(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 September 2014 (25.09.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/151953 A1

(51) International Patent Classification:
A61K 31/505 (2006.01) *A61K 39/395* (2006.01)

(21) International Application Number:
PCT/US2014/026722

(22) International Filing Date:
13 March 2014 (13.03.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/794,094 15 March 2013 (15.03.2013) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2014/151953 A1

(54) Title: COMPOUNDS AND METHODS FOR INDUCING CHONDROGENESIS

(57) Abstract: Described herein are compounds and compositions for the amelioration of arthritis or joint injuries by inducing mesenchymal stem cells into chondrocytes.

COMPOUNDS AND METHODS FOR INDUCING CHONDROGENESIS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Application No. 61/794,094, filed March 15, 2014, which is hereby incorporated by reference in its entirety.

FIELD OF INVENTION

[0002] The present invention relates to compounds, compositions, preparations and their use for inducing chondrogenesis and for the treatment of arthritis or joint injury.

BACKGROUND OF THE INVENTION

[0003] Osteoarthritis (OA) represents the most common musculoskeletal disorder. Approximately 40 million Americans are currently affected and this number is predicted to increase to 60 million within the next twenty years as a result of the aging population and an increase in life expectancy, making it the fourth leading cause of disability. OA is characterized by a slow degenerative breakdown of the joint including both the articular cartilage (containing the cells and matrix which produce lubrication and cushioning for the joint) and the subchondral bone underlying the articular cartilage. Current OA therapies include pain relief with oral NSAIDs or selective cyclooxygenase 2 (COX-2) inhibitors, intra-articular (IA) injection with agents such as corticorsteroids and hyaluronan, and surgical approaches.

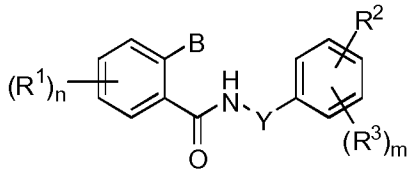
[0004] Mesenchymal stem cells (MSCs) are present in adult articular cartilage and upon isolation can be programmed in vitro to undergo differentiation to chondrocytes and other mesenchymal cell lineages. In part it is regulated by growth factors (TGF s, BMPs), serum conditions and cell-cell contact.

SUMMARY OF THE INVENTION

[0005] Provided herein is a method of ameliorating arthritis or joint injury in a mammal, the method including administering to a joint of the mammal a composition having a therapeutically effective amount of a compound disclosed herein.

[0006] Provided herein is a method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method including contacting mesenchymal stem cells with a sufficient amount of a compound disclosed herein, thereby inducing differentiation of the stem cells into chondrocytes.

[0007] In one aspect, provided herein is a method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula I)

wherein:

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NR^4R^{11}, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

m is 1, 2, 3, or 4;

B is CO_2R^4, CH_2CO_2H, $CH_2CO_2R^4$, or optionally substituted phenyl;

Y is a bond, $-(CR^5R^6)-$, $-(CR^7R^8)(CR^9R^{10})-$, or $-(CR^7R^8)(CR^9R^{10})X-$;

X is O or CR^5R^6;

R^2 is halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$;

each R^3 is independently selected from H, CN, halo, $C(O)R^4$, CO_2H, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$;

each R^4 is independently selected from H and optionally substituted alkyl;

each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, optionally substituted alkyl, OH, CO_2R^4, NR^4R^{11}, and optionally substituted alkoxy; and

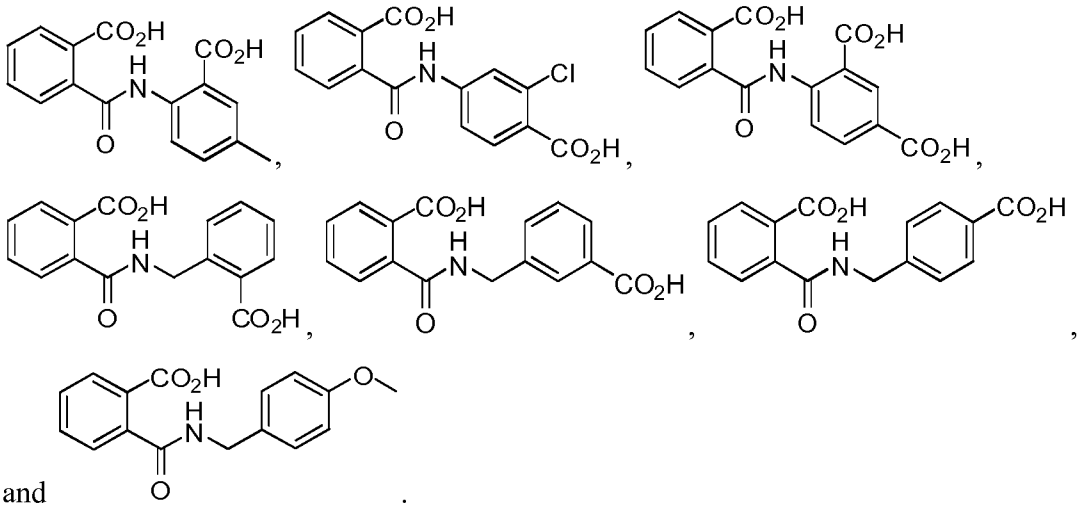
R^{11} is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

provided that

a) if Y is a bond and m is 0, then R^2 is selected from $C(O)NR^4R^{11}$, $(CR^7R^8)OR^4$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$; and

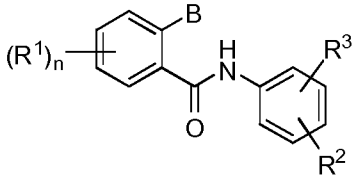
R^2 is not $C(O)NH_2$, p-CH_2OR^4, p-$CH(OH)CH_2OH$, p-CH_2CH_2OH, or p-$CH_2CH_2CH_2OH$; and

b) the compound is not selected from



and .

[0008] In another aspect, provided herein is a method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula Ia, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula Ia)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NR^4R^{11}, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

B is CO_2R^4;

R^2 is halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$;

each R^3 is independently selected from CN, halo, $C(O)R^4$, CO_2H, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$,

$X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$;

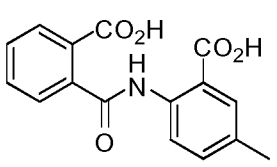
X is O or CR^5R^6;

each R^4 is independently selected from H and optionally substituted alkyl;

each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, optionally substituted alkyl, OH, NR^4R^{11}, and optionally substituted alkoxy; and

R^{11} is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

provided that the compound is not selected from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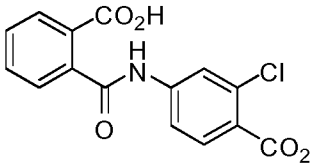
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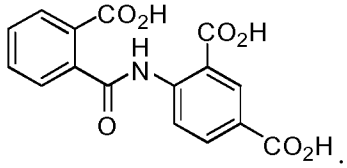
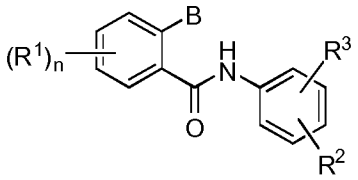

.

[0009] In another aspect, provided herein is a method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula Ib, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula Ib)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NR^4R^{11}, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

B is CO_2R^4;

R^2 is $C(O)NR^4R^{11}$, $(CR^7R^8)OR^4$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$;

R^3 is H;

X is O or CR^5R^6;

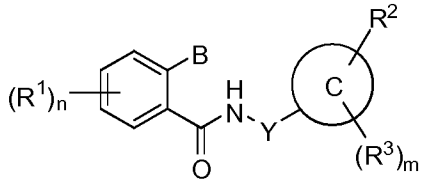
each R^4 is independently selected from H and optionally substituted alkyl;

each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, optionally substituted alkyl, OH, NR^4R^{11}, and optionally substituted alkoxy; and

R^{11} is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

provided that if n is 0, then R^2 is not $C(O)NH_2$, p-CH_2OR^4, p-$CH(OH)CH_2OH$, p-CH_2CH_2OH, or p-$CH_2CH_2CH_2OH$.

[0010] In another aspect, provided herein is a method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula Ic, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula Ic)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NR^4R^{11}, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

m is 1, 2, 3, or 4;

B is CO_2R^4;

Y is -(CR^5R^6)-;

C is aryl or heteroaryl;

X is O or CR^5R^6;

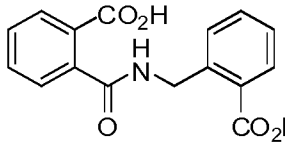
R^2 is halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, SO_2NH_2, SO_3H, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$;

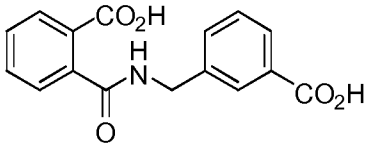
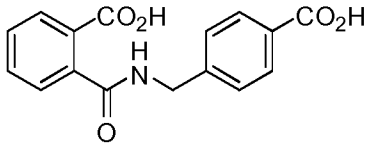
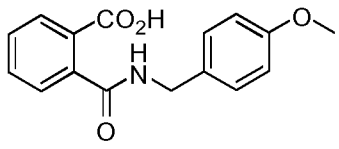
each R^3 is independently selected from H, CN, halo, $C(O)R^4$, CO_2H, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$;

each R^4 is independently selected from H and optionally substituted alkyl;

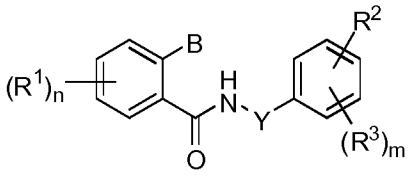
each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, optionally substituted alkyl, OH, CO_2R^4, NR^4R^{11}, and optionally substituted alkoxy; and

R^{11} is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

provided that the compound is not selected from  ,

 ,  , and  .

[0011] In another aspect, provided herein is a method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula I, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula I)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NR^4R^{11}, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

m is 1, 2, 3, or 4;

B is CO_2R^4, CH_2CO_2H, $CH_2CO_2R^3$, or optionally substituted phenyl;

Y is a bond, $-(CR^5R^6)-$, $-(CR^7R^8)(CR^9R^{10})-$, or $-(CR^7R^8)(CR^9R^{10})X-$;

X is O or CR^5R^6;

R^2 is halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$;

each R^3 is independently selected from H, CN, halo, $C(O)R^4$, CO_2H, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$,

$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$;

each R^4 is independently selected from H and optionally substituted alkyl;

each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, optionally substituted alkyl, OH, CO_2R^4, NR^4R^{11}, and optionally substituted alkoxy; and

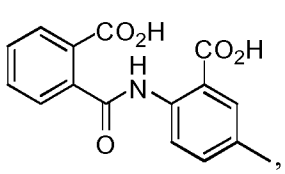
R^{11} is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

provided that

a) if Y is a bond and m is 0, then R^2 is selected from $C(O)NR^4R^{11}$, $(CR^7R^8)OR^4$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$; and

R^2 is not $C(O)NH_2$, p-CH_2OR^4, p-$CH(OH)CH_2OH$, p-CH_2CH_2OH, or p-$CH_2CH_2CH_2OH$; and

b) the compound is not selected from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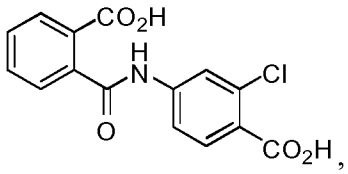
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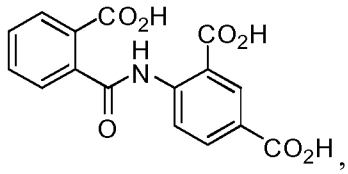
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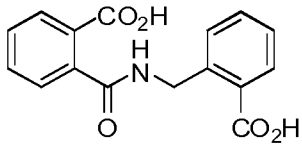
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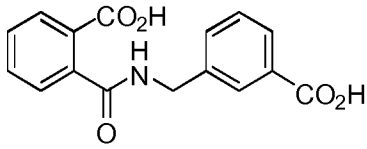
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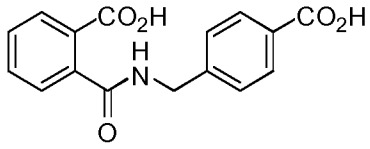
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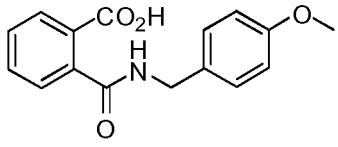
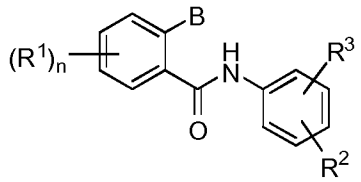

and .

[0012] In another aspect, provided herein is a method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula Ia, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula Ia)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NR^4R^{11}, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

B is CO_2R^4;

R^2 is halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$;

each R^3 is independently selected from CN, halo, $C(O)R^4$, CO_2H, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$;

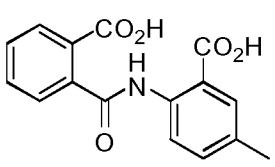
X is O or CR^5R^6;

each R^4 is independently selected from H and optionally substituted alkyl;

each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, optionally substituted alkyl, OH, NR^4R^{11}, and optionally substituted alkoxy; and

R^{11} is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

provided that the compound is not selected from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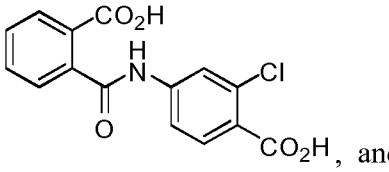
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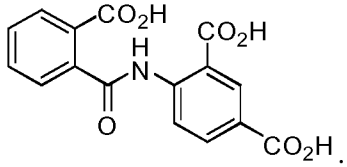
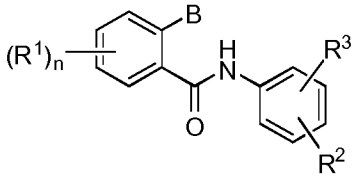

.

[0013] In another aspect, provided herein is a method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula Ib, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula Ib)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NR^4R^{11}, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

B is CO_2R^4;

R^2 is $C(O)NR^4R^{11}$, $(CR^7R^8)OR^4$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$;

R^3 is H;

X is O or CR^5R^6;

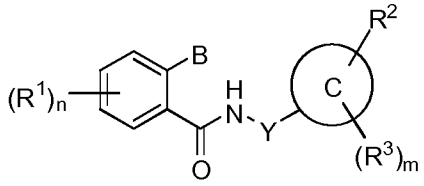
each R^4 is independently selected from H and optionally substituted alkyl;

each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, optionally substituted alkyl, OH, NR^4R^{11}, and optionally substituted alkoxy; and

R^{11} is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

provided that if n is 4 and R^1 is H, then R^2 is not $C(O)NH_2$, p-CH_2OR^4, p-$CH(OH)CH_2OH$, p-CH_2CH_2OH, or p-$CH_2CH_2CH_2OH$.

[0014] In another aspect, provided herein is a method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula Ic, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula Ic)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NR^4R^{11}, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

m is 1, 2, 3, or 4;

B is CO_2R^4;

Y is -(CR^5R^6)-;

C is aryl or heteroaryl;

X is O or CR^5R^6;

R^2 is halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, SO_2NH_2, SO_3H, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$,

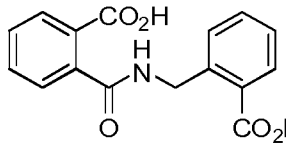
$X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$;

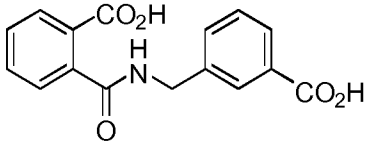
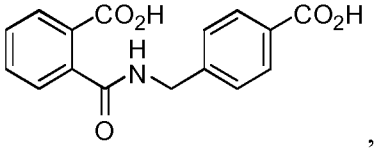
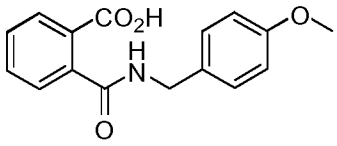
each R^3 is independently selected from H, CN, halo, $C(O)R^4$, CO_2H, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$

each R^4 is independently selected from H and optionally substituted alkyl;

each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, optionally substituted alkyl, OH, CO_2R^4, NR^4R^{11}, and optionally substituted alkoxy; and

R^{11} is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

provided that the compound is not selected from  ,

 ,  , and  .

[0015] In some embodiments described above or below of a compound of Formula I or Ia:

R^2 is halo, $C(O)R^4$, alkyl, optionally substituted alkoxy, haloalkyl, $(CR^7R^8)OR^4$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)C(O)OR^4$, or $X(CR^7R^8)C(O)NR^4R^{11}$; and

each R^3 is independently selected from CN, halo, $C(O)R^4$, CO_2H, $C(O)NR^4R^{11}$, alkyl, or optionally substituted alkoxy;

or R^3 together with an adjacent R^3 or with R^2 form a ring.

[0016] In certain embodiments described above or below of a compound of Formula I or Ia:

R^2 is F, Cl, $C(O)CH_3$, CH_3, CF_3, OCH_3, OEt, OPr, OCF_3, $OCHF_2$, $(CR^7R^8)OR^4$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)C(O)OR^4$, or $X(CR^7R^8)C(O)NR^4R^{11}$; and

each R^3 is independently selected from CN, F, Cl, $C(O)CH_3$, CO_2H, $C(O)NH_2$, CH_3, OCF_3, or OCH_3;

or R^3 together with an adjacent R^3 or with R^2 form a ring.

In certain embodiments, R^3 is independently selected from CN, F, Cl, $C(O)CH_3$, or CO_2H. In certain embodiments, R^2 is F, Cl, $C(O)CH_3$, CH_3, CF_3, OCH_3, OEt, OPr, OCF_3, or $CH_2CH_2CH_2OH$.

[0017] In some embodiments described above or below of a compound of Formula Ib:

R^2 is $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$; and

R^3 is H.

In certain embodiments, R^2 is $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, or $(CR^7R^8)NR^4SO_2R^4$. In certain embodiments, R^2 is CH_2CH_2OH, $CH_2CH_2OCH_3$, CH_2CHCH_3OH, $CHCH_3CH_2OH$, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2NH_2$, $CH_2CH_2CHCH_3OH$, $C(CH_3)_2CH_2CH_2OH$, $CH_2CH_2C(CH_3)_2OH$, OCH_2CH_2OH, $OCH_2CH_2OCH_3$, or $OCH_2CH_2NH_2$. In certain embodiments, R^2 is $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, or $X(CR^7R^8)C(O)NR^4R^{11}$. In certain embodiments, R^2 is $CH_2C(O)CH_3$, $CH_2C(O)NH_2$, $CH_2CH_2C(O)CH_3$, or $CH_2CH_2C(O)NH_2$.

[0018] In some embodiments described above or below of a compound of Formula Ic, C is aryl. In certain embodiments, C is phenyl.

[0019] In some embodiments described above or below of a compound of Formula Ic, C is heteroaryl. In certain embodiments, C is pyridinyl, pyrimidinyl, pyridazinyl, or pyrazinyl.

[0020] In some embodiments described above or below of a compound of Formula Ic:

R^2 is halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2NH_2, SO_3H, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)OR^4$, or $X(CR^7R^8)C(O)NR^4R^{11}$; and

each R^3 is independently selected from H, CN, halo, CO_2H, or haloalkyl.

[0021] In certain embodiments described above or below of a compound of Formula Ic:

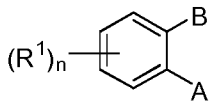
R^2 is Cl, F, $C(O)CH_3$, CO_2H, $C(O)NR^4R^{11}$, CH_3, optionally substituted alkoxy, CF_3, SO_2NH_2, SO_3H, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)OR^4$, or $X(CR^7R^8)C(O)NR^4R^{11}$; and

each R^3 is independently selected from H, CN, Cl, F, CO_2H, or CF_3.

In certain embodiments, R^2 is Cl, F, $C(O)CH_3$, CO_2H, CH_3, OCH_3, CF_3; and each R^3 is independently selected from H, CN, or CO_2H. In certain embodiments, R^2 is $CH_2C(O)NH_2$, $CH_2C(O)CH_3$, $CH_2C(O)OH$, $CH_2CH_2C(O)OH$, or $CH_2CH_2C(O)NH_2$.

[0022] In one aspect, provided herein is a method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a

therapeutically effective amount of a compound of Formula II, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula II)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

B is $NHC(O)R^2$, $NR^3C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NHR^2$, $NHC(O)NR^2R^4$, $NR^3C(O)NH_2$, $NR^3C(O)NHR^2$, $NR^3C(O)NR^2R^4$, $NHC(O)OR^2$, $NR^3C(O)OR^2$, $NHSO_2R^3$, $NR^3SO_2R^3$, $NHSO_2R^4$, $NR^3SO_2R^4$, $NHSO_2NH_2$, $NHSO_2NHR^2$, $NHSO_2NR^2R^4$, $NR^3SO_2NH_2$, $NR^3SO_2NHR^2$, or $NR^3SO_2NR^2R^4$;

each R^2 and R^4 is independently optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted alkyl;

R^3 is optionally substituted alkyl or optionally substituted aralkyl;

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

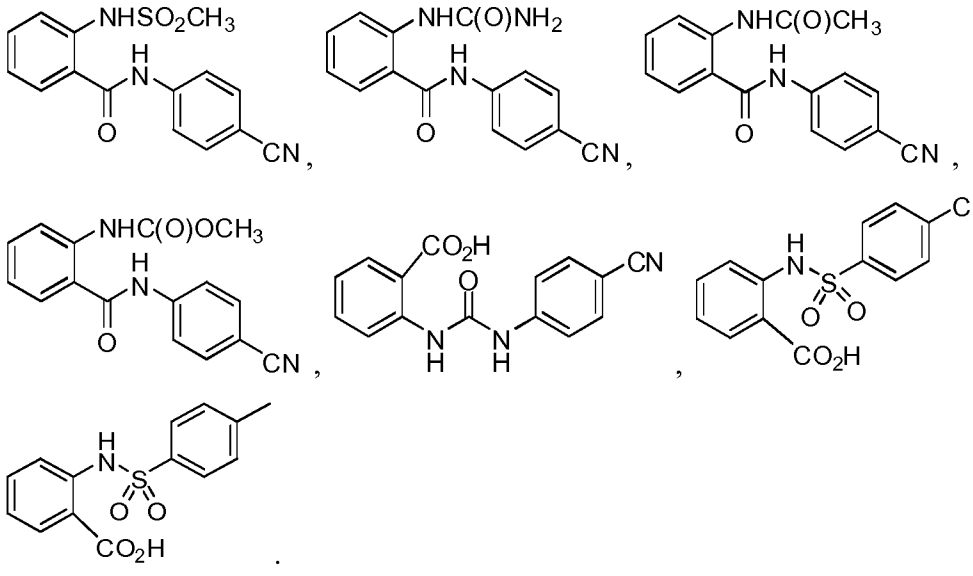
A is CO_2H, CO_2R^3, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^4$, or $SO_2NR^aR^b$; and

each R^a and R^b is independently optionally substituted alkyl or together with the N to which they are attached make a ring;

provided that

a) if B is $NHC(O)R^2$ or $NR^3C(O)R^2$, then A is not CO_2H; and

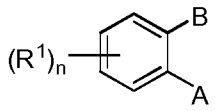
b) the compound is not selected from



, and

.

[0023] In another aspect, provided herein is a method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula IIa, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula IIa)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

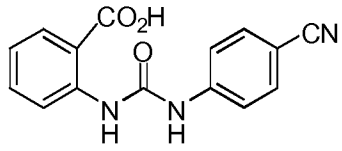
B is $NHC(O)NH_2$, $NHC(O)NHR^2$, $NHC(O)NR^2R^4$, $NR^3C(O)NH_2$, $NR^3C(O)NHR^2$, or $NR^3C(O)NR^2R^4$;

each R^2 and R^4 is independently optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted alkyl;

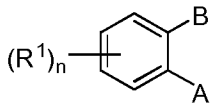
R^3 is optionally substituted alkyl or optionally substituted aralkyl;

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4; and

A is CO_2H or CO_2R^3;

provided that the compound is not  .

[0024] In another aspect, provided herein is a method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula IIb, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula IIb)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

B is $NHC(O)R^2$ or $NR^3C(O)R^2$;

R^2 is optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted alkyl;

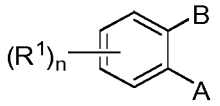
R^3 is optionally substituted alkyl or optionally substituted aralkyl;

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

A is $SO_2NR^aR^b$; and

each R^a and R^b is independently optionally substituted alkyl or together with the N to which they are attached make a ring.

[0025] In another aspect, provided herein is a method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula IIc, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula IIc)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

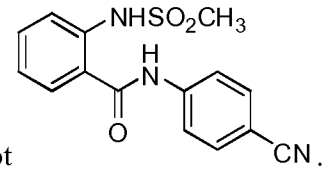
B is $NHSO_2R^3$, $NR^3SO_2R^3$, $NHSO_2R^4$, $NR^3SO_2R^4$, $NHSO_2NH_2$, $NHSO_2NHR^2$, $NHSO_2NR^2R^4$, $NR^3SO_2NH_2$, $NR^3SO_2NHR^2$, or $NR^3SO_2NR^2R^4$;

each R^2 and R^4 is independently optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted alkyl;

each R^3 is independently optionally substituted alkyl or optionally substituted aralkyl;

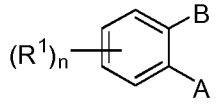
R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4; and

A is $C(O)NHR^2$ or $C(O)NR^2R^4$;

provided that the compound is not 

.

[0026] In another aspect provided herein is a method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula II, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula II)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

B is $NHC(O)R^2$, $NR^3C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NHR^2$, $NHC(O)NR^2R^4$, $NR^3C(O)NH_2$, $NR^3C(O)NHR^2$, $NR^3C(O)NR^2R^4$, $NHC(O)OR^2$, $NR^3C(O)OR^2$, $NHSO_2R^3$, $NR^3SO_2R^3$, $NHSO_2R^4$, $NR^3SO_2R^4$, $NHSO_2NH_2$, $NHSO_2NHR^2$, $NHSO_2NR^2R^4$, $NR^3SO_2NH_2$, $NR^3SO_2NHR^2$, or $NR^3SO_2NR^2R^4$;

each R^2 and R^4 is independently optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted alkyl;

R^3 is optionally substituted alkyl or optionally substituted aralkyl;

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

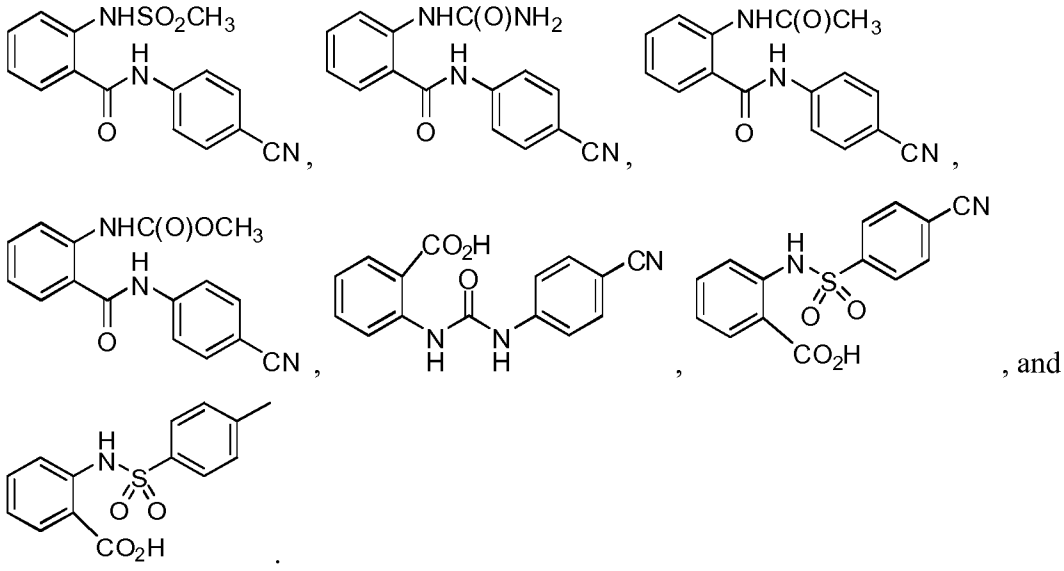
A is CO_2H, CO_2R^3, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^4$, or $SO_2NR^aR^b$; and

each R^a and R^b is independently optionally substituted alkyl or together with the N to which they are attached make a ring;

provided that

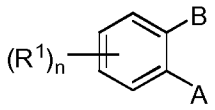
a) if B is $NHC(O)R^2$ or $NR^3C(O)R^2$, then A is not CO_2H; and

b) the compound is not selected from



[0027] In another aspect, provided herein is a method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a

sufficient amount of a compound of Formula IIa, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula IIa)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

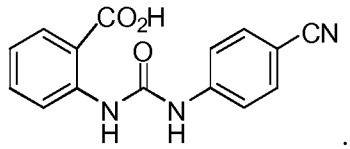
B is $NHC(O)NH_2$, $NHC(O)NHR^2$, $NHC(O)NR^2R^4$, $NR^3C(O)NH_2$, $NR^3C(O)NHR^2$, or $NR^3C(O)NR^2R^4$;

each R^2 and R^4 is independently optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted alkyl;

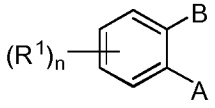
R^3 is optionally substituted alkyl or optionally substituted aralkyl;

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4; and

A is CO_2H or CO_2R^3;

provided that the compound is not  .

[0028] In another aspect, provided herein is a method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula IIb, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula IIb)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

B is $NHC(O)R^2$ or $NR^3C(O)R^2$;

R^2 is optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted alkyl;

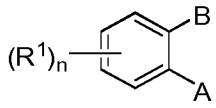
R^3 is optionally substituted alkyl or optionally substituted aralkyl;

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

A is $SO_2NR^aR^b$; and

each R^a and R^b is independently optionally substituted alkyl or together with the N to which they are attached make a ring.

[0029] In another aspect, provided herein is a method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula IIc, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula IIc)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

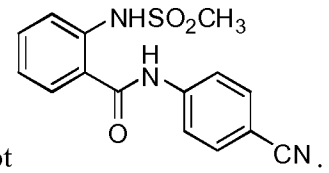
B is $NHSO_2R^3$, $NR^3SO_2R^3$, $NHSO_2R^4$, $NR^3SO_2R^4$, $NHSO_2NH_2$, $NHSO_2NHR^2$, $NHSO_2NR^2R^4$, $NR^3SO_2NH_2$, $NR^3SO_2NHR^2$, or $NR^3SO_2NR^2R^4$;

each R^2 and R^4 is independently optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted alkyl;

each R^3 is independently optionally substituted alkyl or optionally substituted aralkyl;

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4; and

A is $C(O)NHR^2$ or $C(O)NR^2R^4$;

provided that the compound is not 

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[0030] In some embodiments described above or below of a compound of Formula IIa, B is $NHC(O)NHR^2$, $NHC(O)NR^2R^4$, $NR^3C(O)NHR^2$, or $NR^3C(O)NR^2R^4$. In certain embodiments, B is $NHC(O)NHR^2$ or $NR^3C(O)NHR^2$. In certain embodiments, B is $NHC(O)NR^2R^4$ or $NR^3C(O)NR^2R^4$. In certain embodiments, B is $NHC(O)NHR^2$.

[0031] In some embodiments described above or below of a compound of Formula IIa, R^2 is optionally substituted phenyl. In certain embodiments, the phenyl of R^2 is bisubstituted. In certain embodiments, the phenyl of R^2 is monosubstituted. In certain embodiments, the phenyl of R^2 is independently selected from F, Cl, CO_2H, CN, OCH_3, $C(O)CH_3$, CF_3, CH_3, CH_2OH, CH_2CH_2OH, and $CH_2CH_2CH_2OH$.

[0032] In some embodiments described above or below of a compound of Formula IIb, B is $NHC(O)R^2$.

[0033] In some embodiments described above or below of a compound of Formula IIb, B is $NR^3C(O)R^2$. In certain embodiments, R^3 is optionally substituted alkyl.

[0034] In some embodiments described above or below of a compound of Formula IIb, each R^a and R^b is independently optionally substituted alkyl. In some embodiments described above or below of a compound of Formula IIb, R^a and R^b together with the N to which they are attached make a ring.

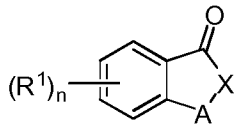
[0035] In some embodiments described above or below of a compound of Formula IIb, R^2 is optionally substituted phenyl. In certain embodiments, the phenyl of R^2 is bisubstituted. In certain embodiments, the phenyl of R^2 is monosubstituted. In certain embodiments, substitution on the phenyl of R^2 is independently selected from F, Cl, CO_2H, CN, OCH_3, $C(O)CH_3$, CF_3, CH_3, CH_2OH, CH_2CH_2OH, and $CH_2CH_2CH_2OH$.

[0036] In some embodiments described above or below of a compound of Formula IIc, B is $NHSO_2R^3$, $NR^3SO_2R^3$, $NHSO_2R^4$, or $NR^3SO_2R^4$. In certain embodiments, B is $NHSO_2R^3$ or $NR^3SO_2R^3$. In certain embodiments, B is $NHSO_2R^3$. In certain embodiments, R^3 is optionally substituted alkyl. In certain embodiments, R^3 is CH_3. In certain embodiments, B is $NHSO_2R^4$ or $NR^3SO_2R^4$. In certain embodiments, R^4 is optionally substituted phenyl.

[0037] In some embodiments described above or below of a compound of Formula IIc, B is $NHSO_2NH_2$, $NHSO_2NHR^2$, $NHSO_2NR^2R^4$, $NR^3SO_2NH_2$, $NR^3SO_2NHR^2$, or $NR^3SO_2NR^2R^4$.

[0038] In some embodiments described above or below of a compound of Formula IIc, A is $C(O)NHR^2$. In some embodiments described above or below of a compound of Formula IIc, A is $C(O)NR^2R^4$. In certain embodiments, R^2 is optionally substituted phenyl. In certain embodiments, the phenyl of R^2 is bisubstituted. In certain embodiments, the phenyl of R^2 is monosubstituted. In certain embodiments, substitution on the phenyl of R^2 is independently selected from F, Cl, CO_2H, CN, OCH_3, $C(O)CH_3$, CF_3, CH_3, CH_2OH, CH_2CH_2OH, and $CH_2CH_2CH_2OH$.

[0039] In another aspect, provided herein is a method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula III, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula III)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

X is O, NH, or NR^6;

A is C(O), CH_2, or $CH\text{-}CR^3R^4\text{-}C(O)R^2$;

R^2 is optionally substituted aryl or optionally substituted heteroaryl;

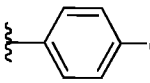
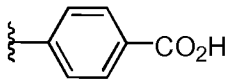
each R^3 and R^4 is independently H or optionally substituted alkyl;

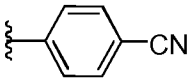
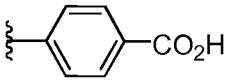
R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4; and

R^6 is optionally substituted phenyl;

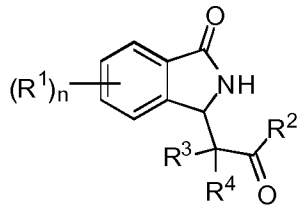
provided that

a) if A is $CH\text{-}CR^3R^4\text{-}C(O)R^2$, then X is O or NH;

b) if n is 0, A is $CHCH_2C(O)R^2$ and X is O, then R^2 is not  or  ; and

c) if A is C(O) or CH_2, then X is NR^6 and R^6 is not  or  .

[0040] In another aspect, provided herein is a method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula IIIa, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula IIIa)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

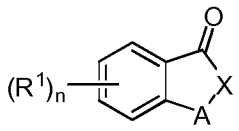
n is 0, 1, 2, 3, or 4;

R^2 is optionally substituted aryl or optionally substituted heteroaryl;

each R^3 and R^4 is independently H or optionally substituted alkyl; and

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4.

[0041] In another aspect, provided herein is a method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula III, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula III)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

X is O, NH, or NR^6;

A is C(O), CH_2, or $CH\text{-}CR^3R^4\text{-}C(O)R^2$;

R^2 is optionally substituted aryl or optionally substituted heteroaryl;

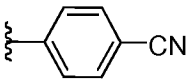
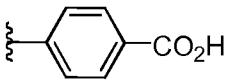
each R^3 and R^4 is independently H or optionally substituted alkyl;

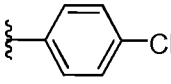
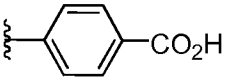
R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4; and

R^6 is optionally substituted phenyl;

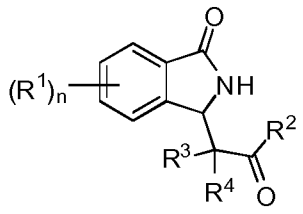
provided that

a) if A is $CH\text{-}CR^3R^4\text{-}C(O)R^2$, then X is O or NH;

b) if n is 0, A is $CHCH_2C(O)R^2$ and X is O, then R^2 is not  or  ; and

c) if A is C(O) or CH_2, then X is NR^6 and R^6 is not  or  .

[0042] In another aspect, provided herein is a method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula IIIa, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula IIIa)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

R^2 is optionally substituted aryl or optionally substituted heteroaryl;

each R^3 and R^4 is independently H or optionally substituted alkyl; and

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4.

[0043] In some embodiments described above or below of a compound of Formula III, X is NR^6 and A is C(O). In some embodiments described above or below of a compound of Formula III, X is NR^6 and A is CH_2. In some embodiments described above or below of a compound of Formula III, X is O and A is $CH\text{-}CR^3R^4\text{-}C(O)R^2$. In some embodiments described above or below of a compound of Formula III, X is NH and A is $CH\text{-}CR^3R^4\text{-}C(O)R^2$.

[0044] In some embodiments described above or below of a compound of Formula III or IIIa, R^3 and R^4 are both hydrogen. In some embodiments described above or below of a compound of Formula III or IIIa, R^3 is optionally substituted alkyl and R^4 is hydrogen. In some embodiments described above or below of a compound of Formula III or IIIa, R^3 and R^4 are independently optionally substituted alkyl.

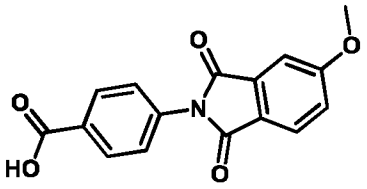
[0045] In some embodiments described above or below of a compound of Formula III or IIIa, R^2 is optionally substituted heteroaryl. In certain embodiments, R^2 is optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted pyridazinyl, or optionally substituted pyrazinyl.

[0046] In some embodiments described above or below of a compound of Formula III or IIIa, R^2 is phenyl. In certain embodiments, the phenyl of R^2 is bisubstituted. In certain embodiments, the phenyl of R^2 is monosubstituted. In certain embodiments, substitution on the phenyl is independently selected from F, Cl, CO_2H, CN, OCH_3, $C(O)CH_3$, CF_3, CH_3, CH_2OH, CH_2CH_2OH, and $CH_2CH_2CH_2OH$.

[0047] In some embodiments described above or below of a compound disclosed herein, B is CO_2R^4 and R^4 is optionally substituted alkyl. In some embodiments described above or below of a compound disclosed herein, B is CO_2R^4 and R^4 is hydrogen.

[0048] In some embodiments described above or below of a compound disclosed herein, n is 0, 1, or 2. In certain embodiments, n is 0. In certain embodiments, n is 1. In certain embodiments, R^1 is independently selected from Cl, F, CH_2OH, CH_2NH_2, OCH_3, OCF_3, $OCHF_2$, CN, NO_2, CO_2H, and CO_2CH_3.

[0049] In one aspect, provided herein is a method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof, selected from: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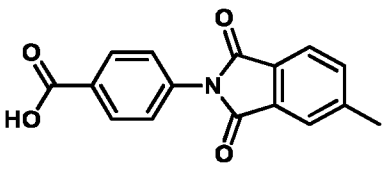
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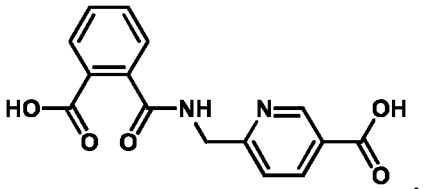
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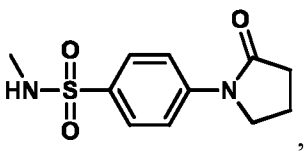
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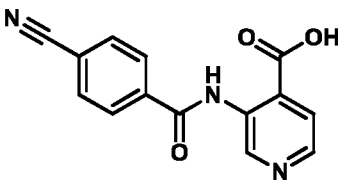
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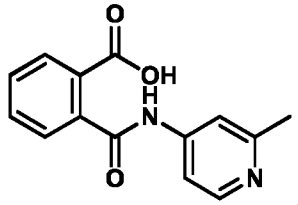
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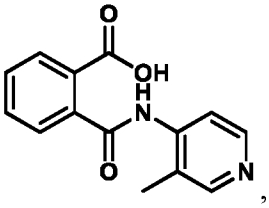
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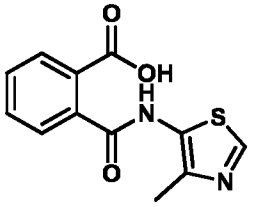
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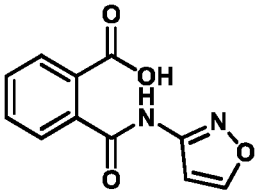
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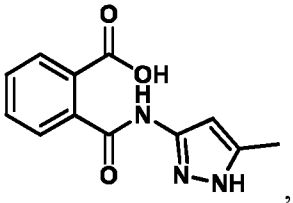
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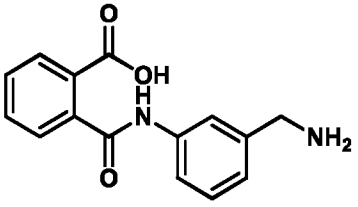
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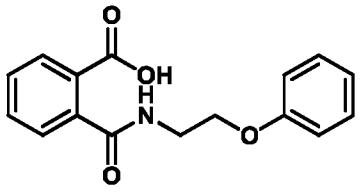
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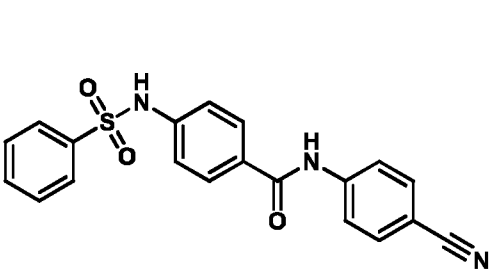
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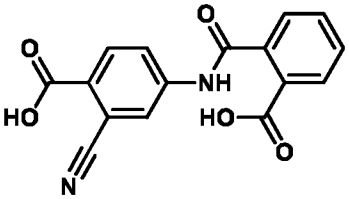
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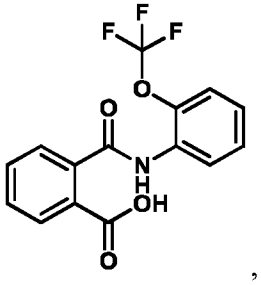
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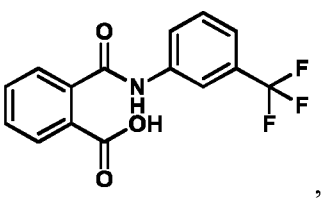
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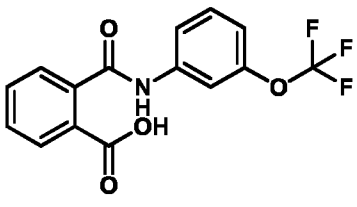
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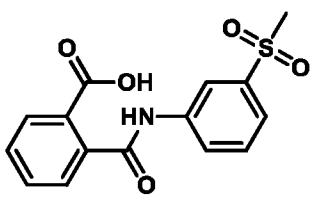
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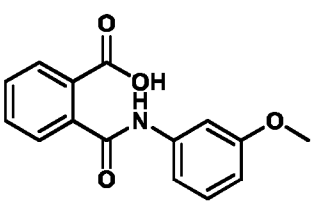
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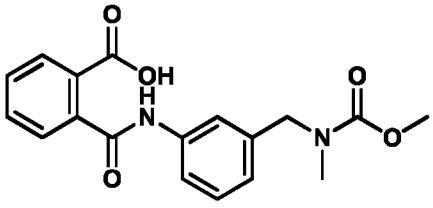
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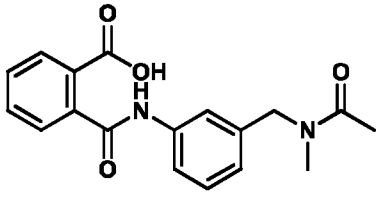
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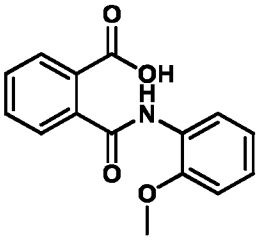
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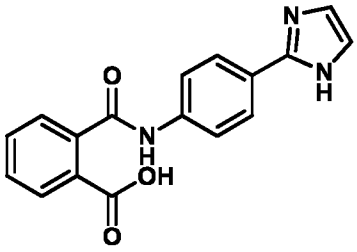
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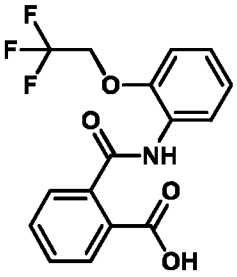
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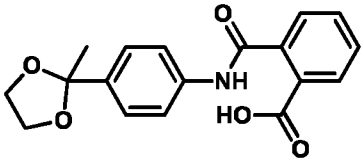
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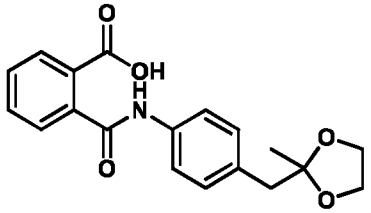
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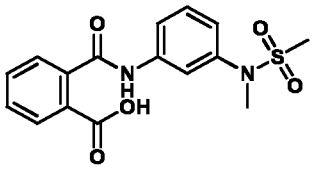
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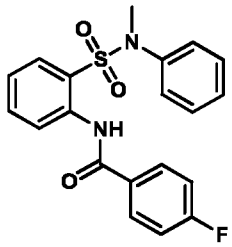
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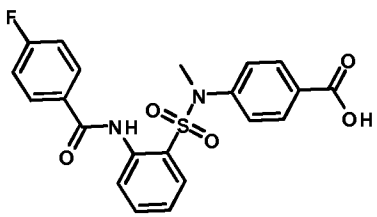
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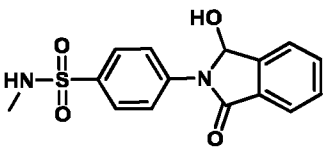
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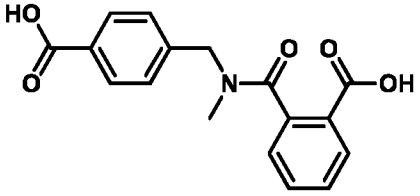
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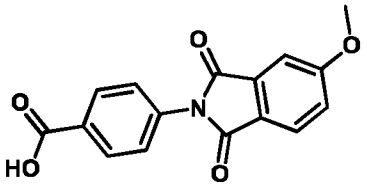
[0050] In another aspect, provided herein is a method of of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof, selected from: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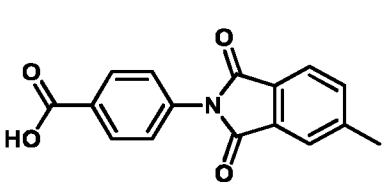
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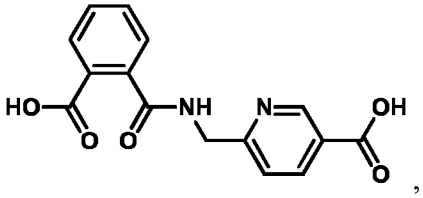
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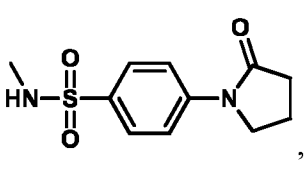
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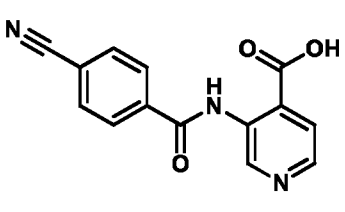
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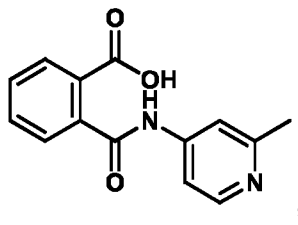
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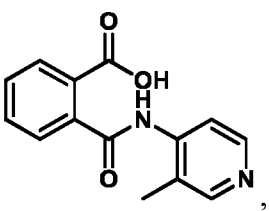
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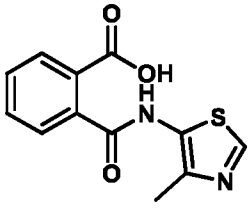
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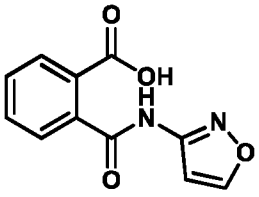
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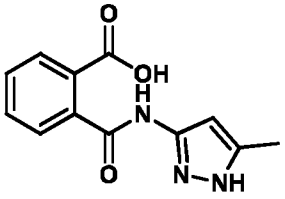
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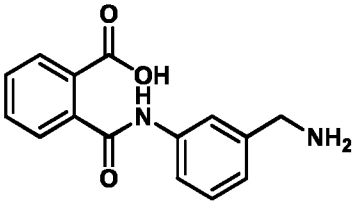
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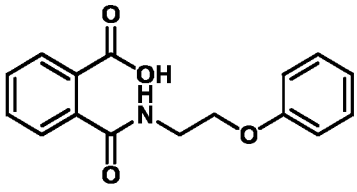
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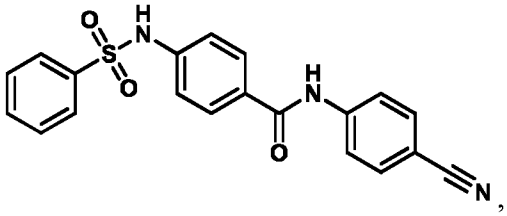
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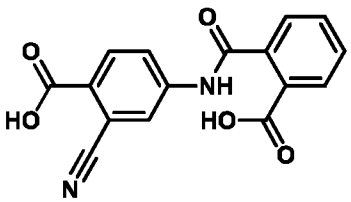
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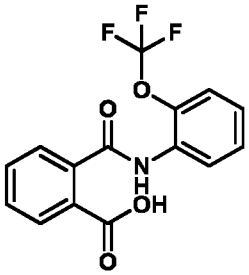
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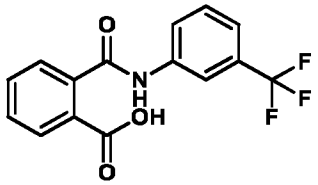
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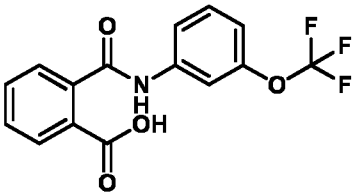
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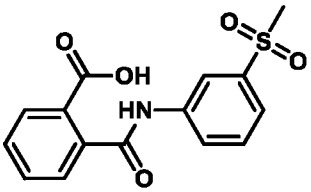
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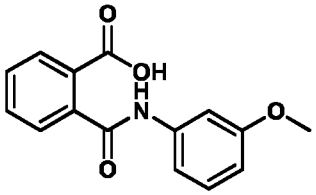
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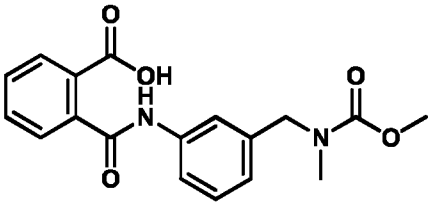
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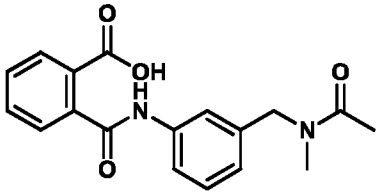
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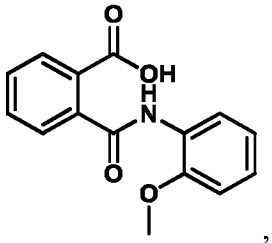
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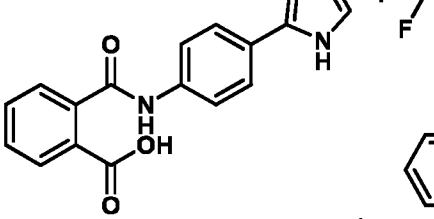
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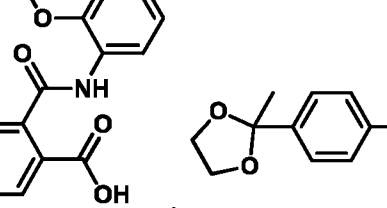
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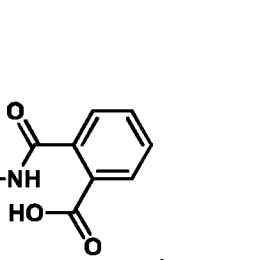
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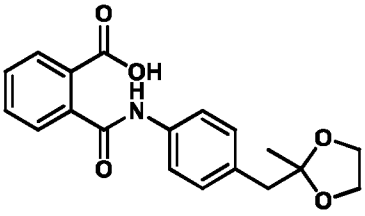
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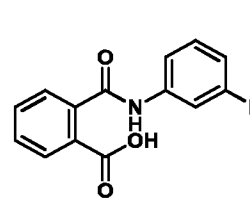
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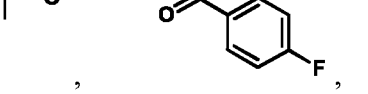
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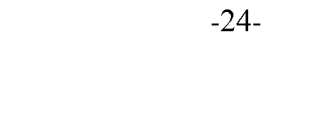
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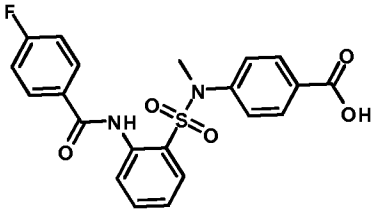
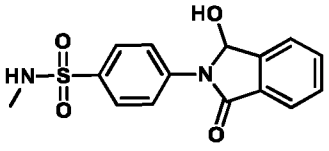
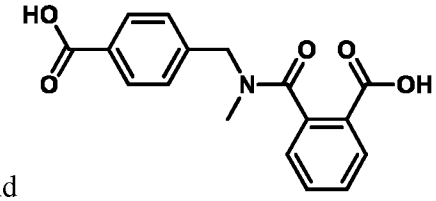
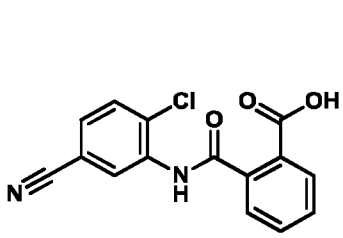
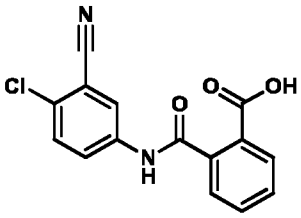
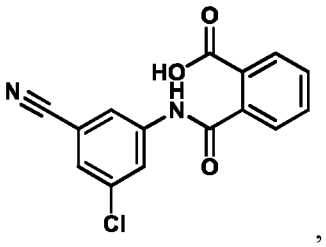
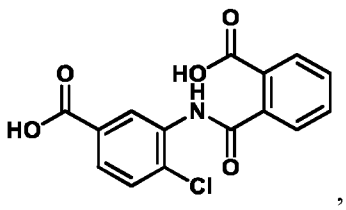
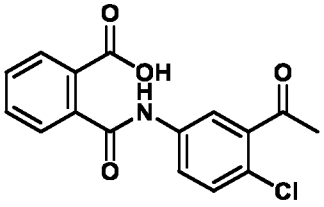
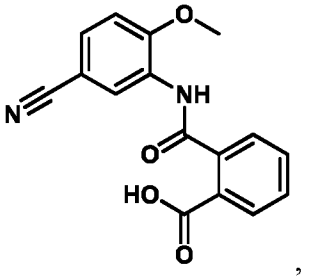
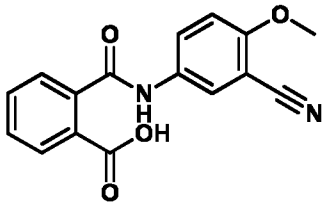
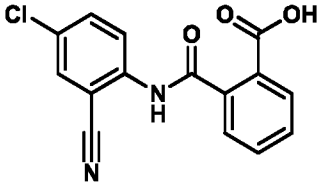
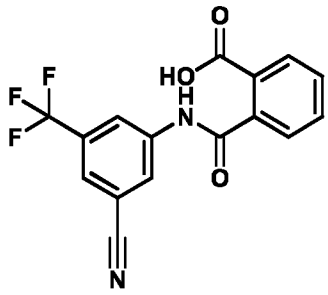
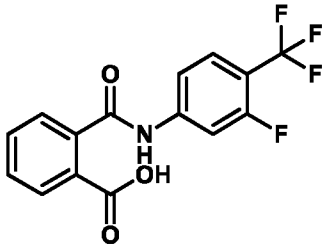
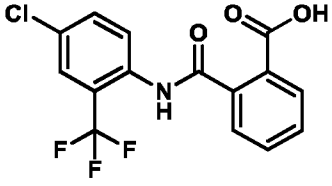
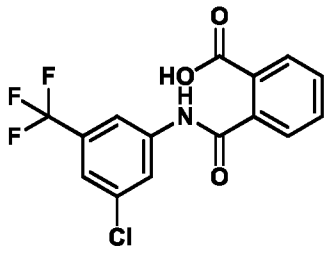



, and .

[0051] In some embodiments described above, the method is performed *in vitro.*

[0052] In some embodiments described above, the method is performed *in vivo* in a mammal and the stem cells are present in the mammal. In some embodiments, the mammal is a domesticated animal or livestock. In certain embodiments, the mammal is a human, a dog, a cat, or a horse.

[0053] In one aspect, provided herein are compounds of Formula I, or pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, esters, metabolites, N-oxides, stereoisomers, or isomers thereof, selected from: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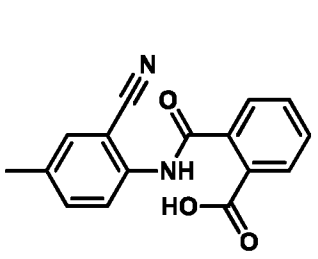

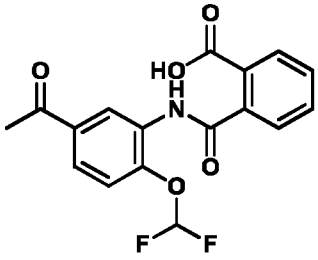

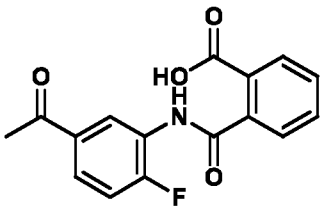

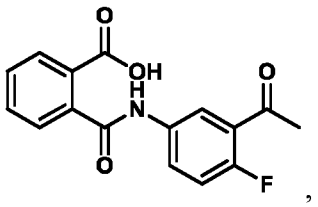

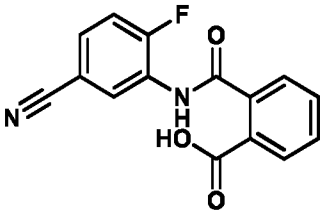

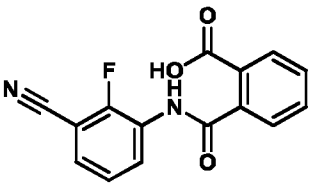

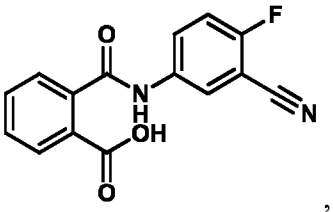

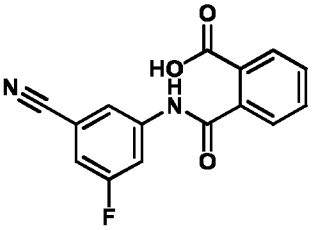

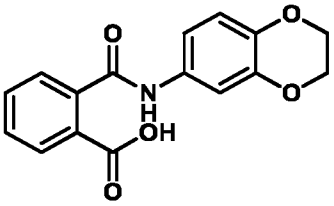

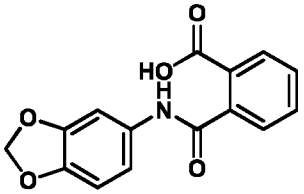

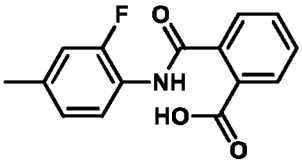

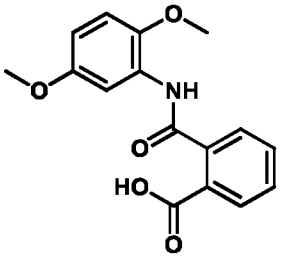

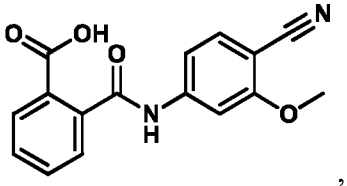

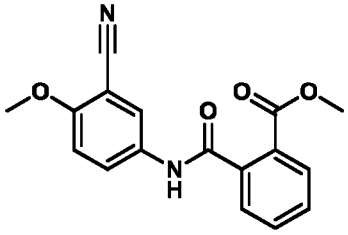

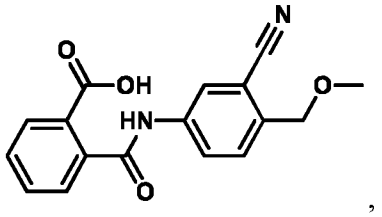

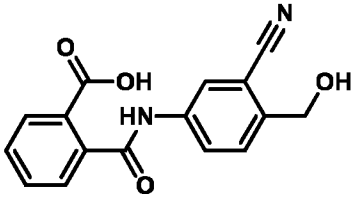

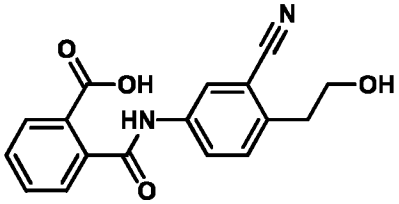

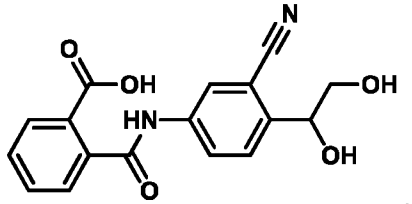

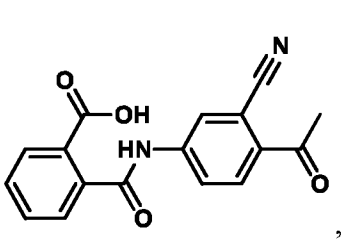

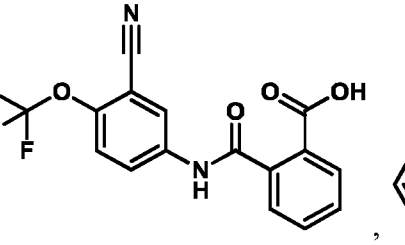

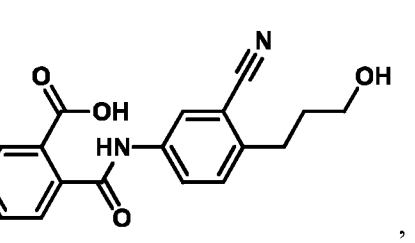

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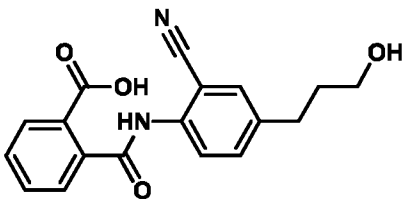
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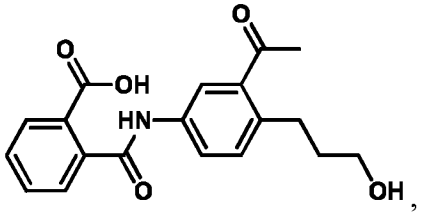
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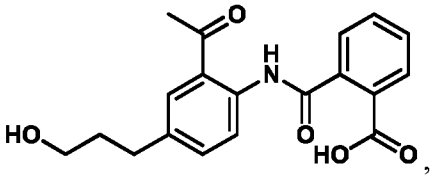
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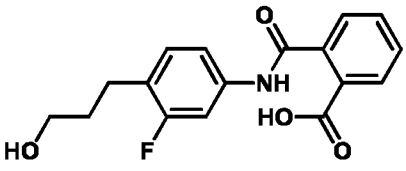
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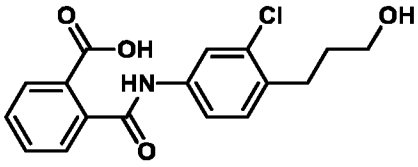
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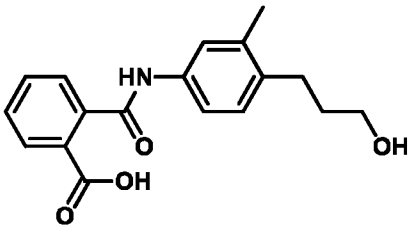
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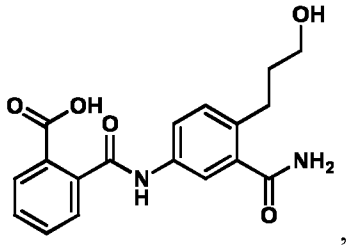
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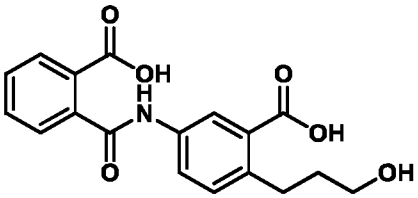
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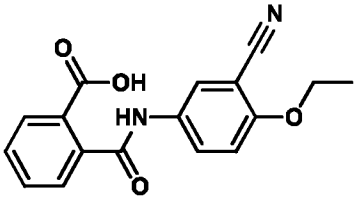
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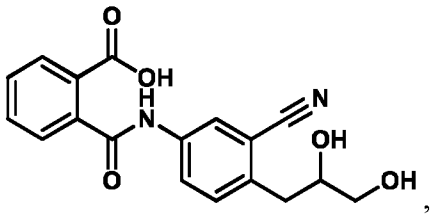
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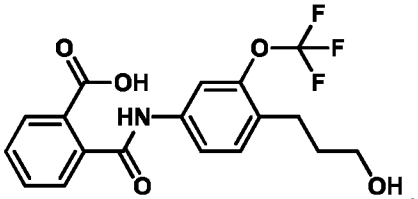
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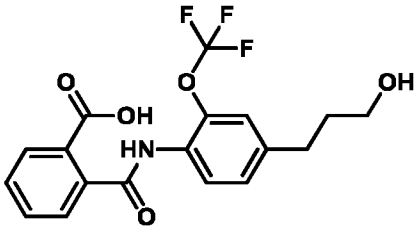
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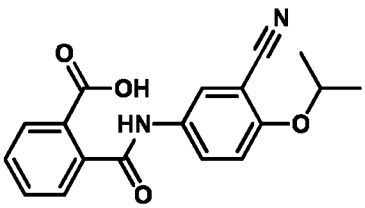
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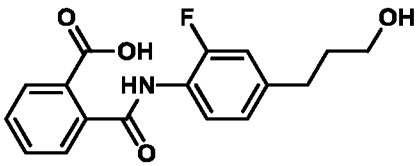
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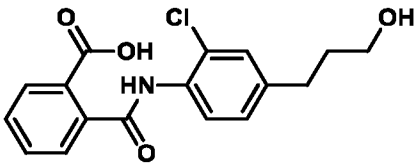
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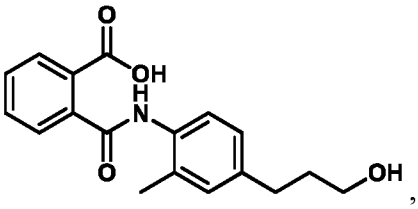
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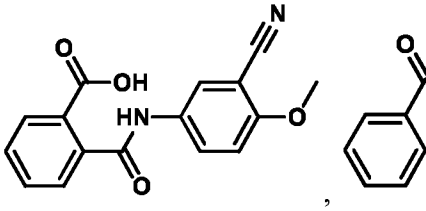
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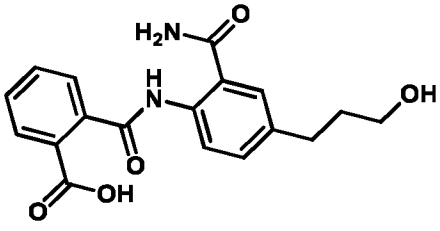
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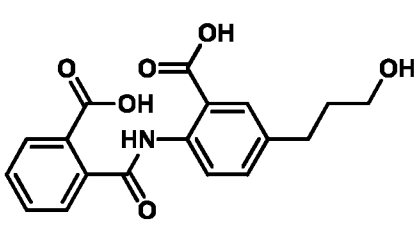
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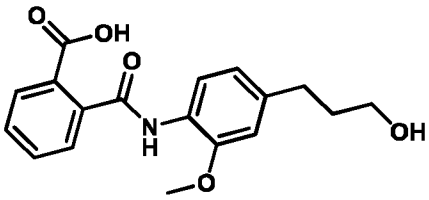
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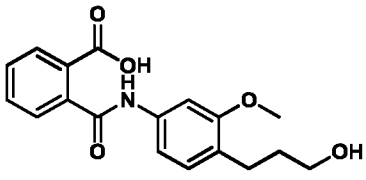
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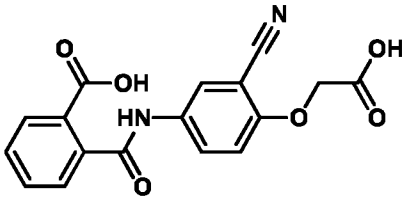
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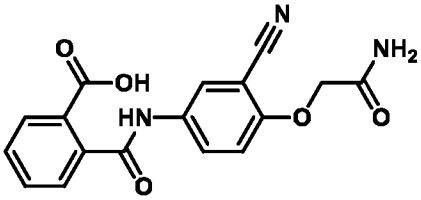
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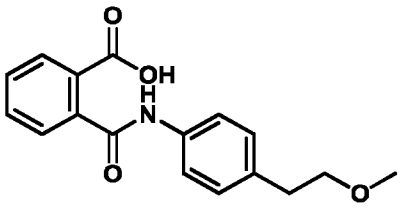
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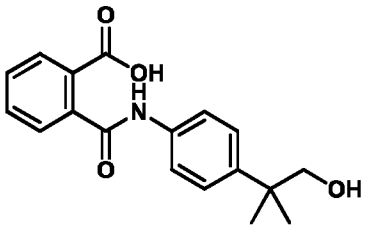
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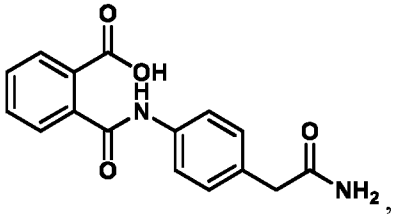
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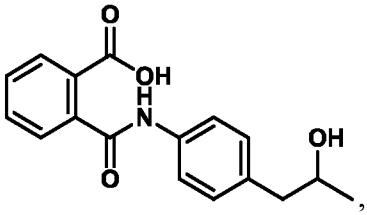
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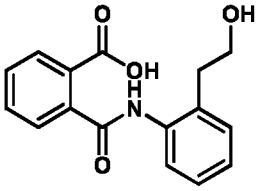
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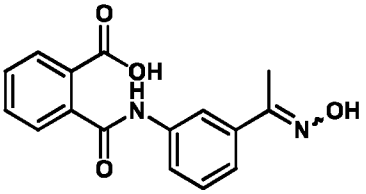
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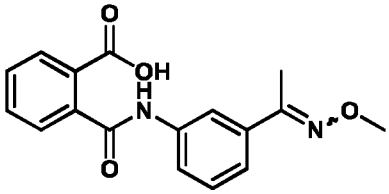
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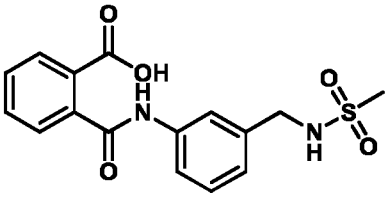
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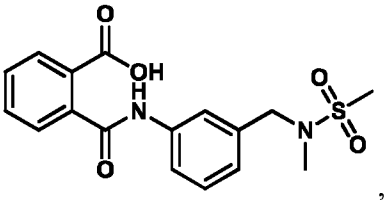
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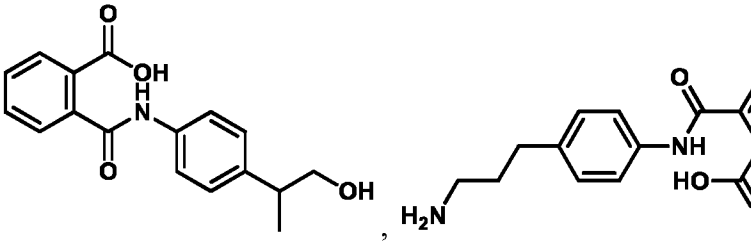
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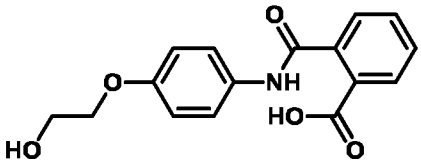
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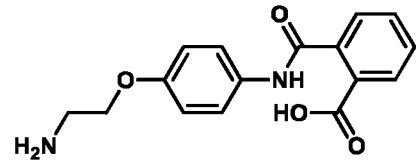
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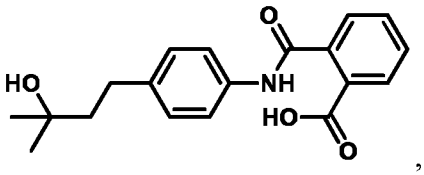
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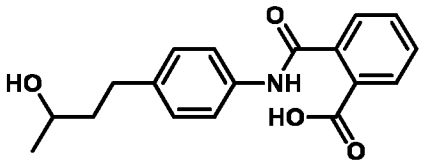
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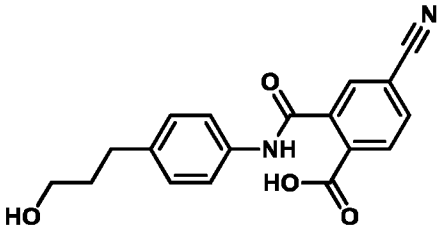
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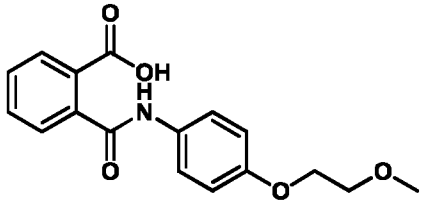
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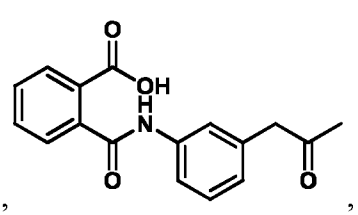
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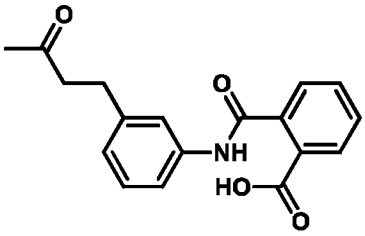
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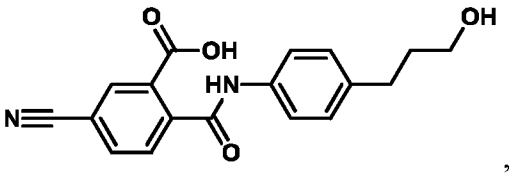
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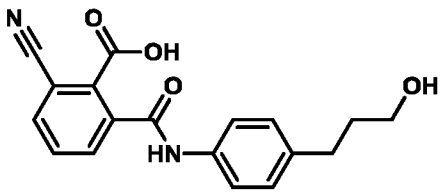
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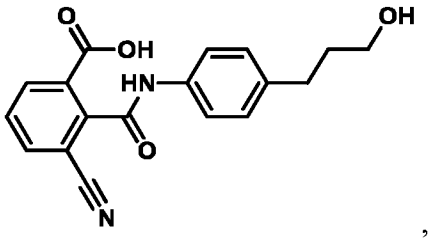
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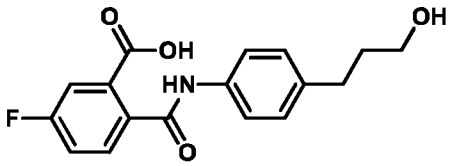
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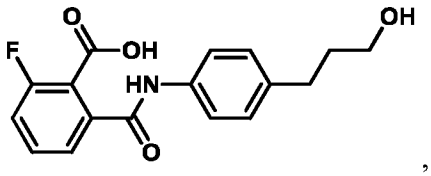
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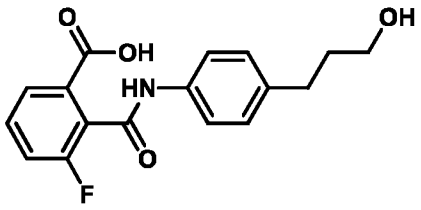
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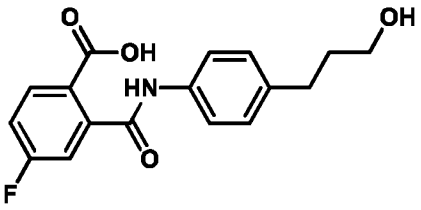
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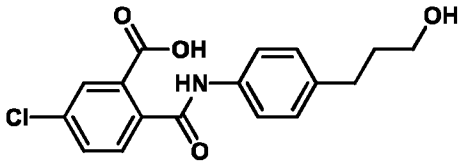
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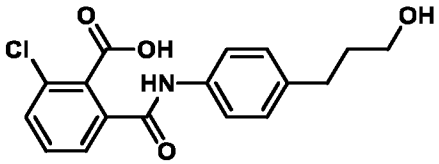
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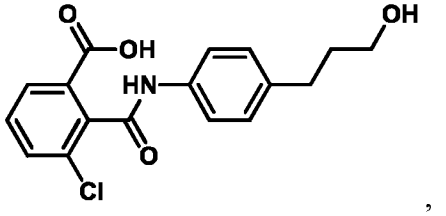
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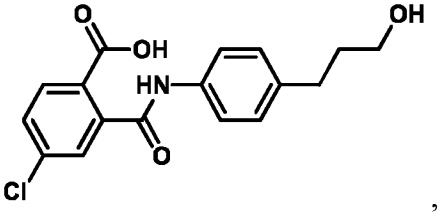
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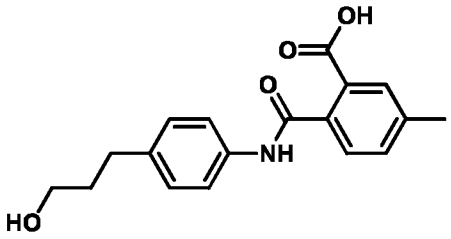
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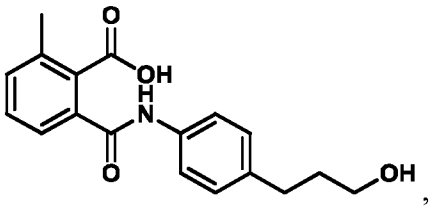
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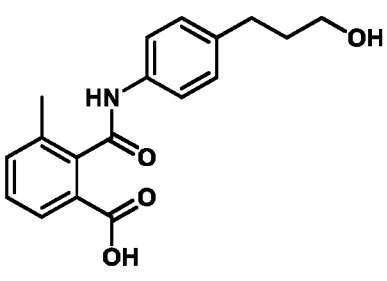
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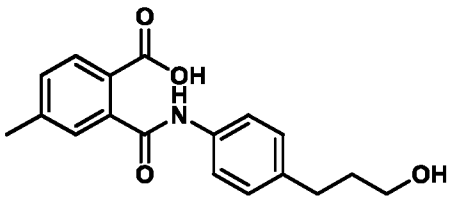
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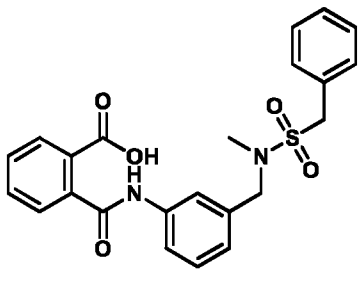

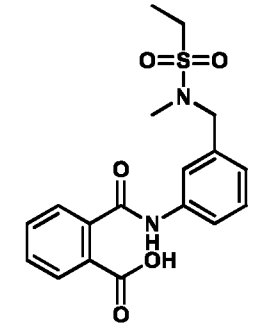
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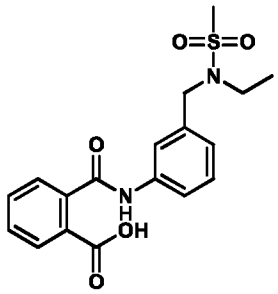
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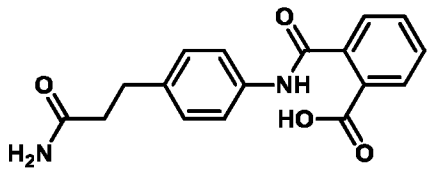
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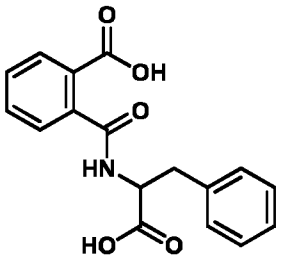
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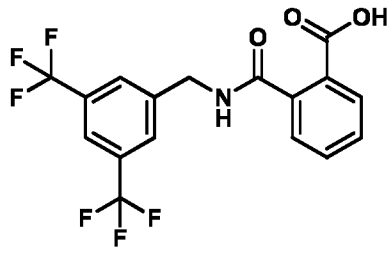
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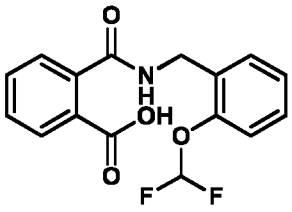
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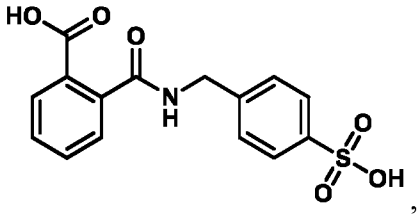
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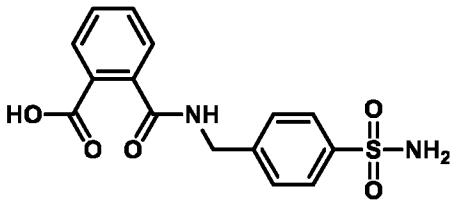
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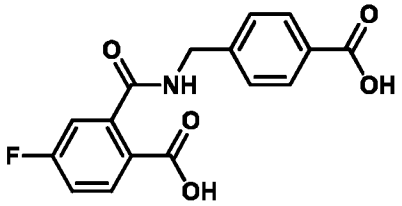
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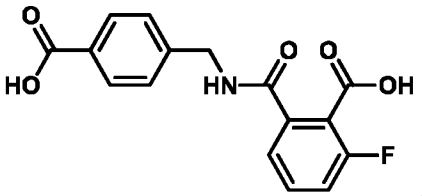
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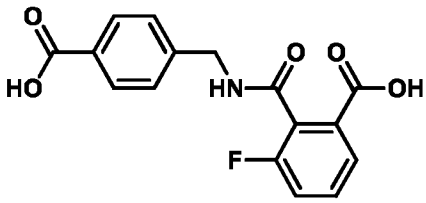
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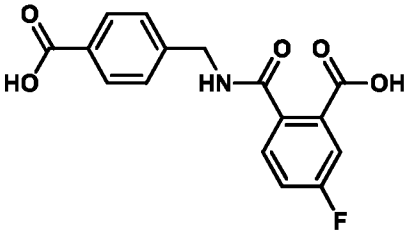
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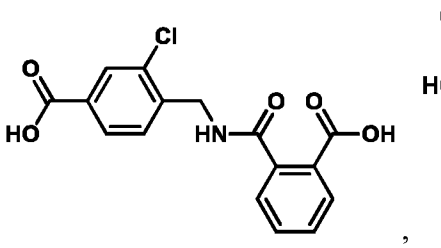
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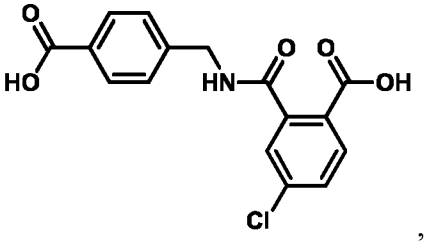
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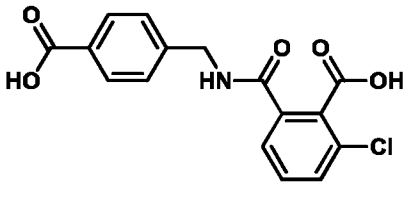
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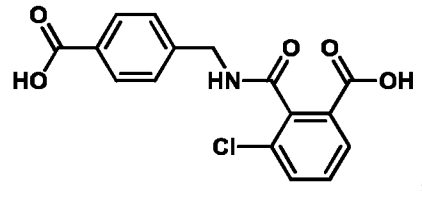
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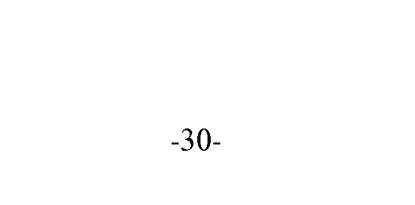
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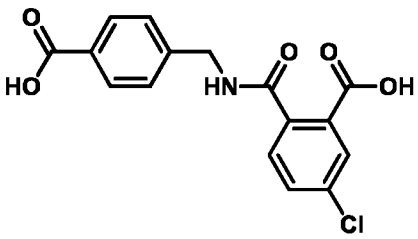
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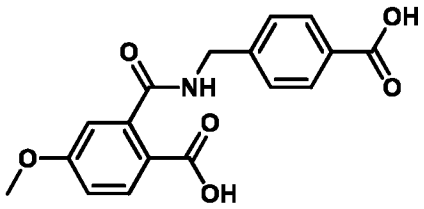
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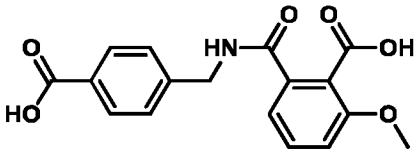
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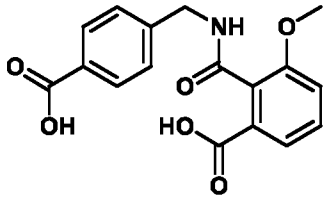
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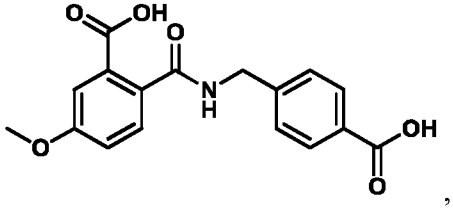
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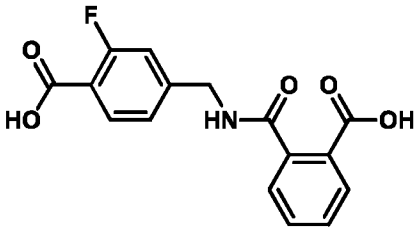
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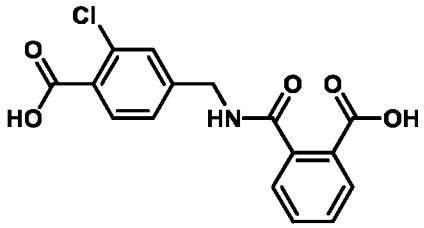
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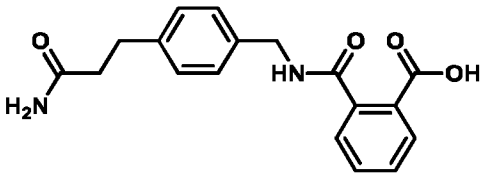
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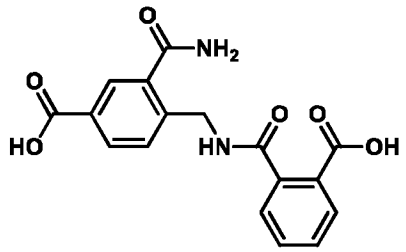
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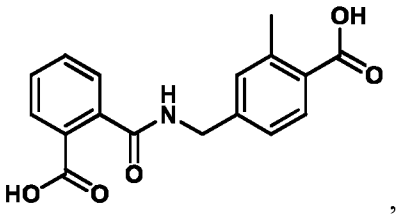
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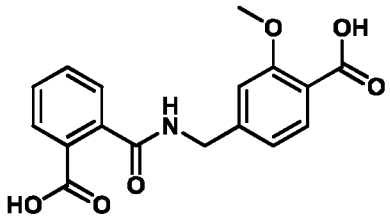
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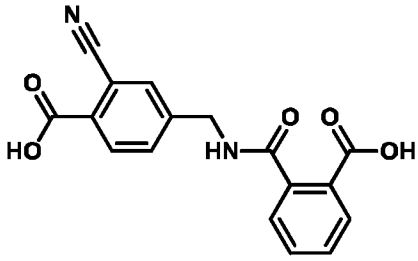
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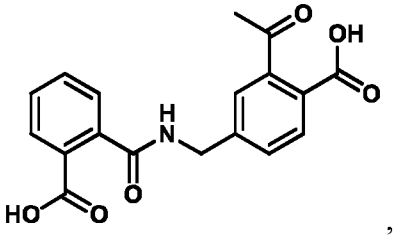
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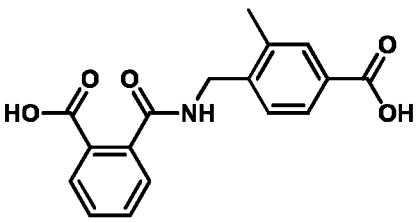
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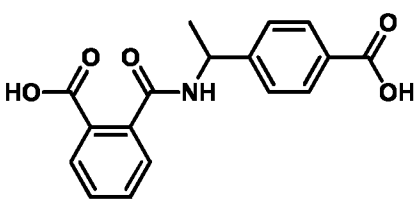
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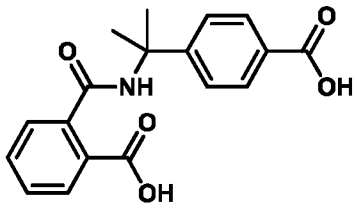
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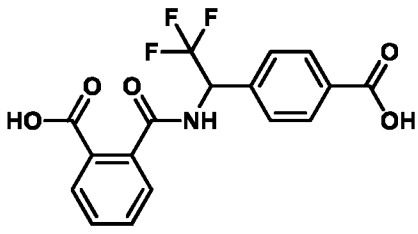
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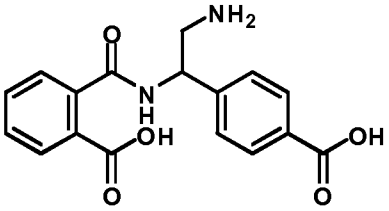
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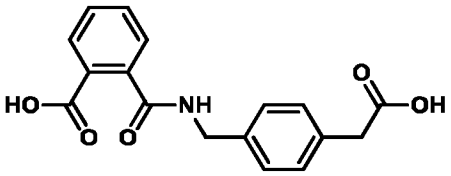
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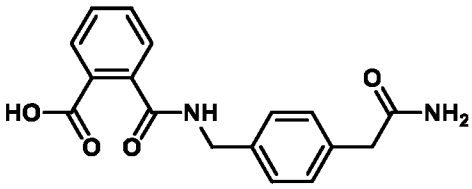
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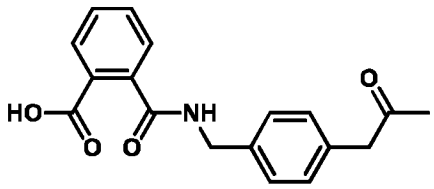
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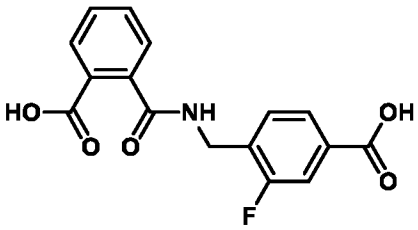
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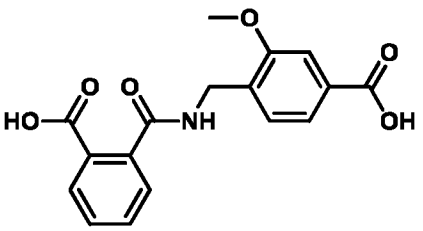
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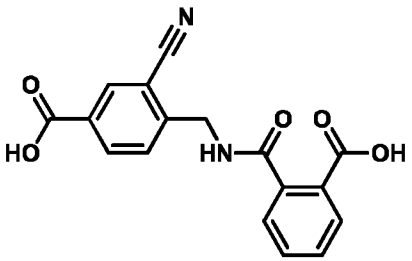
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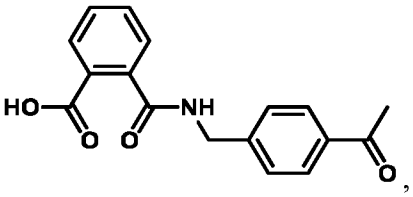
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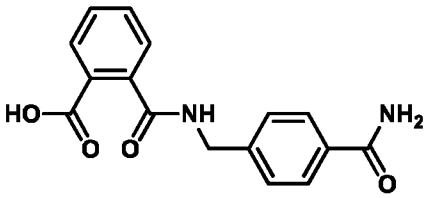
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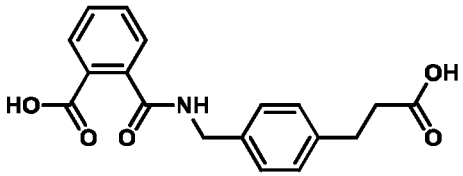
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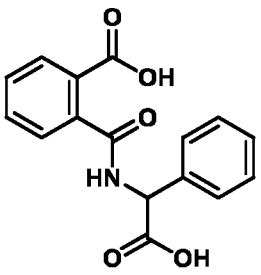
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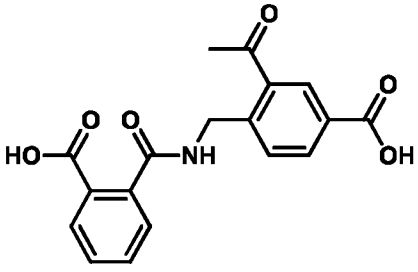
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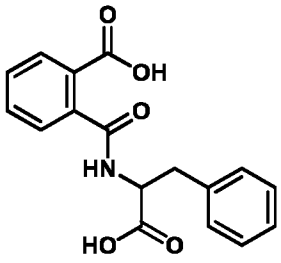
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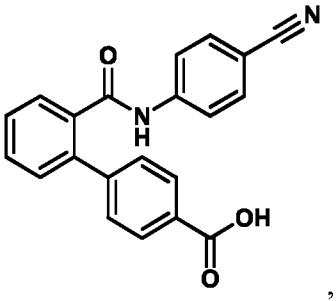
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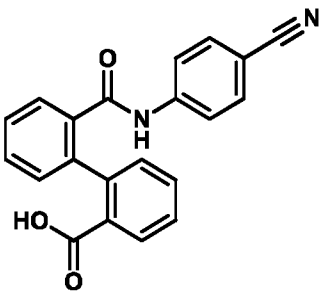
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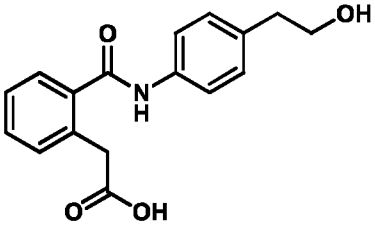
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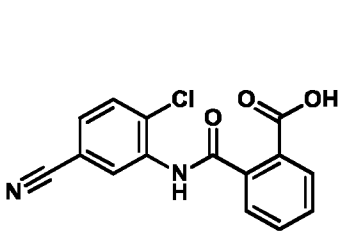
[0054] In another aspect, provided herein are compounds of Formula Ia, or pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, esters, metabolites, N-oxides, stereoisomers, or isomers thereof, selected from: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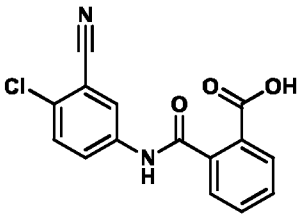
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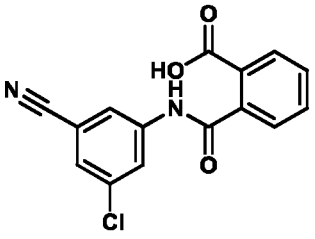
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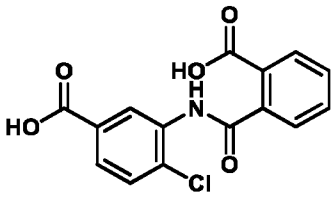
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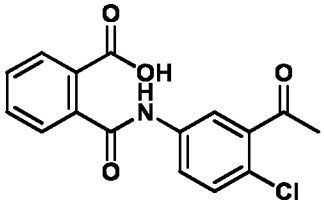
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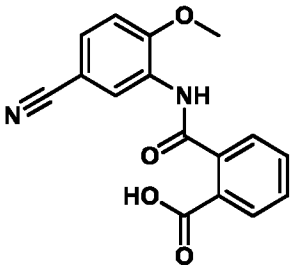
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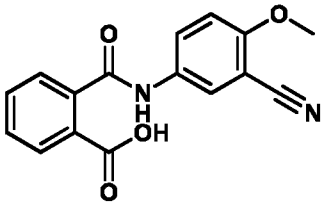
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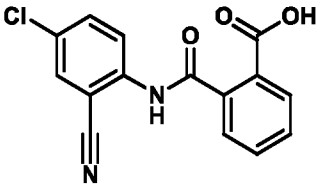
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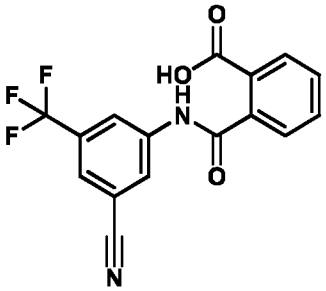
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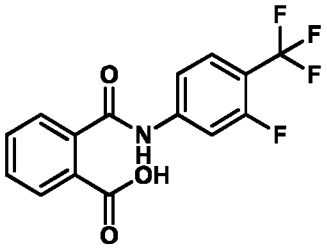
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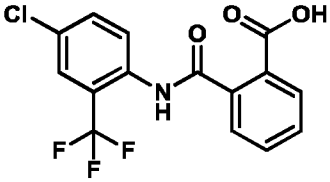
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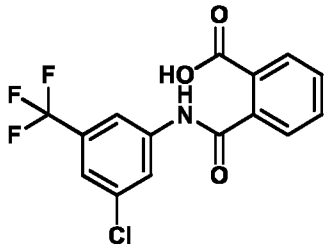
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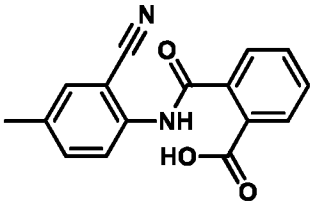
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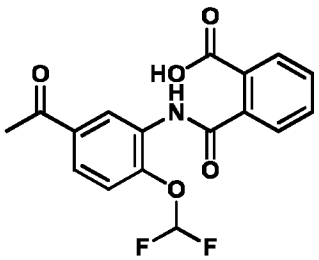
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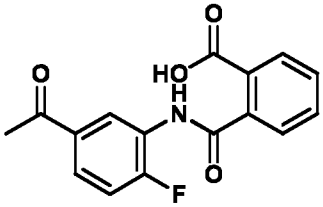
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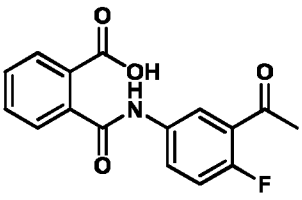
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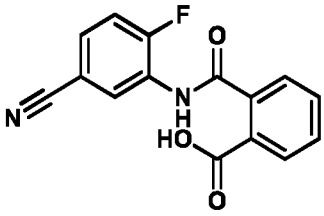
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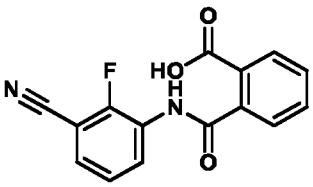
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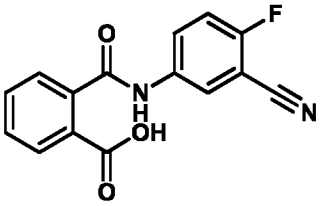
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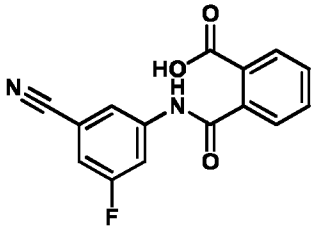
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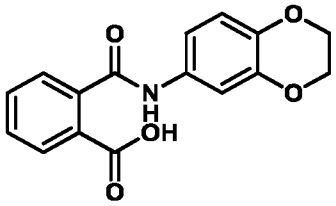
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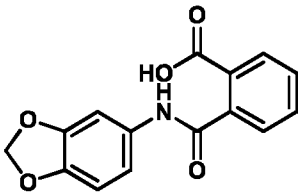
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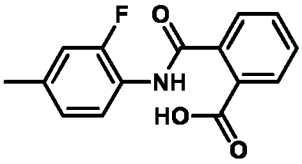
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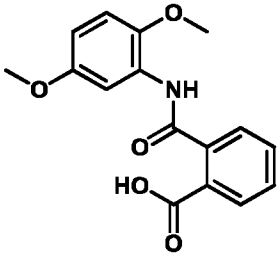
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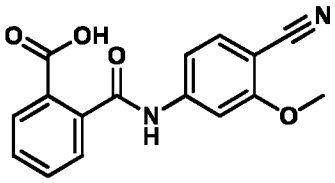
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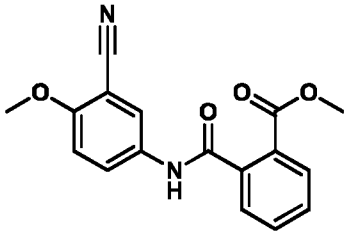
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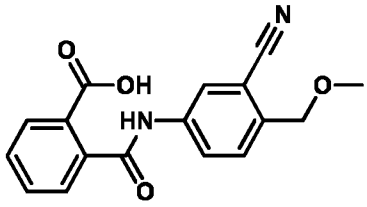
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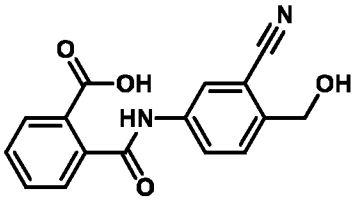
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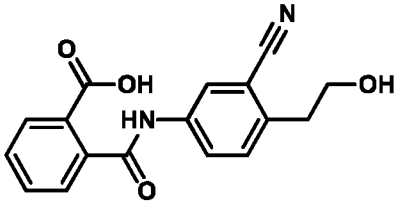
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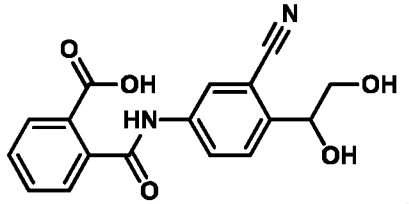
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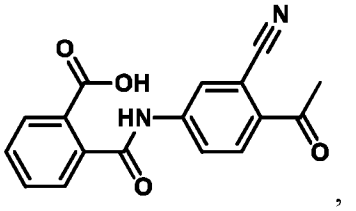
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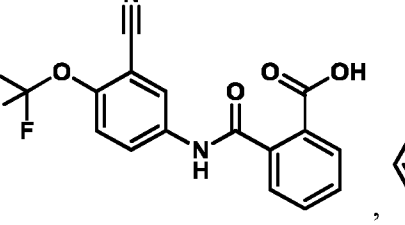
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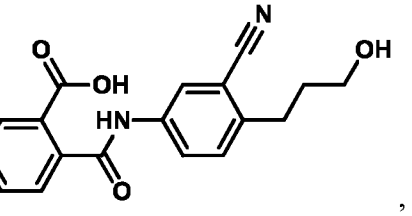
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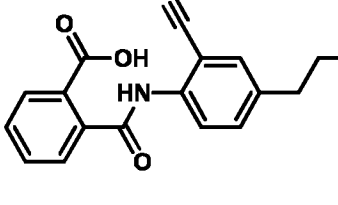
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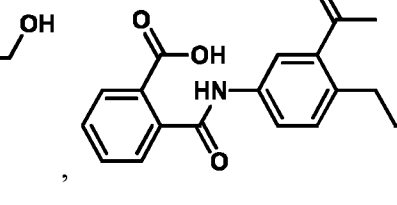
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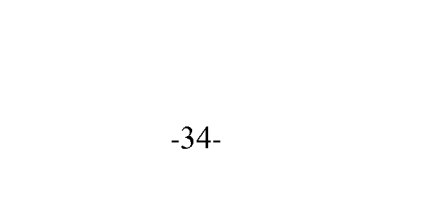
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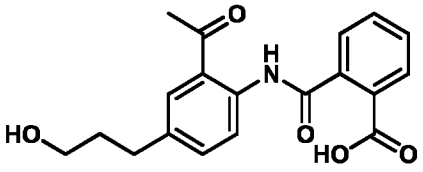
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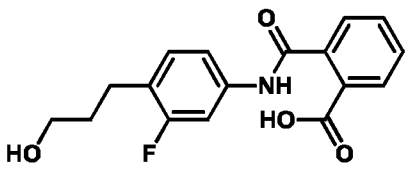
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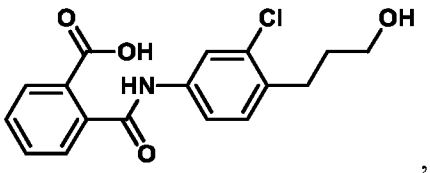
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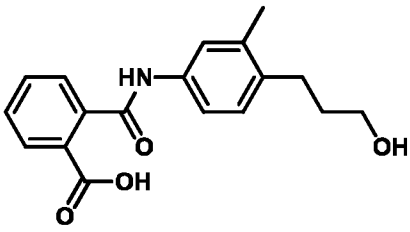
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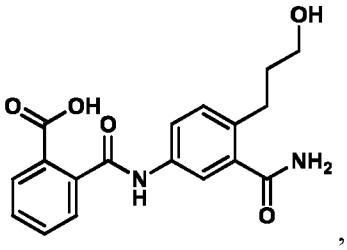
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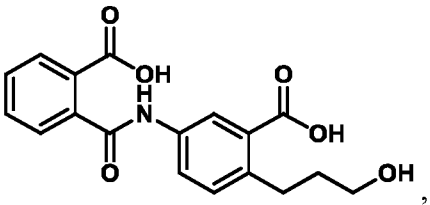
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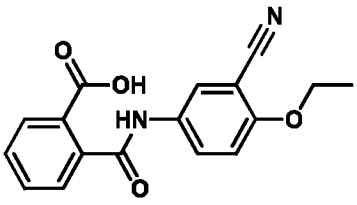
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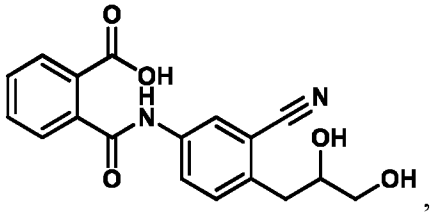
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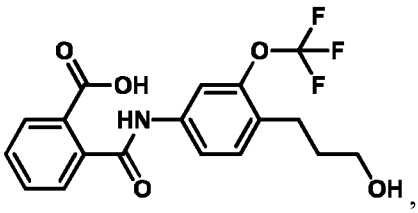
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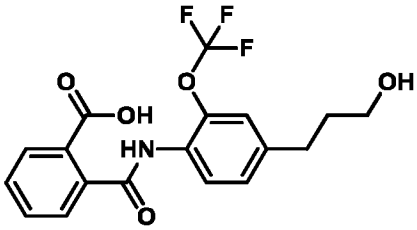
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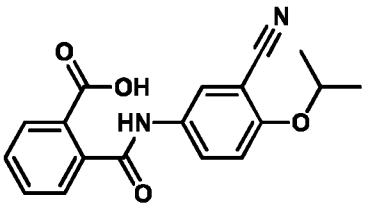
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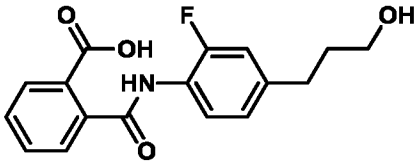
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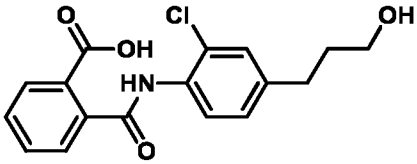
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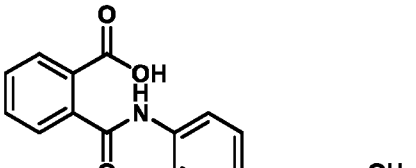
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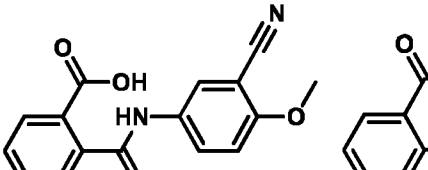
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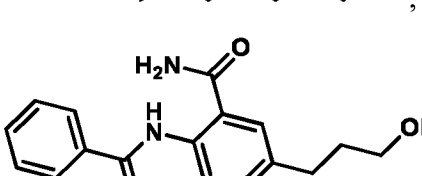
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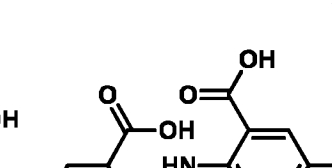
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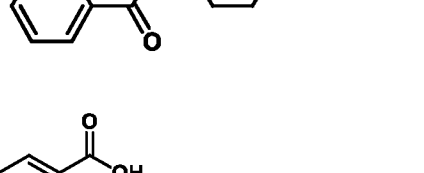
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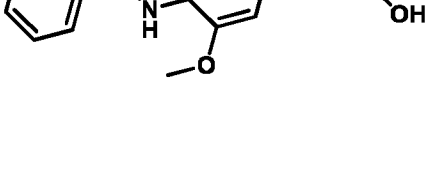
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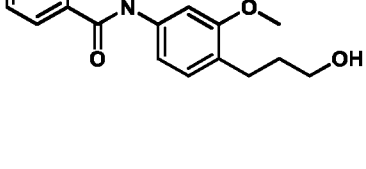
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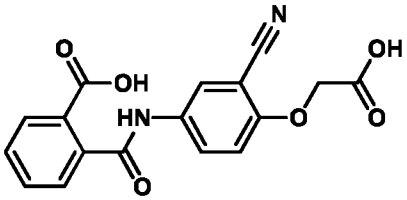
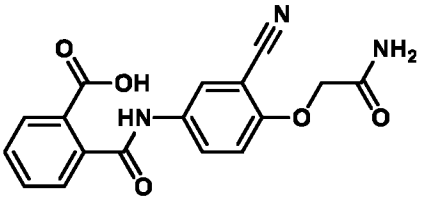

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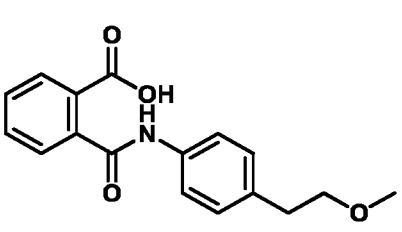
[0055] In another aspect, provided herein are compounds of Formula Ib, or pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, esters, metabolites, N-oxides, stereoisomers, or isomers thereof, selected from: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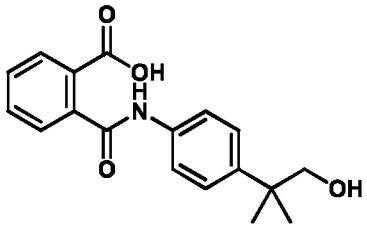
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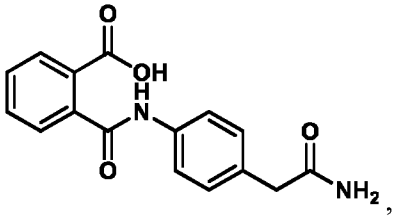
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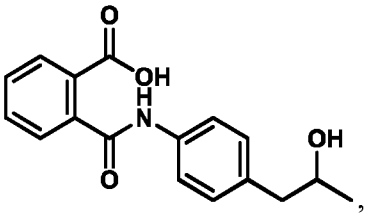
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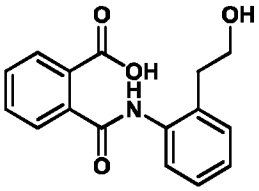
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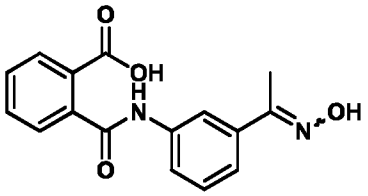
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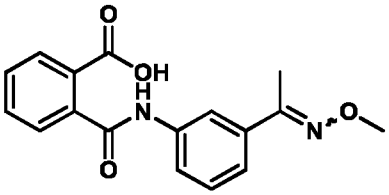
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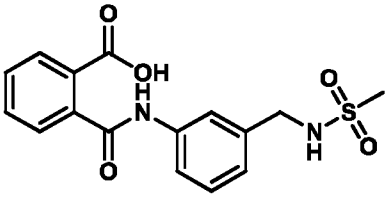
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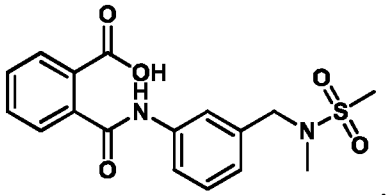
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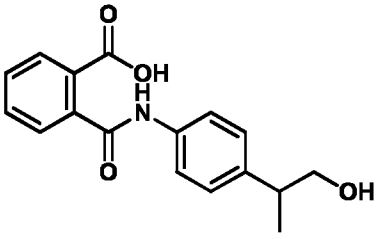
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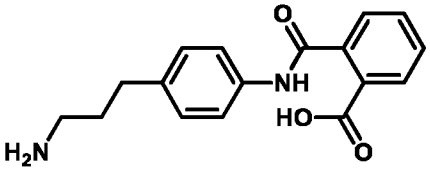
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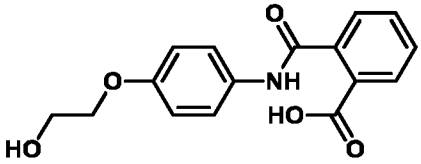
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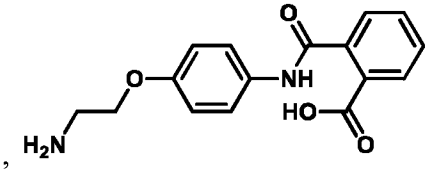
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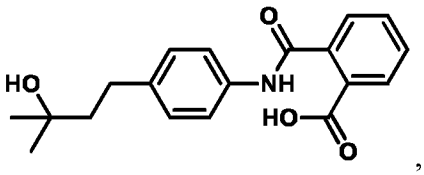
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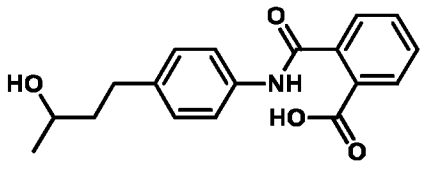
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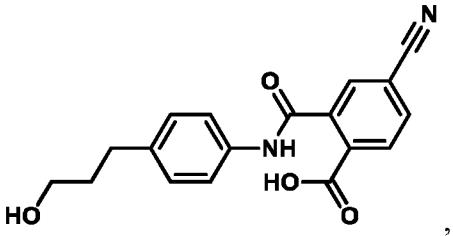
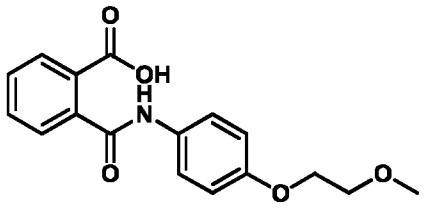
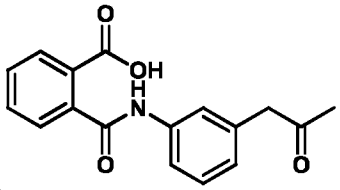
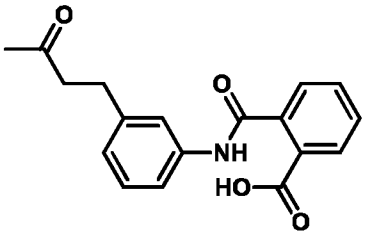
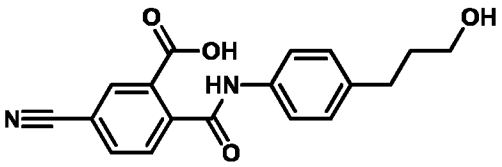
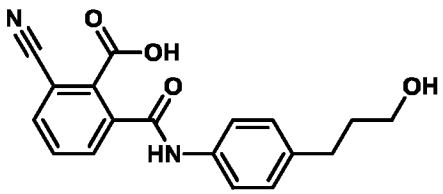
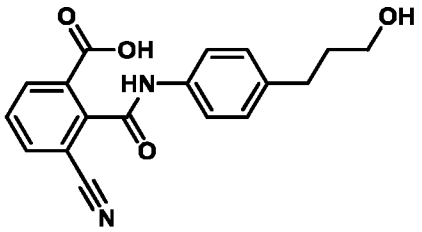
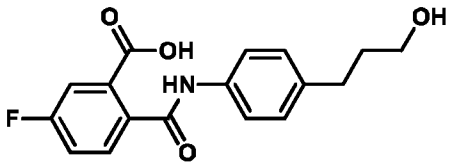
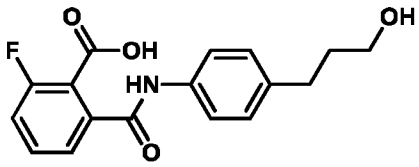
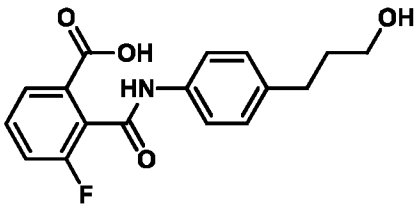
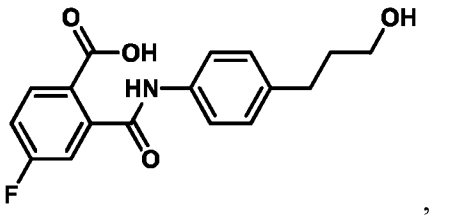
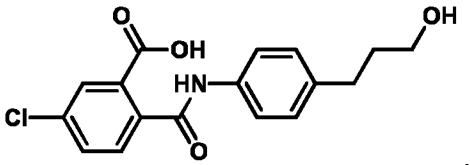
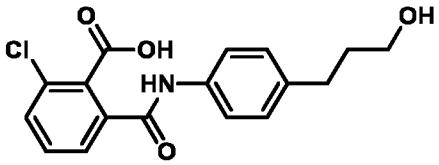
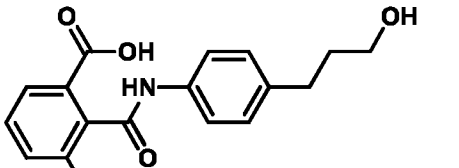
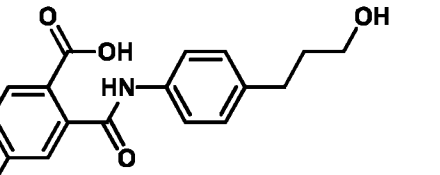
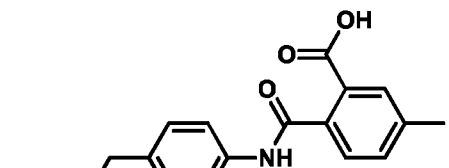
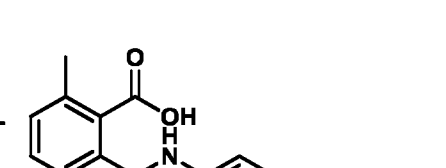

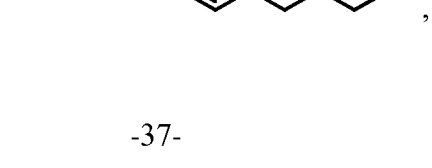

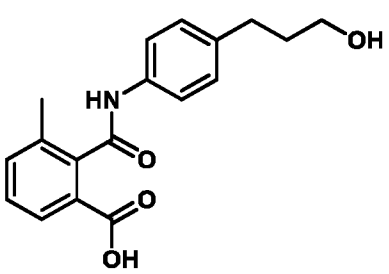
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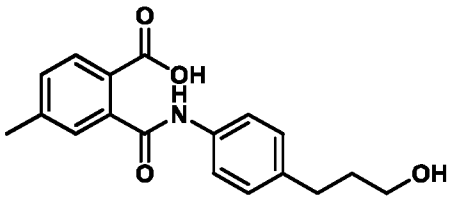
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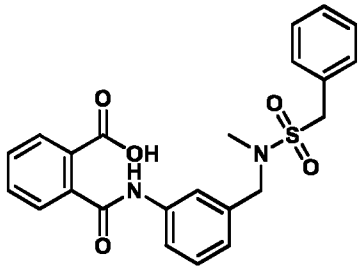
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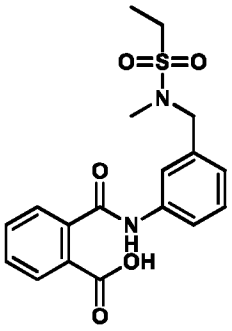
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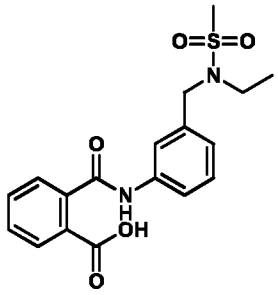
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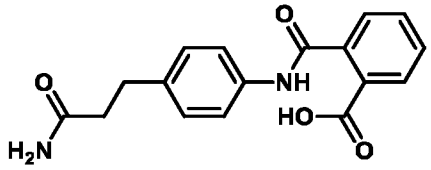
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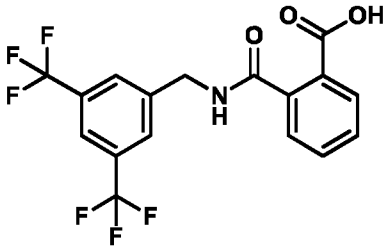
[0056] In another aspect, provided herein are compounds of Formula Ic, or pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, esters, metabolites, N-oxides, stereoisomers, or isomers thereof, selected from: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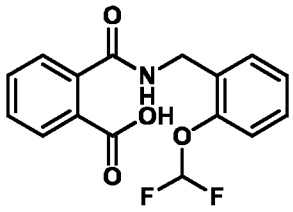
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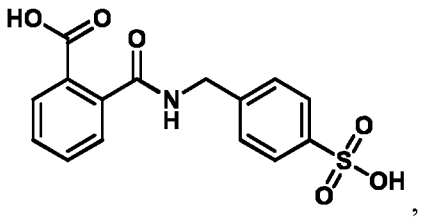
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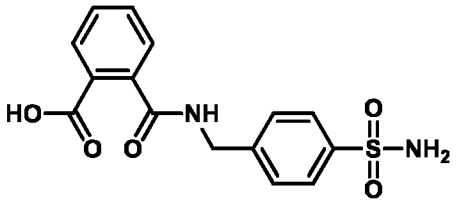
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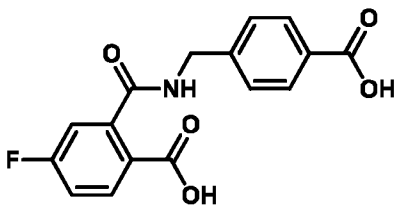
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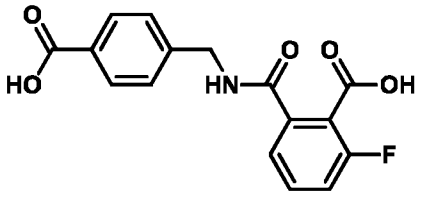
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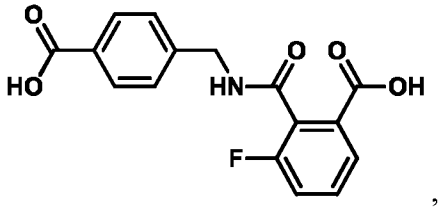
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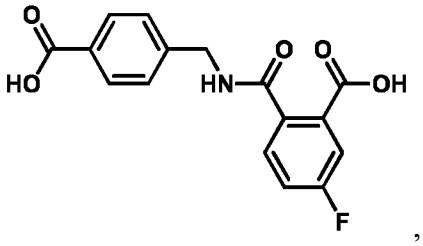
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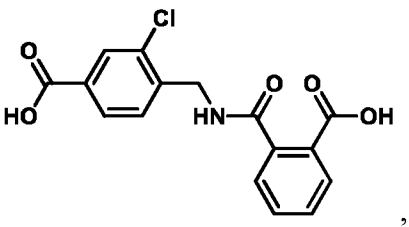
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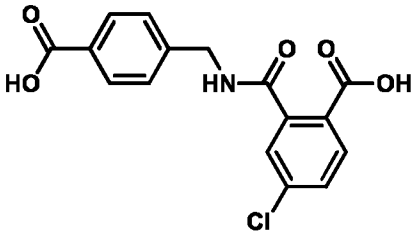
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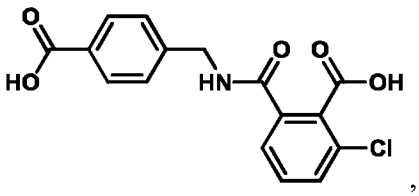
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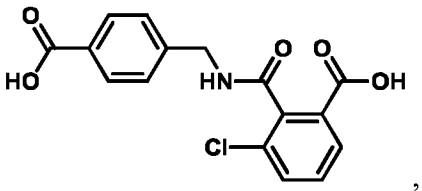
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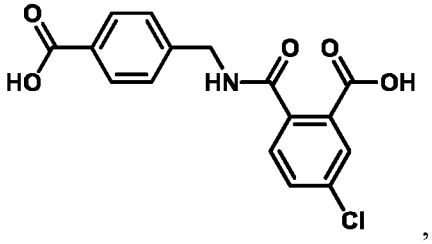
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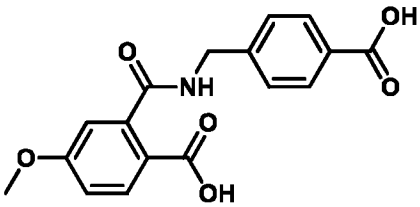
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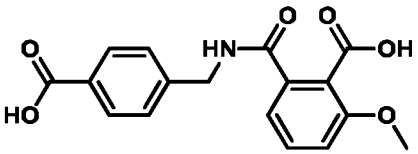
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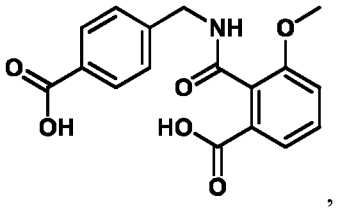
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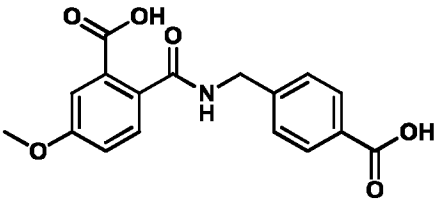
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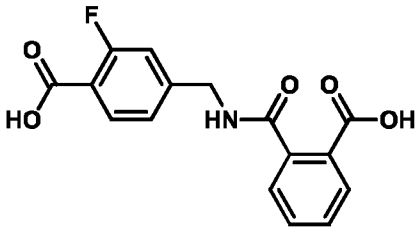
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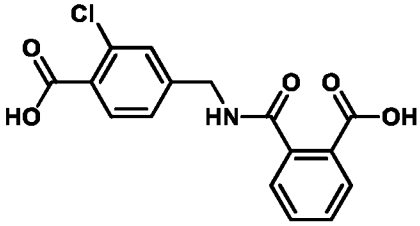
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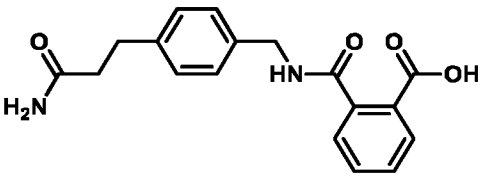
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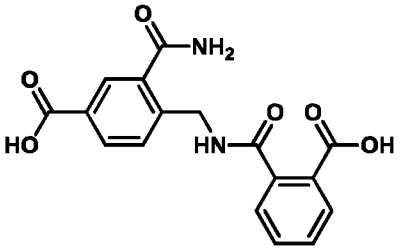
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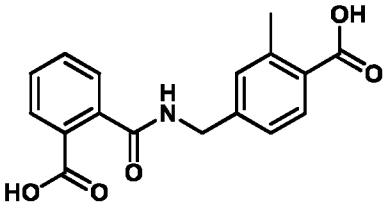
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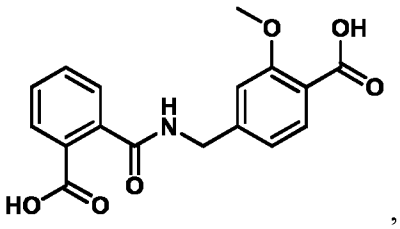
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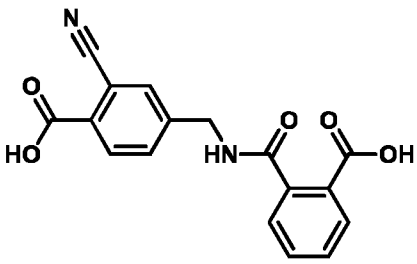
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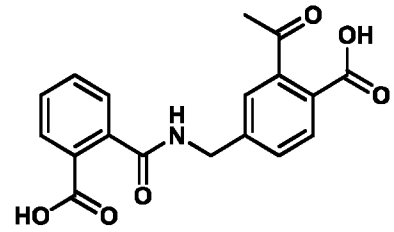
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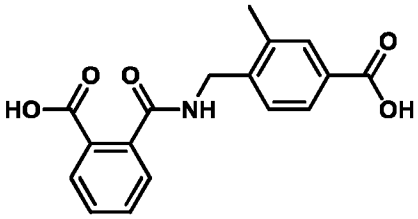
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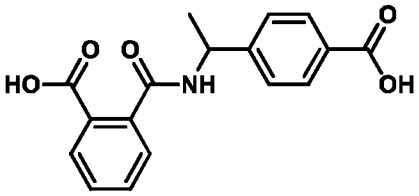
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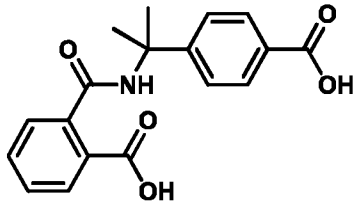
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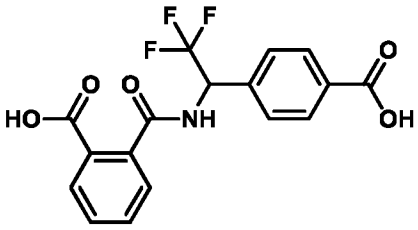
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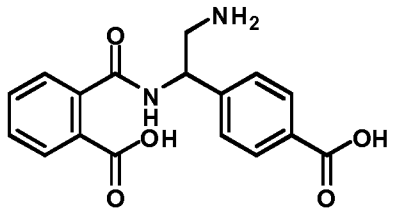
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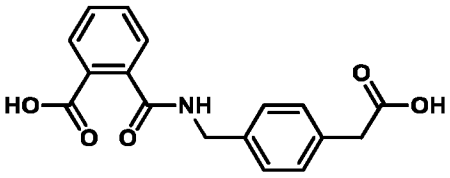
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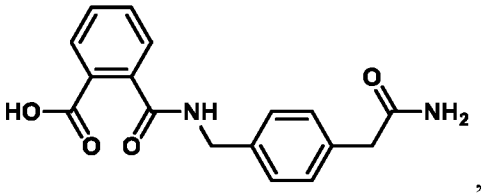
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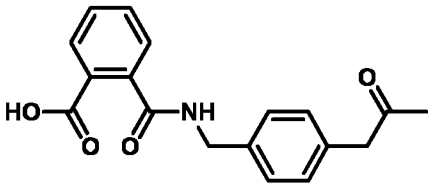
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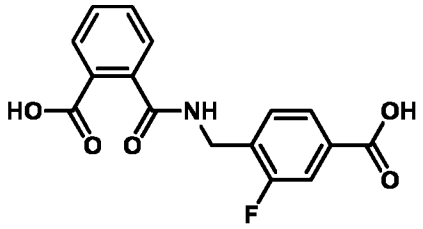
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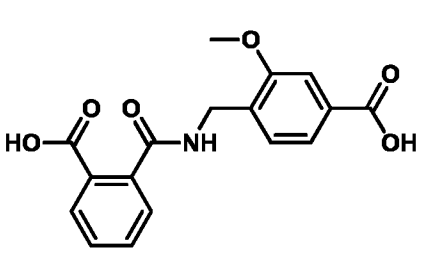
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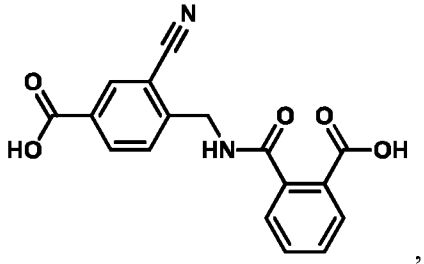
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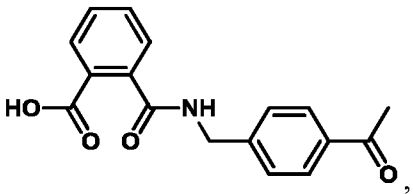
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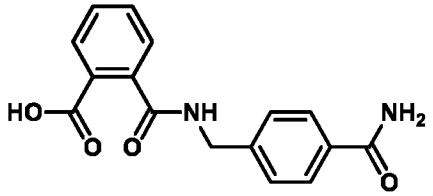
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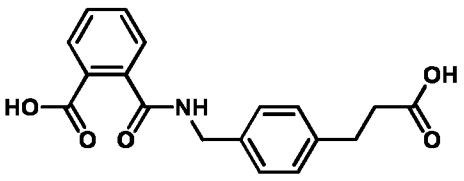
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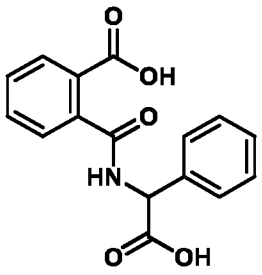
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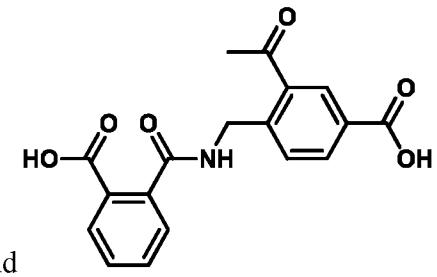
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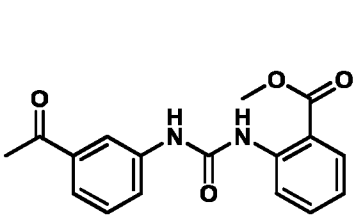
[0057] In another aspect, provided herein are compounds of Formula II, or pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, esters, metabolites, N-oxides, stereoisomers, or isomers thereof, selected from: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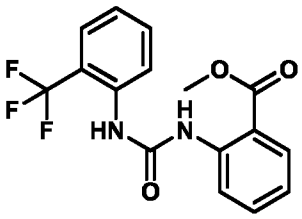
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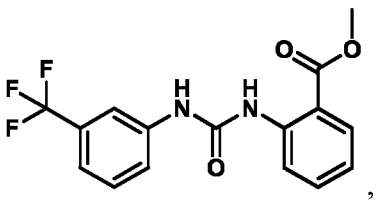
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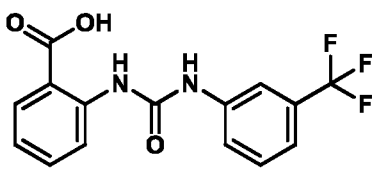
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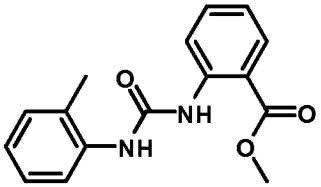
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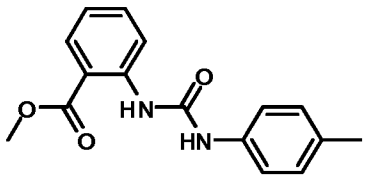
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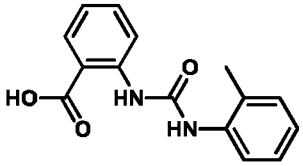
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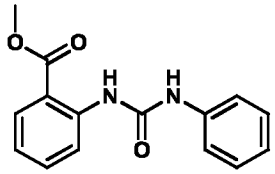
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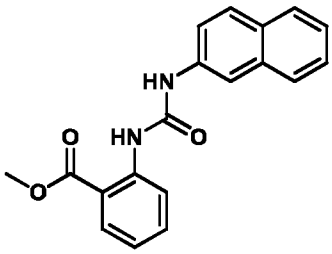
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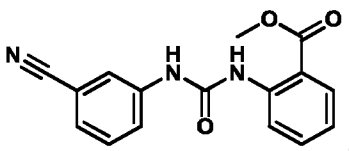
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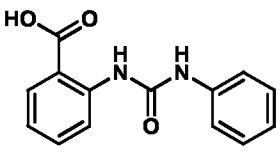
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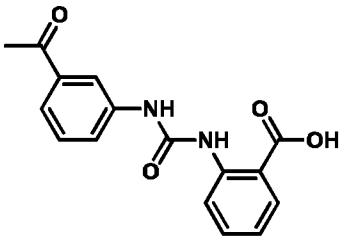
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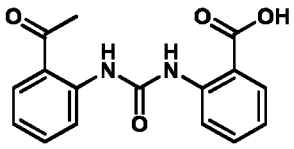
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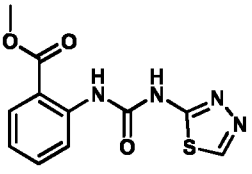
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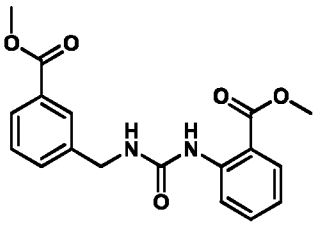
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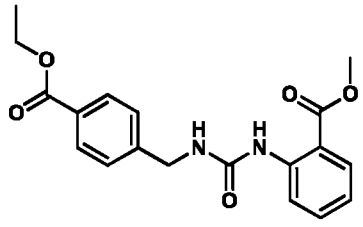
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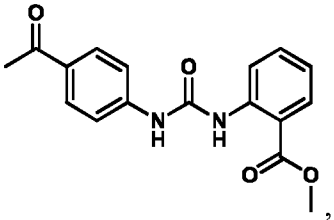
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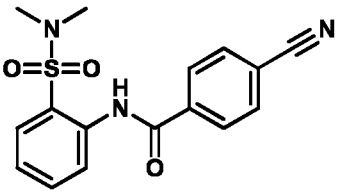
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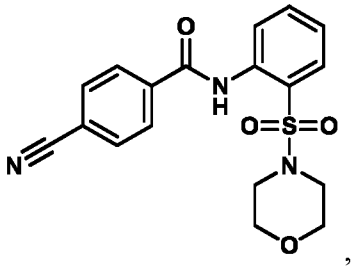
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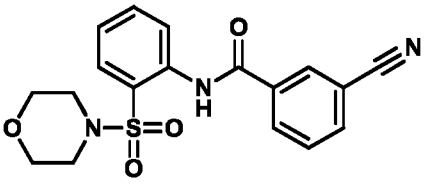
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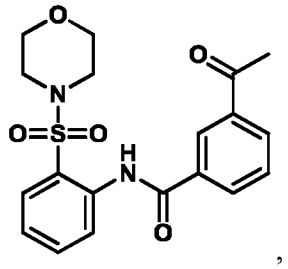
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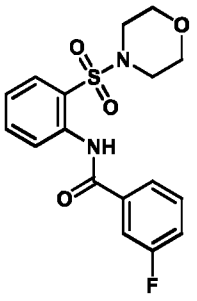
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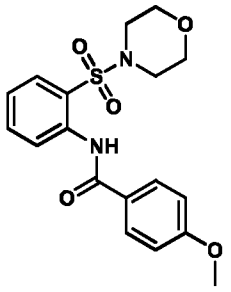
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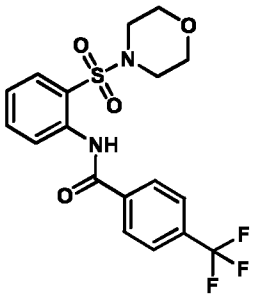
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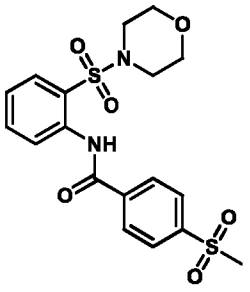
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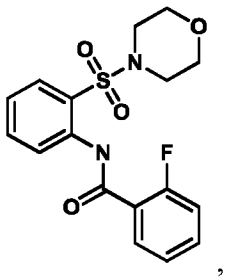
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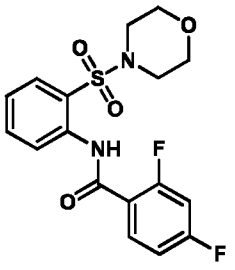
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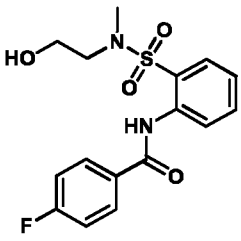
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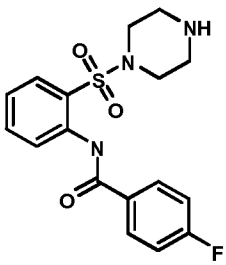
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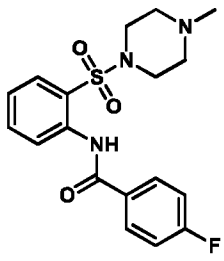
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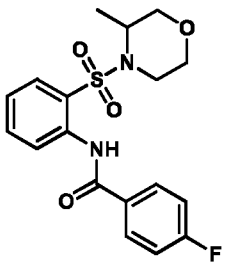
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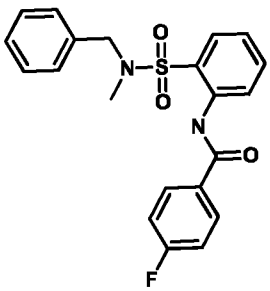
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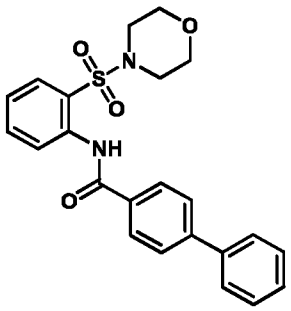
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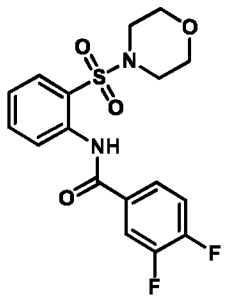
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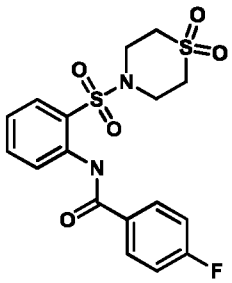
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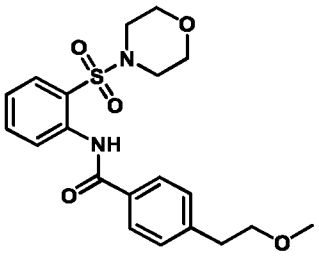
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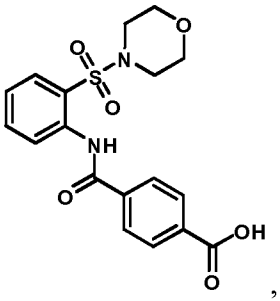
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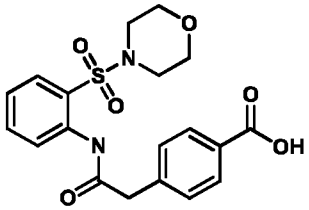
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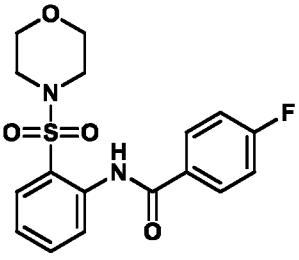
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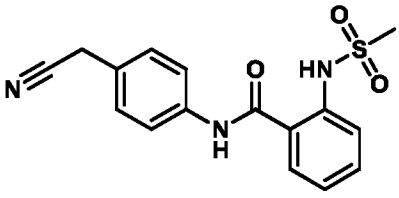
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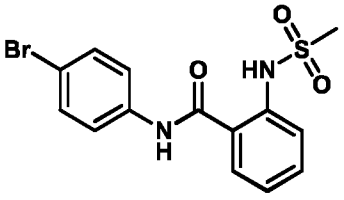
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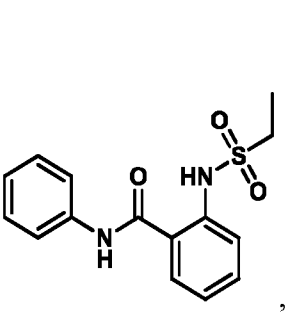
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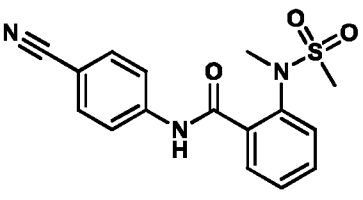
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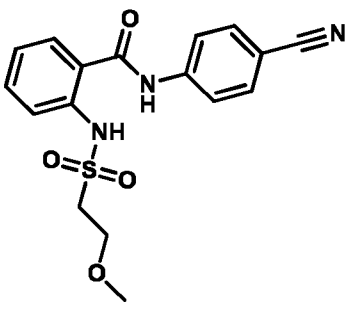
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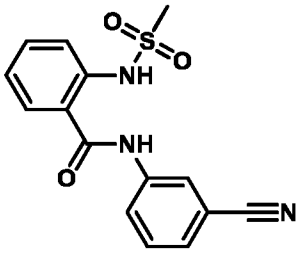
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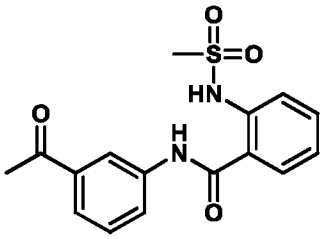
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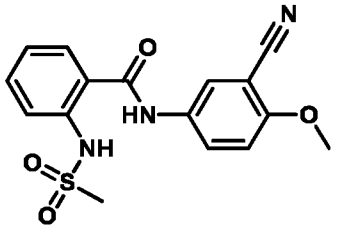
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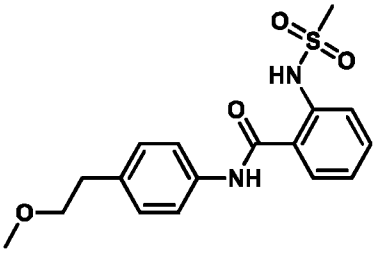
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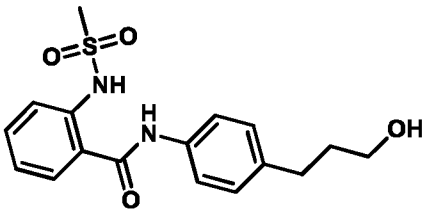
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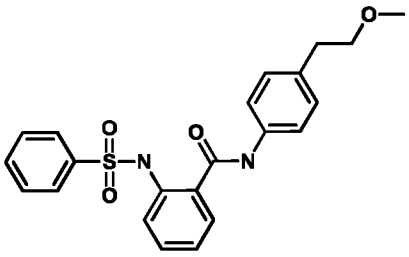
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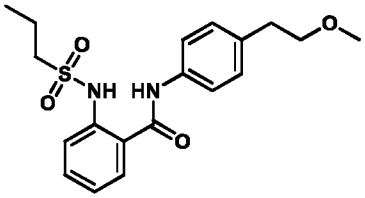
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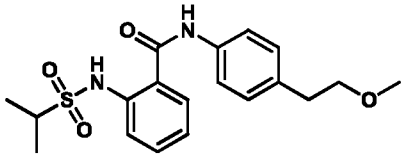
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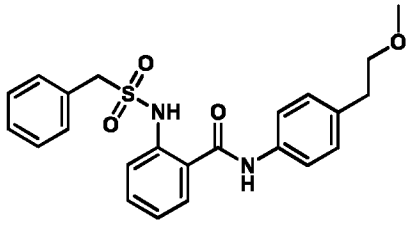
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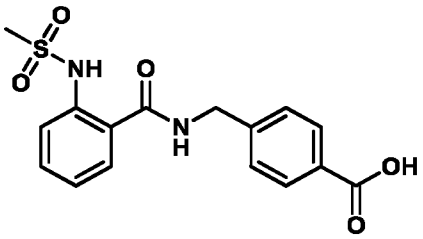
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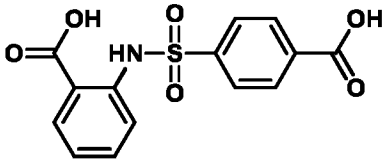
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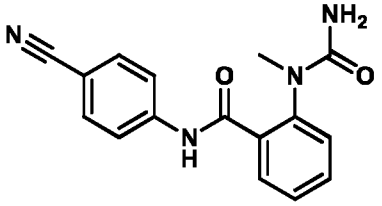
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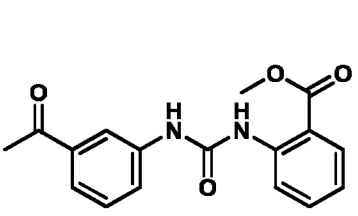
[0058] In another aspect, provided herein are compounds of Formula IIa, or pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, esters, metabolites, N-oxides, stereoisomers, or isomers thereof, selected from: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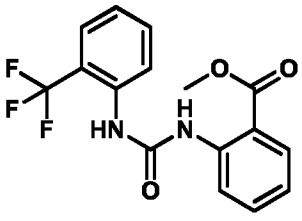
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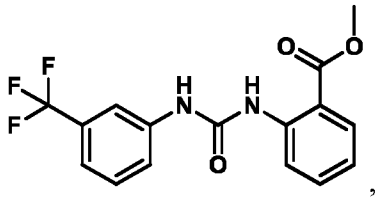
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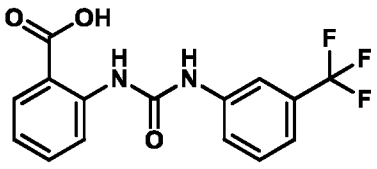
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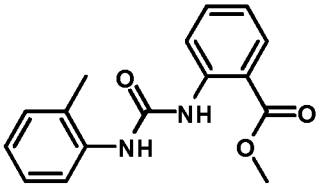
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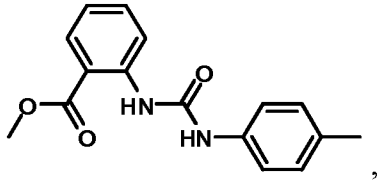
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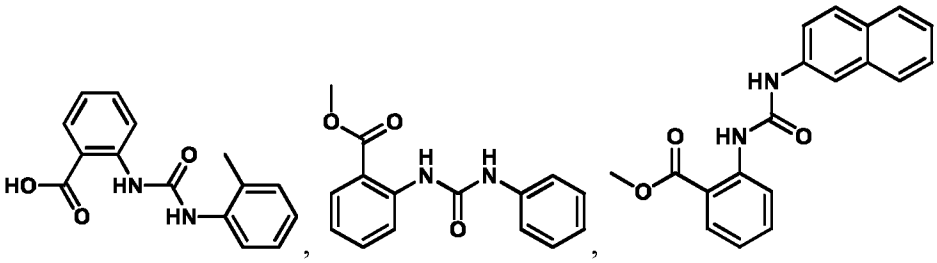
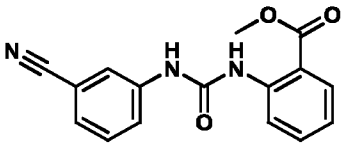
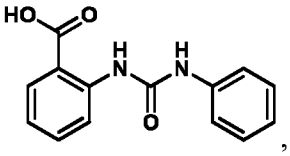
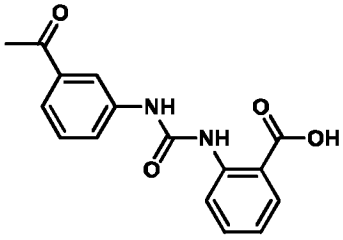
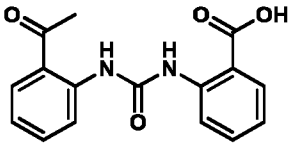
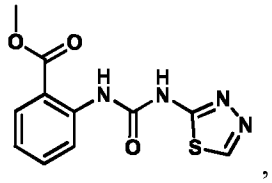
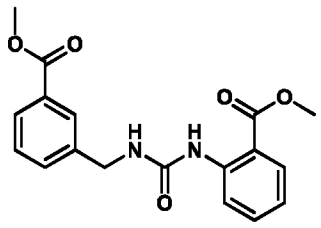
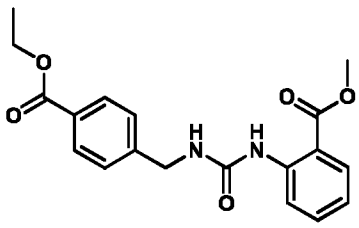
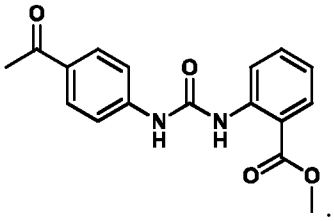
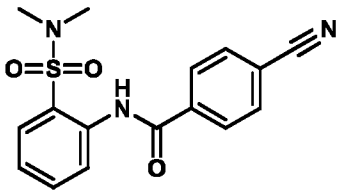
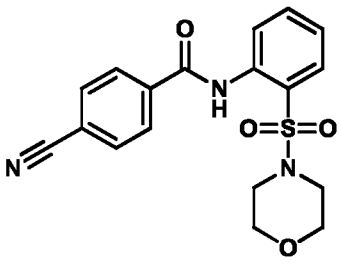
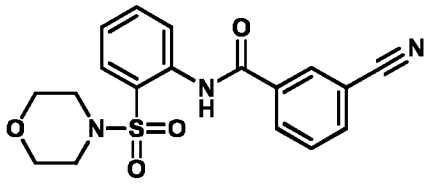
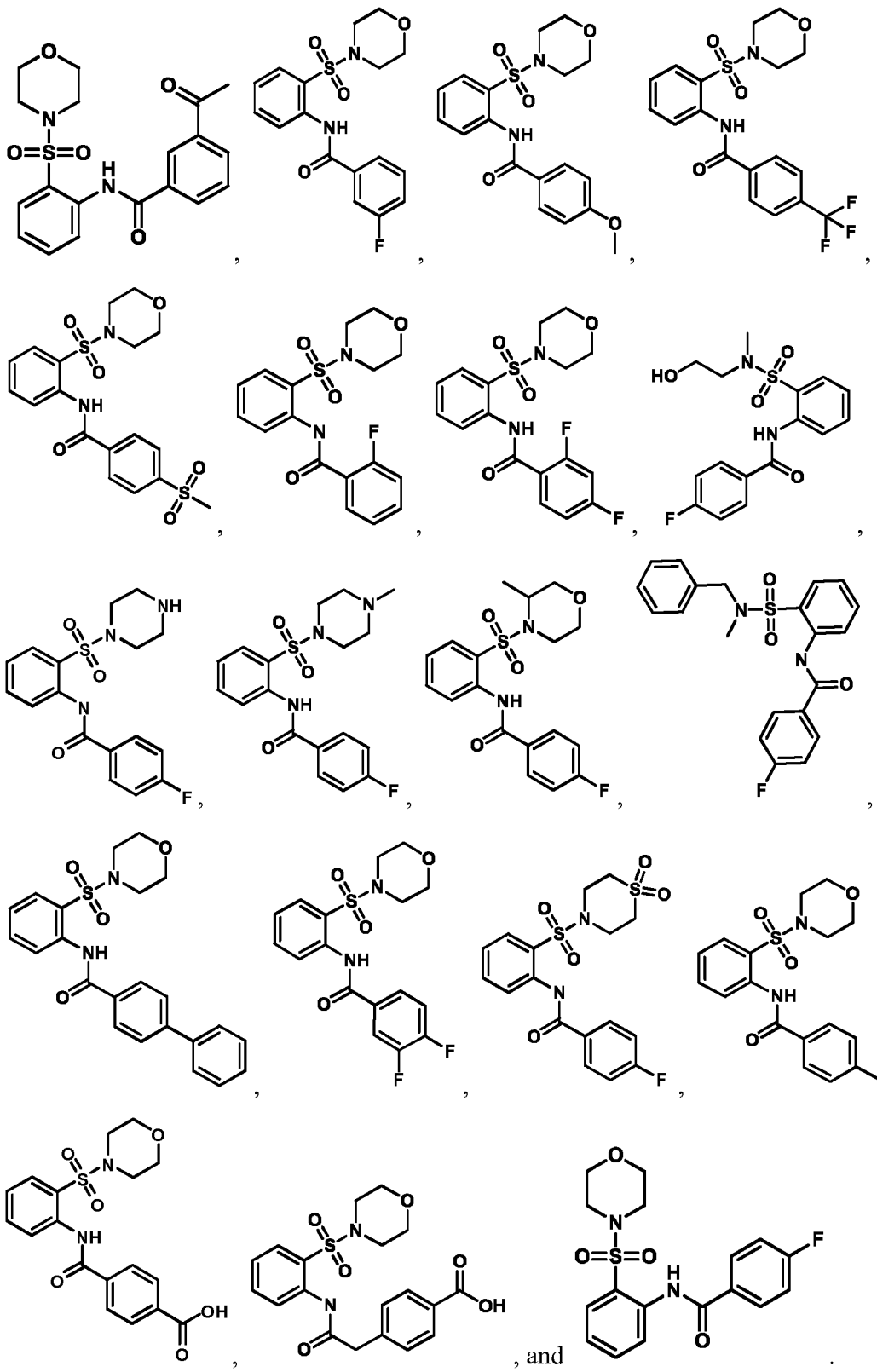


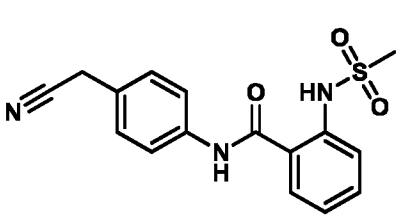









[0059] In another aspect, provided herein are compounds of Formula IIb, or pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, esters, metabolites, N-oxides, stereoisomers, or isomers thereof, selected from:



[0060] In another aspect, provided herein are compounds of Formula IIc, or pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, esters, metabolites, N-oxides, stereoisomers, or isomers thereof, selected from: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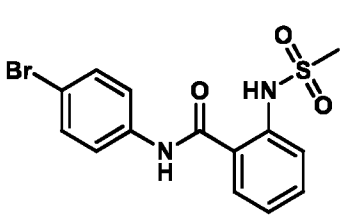
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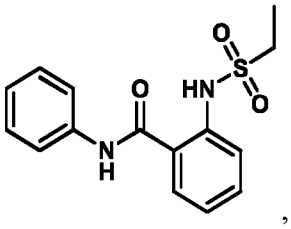
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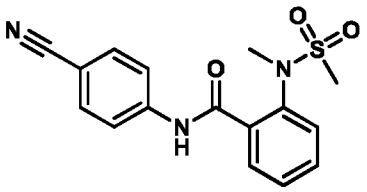
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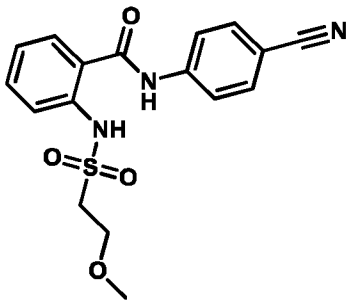
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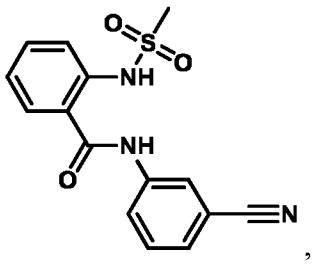
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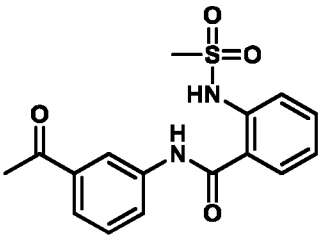
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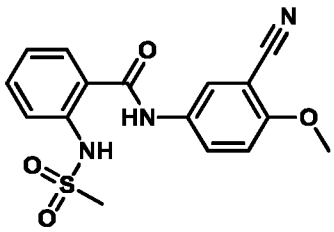
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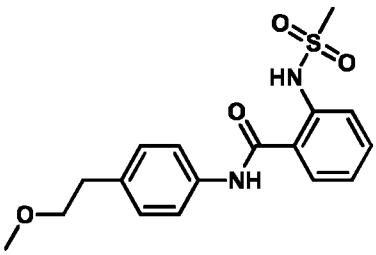
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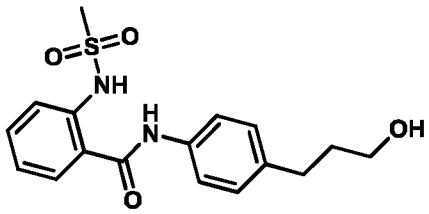
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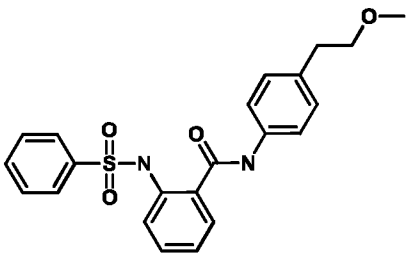
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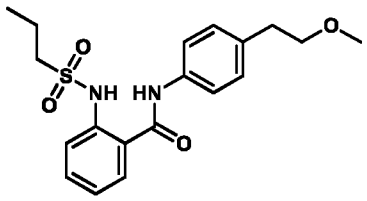
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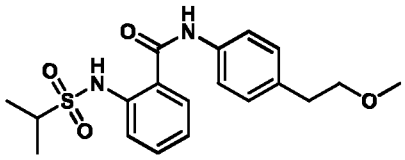
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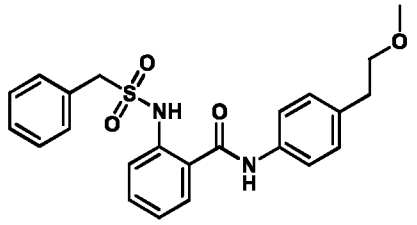
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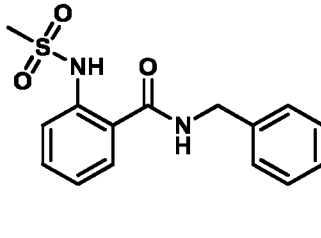
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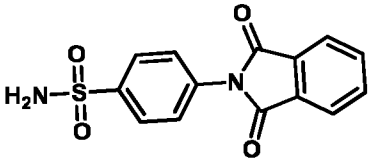
[0061] In another aspect, provided herein are compounds of Formula III, or pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, esters, metabolites, N-oxides, stereoisomers, or isomers thereof, selected from: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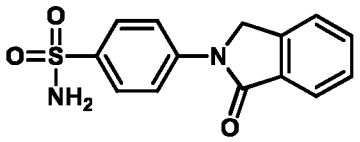
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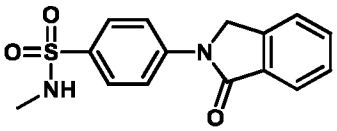
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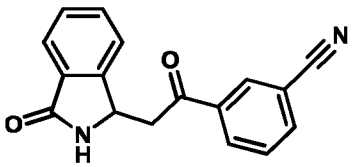
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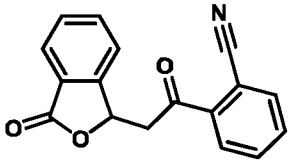
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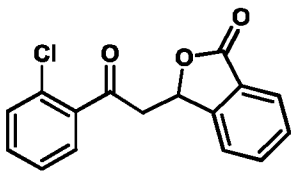
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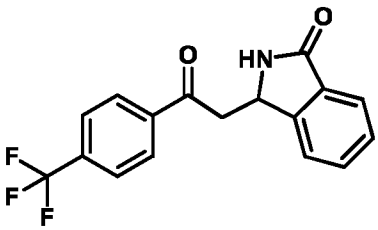
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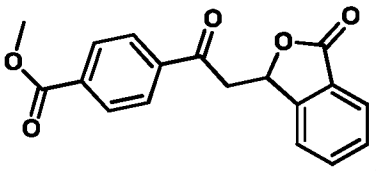
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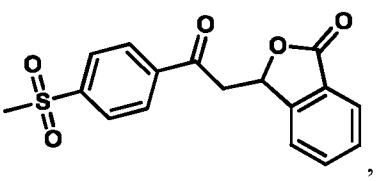
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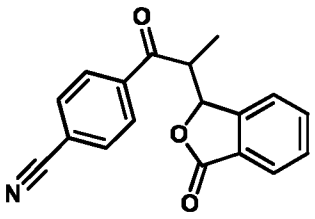
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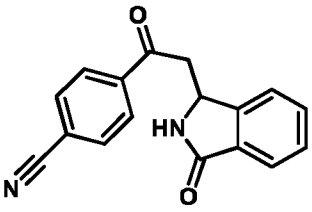
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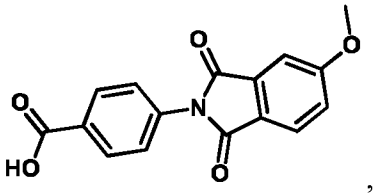
[0062] In another aspect, provided herein are compounds, or pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, esters, metabolites, N-oxides, stereoisomers, or isomers thereof, selected from: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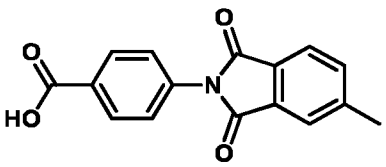
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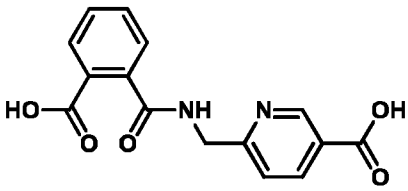
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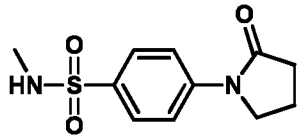
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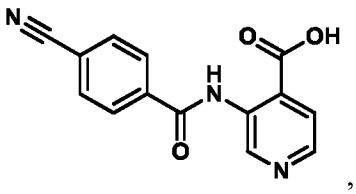
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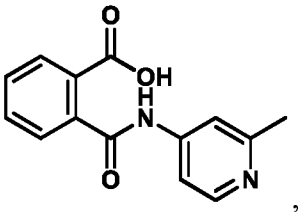
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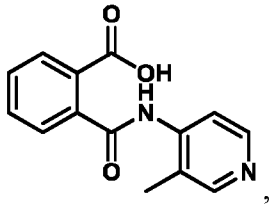
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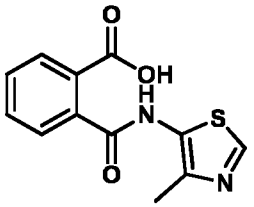
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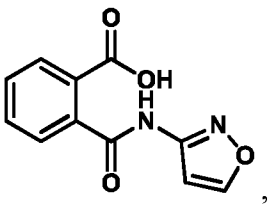
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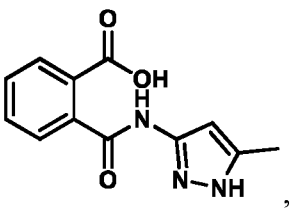
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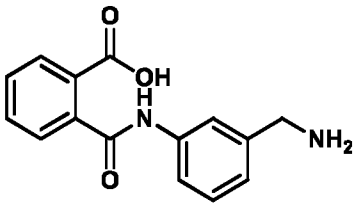
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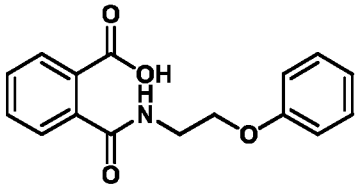
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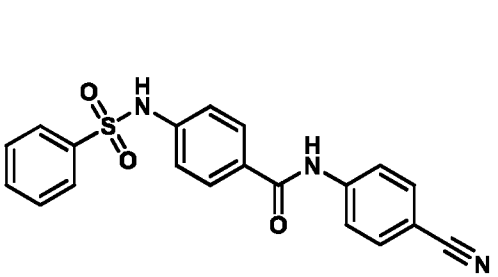
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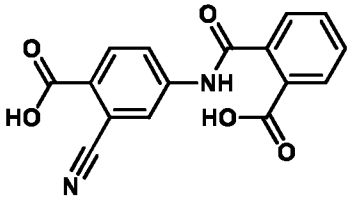
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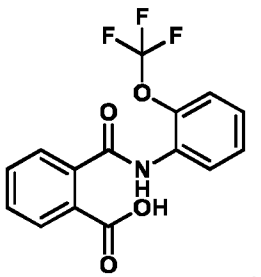
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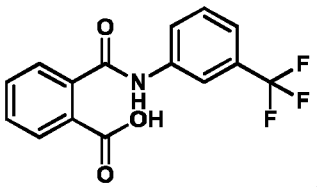
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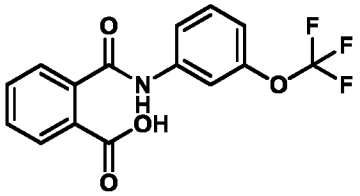
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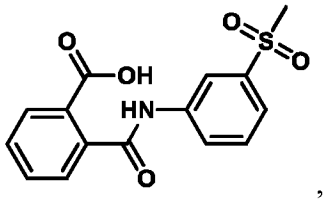
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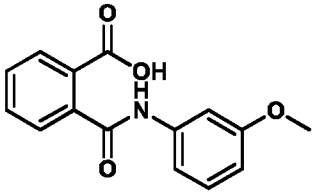
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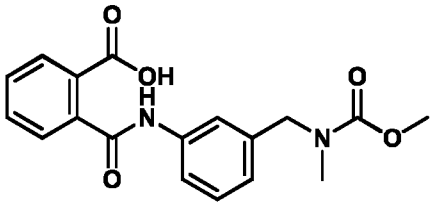
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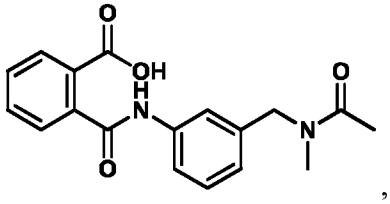
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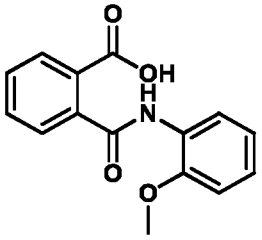
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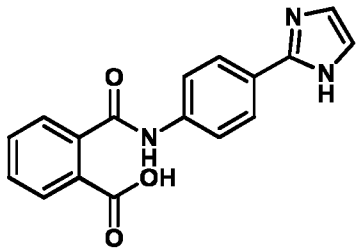
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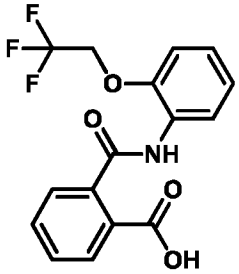
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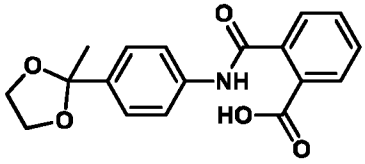
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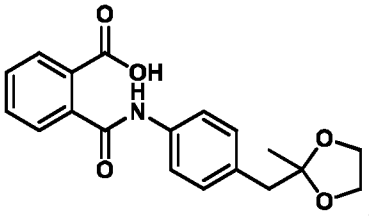
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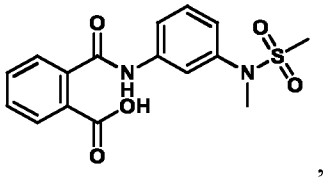
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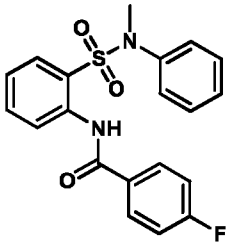
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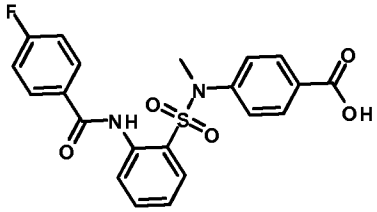
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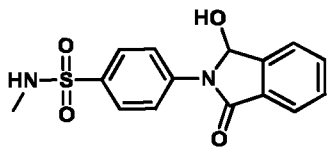
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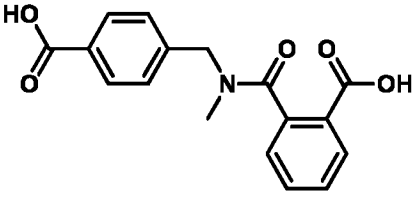
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[0063] In one aspect, provided herein is a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester,

metabolite, N-oxide, stereoisomer, or isomer thereof, and a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition further comprises an additional compound which is therapeutically effective for the treatment of arthritis or joint injury and/or the symptoms associated with arthritis or joint injury in a mammal. In certain embodiments, the additional compound is selected from NSAIDS, analgesics, angiopoietin-like 3 protein (ANGPTL3) or chondrogenic variant thereof, oral salmon calcitonin, SD-6010 (iNOS inhibitor), vitamin D3 (cholecalciferol), apoptosis/caspase inhibitors (emricasan), collagen hydrolysate, FGF18, BMP7, avocado soy unsaponifiables (ASU), and hyaluronic acid. In some embodiments, the mammal is human. In other embodiments, the mammal is a companion animal or livestock. In further embodiments, the companion animal or livestock is a dog, cat, or horse.

INCORPORATION BY REFERENCE

[0064] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION OF THE INVENTION

[0065] Osteoarthritis (OA) is characterized by progressive breakdown of articular cartilage, and ultimately leads to functional failure of synovial joints [Reginster, J.Y. and N.G. Khaltaev, *Introduction and WHO perspective on the global burden of musculoskeletal conditions.* Rheumatology (Oxford), 2002. 41 Supp 1: p. 1-2]. OA is mediated by several pathogenic mechanisms including enzymatic degradation of extracellular matrix, deficient new matrix formation, cell death, and abnormal activation and hypertrophic differentiation of cartilage cells [Goldring, M.B. and S.R. Goldring, *Articular cartilage and subchondral bone in the pathogenesis of osteoarthritis.* Ann N Y Acad Sci, 2010. 1192(1): p. 230-7]. The only current therapeutic options for OA are pain management and surgical intervention [Hunter, D.J., *Pharmacologic therapy for osteoarthritis-the era of disease modification.* Nat Rev Rheumatol, 2011. 7(1): p. 13-22].

[0066] Mesenchymal stem cells (MSCs), residing in bone marrow and most adult tissues, are capable of self-renewal and differentiation into a variety of cell lineages including chondrocytes, osteoblasts and adipocytes [Pittenger, M.F., et al., *Multilineage potential of adult human mesenchymal stem cells.* Science, 1999. **284**(5411): p. 143-7]. Recent studies found that adult articular cartilage contains MSCs (approximately 3% of the cells) that are capable of multi-lineage differentiation. In OA cartilage, the number of these cells approximately doubles. These resident stem cells still retain the capability to differentiate into chondrocytes and thus the capacity to repair the damaged cartilage [Grogan, S.P., et al., *Mesenchymal progenitor cell markers in human articular cartilage: normal distribution and changes in osteoarthritis.* Arthritis Res Ther, 2009. **11**(3): p. R85;

Koelling, S., et al., *Migratory chondrogenic progenitor cells from repair tissue during the later stages of human osteoarthritis.* Cell Stem Cell, 2009. **4**(4): p. 324-35].

[0067] The present invention is based, in part, on the discovery that the compounds of the present invention stimulate chondrocyte differentiation in mesenchymal stem cells. Accordingly, the present invention provides for methods of induction of mesenchymal stem cell differentiation into chondrocytes. Further, the present invention provides for administration of compounds and compositions of the present invention to prevent or ameliorate arthritis or joint injury by administrating the compound or composition into a joint, the vertebrae, vertebral disc or systemically.

Definitions

[0068] In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments. However, one skilled in the art will understand that the invention may be practiced without these details. In other instances, well-known structures have not been shown or described in detail to avoid unnecessarily obscuring descriptions of the embodiments. Unless the context requires otherwise, throughout the specification and claims which follow, the word "comprise" and variations thereof, such as, "comprises" and "comprising" are to be construed in an open, inclusive sense, that is, as "including, but not limited to." Further, headings provided herein are for convenience only and do not interpret the scope or meaning of the claimed invention.

[0069] Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments. Also, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the content clearly dictates otherwise. It should also be noted that the term "or" is generally employed in its sense including "and/or" unless the content clearly dictates otherwise.

[0070] The terms below, as used herein, have the following meanings, unless indicated otherwise:

[0071] "Amino" refers to the $-NH_2$ radical.

[0072] "Cyano" or "nitrile" refers to the -CN radical.

[0073] "Hydroxy" or "hydroxyl" refers to the -OH radical.

[0074] "Nitro" refers to the $-NO_2$ radical.

[0075] "Oxo" refers to the =O substituent.

[0076] "Oxime" refers to the =N-OH substituent.

[0077] "Thioxo" refers to the =S substituent.

[0078] "Alkyl" refers to a straight or branched hydrocarbon chain radical, which is fully saturated or comprises unsaturations, has from one to thirty carbon atoms, and is attached to the rest of the molecule by a single bond. Alkyls comprising any number of carbon atoms from 1 to 30 are included. An alkyl comprising up to 30 carbon atoms is referred to as a C_1-C_{30} alkyl, likewise, for example, an alkyl comprising up to 12 carbon atoms is a C_1-C_{12} alkyl. Alkyls (and other moieties defined herein) comprising other numbers of carbon atoms are represented similarly. Alkyl groups include, but are not limited to, C_1-C_{30} alkyl, C_1-C_{20} alkyl, C_1-C_{15} alkyl, C_1-C_{10} alkyl, C_1-C_8 alkyl, C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_3 alkyl, C_1-C_2 alkyl, C_2-C_8 alkyl, C_3-C_8 alkyl and C_4-C_8 alkyl. Representative alkyl groups include, but are not limited to, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *i*-butyl, *s*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), 3-methylhexyl, 2-methylhexyl, vinyl, allyl, propynyl, and the like. Alkyl comprising unsaturations include alkenyl and alkynyl groups. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted as described below.

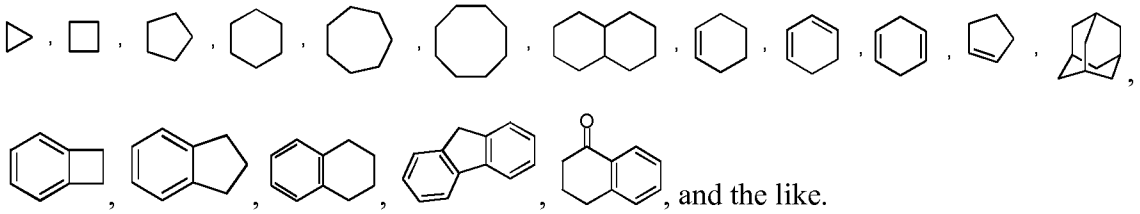
[0079] "Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain, as described for alkyl above. Unless stated otherwise specifically in the specification, an alkylene group may be optionally substituted as described below.

[0080] "Alkoxy" refers to a radical of the formula -OR_a where R_a is an alkyl radical as defined. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted as described below.

[0081] "Aryl" refers to a radical derived from a hydrocarbon ring system comprising hydrogen, 6 to 30 carbon atoms and at least one aromatic ring. The aryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems. Aryl radicals include, but are not limited to, aryl radicals derived from the hydrocarbon ring systems of aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals that are optionally substituted.

[0082] "Cycloalkyl" or "carbocycle" refers to a stable, non-aromatic, monocyclic or polycyclic carbocyclic ring, which may include fused or bridged ring systems, which is saturated or unsaturated. Representative cycloalkyls or carbocycles include, but are not limited to, cycloalkyls having from three to fifteen carbon atoms, from three to ten carbon atoms, from three to eight carbon atoms, from three to six carbon atoms, from three to five carbon atoms, or three to four carbon atoms. Monocyclic cycloalkyls or carbocycles include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls or carbocycles include, for example, adamantyl, norbornyl, decalinyl, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, cis-decalin,

trans-decalin, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, and bicyclo[3.3.2]decane, and 7,7-dimethyl-bicyclo[2.2.1]heptanyl. Unless otherwise stated specifically in the specification, a cycloalkyl or carbocycle group may be optionally substituted. Illustrative examples of cycloalkyl groups include, but are not limited to, the following moieties:



, and the like.

[0083] "Fused" refers to any ring structure described herein which is fused to an existing ring structure. When the fused ring is a heterocyclyl ring or a heteroaryl ring, any carbon atom on the existing ring structure which becomes part of the fused heterocyclyl ring or the fused heteroaryl ring may be replaced with a nitrogen atom.

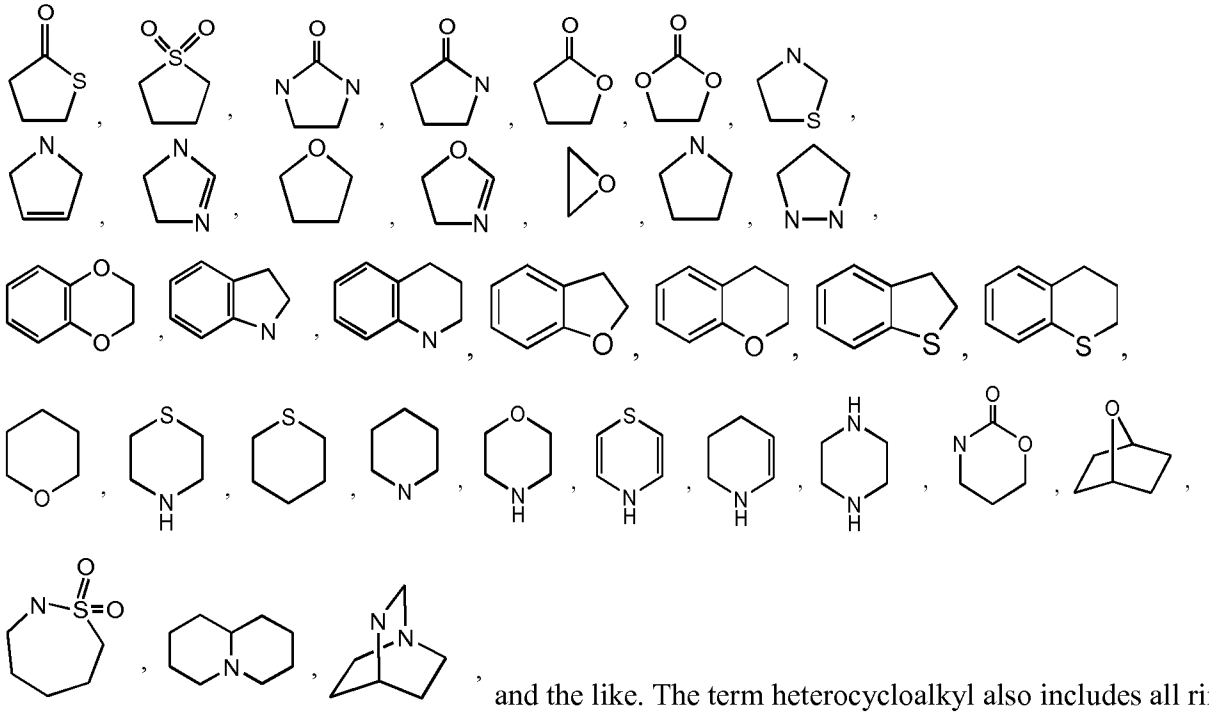
[0084] "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo.

[0085] "Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like. Unless stated otherwise specifically in the specification, a haloalkyl group may be optionally substituted.

[0086] "Haloalkoxy" similarly refers to a radical of the formula $-OR_a$ where R_a is a haloalkyl radical as defined. Unless stated otherwise specifically in the specification, a haloalkoxy group may be optionally substituted as described below.

[0087] "Heterocycloalkyl" or "heterocyclyl" or "heterocyclic ring" or "heterocycle" refers to a stable 3- to 24-membered non-aromatic ring radical comprising 2 to 23 carbon atoms and from one to 8 heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous and sulfur. Unless stated otherwise specifically in the specification, the heterocyclyl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the heterocyclyl radical may be partially or fully saturated. Examples of such heterocyclyl radicals include, but are not limited to, azetidinyl, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, 12-crown-4, 15-crown-5, 18-crown-6, 21-crown-7, aza-18-crown-6,

diaza-18-crown-6, aza-21-crown-7, and diaza-21-crown-7. Unless stated otherwise specifically in the specification, a heterocyclyl group may be optionally substituted. Illustrative examples of heterocycloalkyl groups, also referred to as non-aromatic heterocycles, include:



and the like. The term heterocycloalkyl also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. Unless otherwise noted, heterocycloalkyls have from 2 to 10 carbons in the ring. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e. skeletal atoms of the heterocycloalkyl ring). Unless stated otherwise specifically in the specification, a heterocycloalkyl group may be optionally substituted.

[0088] "Heteroaryl" refers to a 5- to 14-membered ring system radical comprising hydrogen atoms, one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous and sulfur, and at least one aromatic ring. For purposes of this invention, the heteroaryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, naphthyridinyl,

oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (*i.e.*, thienyl). Unless stated otherwise specifically in the specification, a heteroaryl group may be optionally substituted.

[0089] All the above groups may be either substituted or unsubstituted. The term "substituted" as used herein means any of the above groups (*e.g.* alkyl, alkylene, alkoxy, aryl, cycloalkyl, haloalkyl, heterocyclyl and/or heteroaryl) may be further functionalized wherein at least one hydrogen atom is replaced by a bond to a non-hydrogen atom substituent. Unless stated specifically in the specification, a substituted group may include one or more substituents selected from: oxo, amino, $-CO_2H$, nitrile, nitro, hydroxyl, thiooxy, alkyl, alkylene, alkoxy, aryl, cycloalkyl, heterocyclyl, heteroaryl, dialkylamines, arylamines, alkylarylamines, diarylamines, trialkylammonium ($-N^+R_3$), N-oxides, imides, and enamines; a silicon atom in groups such as trialkylsilyl groups, dialkylarylsilyl groups, alkyldiarylsilyl groups, triarylsilyl groups, perfluoroalkyl or perfluoroalkoxy, for example, trifluoromethyl or trifluoromethoxy. "Substituted" also means any of the above groups in which one or more hydrogen atoms are replaced by a higher-order bond (*e.g.*, a double- or triple-bond) to a heteroatom such as oxygen in oxo, carbonyl, carboxyl, and ester groups; and nitrogen in groups such as imines, oximes, hydrazones, and nitriles. For example, "substituted" includes any of the above groups in which one or more hydrogen atoms are replaced with $-NH_2$, $-NR_gC(=O)NR_gR_h$, $-NR_gC(=O)OR_h$, $-NR_gSO_2R_h$, $-OC(=O)NR_gR_h$, $-OR_g$, $-SR_g$, $-SOR_g$, $-SO_2R_g$, $-OSO_2R_g$, $-SO_2OR_g$, $=NSO_2R_g$, and $-SO_2NR_gR_h$. In the foregoing, R_g and R_h are the same or different and independently hydrogen, alkyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl. In addition, each of the foregoing substituents may also be optionally substituted with one or more of the above substituents. Furthermore, any of the above groups may be substituted to include one or more internal oxygen, sulfur, or nitrogen atoms. For example, an alkyl group may be substituted with one or more internal oxygen atoms to form an ether or polyether group. Similarily, an alkyl group may be substituted with one or more internal sulfur atoms to form a thioether, disulfide, etc.

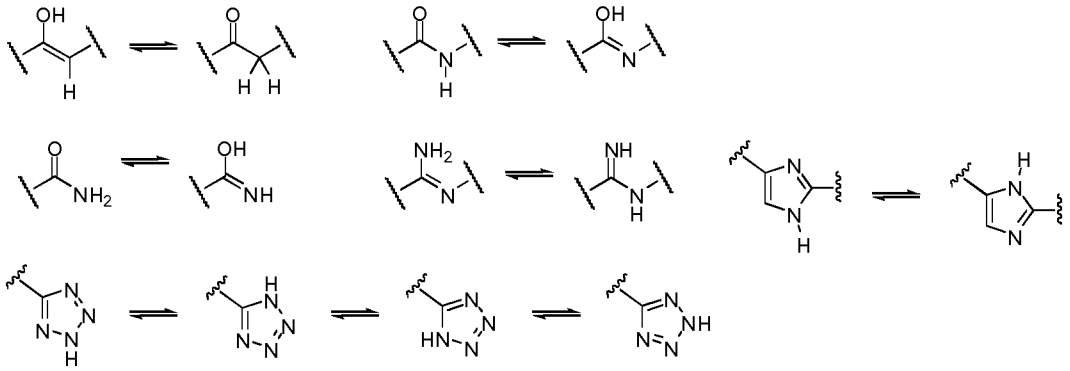
[0090] The term "optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted alkyl" means either "alkyl" or "substituted alkyl" as defined above. Further, an optionally substituted group may be un-substituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), mono-substituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and mono-substituted

(e.g., $-CH_2CHF_2$, $-CH_2CF_3$, $-CF_2CH_3$, $-CFHCHF_2$, etc). It will be understood by those skilled in the art with respect to any group containing one or more substituents that such groups are not intended to introduce any substitution or substitution patterns (e.g., substituted alkyl includes optionally substituted cycloalkyl groups, which in turn are defined as including optionally substituted alkyl groups, potentially ad infinitum) that are sterically impractical and/or synthetically non-feasible. Thus, any substituents described should generally be understood as having a maximum molecular weight of about 1,000 daltons, and more typically, up to about 500 daltons.

[0091] An "effective amount" or "therapeutically effective amount" refers to an amount of a compound administered to a mammalian subject, either as a single dose or as part of a series of doses, which is effective to produce a desired therapeutic effect.

[0092] "Treatment" of an individual (e.g. a mammal, such as a human) or a cell is any type of intervention used in an attempt to alter the natural course of the individual or cell. In some embodiments, treatment includes administration of a pharmaceutical composition, subsequent to the initiation of a pathologic event or contact with an etiologic agent and includes stabilization of the condition (e.g., condition does not worsen) or alleviation of the condition. In other embodiments, treatment also includes prophylactic treatment (e.g., administration of a composition described herein when an individual is suspected to be suffering from a bacterial infection).

[0093] A "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule. The compounds presented herein may exist as tautomers. Tautomers are compounds that are interconvertible by migration of a hydrogen atom, accompanied by a switch of a single bond and adjacent double bond. In bonding arrangements where tautomerization is possible, a chemical equilibrium of the tautomers will exist. All tautomeric forms of the compounds disclosed herein are contemplated. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Some examples of tautomeric interconversions include:



[0094] A "metabolite" of a compound disclosed herein is a derivative of that compound that is formed when the compound is metabolized. The term "active metabolite" refers to a biologically active derivative of a compound that is formed when the compound is metabolized. The term "metabolized," as used herein, refers to the sum of the processes (including, but not limited to, hydrolysis reactions and reactions catalyzed by enzymes, such as, oxidation reactions) by which a

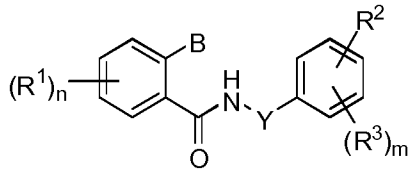
particular substance is changed by an organism. Thus, enzymes may produce specific structural alterations to a compound. For example, cytochrome P450 catalyzes a variety of oxidative and reductive reactions while uridine diphosphate glucuronyl transferases catalyze the transfer of an activated glucuronic-acid molecule to aromatic alcohols, aliphatic alcohols, carboxylic acids, amines and free sulfhydryl groups. Further information on metabolism may be obtained from The Pharmacological Basis of Therapeutics, 9th Edition, McGraw-Hill (1996). Metabolites of the compounds disclosed herein can be identified either by administration of compounds to a host and analysis of tissue samples from the host, or by incubation of compounds with hepatic cells in vitro and analysis of the resulting compounds. Both methods are well known in the art. In some embodiments, metabolites of a compound are formed by oxidative processes and correspond to the corresponding hydroxy-containing compound. In some embodimets, a compound is metabolized to pharmacologically active metabolites.

Methods

[0095] Provided herein is a method of ameliorating arthritis or joint injury in a mammal, the method including administering to a joint of the mammal a composition having a therapeutically effective amount of a compound disclosed herein.

[0096] Provided herein is a method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method including contacting mesenchymal stem cells with a sufficient amount of a compound disclosed herein, thereby inducing differentiation of the stem cells into chondrocytes.

[0097] In one aspect, provided herein is a method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula I)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NR^4R^{11}, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

m is 1, 2, 3, or 4;

B is CO_2R^4, CH_2CO_2H, $CH_2CO_2R^4$, or optionally substituted phenyl;

Y is a bond, $-(CR^5R^6)-$, $-(CR^7R^8)(CR^9R^{10})-$, or $-(CR^7R^8)(CR^9R^{10})X-$;

X is O or CR^5R^6;

R^2 is halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$;

each R^3 is independently selected from H, CN, halo, $C(O)R^4$, CO_2H, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$;

or R^3 together with an adjacent R^3 or with R^2 form a ring;

each R^4 is independently selected from H and optionally substituted alkyl;

each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, optionally substituted alkyl, OH, CO_2R^4, NR^4R^{11}, and optionally substituted alkoxy; and

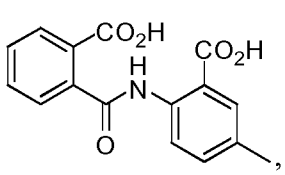
R^{11} is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

provided that

a) if Y is a bond and m is 0, then R^2 is selected from $C(O)NR^4R^{11}$, $(CR^7R^8)OR^4$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$; and

R^2 is not $C(O)NH_2$, p-CH_2OR^4, p-$CH(OH)CH_2OH$, p-CH_2CH_2OH, or p-$CH_2CH_2CH_2OH$; and

b) the compound is not selected from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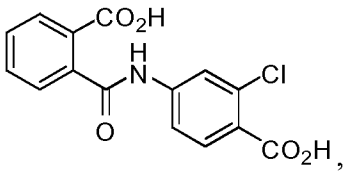
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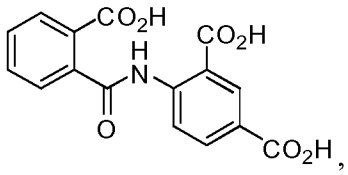
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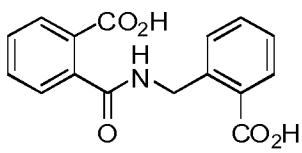
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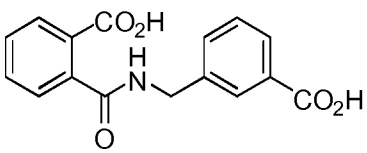
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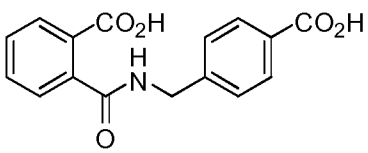
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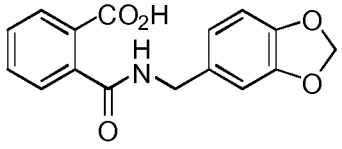

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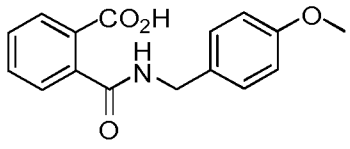

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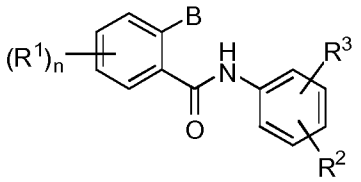
[0098] In another aspect, provided herein is a method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula Ia, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula Ia)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NR^4R^{11}, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

B is CO_2R^4;

R^2 is halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$;

each R^3 is independently selected from CN, halo, $C(O)R^4$, CO_2H, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$;

or R^3 together with an adjacent R^3 or with R^2 form a ring;

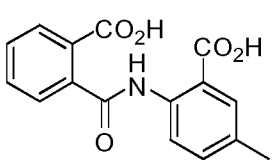
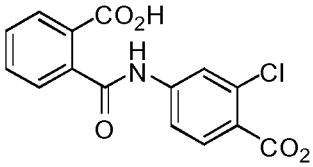
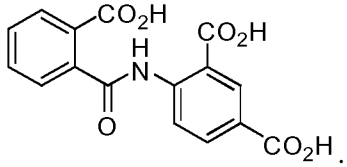
X is O or CR^5R^6;

each R^4 is independently selected from H and optionally substituted alkyl;

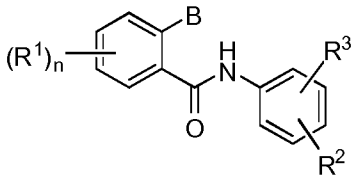
each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, optionally substituted alkyl, OH, NR^4R^{11}, and optionally substituted alkoxy; and

R^{11} is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

provided that the compound is not selected from

[0099] In another aspect, provided herein is a method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula Ib, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula Ib)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NR^4R^{11}, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

B is CO_2R^4;

R^2 is $C(O)NR^4R^{11}$, $(CR^7R^8)OR^4$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$;

R^3 is H;

X is O or CR^5R^6;

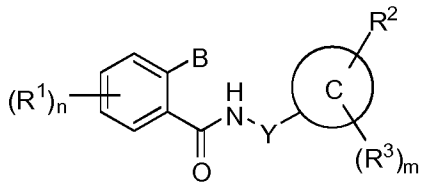
each R^4 is independently selected from H and optionally substituted alkyl;

each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, optionally substituted alkyl, OH, NR^4R^{11}, and optionally substituted alkoxy; and

R^{11} is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

provided that if n is 0, then R^2 is not $C(O)NH_2$, p-CH_2OR^4, p-$CH(OH)CH_2OH$, p-CH_2CH_2OH, or p-$CH_2CH_2CH_2OH$.

[00100] In another aspect, provided herein is a method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula Ic, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula Ic)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NR^4R^{11}, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

m is 1, 2, 3, or 4;

B is CO_2R^4;

Y is $-(CR^5R^6)-$;

C is aryl or heteroaryl;

X is O or CR^5R^6;

R^2 is halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, SO_2NH_2, SO_3H, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$;

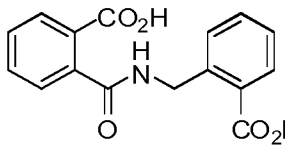
each R^3 is independently selected from H, CN, halo, $C(O)R^4$, CO_2H, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$;

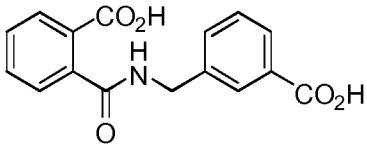
or R^3 together with an adjacent R^3 or with R^2 form a ring;

each R^4 is independently selected from H and optionally substituted alkyl;

each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, optionally substituted alkyl, OH, CO_2R^4, NR^4R^{11}, and optionally substituted alkoxy; and

R^{11} is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

provided that the compound is not selected from  ,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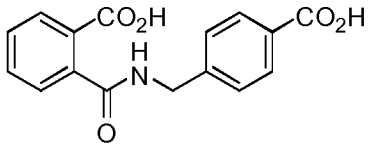
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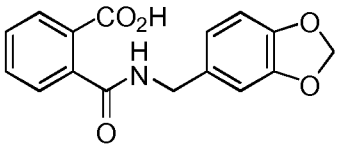
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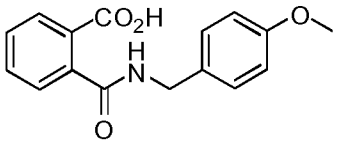
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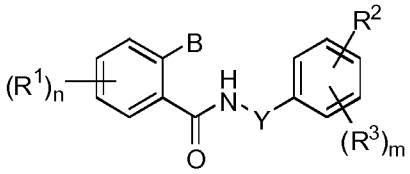
[00101] In another aspect, provided herein is a method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula I, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula I)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NR^4R^{11}, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

m is 1, 2, 3, or 4;

B is CO_2R^4, CH_2CO_2H, $CH_2CO_2R^3$, or optionally substituted phenyl;

Y is a bond, $-(CR^5R^6)-$, $-(CR^7R^8)(CR^9R^{10})-$, or $-(CR^7R^8)(CR^9R^{10})X-$;

X is O or CR^5R^6;

R^2 is halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$;

each R^3 is independently selected from H, CN, halo, $C(O)R^4$, CO_2H, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$;

or R^3 together with an adjacent R^3 or with R^2 form a ring;

each R^4 is independently selected from H and optionally substituted alkyl;

each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, optionally substituted alkyl, OH, CO_2R^4, NR^4R^{11}, and optionally substituted alkoxy; and

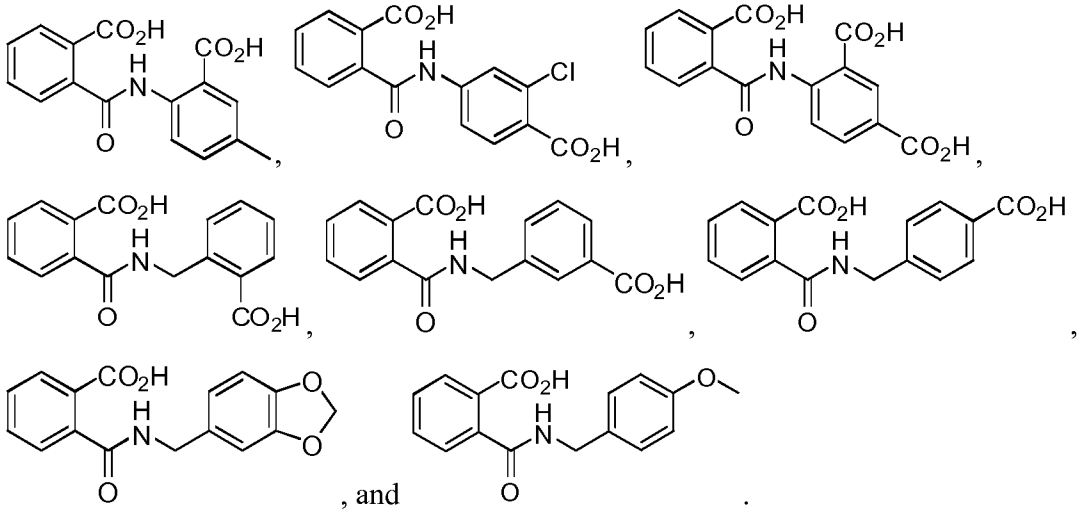
R^{11} is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

provided that

a) if Y is a bond and m is 0, then R^2 is selected from $C(O)NR^4R^{11}$, $(CR^7R^8)OR^4$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$; and

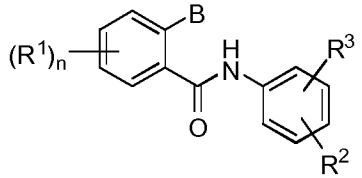
R^2 is not $C(O)NH_2$, p-CH_2OR^4, p-$CH(OH)CH_2OH$, p-CH_2CH_2OH, or p-$CH_2CH_2CH_2OH$; and

b) the compound is not selected from



, and .

[00102] In another aspect, provided herein is a method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula Ia, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula Ia)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NR^4R^{11}, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

B is CO_2R^4;

R^2 is halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$;

each R^3 is independently selected from CN, halo, $C(O)R^4$, CO_2H, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$;

or R^3 together with an adjacent R^3 or with R^2 form a ring;

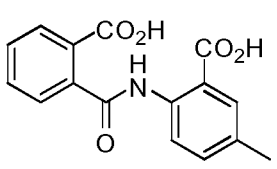
X is O or CR^5R^6;

each R^4 is independently selected from H and optionally substituted alkyl;

each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, optionally substituted alkyl, OH, NR^4R^{11}, and optionally substituted alkoxy; and

R^{11} is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

provided that the compound is not selected from



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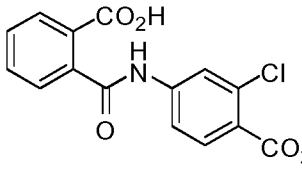

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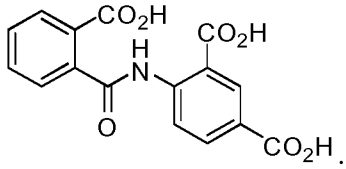

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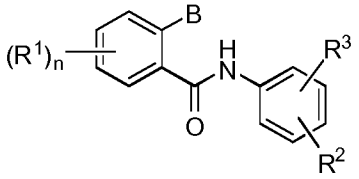
[00103] In another aspect, provided herein is a method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula Ib, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula Ib)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NR^4R^{11}, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

B is CO_2R^4;

R^2 is $C(O)NR^4R^{11}$, $(CR^7R^8)OR^4$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$;

R^3 is H;

X is O or CR^5R^6;

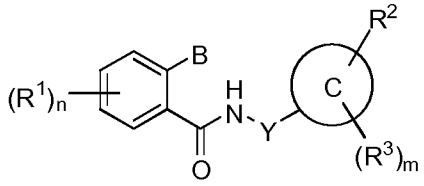
each R^4 is independently selected from H and optionally substituted alkyl;

each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, optionally substituted alkyl, OH, NR^4R^{11}, and optionally substituted alkoxy; and

R^{11} is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

provided that if n is 4 and R^1 is H, then R^2 is not $C(O)NH_2$, p-CH_2OR^4, p-$CH(OH)CH_2OH$, p-CH_2CH_2OH, or p-$CH_2CH_2CH_2OH$.

[00104] In another aspect, provided herein is a method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula Ic, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula Ic)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NR^4R^{11}, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

m is 1, 2, 3, or 4;

B is CO_2R^4;

Y is -(CR^5R^6)-;

C is aryl or heteroaryl;

X is O or CR^5R^6;

R^2 is halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, SO_2NH_2, SO_3H, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$,

$X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$;

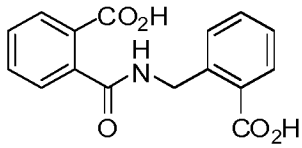
each R^3 is independently selected from H, CN, halo, $C(O)R^4$, CO_2H, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$

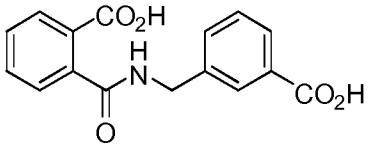
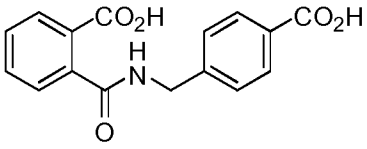
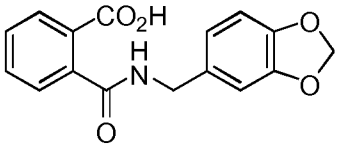
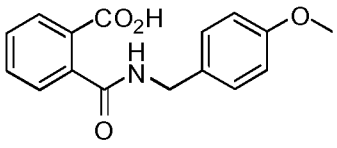
or R^3 together with an adjacent R^3 or with R^2 form a ring;

each R^4 is independently selected from H and optionally substituted alkyl;

each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, optionally substituted alkyl, OH, CO_2R^4, NR^4R^{11}, and optionally substituted alkoxy; and

R^{11} is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

provided that the compound is not selected from  ,

 ,  ,  , and  .

[00105] In some embodiments described above or below of a compound of Formula I or Ia:

R^2 is halo, $C(O)R^4$, alkyl, optionally substituted alkoxy, haloalkyl, $(CR^7R^8)OR^4$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)C(O)OR^4$, or $X(CR^7R^8)C(O)NR^4R^{11}$; and

each R^3 is independently selected from CN, halo, $C(O)R^4$, CO_2H, $C(O)NR^4R^{11}$, alkyl, or optionally substituted alkoxy;

or R^3 together with an adjacent R^3 or with R^2 form a ring.

[00106] In certain embodiments described above or below of a compound of Formula I or Ia:

R^2 is F, Cl, $C(O)CH_3$, CH_3, CF_3, OCH_3, OEt, OPr, OCF_3, $OCHF_2$, $(CR^7R^8)OR^4$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)C(O)OR^4$, or $X(CR^7R^8)C(O)NR^4R^{11}$; and

each R^3 is independently selected from CN, F, Cl, $C(O)CH_3$, CO_2H, $C(O)NH_2$, CH_3, OCF_3, or OCH_3;

or R^3 together with an adjacent R^3 or with R^2 form a ring.

In certain embodiments, R^3 is independently selected from CN, F, Cl, $C(O)CH_3$, or CO_2H. In certain embodiments, R^3 is CN or CO_2H. In certain embodiments, R^2 is F, Cl, $C(O)CH_3$, CH_3, CF_3, OCH_3, OEt, OPr, OCF_3, or $CH_2CH_2CH_2OH$. In certain embodiments, R^2 is $CH_2CH_2CH_2OH$. In certain embodiments, R^3 together with an adjacent R^3 or with R^2 form a ring.

[00107] In certain embodiments, R^2 is $(CR^7R^8)OR^4$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)C(O)OR^4$, or $X(CR^7R^8)C(O)NR^4R^{11}$; and each R^3 is independently selected from CN, F, Cl, $C(O)CH_3$, CO_2H, $C(O)NH_2$, CH_3, OCF_3, or OCH_3. In certain embodiments, R^2 is F, Cl, $C(O)CH_3$, CH_3, CF_3, OCH_3, OEt, OPr, OCF_3, or $CH_2CH_2CH_2OH$; and R^3 is independently selected from CN, F, Cl, $C(O)CH_3$, or CO_2H. In certain embodiments, R^2 is F, Cl, $C(O)CH_3$, CH_3, CF_3, OCH_3, OEt, OPr, OCF_3, or $CH_2CH_2CH_2OH$; and R^3 is independently selected from CN or CO_2H. In certain embodiments, R^2 is $CH_2CH_2CH_2OH$ and R^3 is independently selected from CN, F, Cl, $C(O)CH_3$, or CO_2H.

[00108] In some embodiments described above or below of a compound of Formula I:

R^2 is halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$; and

each R^3 is independently selected from CN, halo, $C(O)R^4$, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$.

[00109] In some embodiments described above or below of a compound of Formula Ia:

R^2 is halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$; and

each R^3 is independently selected from CN, halo, $C(O)R^4$, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$.

[00110] In some embodiments described above or below of a compound of Formula Ib:

R^2 is $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$; and

R^3 is H.

In certain embodiments, R^2 is $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, or $(CR^7R^8)NR^4SO_2R^4$. In certain embodiments, R^2 is CH_2CH_2OH, $CH_2CH_2OCH_3$, CH_2CHCH_3OH, $CHCH_3CH_2OH$, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2NH_2$, $CH_2CH_2CHCH_3OH$, $C(CH_3)_2CH_2CH_2OH$, $CH_2CH_2C(CH_3)_2OH$, OCH_2CH_2OH, $OCH_2CH_2OCH_3$, or $OCH_2CH_2NH_2$. In certain embodiments, R^2 is $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, or $X(CR^7R^8)C(O)NR^4R^{11}$. In certain embodiments, R^2 is $CH_2C(O)CH_3$, $CH_2C(O)NH_2$, $CH_2CH_2C(O)CH_3$, or $CH_2CH_2C(O)NH_2$.

[00111] In some embodiments described above or below of a compound of Formula Ic, C is aryl. In certain embodiments, C is phenyl. In certain embodiments, C is naphthyl.

[00112] In some embodiments described above or below of a compound of Formula Ic, C is heteroaryl. In certain embodiments, C is pyridinyl, pyrimidinyl, pyridazinyl, or pyrazinyl. In certain embodiments, C is pyridinyl. In certain embodiments, C is pyrimidinyl. In certain embodiments, C is pyridazinyl. In certain embodiments, C is a 5-membered heteroaryl ring. In certain embodiments, C is thiophene, benzofuran, pyrrole, thiazole, imidazole, oxazole, pyrazole, or triazole.

[00113] In some embodiments described above or below of a compound of Formula Ic:

R^2 is halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, SO_2NH_2, SO_3H, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$; and

each R^3 is independently selected from H, CN, halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$,

$X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$;

provided that if n = 0 and C is phenyl, R^2 is not CO_2H or p-OCH_3.

[00114] In some embodiments described above or below of a compound of Formula Ic:

R^2 is halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2NH_2, SO_3H, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)OR^4$, or $X(CR^7R^8)C(O)NR^4R^{11}$; and

each R^3 is independently selected from H, CN, halo, CO_2H, or haloalkyl.

[00115] In certain embodiments described above or below of a compound of Formula Ic:

R^2 is Cl, F, $C(O)CH_3$, CO_2H, $C(O)NR^4R^{11}$, CH_3, optionally substituted alkoxy, CF_3, SO_2NH_2, SO_3H, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)OR^4$, or $X(CR^7R^8)C(O)NR^4R^{11}$; and

each R^3 is independently selected from H, CN, Cl, F, CO_2H, or CF_3.

In certain embodiments, R^2 is Cl, F, $C(O)CH_3$, CO_2H, CH_3, OCH_3, CF_3; and each R^3 is independently selected from H, CN, or CO_2H. In certain embodiments, R^2 is $CH_2C(O)NH_2$, $CH_2C(O)CH_3$, $CH_2C(O)OH$, $CH_2CH_2C(O)OH$, or $CH_2CH_2C(O)NH_2$. In certain embodiments, R^2 is CO_2H. In certain embodiments, R^2 is CO_2H and each R^3 is independently selected from H, CN, Cl, F, or CF_3.

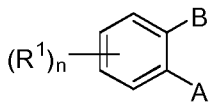
[00116] In certain embodiments described above or below of a compound of Formula Ic:

R^2 is Cl, F, $C(O)CH_3$, CO_2H, $C(O)NR^4R^{11}$, CH_3, optionally substituted alkoxy, CF_3, SO_2NH_2, SO_3H, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)OR^4$, or $X(CR^7R^8)C(O)NR^4R^{11}$; and

each R^3 is independently selected from H, CN, or CO_2H.

In certain embodiments, R^2 is $CH_2C(O)NH_2$, $CH_2C(O)CH_3$, $CH_2C(O)OH$, $CH_2CH_2C(O)OH$, or $CH_2CH_2C(O)NH_2$; and each R^3 is independently selected from H, CN, or CO_2H.

[00117] In one aspect, provided herein is a method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula II, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula II)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

B is $NHC(O)R^2$, $NR^3C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NHR^2$, $NHC(O)NR^2R^4$, $NR^3C(O)NH_2$, $NR^3C(O)NHR^2$, $NR^3C(O)NR^2R^4$, $NHC(O)OR^2$, $NR^3C(O)OR^2$, $NHSO_2R^3$, $NR^3SO_2R^3$, $NHSO_2R^4$, $NR^3SO_2R^4$, $NHSO_2NH_2$, $NHSO_2NHR^2$, $NHSO_2NR^2R^4$, $NR^3SO_2NH_2$, $NR^3SO_2NHR^2$, or $NR^3SO_2NR^2R^4$;

each R^2 and R^4 is independently optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted alkyl;

R^3 is optionally substituted alkyl or optionally substituted aralkyl;

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

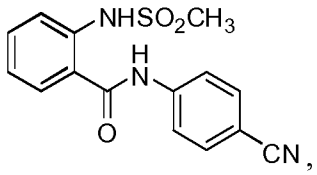
A is CO_2H, CO_2R^3, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^4$, or $SO_2NR^aR^b$; and

each R^a and R^b is independently optionally substituted alkyl or together with the N to which they are attached make a ring;

provided that

a) if B is $NHC(O)R^2$ or $NR^3C(O)R^2$, then A is not CO_2H; and

b) the compound is not selected from



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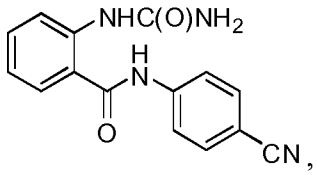

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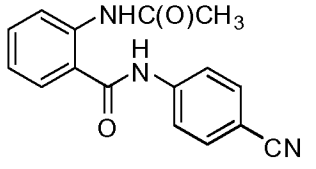

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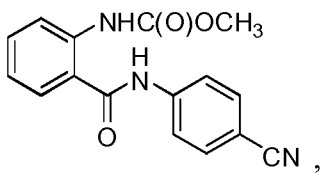

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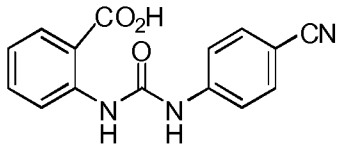

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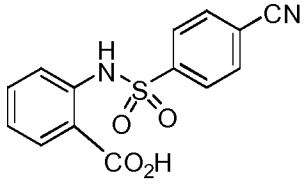

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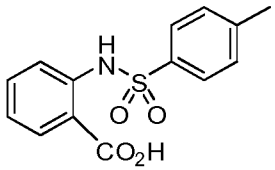
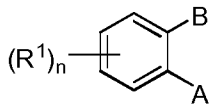


.

[00118] In another aspect, provided herein is a method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula IIa, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula IIa)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

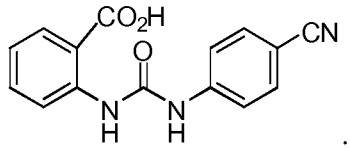
B is $NHC(O)NH_2$, $NHC(O)NHR^2$, $NHC(O)NR^2R^4$, $NR^3C(O)NH_2$, $NR^3C(O)NHR^2$, or $NR^3C(O)NR^2R^4$;

each R^2 and R^4 is independently optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted alkyl;

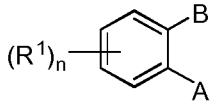
R^3 is optionally substituted alkyl or optionally substituted aralkyl;

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4; and

A is CO_2H or CO_2R^3;

provided that the compound is not  .

[00119] In another aspect, provided herein is a method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula IIb, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula IIb)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

B is $NHC(O)R^2$ or $NR^3C(O)R^2$;

R^2 is optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted alkyl;

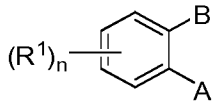
R^3 is optionally substituted alkyl or optionally substituted aralkyl;

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

A is $SO_2NR^aR^b$; and

each R^a and R^b is independently optionally substituted alkyl or together with the N to which they are attached make a ring.

[00120] In another aspect, provided herein is a method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula IIc, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula IIc)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

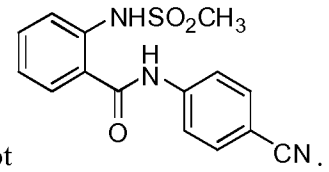
B is $NHSO_2R^3$, $NR^3SO_2R^3$, $NHSO_2R^4$, $NR^3SO_2R^4$, $NHSO_2NH_2$, $NHSO_2NHR^2$, $NHSO_2NR^2R^4$, $NR^3SO_2NH_2$, $NR^3SO_2NHR^2$, or $NR^3SO_2NR^2R^4$;

each R^2 and R^4 is independently optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted alkyl;

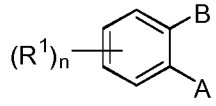
each R^3 is independently optionally substituted alkyl or optionally substituted aralkyl;

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4; and

A is $C(O)NHR^2$ or $C(O)NR^2R^4$;

provided that the compound is not  .

[00121] In another aspect provided herein is a method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula II, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula II)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

B is $NHC(O)R^2$, $NR^3C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NHR^2$, $NHC(O)NR^2R^4$, $NR^3C(O)NH_2$, $NR^3C(O)NHR^2$, $NR^3C(O)NR^2R^4$, $NHC(O)OR^2$, $NR^3C(O)OR^2$, $NHSO_2R^3$, $NR^3SO_2R^3$, $NHSO_2R^4$, $NR^3SO_2R^4$, $NHSO_2NH_2$, $NHSO_2NHR^2$, $NHSO_2NR^2R^4$, $NR^3SO_2NH_2$, $NR^3SO_2NHR^2$, or $NR^3SO_2NR^2R^4$;

each R^2 and R^4 is independently optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted alkyl;

R^3 is optionally substituted alkyl or optionally substituted aralkyl;

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

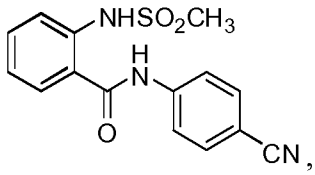
A is CO_2H, CO_2R^3, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^4$, or $SO_2NR^aR^b$; and

each R^a and R^b is independently optionally substituted alkyl or together with the N to which they are attached make a ring;

provided that

a) if B is $NHC(O)R^2$ or $NR^3C(O)R^2$, then A is not CO_2H; and

b) the compound is not selected from



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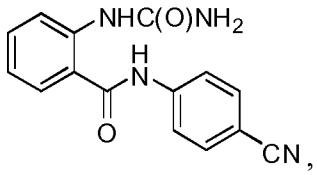

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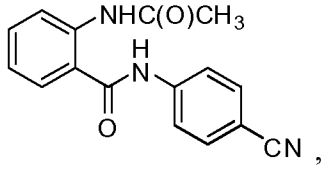

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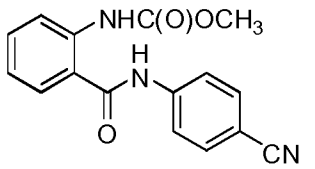

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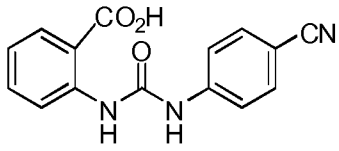

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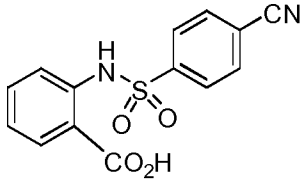

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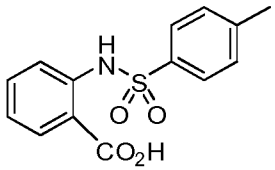

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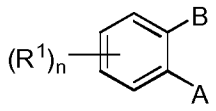
[00122] In another aspect, provided herein is a method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula IIa, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula IIa)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

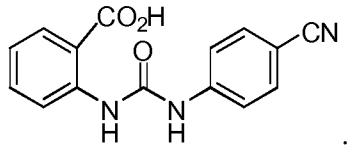
B is $NHC(O)NH_2$, $NHC(O)NHR^2$, $NHC(O)NR^2R^4$, $NR^3C(O)NH_2$, $NR^3C(O)NHR^2$, or $NR^3C(O)NR^2R^4$;

each R^2 and R^4 is independently optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted alkyl;

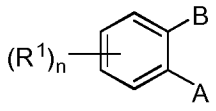
R^3 is optionally substituted alkyl or optionally substituted aralkyl;

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4; and

A is CO_2H or CO_2R^3;

provided that the compound is not  .

[00123] In another aspect, provided herein is a method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula IIb, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula IIb)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

B is $NHC(O)R^2$ or $NR^3C(O)R^2$;

R^2 is optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted alkyl;

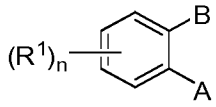
R^3 is optionally substituted alkyl or optionally substituted aralkyl;

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

A is $SO_2NR^aR^b$; and

each R^a and R^b is independently optionally substituted alkyl or together with the N to which they are attached make a ring.

[00124] In another aspect, provided herein is a method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula IIc, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula IIc)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

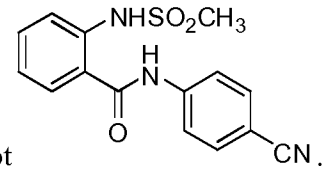
B is $NHSO_2R^3$, $NR^3SO_2R^3$, $NHSO_2R^4$, $NR^3SO_2R^4$, $NHSO_2NH_2$, $NHSO_2NHR^2$, $NHSO_2NR^2R^4$, $NR^3SO_2NH_2$, $NR^3SO_2NHR^2$, or $NR^3SO_2NR^2R^4$;

each R^2 and R^4 is independently optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted alkyl;

each R^3 is independently optionally substituted alkyl or optionally substituted aralkyl;

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4; and

A is $C(O)NHR^2$ or $C(O)NR^2R^4$;

provided that the compound is not 

.

[00125] In some embodiments described above or below of a compound of Formula IIa, B is $NHC(O)NHR^2$, $NHC(O)NR^2R^4$, $NR^3C(O)NHR^2$, or $NR^3C(O)NR^2R^4$. In certain embodiments, B is $NHC(O)NHR^2$ or $NR^3C(O)NHR^2$. In certain embodiments, B is $NHC(O)NR^2R^4$ or $NR^3C(O)NR^2R^4$. In certain embodiments, B is $NHC(O)NHR^2$.

[00126] In some embodiments described above or below of a compound of Formula IIa, B is $NHC(O)NHR^2$, $NHC(O)NR^2R^4$, $NR^3C(O)NHR^2$, or $NR^3C(O)NR^2R^4$; and A is CO_2H. In certain embodiments, B is $NHC(O)NHR^2$ or $NR^3C(O)NHR^2$; and A is CO_2H. In certain embodiments, B is

$NHC(O)NHR^2$ and A is CO_2H. In certain embodiments, B is $NHC(O)NHR^2$ and A is CO_2H, , wherein R^2 is optionally substituted phenyl.

[00127] In some embodiments described above or below of a compound of Formula IIa, B is $NHC(O)NHR^2$, $NHC(O)NR^2R^4$, $NR^3C(O)NHR^2$, or $NR^3C(O)NR^2R^4$; and A is CO_2R^3. In certain embodiments, B is $NHC(O)NHR^2$ or $NR^3C(O)NHR^2$; and A is CO_2R^3. In certain embodiments, B is $NHC(O)NHR^2$ and A is CO_2R^3. In certain embodiments, B is $NHC(O)NHR^2$ and A is CO_2R^3, wherein R^2 is optionally substituted phenyl.

[00128] In some embodiments described above or below of a compound of Formula IIa, R^2 is optionally substituted phenyl. In certain embodiments, the phenyl of R^2 is bisubstituted. In certain embodiments, the phenyl of R^2 is monosubstituted. In certain embodiments, substitution on the phenyl of R^2 is independently selected from optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, halo, CN, CO_2H, amino, monoalkylamine, dialkylamine, monoarylamine, alkylarylamine, cycloalkyl, hydroxy, C(O)-(optionally substituted alkyl), $C(O)NH_2$, C(O)NH-(optionally substituted alkyl), alkylthioether, alkylsulfoxide, alkylsulfone, C(O)-(optionally substituted aryl), C(O)NH-(optionally substituted aryl), arylthioether, arylsulfoxide, or arylsulfone. In certain embodiments, substitution on the phenyl of R^2 is independently selected from F, Cl, CO_2H, CN, OCH_3, $C(O)CH_3$, CF_3, CH_3, CH_2OH, CH_2CH_2OH, and $CH_2CH_2CH_2OH$. In certain embodiments, bisubstitution on the phenyl of R^2 consists of CN and a group selected from F, Cl, CO_2H, OCH_3, $C(O)CH_3$, CF_3, CH_3, CH_2OH, CH_2CH_2OH, and $CH_2CH_2CH_2OH$. In certain embodiments, bisubstitution on the phenyl of R^2 consists of CO_2H and a group selected from F, Cl, CN, OCH_3, $C(O)CH_3$, CF_3, CH_3, CH_2OH, CH_2CH_2OH, and $CH_2CH_2CH_2OH$. In certain embodiments, bisubstitution on the phenyl of R^2 consists of $CH_2CH_2CH_2OH$ and a group selected from F, Cl, CN, OCH_3, $C(O)CH_3$, CF_3, CH_3, CH_2OH, CH_2CH_2OH, and CO_2H.

[00129] In some embodiments described above or below of a compound of Formula IIa, R^2 is optionally substituted naphthyl.

[00130] In some embodiments described above or below of a compound of Formula IIa, R^2 is optionally substituted heteroaryl. In certain embodiments, R^2 is optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted pyridazinyl, or optionally substituted pyrazinyl. In certain embodiments, R^2 is an optionally substituted 5-membered heteroaryl ring. In certain embodiments, the 5-membered heteroaryl ring is thiophene, benzofuran, pyrrole, thiazole, imidazole, oxazole, pyrazole, or triazole. In certain embodiments, R^2 is an optionally substituted bicyclic heteroaryl. In certain embodiments, the bicyclic heteroaryl is benzimidazole, benzthiazole, benzoxazole, indazole, quinoline, or naphthyridine.

[00131] In some embodiments described above or below of a compound of Formula IIb, B is $NHC(O)R^2$. In certain embodiments, B is $NHC(O)R^2$ and R^2 is optionally substituted phenyl. In certain embodiments, B is $NHC(O)R^2$ and R^2 is optionally substituted heteroaryl.

[00132] In some embodiments described above or below of a compound of Formula IIb, B is $NR^3C(O)R^2$. In certain embodiments, R^3 is optionally substituted alkyl.

[00133] In some embodiments described above or below of a compound of Formula IIb, each R^a and R^b is independently optionally substituted alkyl. In certain embodiments, each R^a and R^b is independently alkyl. In some embodiments described above or below of a compound of Formula IIb, R^a and R^b together with the N to which they are attached make a ring. In certain embodiments, the ring is morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, azetidinyl, aziridinyl, azepanyl, homopiperazinyl, or piperazinyl.

[00134] In some embodiments described above or below of a compound of Formula IIb, R^2 is optionally substituted phenyl. In certain embodiments, the phenyl of R^2 is bisubstituted. In certain embodiments, the phenyl of R^2 is monosubstituted. In certain embodiments, substitution on the phenyl of R^2 is independently selected from optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, halo, CN, CO_2H, amino, monoalkylamine, dialkylamine, monoarylamine, alkylarylamine, cycloalkyl, hydroxy, C(O)-(optionally substituted alkyl), $C(O)NH_2$, C(O)NH-(optionally substituted alkyl), alkylthioether, alkylsulfoxide, alkylsulfone, C(O)-(optionally substituted aryl), C(O)NH-(optionally substituted aryl), arylthioether, arylsulfoxide, or arylsulfone. In certain embodiments, substitution on the phenyl of R^2 is independently selected from F, Cl, CO_2H, CN, OCH_3, $C(O)CH_3$, CF_3, CH_3, CH_2OH, CH_2CH_2OH, and $CH_2CH_2CH_2OH$. In certain embodiments, bisubstitution on the phenyl of R^2 consists of CN and a group selected from F, Cl, CO_2H, OCH_3, $C(O)CH_3$, CF_3, CH_3, CH_2OH, CH_2CH_2OH, and $CH_2CH_2CH_2OH$. In certain embodiments, bisubstitution on the phenyl of R^2 consists of CO_2H and a group selected from F, Cl, CN, OCH_3, $C(O)CH_3$, CF_3, CH_3, CH_2OH, CH_2CH_2OH, and $CH_2CH_2CH_2OH$. In certain embodiments, bisubstitution on the phenyl of R^2 consists of $CH_2CH_2CH_2OH$ and a group selected from F, Cl, CN, OCH_3, $C(O)CH_3$, CF_3, CH_3, CH_2OH, CH_2CH_2OH, and CO_2H.

[00135] In some embodiments described above or below of a compound of Formula IIb, R^2 is optionally substituted naphthyl.

[00136] In some embodiments described above or below of a compound of Formula IIb, R^2 is optionally substituted heteroaryl. In certain embodiments, R^2 is optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted pyridazinyl, or optionally substituted pyrazinyl. In certain embodiments, R^2 is an optionally substituted 5-membered heteroaryl ring. In certain embodiments, the 5-membered heteroaryl ring is thiophene, benzofuran, pyrrole, thiazole, imidazole, oxazole, pyrazole, or triazole. In certain embodiments, R^2 is an optionally substituted bicyclic heteroaryl. In certain embodiments, the bicyclic heteroaryl is benzimidazole, benzthiazole, benzoxazole, indazole, quinoline, or naphthyridine.

[00137] In some embodiments described above or below of a compound of Formula IIc, B is $NHSO_2R^3$, $NR^3SO_2R^3$, $NHSO_2R^4$, or $NR^3SO_2R^4$. In certain embodiments, B is $NHSO_2R^3$ or

$NR^3SO_2R^3$. In certain embodiments, B is $NHSO_2R^3$. In certain embodiments, R^3 is optionally substituted alkyl. In certain embodiments, R^3 is alkyl. In certain embodiments, R^3 is CH_3. In certain embodiments, B is $NHSO_2R^4$ or $NR^3SO_2R^4$. In certain embodiments, R^4 is optionally substituted phenyl. In certain embodiments, R^4 is optionally substituted naphthyl. In certain embodiments, R^4 is optionally substituted heteroaryl. In certain embodiments, R^4 is optionally substituted heterocyclyl.

[00138] In some embodiments described above or below of a compound of Formula IIc, B is $NHSO_2R^3$, $NR^3SO_2R^3$, $NHSO_2R^4$, or $NR^3SO_2R^4$ and A is $C(O)NHR^2$. In certain embodiments, B is $NHSO_2R^3$ or $NR^3SO_2R^3$ and A is $C(O)NHR^2$. In certain embodiments, B is $NHSO_2R^3$ and A is $C(O)NHR^2$. In certain embodiments, B is $NHSO_2R^3$ and A is $C(O)NHR^2$, wherein R^3 is optionally substituted alkyl. In certain embodiments, B is $NHSO_2R^3$ and A is $C(O)NHR^2$, wherein R^3 is optionally substituted alkyl and R^2 is optionally substituted phenyl. In certain embodiments, B is $NHSO_2R^3$ and A is $C(O)NHR^2$, wherein R^3 is optionally substituted alkyl and R^2 is optionally substituted heteroaryl.

[00139] In some embodiments described above or below of a compound of Formula IIc, B is $NHSO_2R^3$, $NR^3SO_2R^3$, $NHSO_2R^4$, or $NR^3SO_2R^4$ and A is $C(O)NR^2R^4$. In certain embodiments, B is $NHSO_2R^3$ or $NR^3SO_2R^3$ and A is $C(O)NR^2R^4$. In certain embodiments, B is $NHSO_2R^3$ and A is $C(O)NR^2R^4$. In certain embodiments, B is $NHSO_2R^3$ and A is $C(O)NR^2R^4$, wherein R^3 is optionally substituted alkyl. In certain embodiments, B is $NHSO_2R^3$ and A is $C(O)NR^2R^4$, wherein R^3 is optionally substituted alkyl and R^2 is optionally substituted phenyl. In certain embodiments, B is $NHSO_2R^3$ and A is $C(O)NR^2R^4$, wherein R^3 is optionally substituted alkyl and R^2 is optionally substituted heteroaryl.

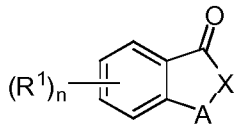
[00140] In some embodiments described above or below of a compound of Formula IIc, B is $NHSO_2NH_2$, $NHSO_2NHR^2$, $NHSO_2NR^2R^4$, $NR^3SO_2NH_2$, $NR^3SO_2NHR^2$, or $NR^3SO_2NR^2R^4$. In certain embodiments, B is $NHSO_2NH_2$, $NHSO_2NHR^2$, $NHSO_2NR^2R^4$, $NR^3SO_2NH_2$, $NR^3SO_2NHR^2$, or $NR^3SO_2NR^2R^4$ and A is $C(O)NHR^2$. In certain embodiments, B is $NHSO_2NH_2$, $NHSO_2NHR^2$, $NHSO_2NR^2R^4$, $NR^3SO_2NH_2$, $NR^3SO_2NHR^2$, or $NR^3SO_2NR^2R^4$ and A is $C(O)NR^2R^4$.

[00141] In some embodiments described above or below of a compound of Formula IIc, A is $C(O)NHR^2$. In some embodiments described above or below of a compound of Formula IIc, A is $C(O)NR^2R^4$. In certain embodiments, R^2 is optionally substituted phenyl. In certain embodiments, the phenyl of R^2 is bisubstituted. In certain embodiments, the phenyl of R^2 is monosubstituted. In certain embodiments, substitution on the phenyl of R^2 is independently selected from optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, halo, CN, CO_2H, amino, monoalkylamine, dialkylamine, monoarylamine, alkylarylamine, cycloalkyl, hydroxy, C(O)-(optionally substituted alkyl), $C(O)NH_2$, C(O)NH-(optionally substituted alkyl), alkylthioether, alkylsulfoxide, alkylsulfone, C(O)-(optionally substituted aryl), C(O)NH-(optionally substituted aryl), arylthioether, arylsulfoxide, or arylsulfone. In certain embodiments, substitution on the phenyl

of R^2 is independently selected from F, Cl, CO_2H, CN, OCH_3, $C(O)CH_3$, CF_3, CH_3, CH_2OH, CH_2CH_2OH, and $CH_2CH_2CH_2OH$. In certain embodiments, bisubstitution on the phenyl of R^2 consists of CN and a group selected from F, Cl, CO_2H, OCH_3, $C(O)CH_3$, CF_3, CH_3, CH_2OH, CH_2CH_2OH, and $CH_2CH_2CH_2OH$. In certain embodiments, bisubstitution on the phenyl of R^2 consists of CO_2H and a group selected from F, Cl, CN, OCH_3, $C(O)CH_3$, CF_3, CH_3, CH_2OH, CH_2CH_2OH, and $CH_2CH_2CH_2OH$. In certain embodiments, bisubstitution on the phenyl of R^2 consists of $CH_2CH_2CH_2OH$ and a group selected from F, Cl, CN, OCH_3, $C(O)CH_3$, CF_3, CH_3, CH_2OH, CH_2CH_2OH, and CO_2H.In certain embodiments, R^2 is optionally substituted naphthyl.

[00142] In some embodiments described above or below of a compound of Formula IIc, R^2 is optionally substituted heteroaryl. In certain embodiments, R^2 is optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted pyridazinyl, or optionally substituted pyrazinyl. In certain embodiments, R^2 is an optionally substituted 5-membered heteroaryl ring. In certain embodiments, the 5-membered heteroaryl ring is thiophene, benzofuran, pyrrole, thiazole, imidazole, oxazole, pyrazole, or triazole. In certain embodiments, R^2 is an optionally substituted bicyclic heteroaryl. In certain embodiments, the bicyclic heteroaryl is benzimidazole, benzthiazole, benzoxazole, indazole, quinoline, or naphthyridine.

[00143] In another aspect, provided herein is a method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula III, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula III)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

X is O, NH, or NR^6;

A is C(O), CH_2, or $CH\text{-}CR^3R^4\text{-}C(O)R^2$;

R^2 is optionally substituted aryl or optionally substituted heteroaryl;

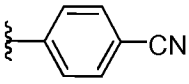
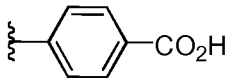
each R^3 and R^4 is independently H or optionally substituted alkyl;

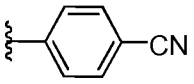
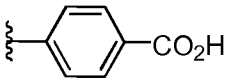
R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4; and

R^6 is optionally substituted phenyl;

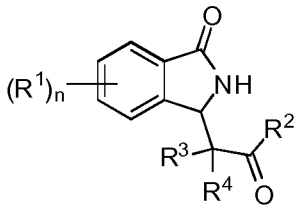
provided that

a) if A is CH-CR^{3}R^4-C(O)R^2, then X is O or NH;

b) if n is 0, A is CHCH$_2$C(O)R^2 and X is O, then R^2 is not  or  ; and

c) if A is C(O) or CH$_2$, then X is NR^6 and R^6 is not  or  .

[00144] In another aspect, provided herein is a method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula IIIa, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula IIIa)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO$_2$, SR^4, S(O)R^4, SO$_2$R^4, NHR^5, NR^{4}R^5, CO$_2$H, or CO$_2$R^4;

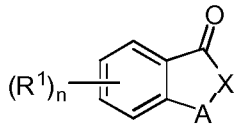
n is 0, 1, 2, 3, or 4;

R^2 is optionally substituted aryl or optionally substituted heteroaryl;

each R^3 and R^4 is independently H or optionally substituted alkyl; and

R^5 is H, optionally substituted alkyl, C(O)R^4, C(O)OR^4, C(O)NR^{4}R^4, or SO$_2$R^4.

[00145] In another aspect, provided herein is a method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula III, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula III)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO$_2$, SR^4, S(O)R^4, SO$_2$R^4, NHR^5, NR^{4}R^5, CO$_2$H, or CO$_2$R^4;

n is 0, 1, 2, 3, or 4;

X is O, NH, or NR^6;

A is C(O), CH_2, or $CH\text{-}CR^3R^4\text{-}C(O)R^2$;

R^2 is optionally substituted aryl or optionally substituted heteroaryl;

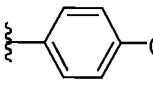
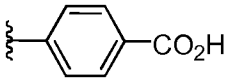
each R^3 and R^4 is independently H or optionally substituted alkyl;

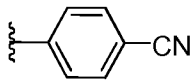
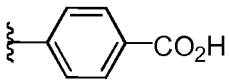
R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4; and

R^6 is optionally substituted phenyl;

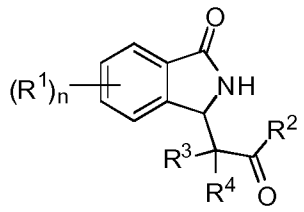
provided that

d) if A is $CH\text{-}CR^3R^4\text{-}C(O)R^2$, then X is O or NH;

e) if n is 0, A is $CHCH_2C(O)R^2$ and X is O, then R^2 is not  or  ; and

if A is C(O) or CH_2, then X is NR^6 and R^6 is not  or  .

[00146] In another aspect, provided herein is a method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula IIIa, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula IIIa)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

R^2 is optionally substituted aryl or optionally substituted heteroaryl;

each R^3 and R^4 is independently H or optionally substituted alkyl; and

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4.

[00147] In some embodiments described above or below of a compound of Formula III, X is NR^6 and A is C(O). In some embodiments described above or below of a compound of Formula III, X is NR^6 and A is CH_2. In some embodiments described above or below of a compound of Formula III, X

is O and A is CH-CR^3R^4-$C(O)R^2$. In some embodiments described above or below of a compound of Formula III, X is NH and A is CH-CR^3R^4-$C(O)R^2$.

[00148] In some embodiments described above or below of a compound of Formula III or IIIa, R^3 and R^4 are both hydrogen. In some embodiments described above or below of a compound of Formula III or IIIa, R^3 is optionally substituted alkyl and R^4 is hydrogen. In some embodiments described above or below of a compound of Formula III or IIIa, R^3 and R^4 are independently optionally substituted alkyl.

[00149] In some embodiments described above or below of a compound of Formula III or IIIa, R^2 is heteroaryl. In certain embodiments, R^2 is optionally substituted optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted pyridazinyl, or optionally substituted pyrazinyl. In certain embodiments, R^2 is 5-membered heteroaryl. In certain embodiments, the 5-membered heteroaryl is thiophene, benzofuran, pyrrole, thiazole, imidazole, oxazole, pyrazole, or triazole. In certain embodiments, R^2 is bicyclic heteroaryl. In certain embodiments, the bicyclic heteroaryl is benzimidazole, benzthiazole, benzoxazole, indazole, quinoline, or naphthyridine.

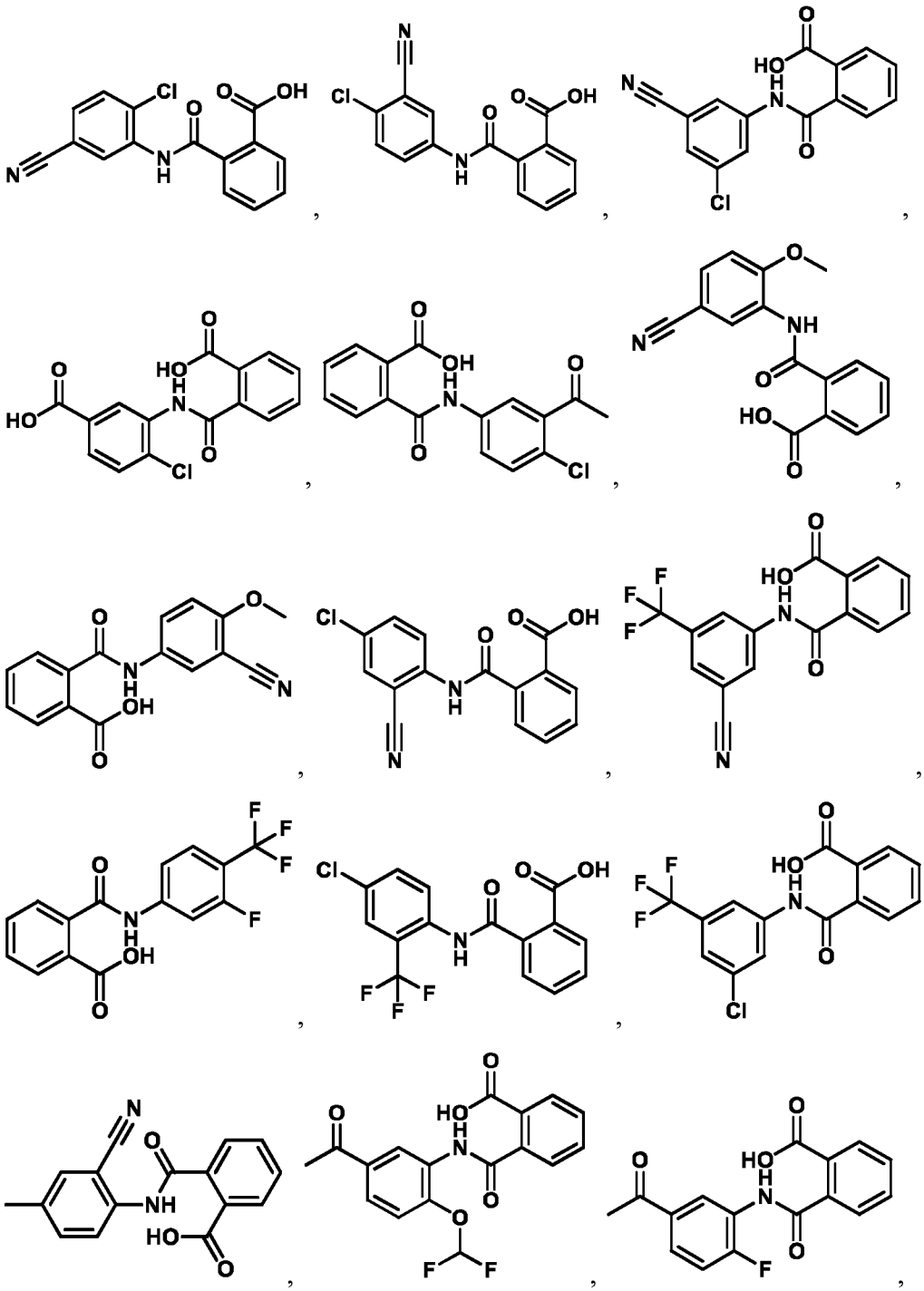
[00150] In some embodiments described above or below of a compound of Formula III or IIIa, R^2 is phenyl. In certain embodiments, the phenyl of R^2 is bisubstituted. In certain embodiments, the phenyl of R^2 is monosubstituted. In certain embodiments, substitution on the phenyl of R^2 is independently selected from optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, halo, CN, CO_2H, amino, monoalkylamine, dialkylamine, monoarylamine, alkylarylamine, cycloalkyl, hydroxy, C(O)-(optionally substituted alkyl), $C(O)NH_2$, C(O)NH-(optionally substituted alkyl), alkylthioether, alkylsulfoxide, alkylsulfone, C(O)-(optionally substituted aryl), C(O)NH-(optionally substituted aryl), arylthioether, arylsulfoxide, or arylsulfone. In certain embodiments, substitution on the phenyl is independently selected from F, Cl, CO_2H, CN, OCH_3, $C(O)CH_3$, CF_3, CH_3, CH_2OH, CH_2CH_2OH, and $CH_2CH_2CH_2OH$. In certain embodiments, bisubstitution on the phenyl of R^2 consists of CN and a group selected from F, Cl, CO_2H, OCH_3, $C(O)CH_3$, CF_3, CH_3, CH_2OH, CH_2CH_2OH, and $CH_2CH_2CH_2OH$. In certain embodiments, bisubstitution on the phenyl of R^2 consists of CO_2H and a group selected from F, Cl, CN, OCH_3, $C(O)CH_3$, CF_3, CH_3, CH_2OH, CH_2CH_2OH, and $CH_2CH_2CH_2OH$. In certain embodiments, bisubstitution on the phenyl of R^2 consists of $CH_2CH_2CH_2OH$ and a group selected from F, Cl, CN, OCH_3, $C(O)CH_3$, CF_3, CH_3, CH_2OH, CH_2CH_2OH, and CO_2H.

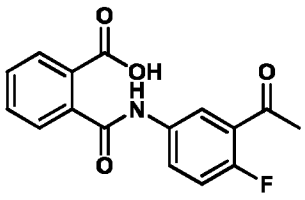
[00151] In some embodiments described above or below of a compound of Formula III or IIIa, R^2 is naphthyl.

[00152] In some embodiments described above or below of a compound disclosed herein, B is CO_2R^4 and R^4 is optionally substituted alkyl. In some embodiments described above or below of a compound disclosed herein, B is CO_2R^4 and R^4 is hydrogen.

[00153] In some embodiments described above or below of a compound disclosed herein, n is 0, 1, or 2. In certain embodiments, n is 0. In certain embodiments, n is 1. In certain embodiments, R^1 is independently selected from Cl, F, CH_2OH, CH_2NH_2, OCH_3, OCF_3, $OCHF_2$, CN, NO_2, CO_2H, and CO_2CH_3.

[00154] In some embodiments described above or below of a compound of Formula I, the compound is selected from:

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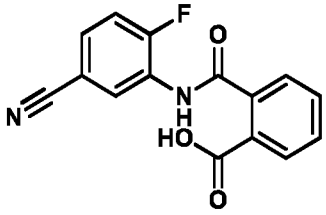
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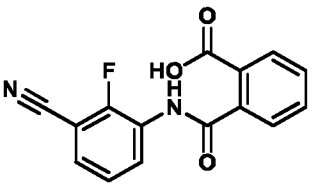
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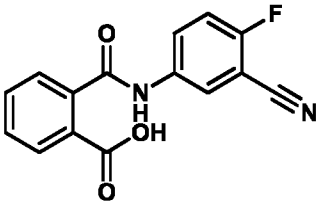
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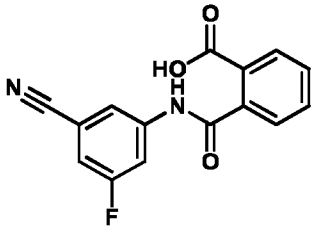
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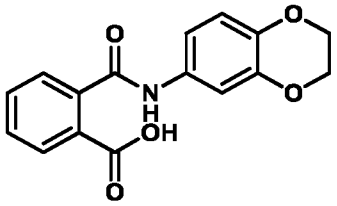
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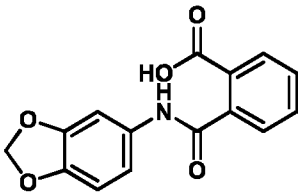
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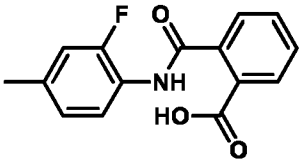
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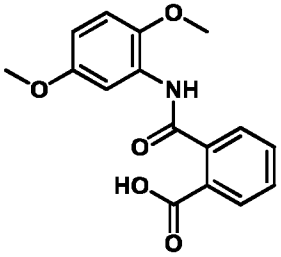
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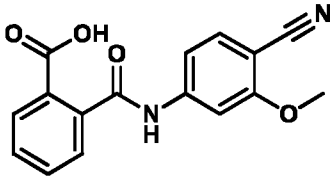
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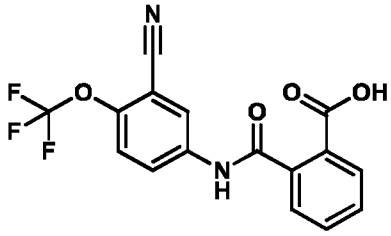
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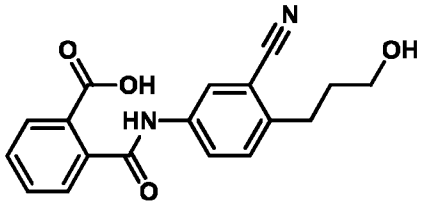
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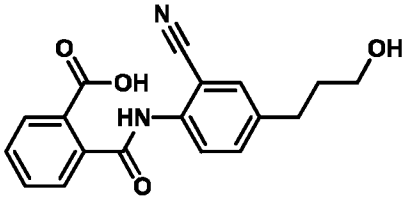
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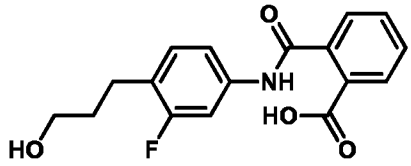
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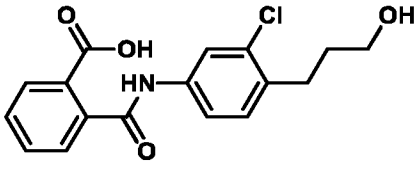
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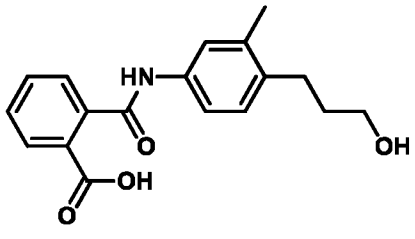
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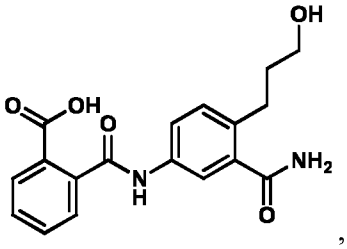
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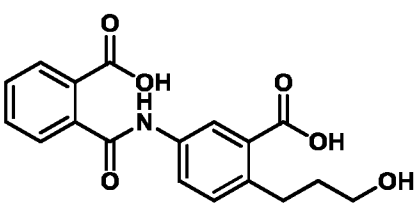
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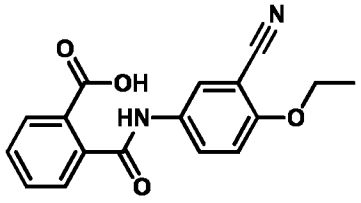
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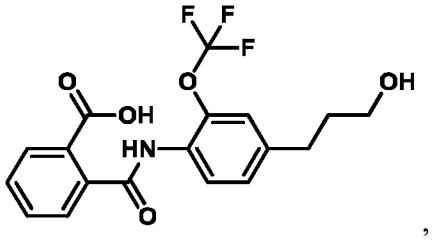
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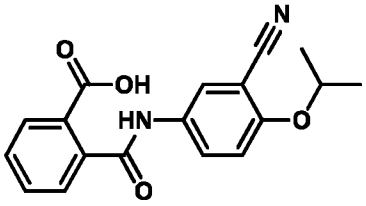
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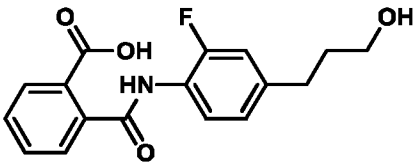
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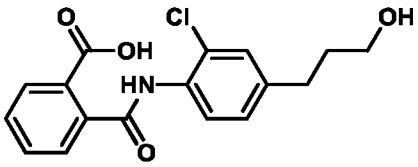
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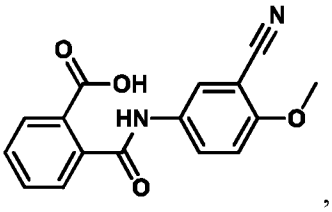
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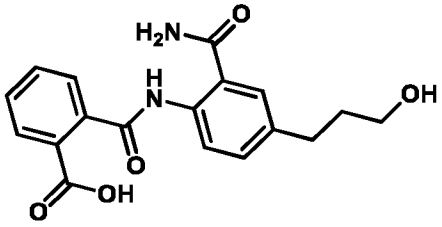
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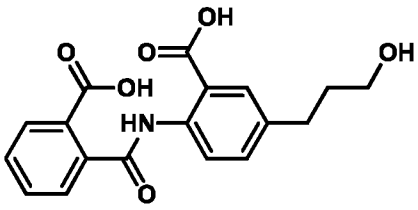
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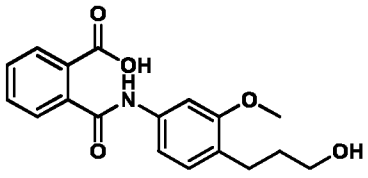
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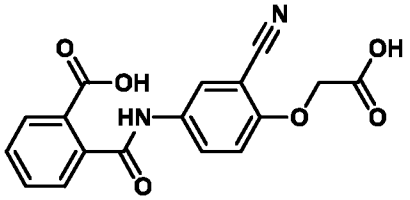
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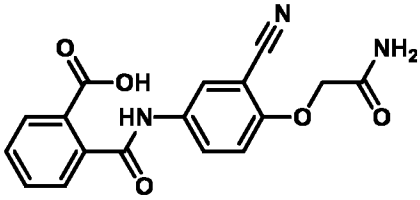
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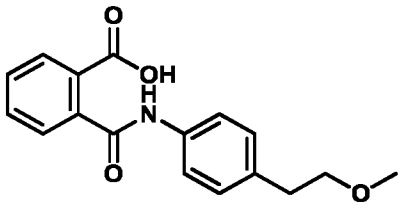
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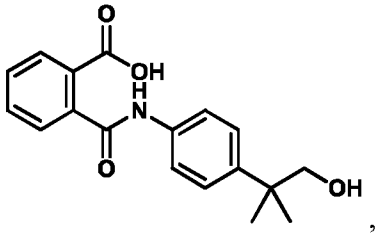
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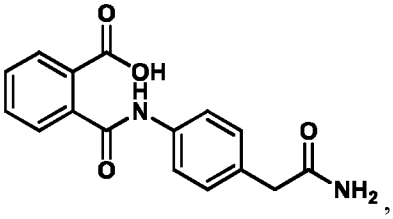
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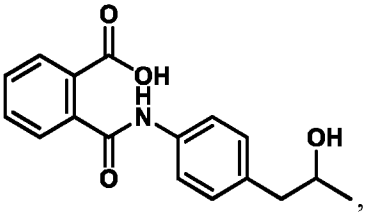
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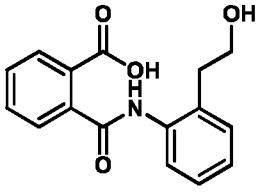
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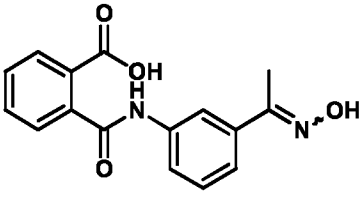
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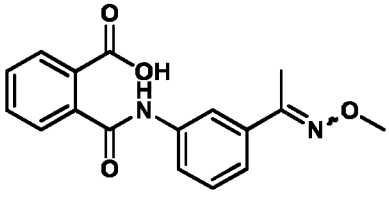
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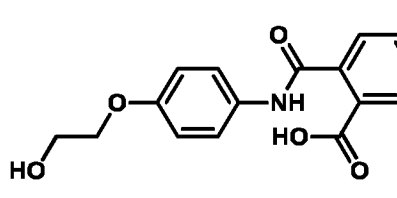
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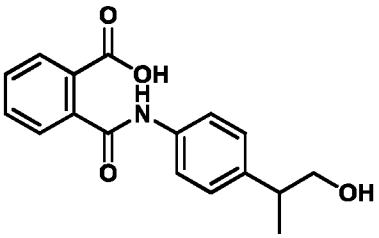
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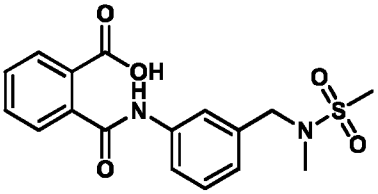
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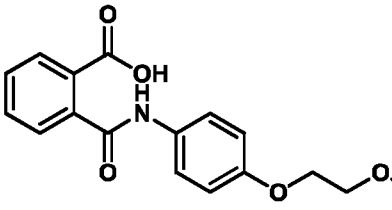
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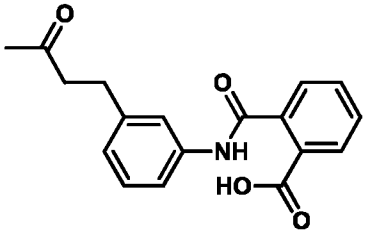
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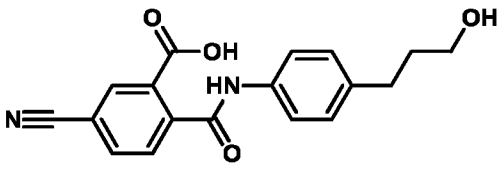
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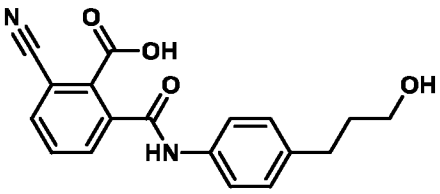
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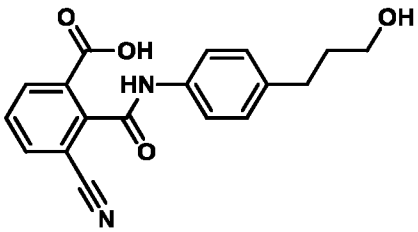
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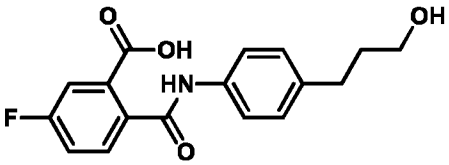
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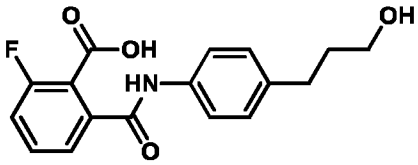
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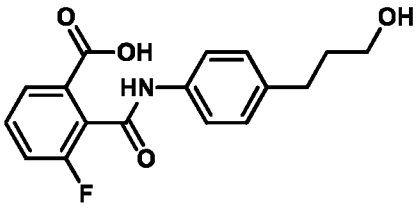
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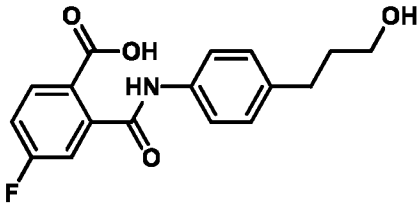
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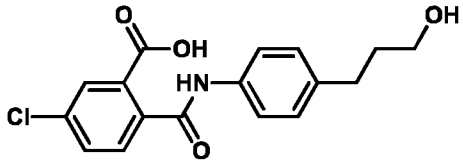
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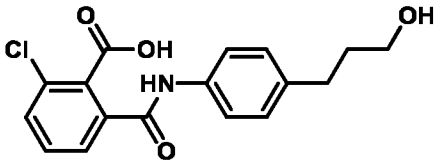
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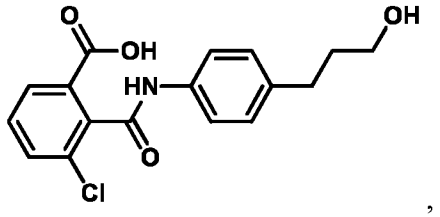
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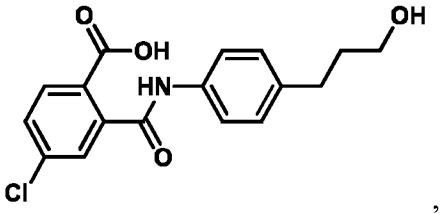
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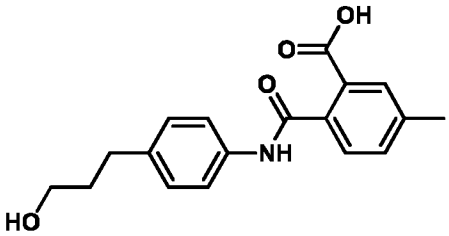
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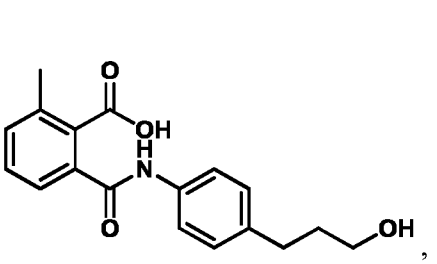
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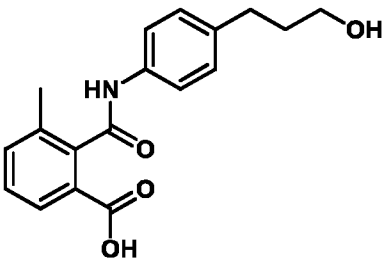
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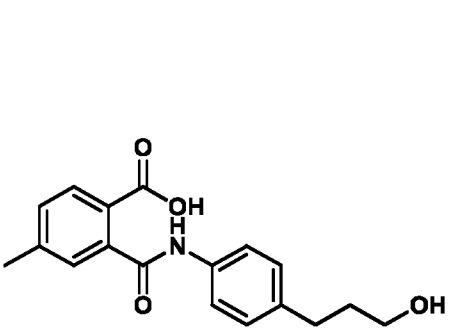
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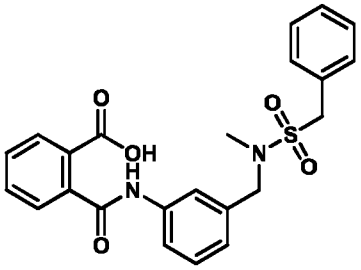
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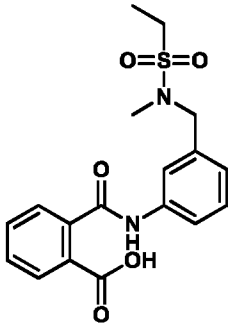
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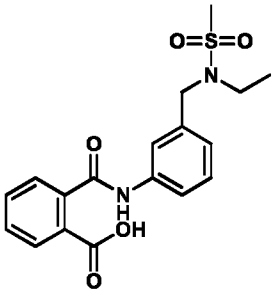
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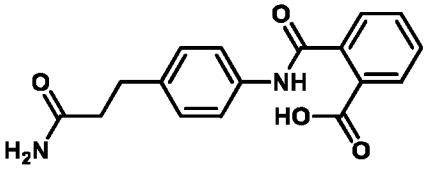
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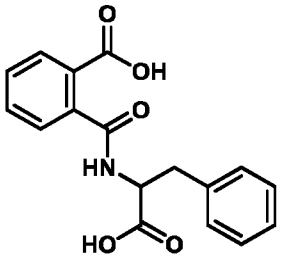
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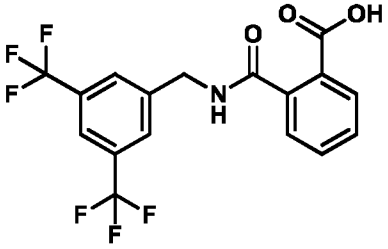
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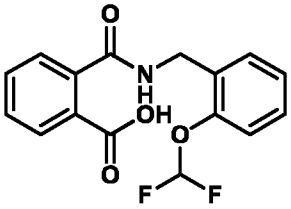
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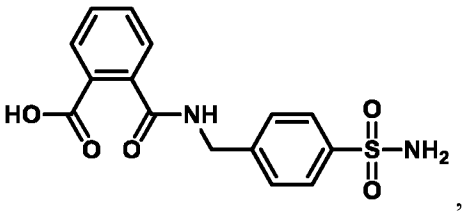
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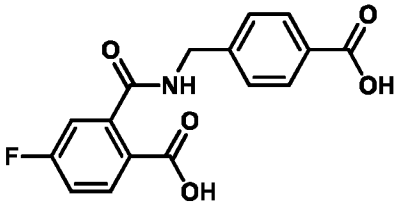
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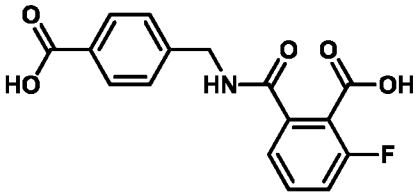
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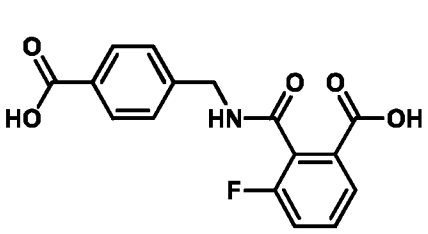
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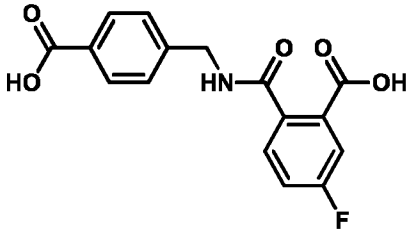
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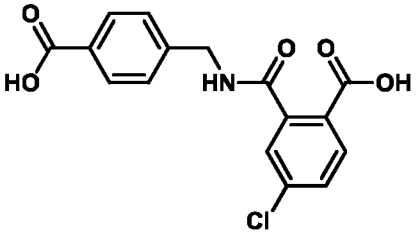
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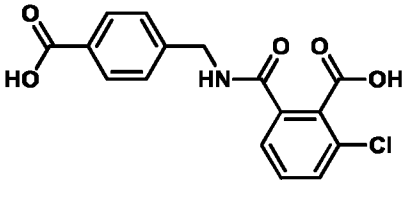
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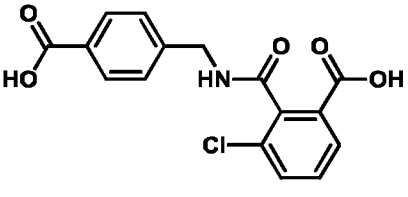
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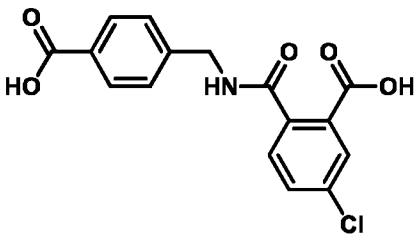
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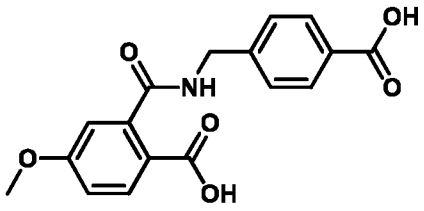
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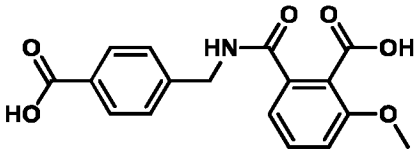
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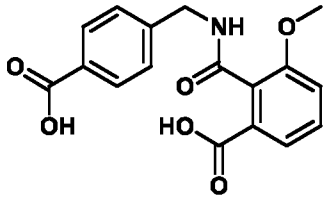
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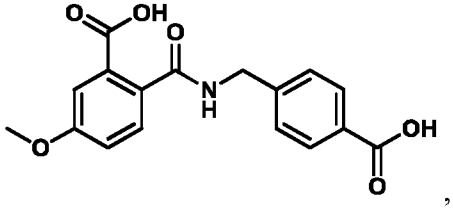
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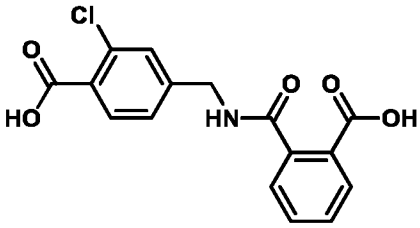
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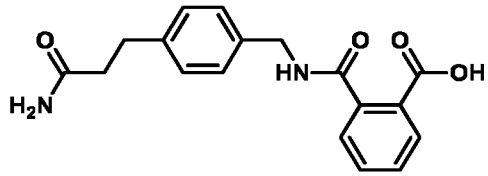
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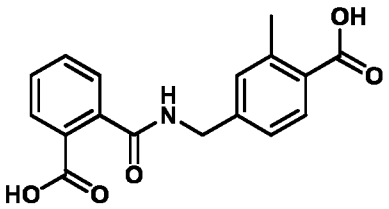
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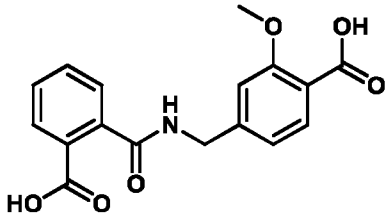
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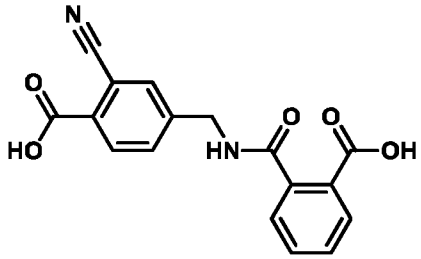
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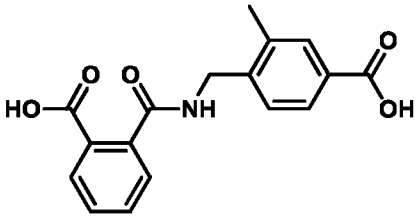
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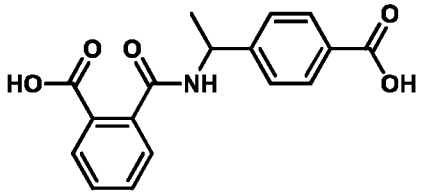
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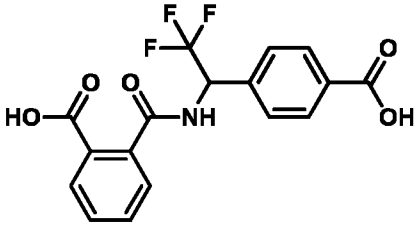
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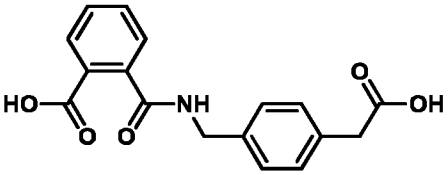
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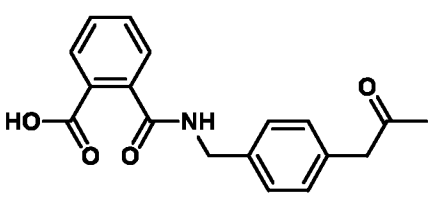
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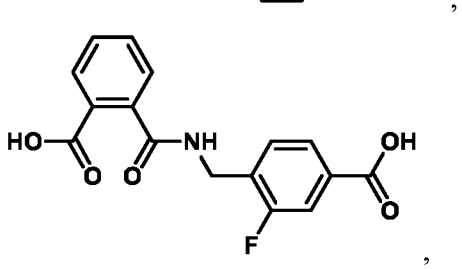
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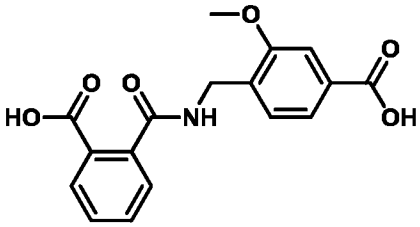
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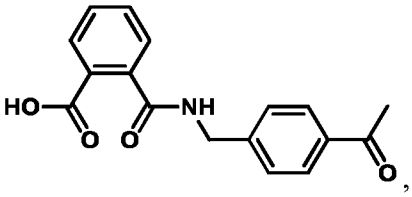
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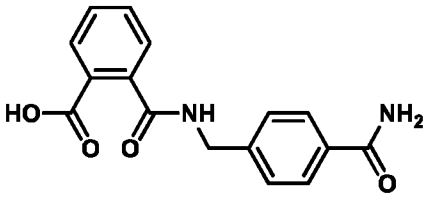
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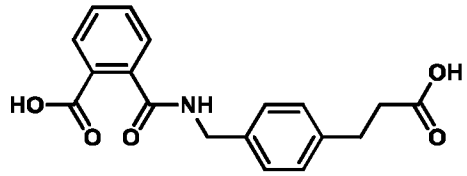
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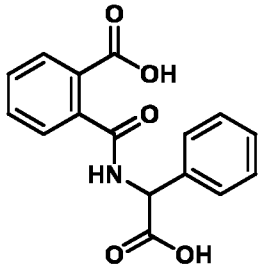
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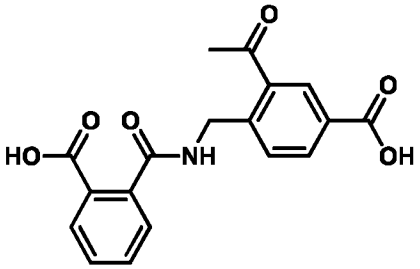
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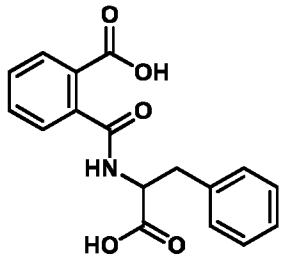
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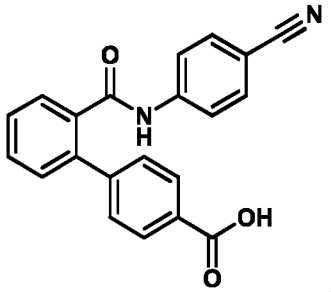
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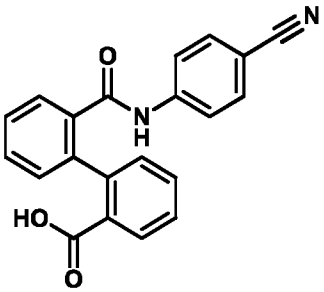
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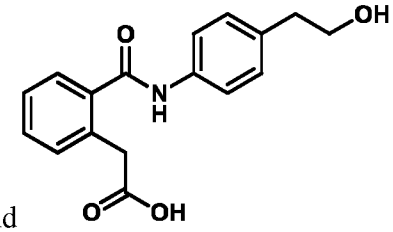
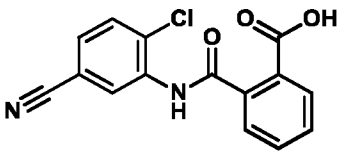

; or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

[00155] In some embodiments described above or below of a compound of Formula Ia, the compound is selected from: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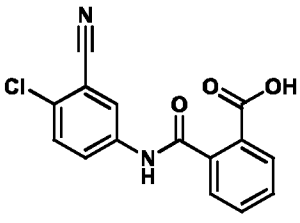
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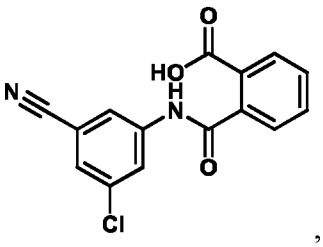
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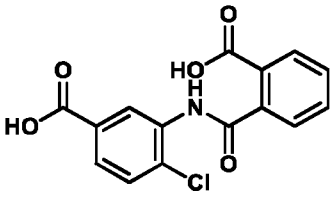
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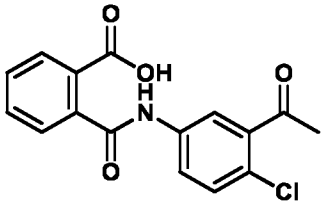
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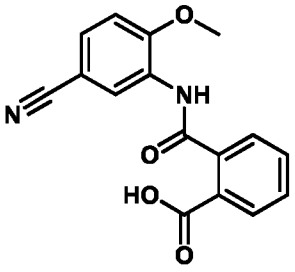
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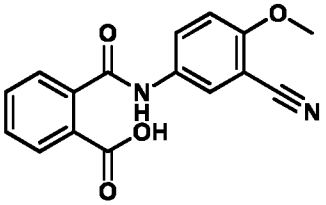
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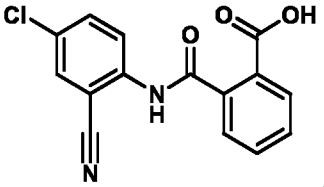
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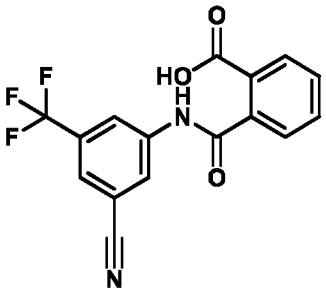
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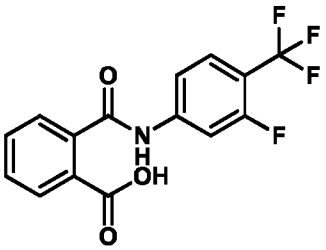
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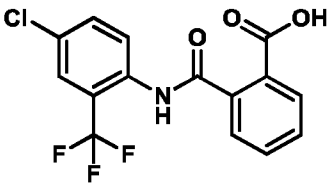
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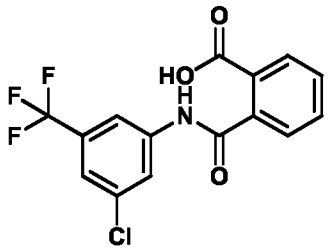
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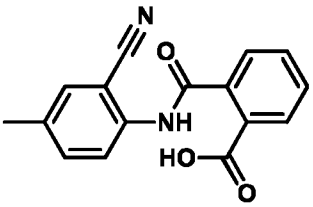
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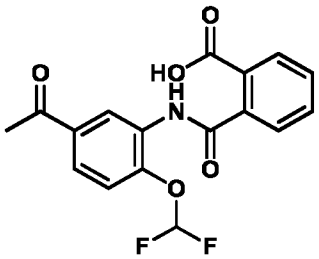
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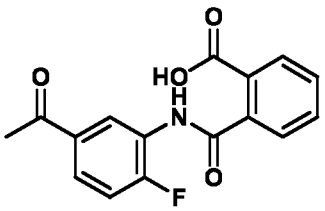
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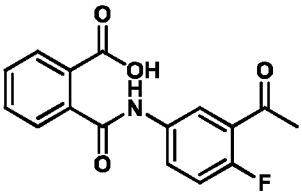
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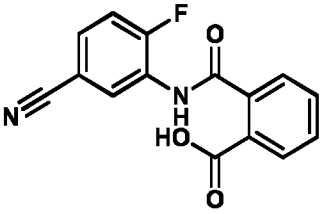
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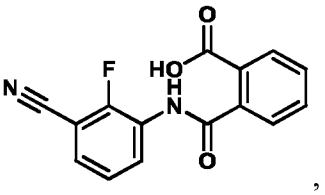
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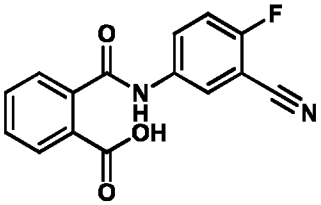
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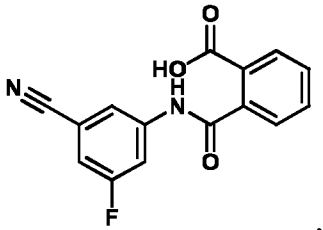
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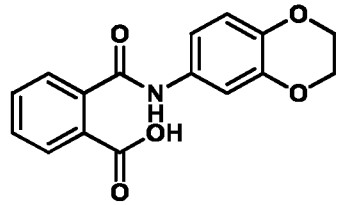
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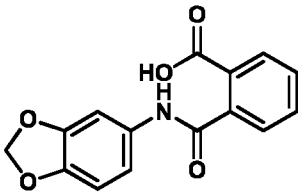
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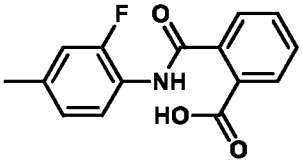
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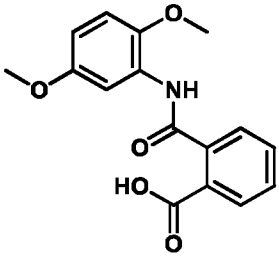
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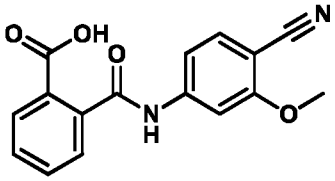
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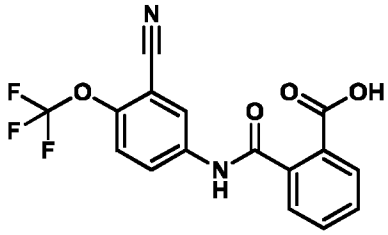
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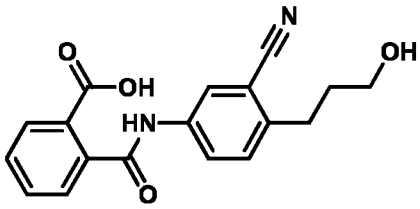
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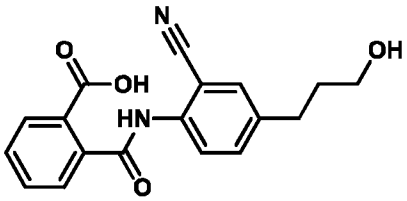
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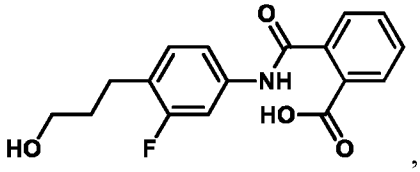
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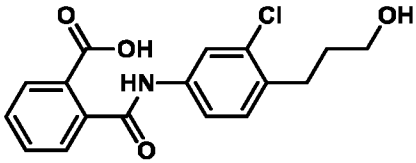
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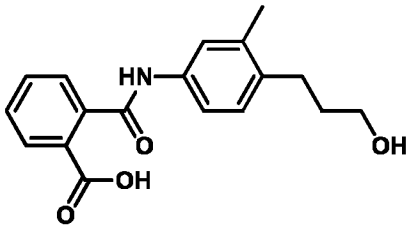
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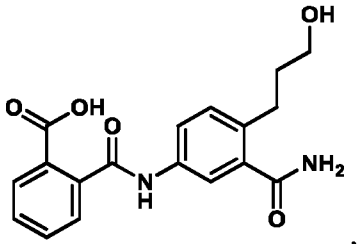
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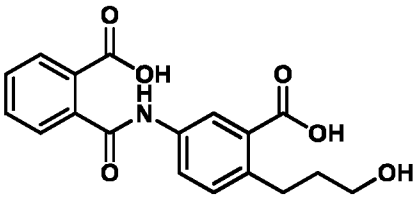
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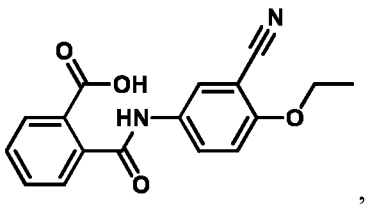
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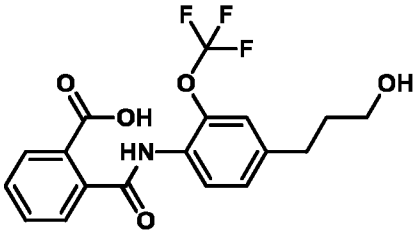
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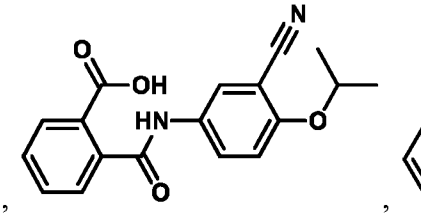
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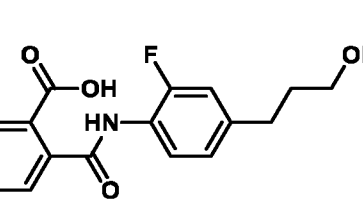
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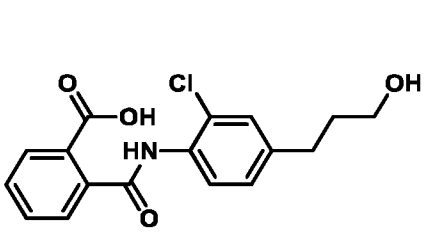
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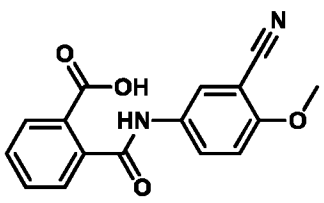
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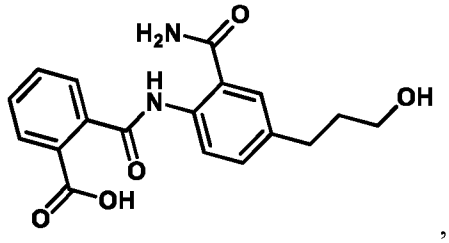
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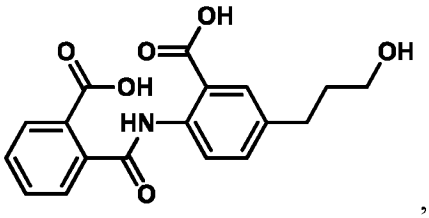
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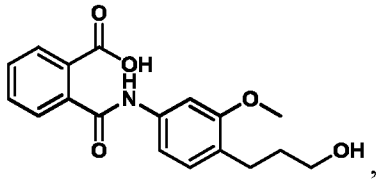
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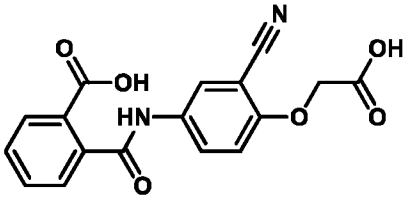
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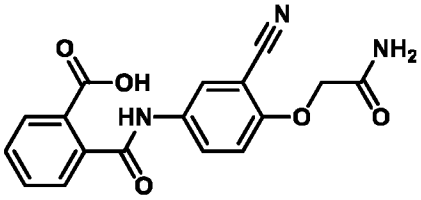
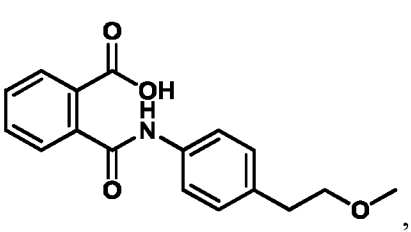

; or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

[00156] In some embodiments described above or below of a compound of Formula Ib, the compound is selected from: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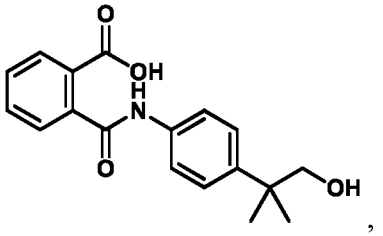
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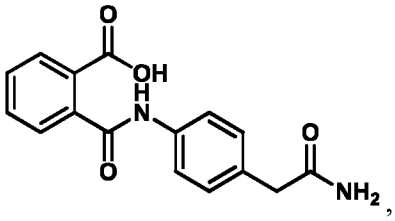
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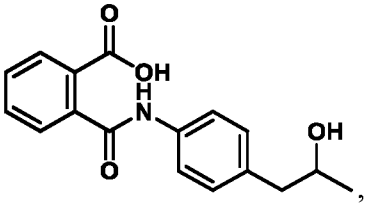
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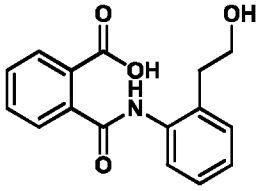
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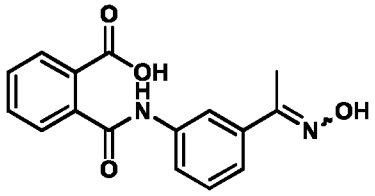
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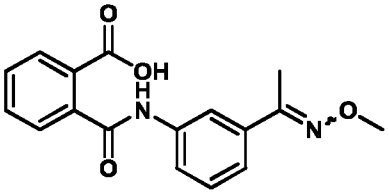
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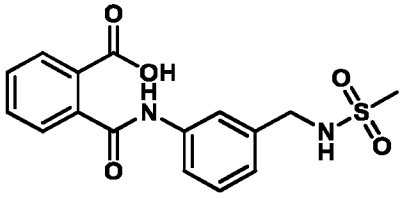
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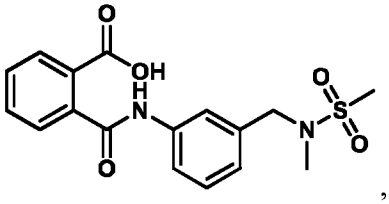
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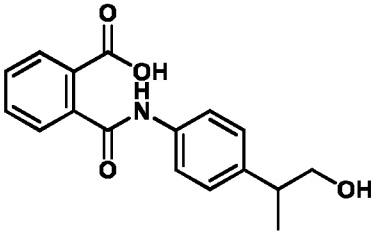
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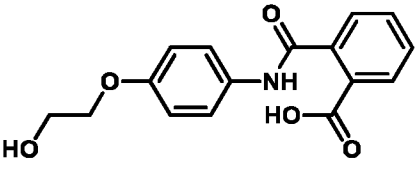
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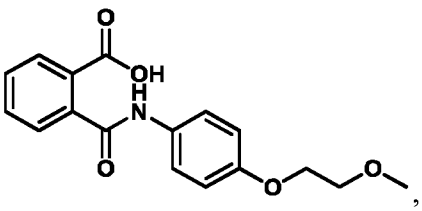
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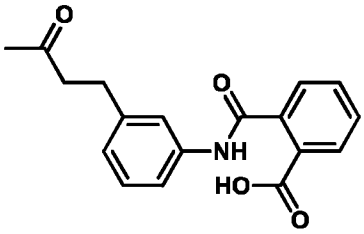
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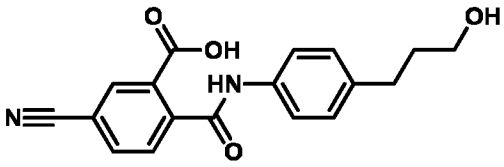
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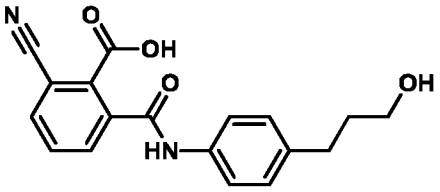
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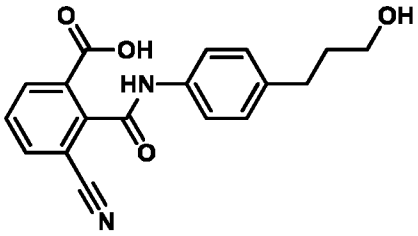
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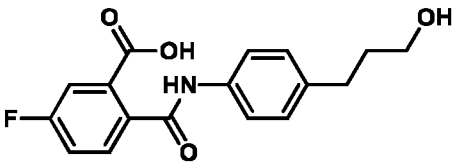
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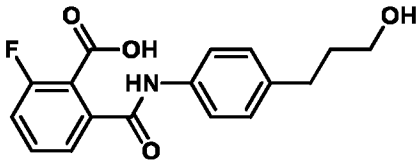
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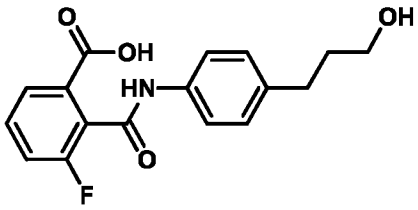
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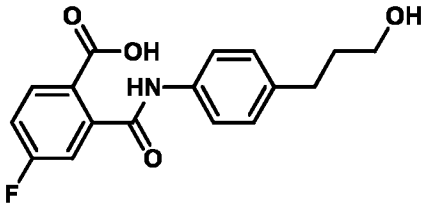
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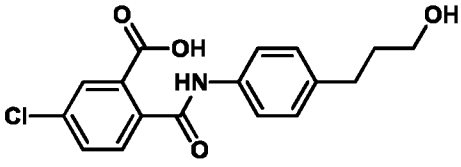
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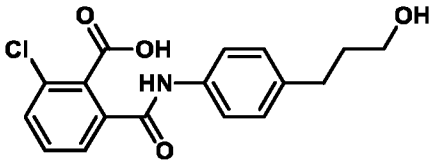
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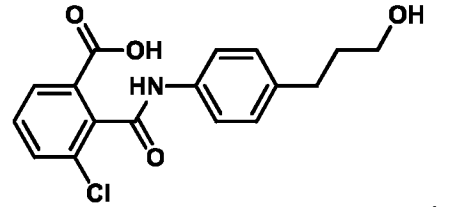
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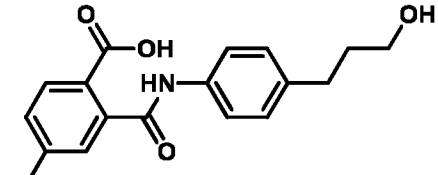
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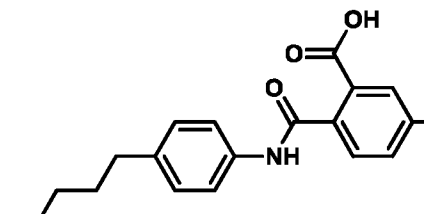
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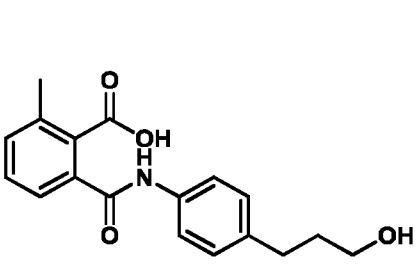
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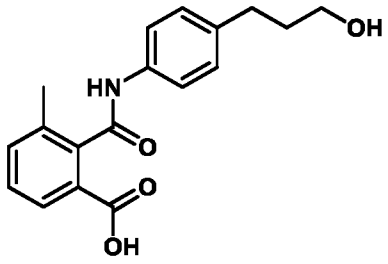
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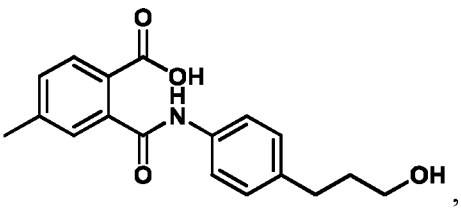
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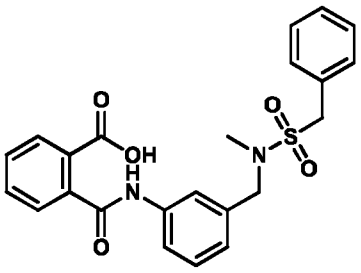
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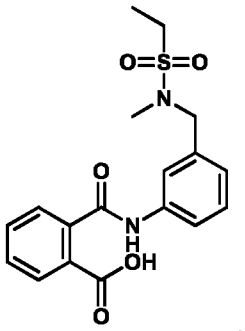
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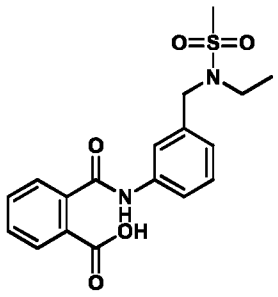
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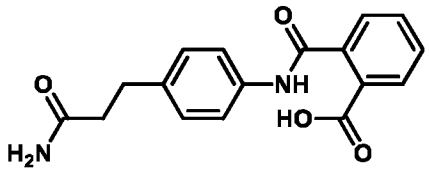
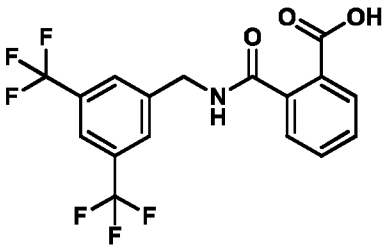

; or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

[00157] In some embodiments described above or below of a compound of Formula Ic, the compound is selected from: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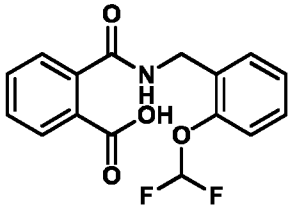
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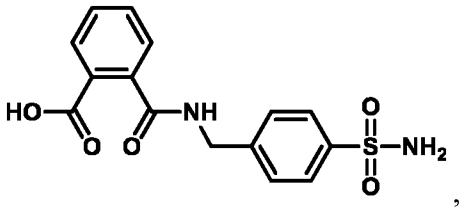
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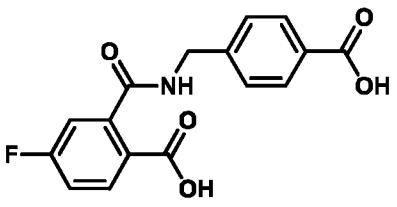
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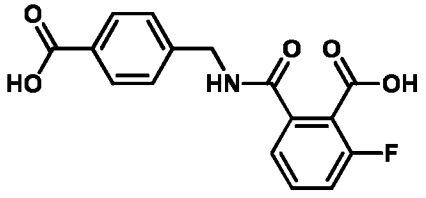
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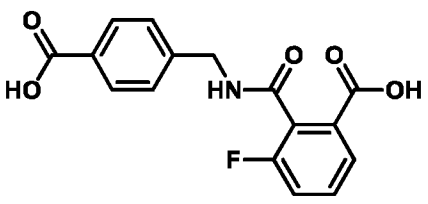
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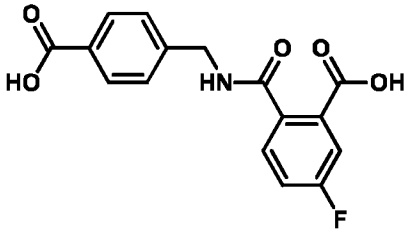
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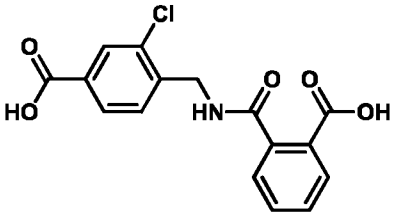
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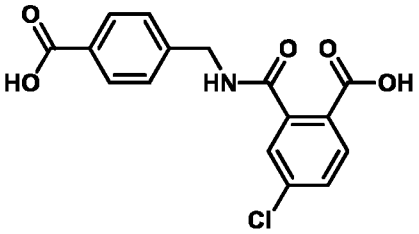
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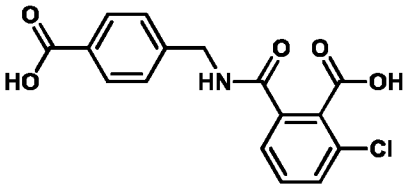
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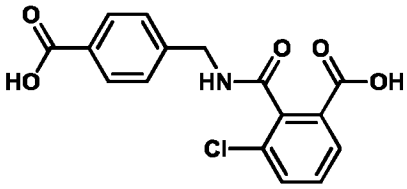
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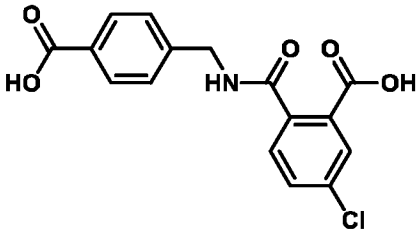
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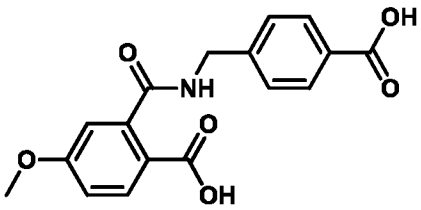
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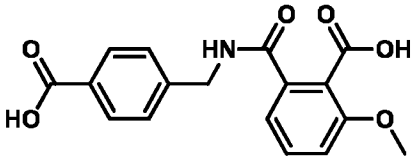
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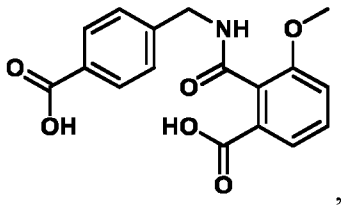
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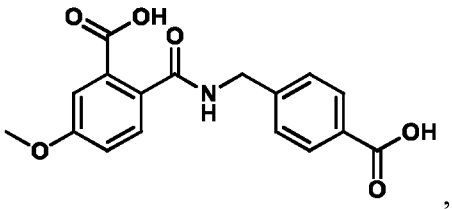
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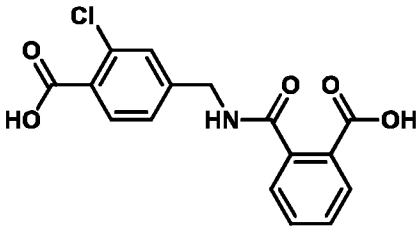
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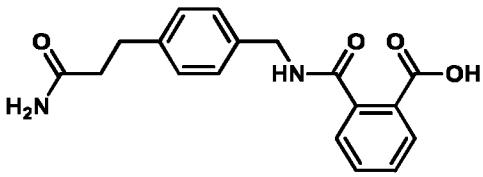
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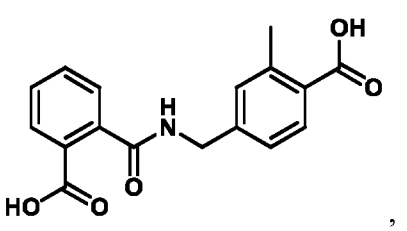
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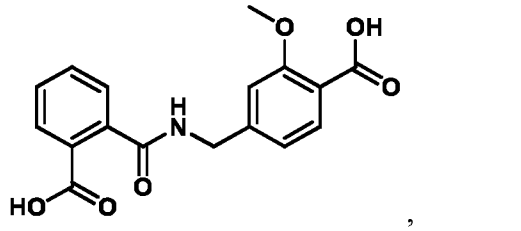
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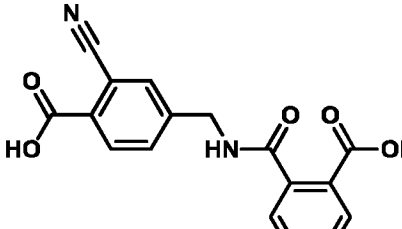
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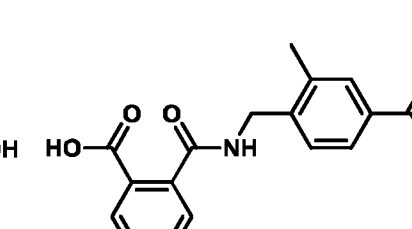
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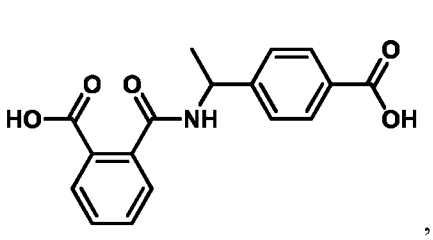
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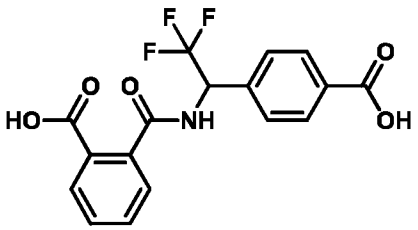
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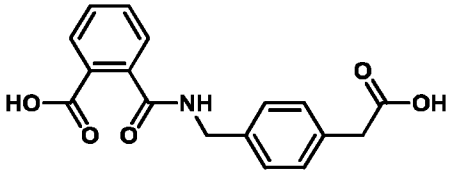
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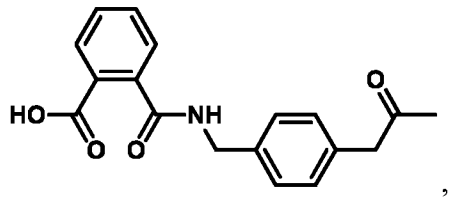
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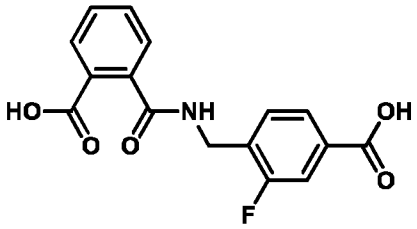
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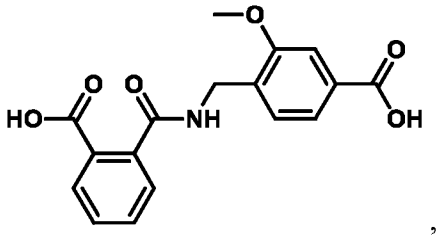
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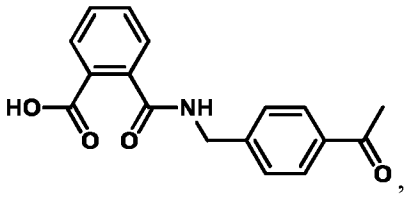
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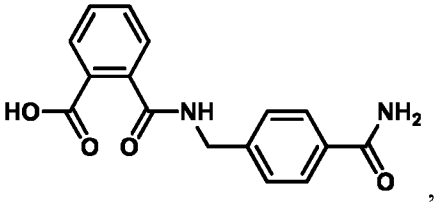
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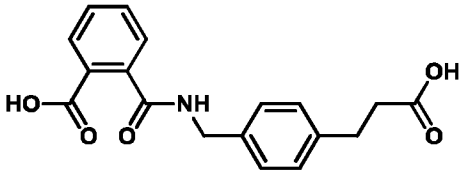
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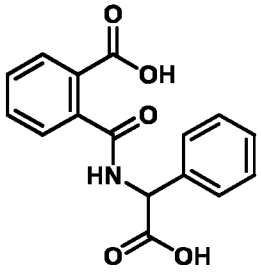
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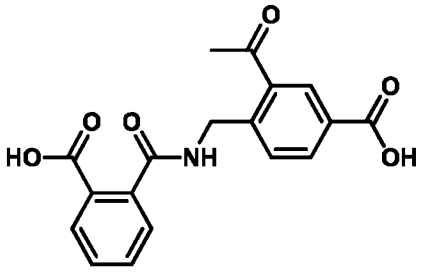
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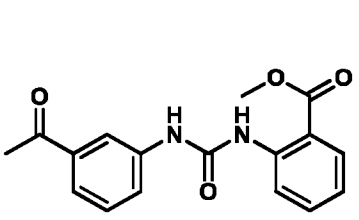
or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

[00158] In some embodiments described above or below of a compound of Formula II, the compound is selected from: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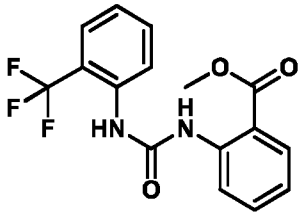
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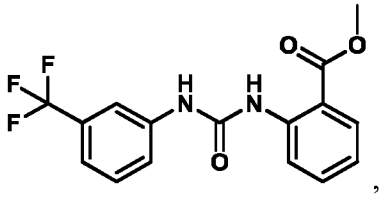
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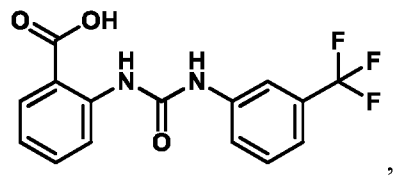
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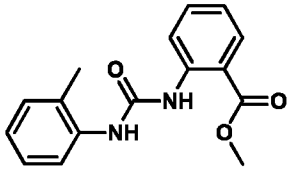
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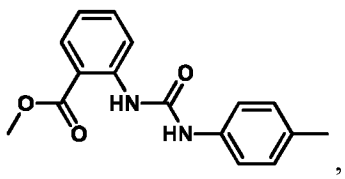
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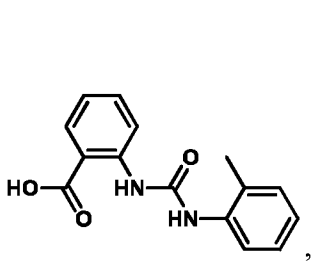
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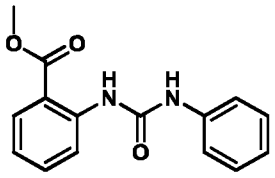
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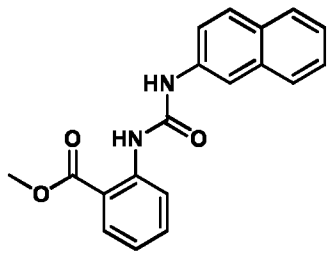
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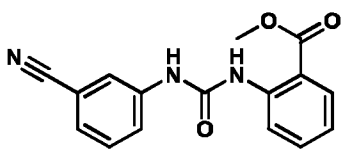
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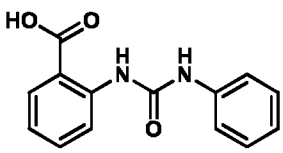
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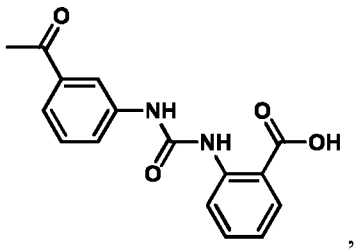
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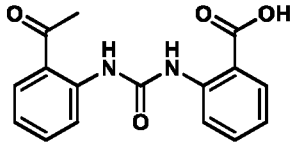
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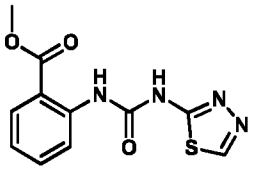
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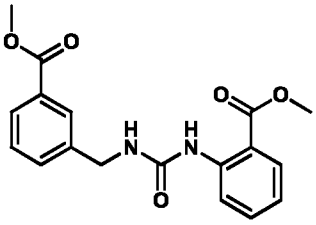
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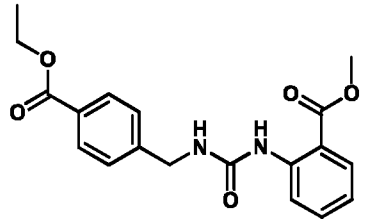
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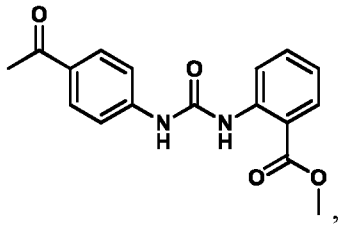
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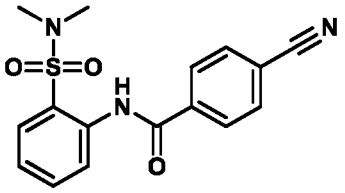
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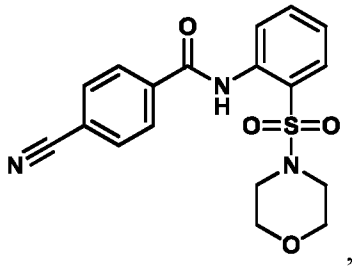
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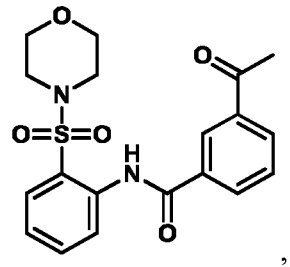
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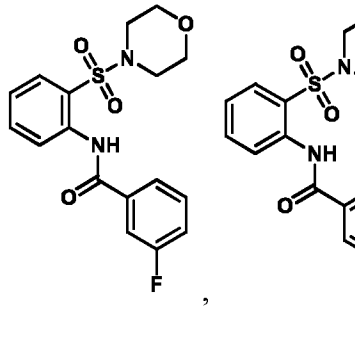
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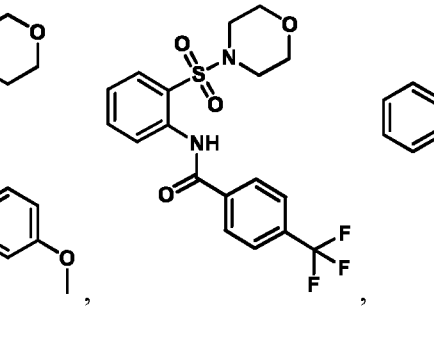
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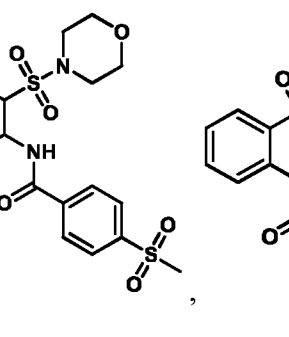
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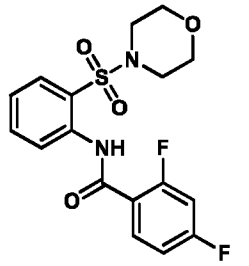
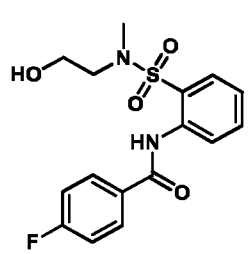
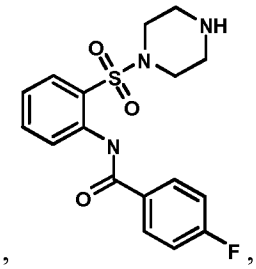
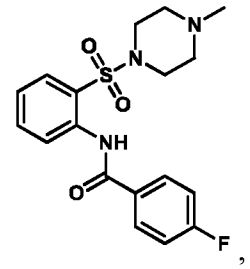
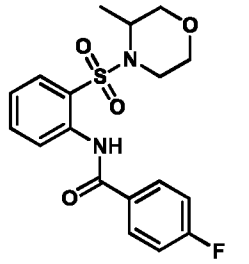
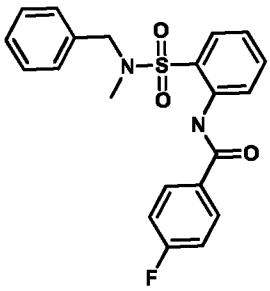
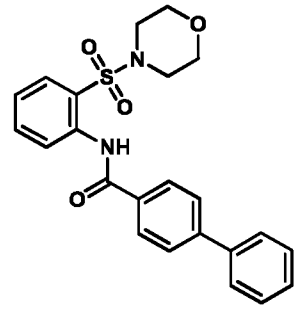
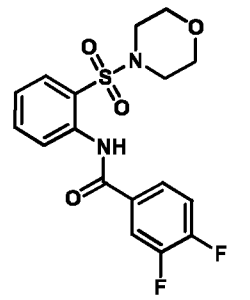
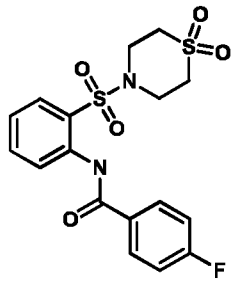
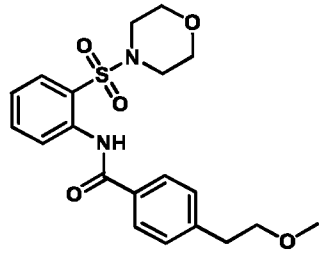
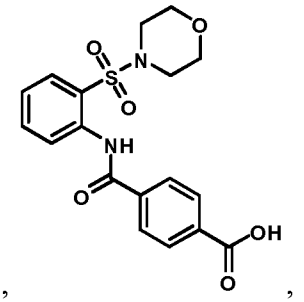
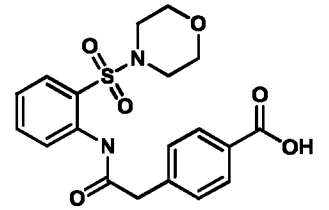
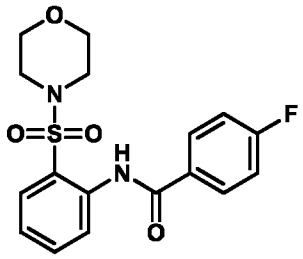
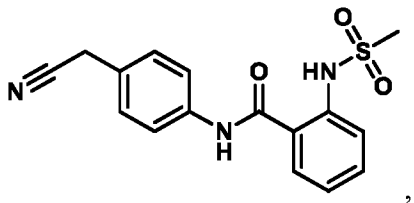
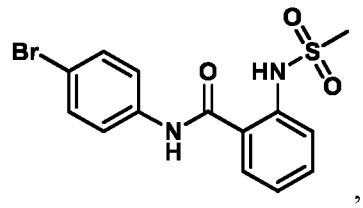
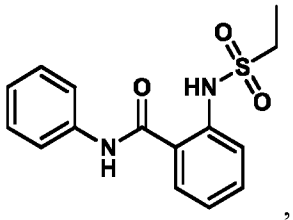
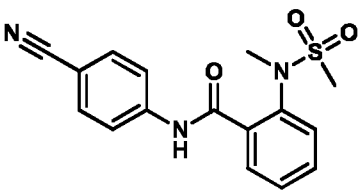
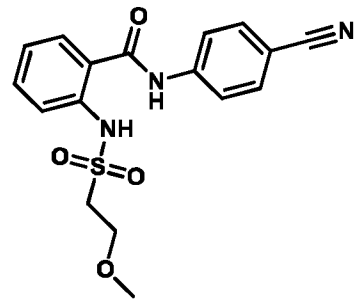
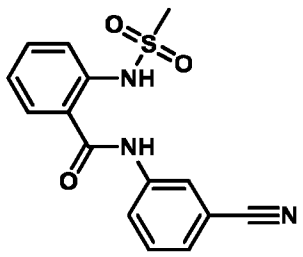
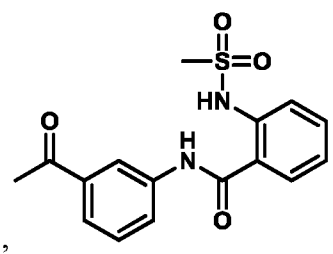
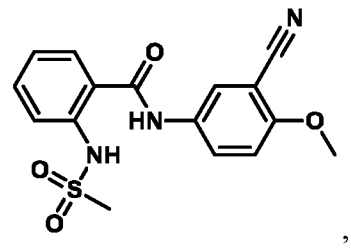

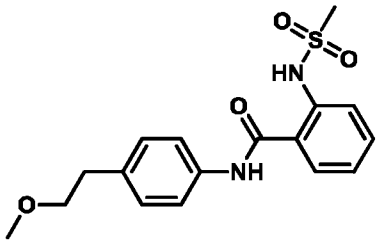
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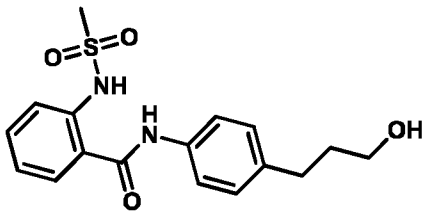
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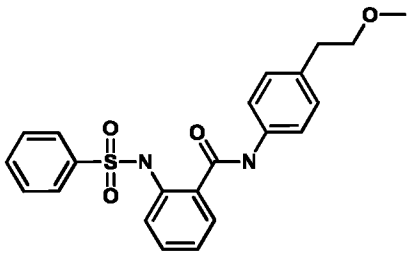
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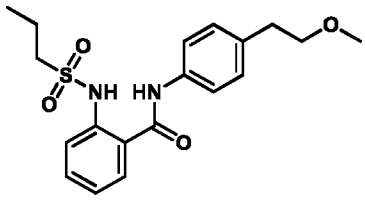
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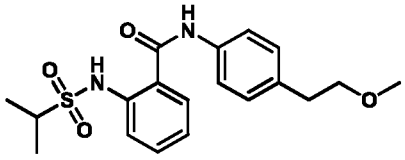
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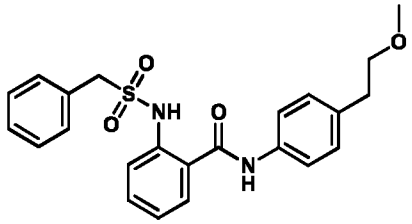
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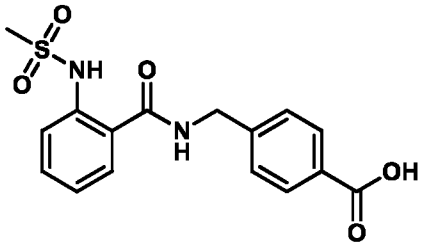
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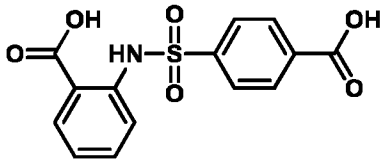
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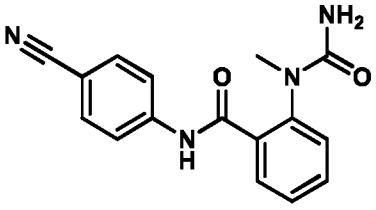
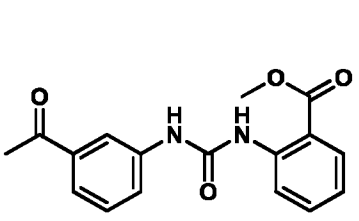

; or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

[00159] In some embodiments described above or below of a compound of Formula IIa, the compound is selected from: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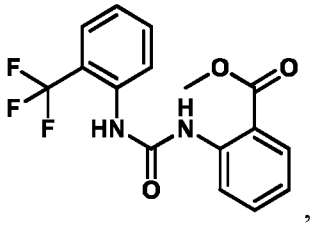
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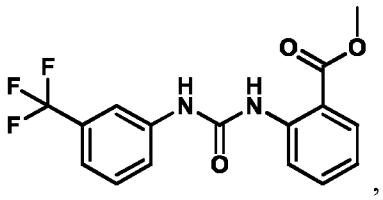
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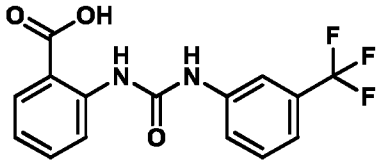
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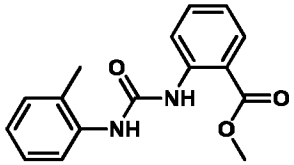
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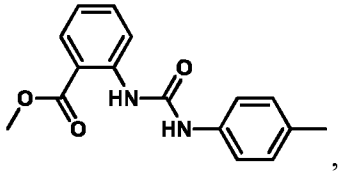
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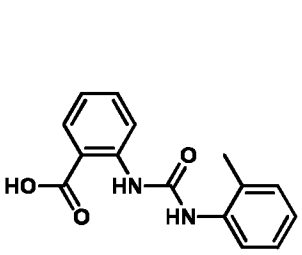
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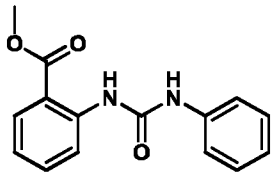
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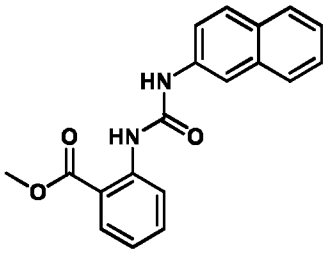
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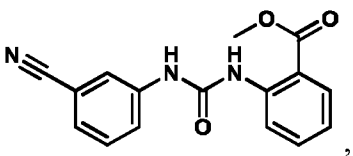
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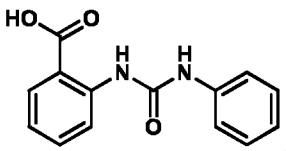
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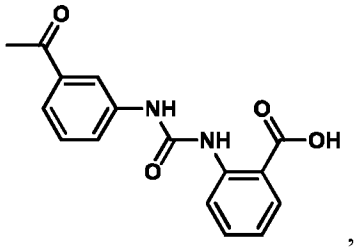
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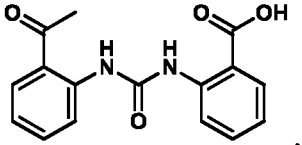
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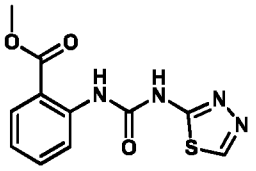
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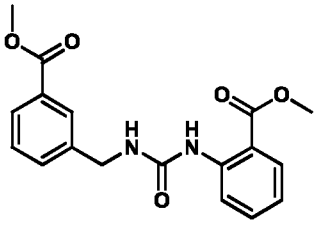
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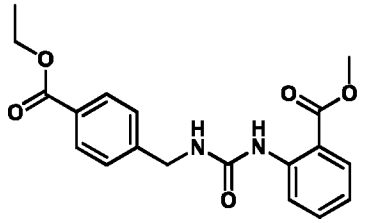
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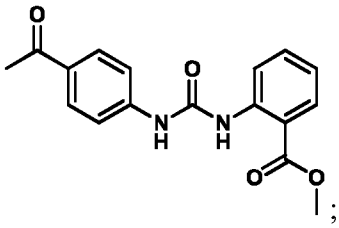
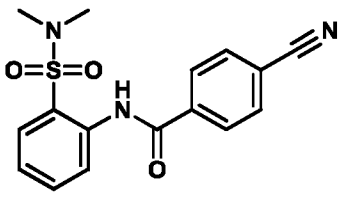

; or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

[00160] In some embodiments described above or below of a compound of Formula IIb, the compound is selected from: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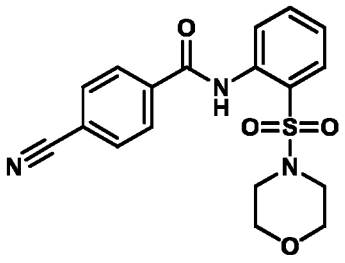
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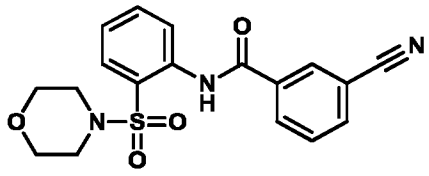
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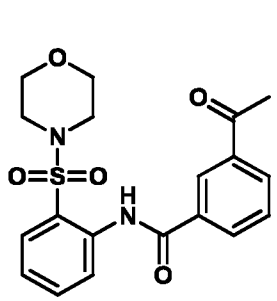
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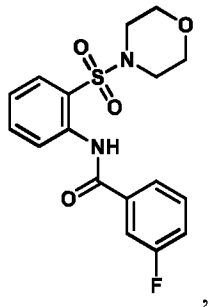
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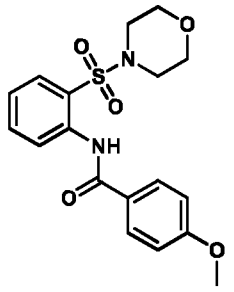
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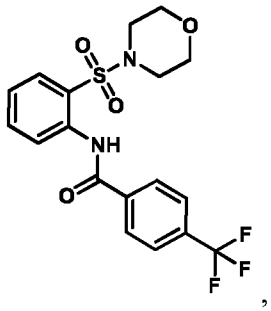
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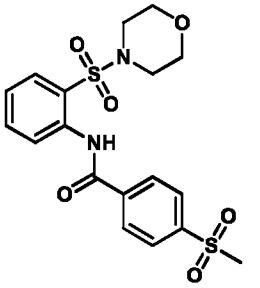
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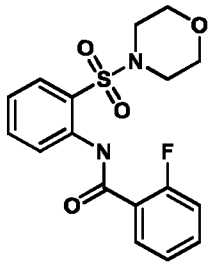
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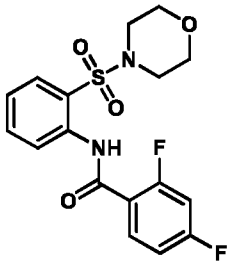
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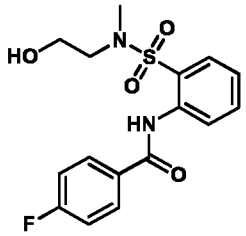
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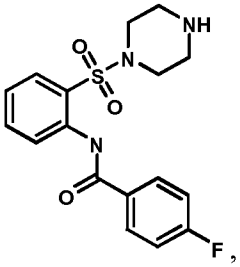
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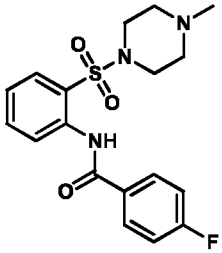
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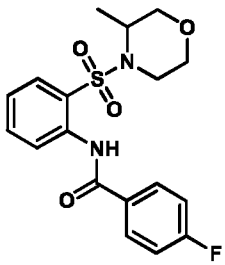
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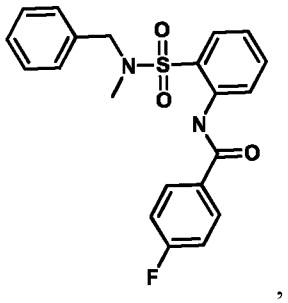
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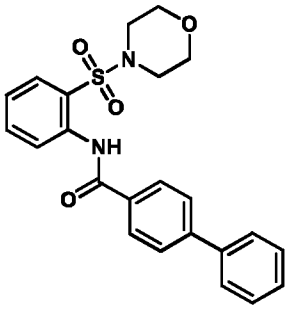
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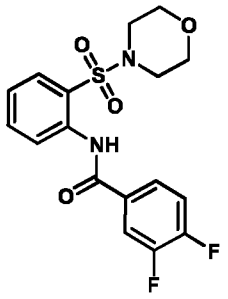
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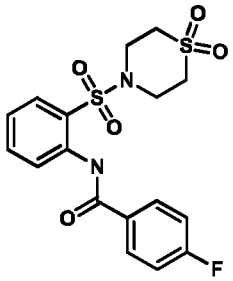
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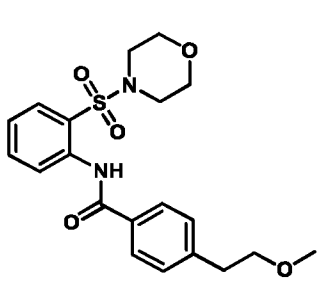
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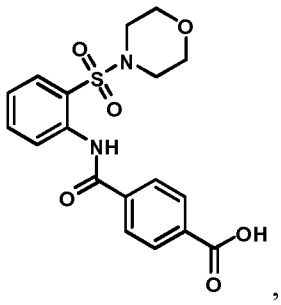
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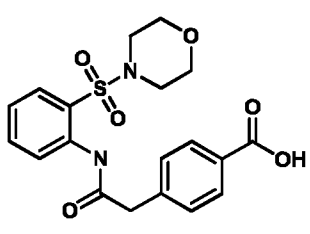
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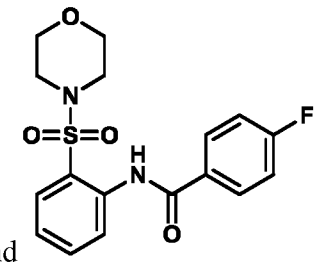
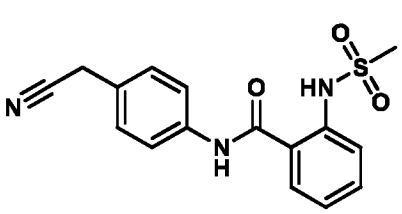

; or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

[00161] In some embodiments described above or below of a compound of Formula IIc, the compound is selected from: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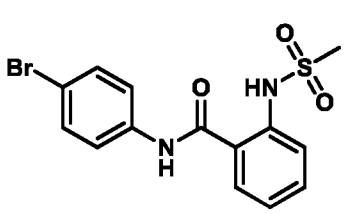
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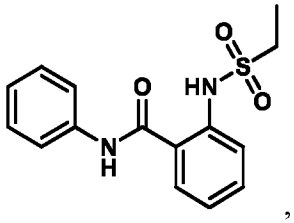
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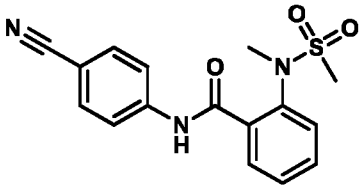
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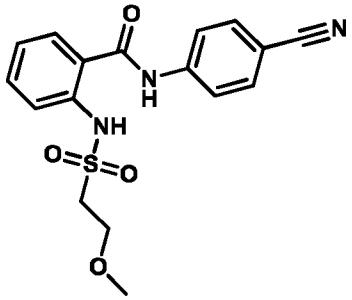
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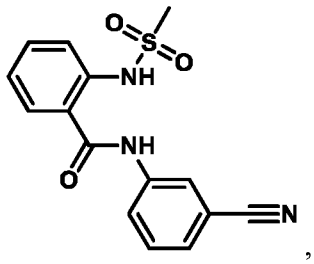
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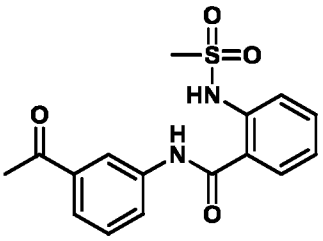
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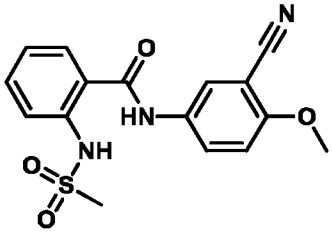
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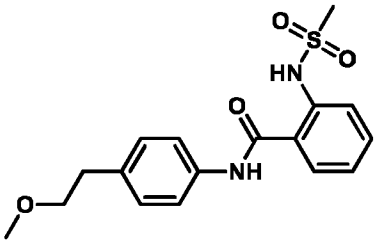
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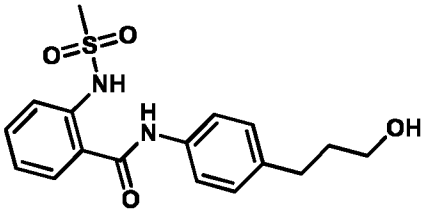
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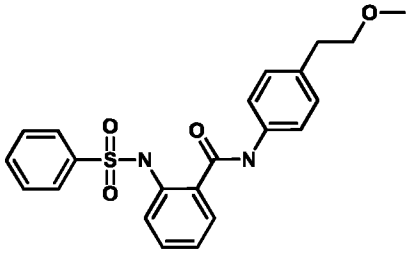
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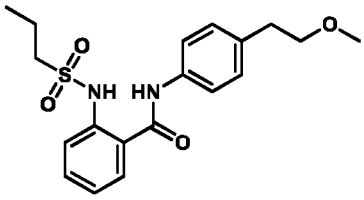
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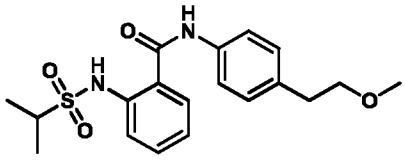
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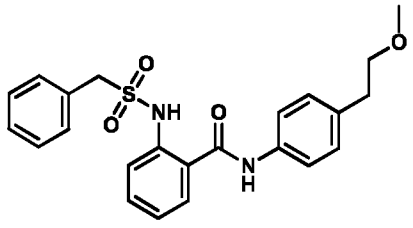
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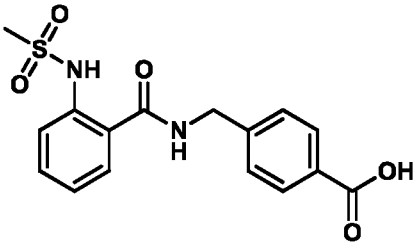
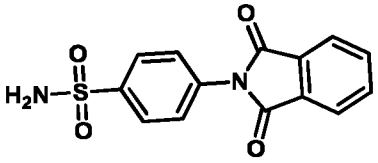

; or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

[00162] In some embodiments described above or below of a compound of Formula III, the compound is selected from: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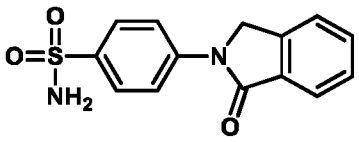
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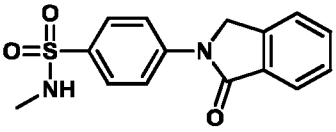
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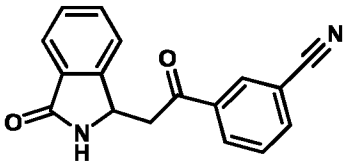
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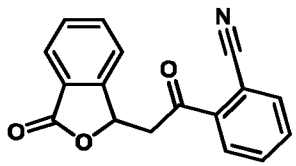
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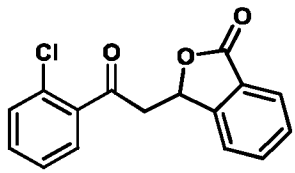
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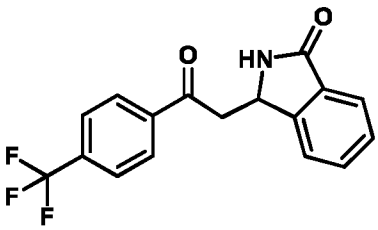
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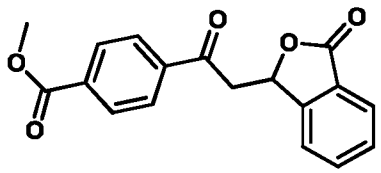
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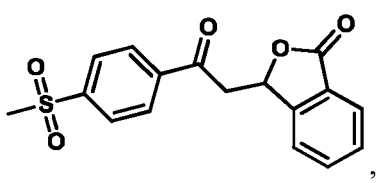
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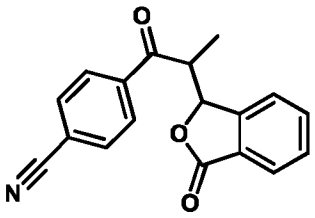
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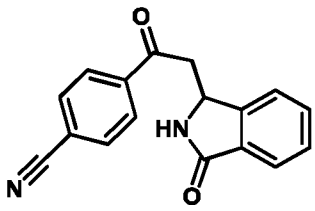
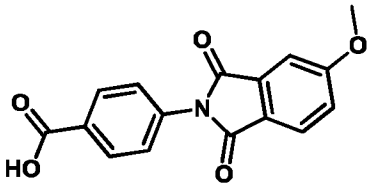

; or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

[00163] In one aspect, provided herein is a method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof, selected from: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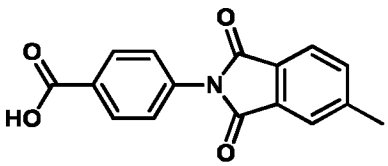
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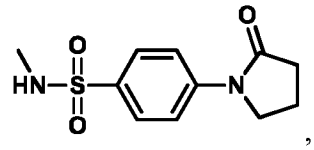
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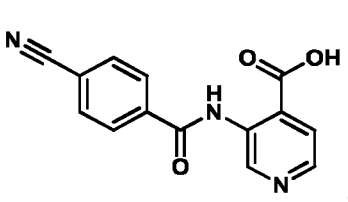
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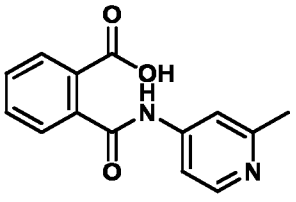
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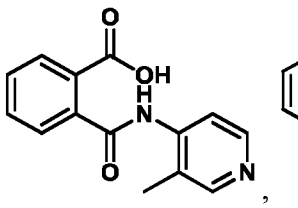
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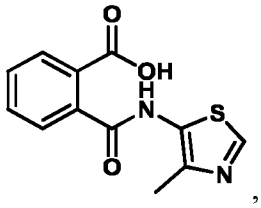
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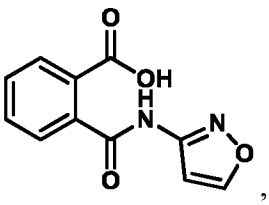
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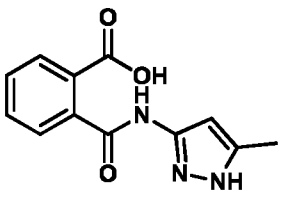
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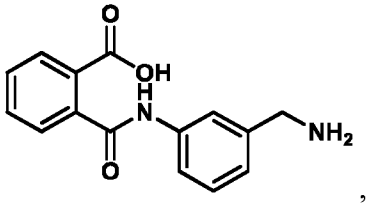
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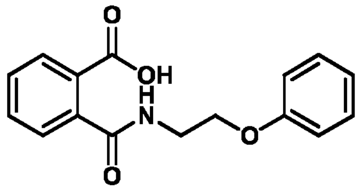
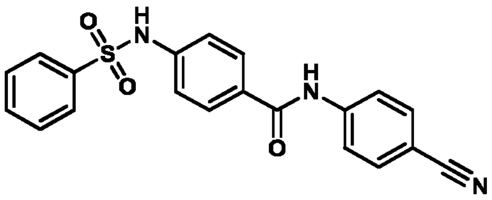
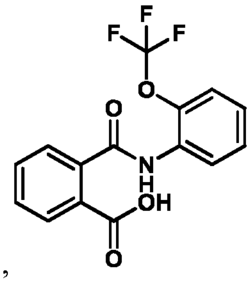
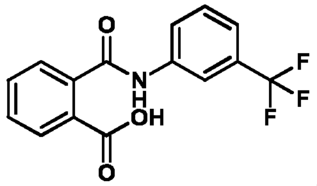
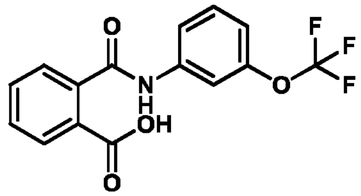
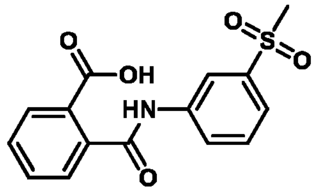
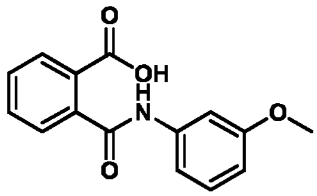
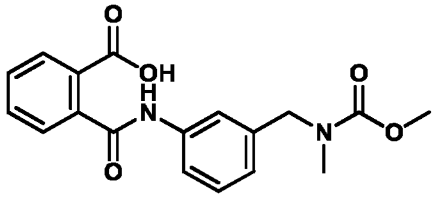
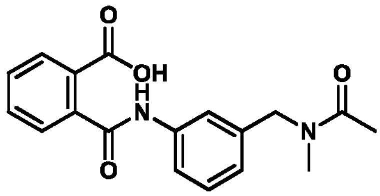
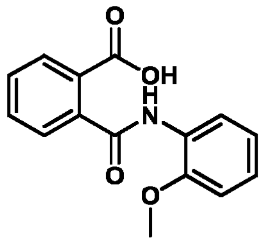
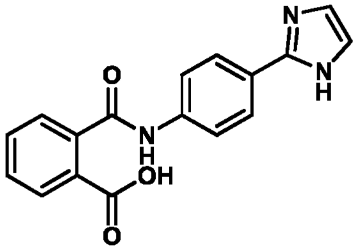
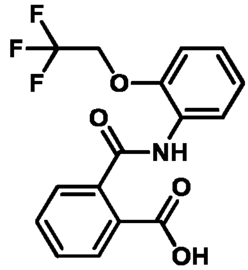
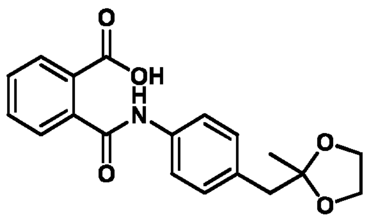
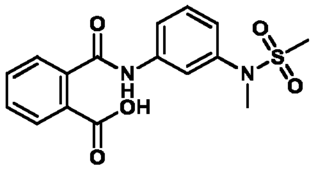
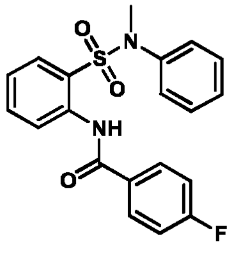
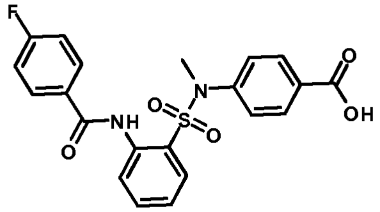
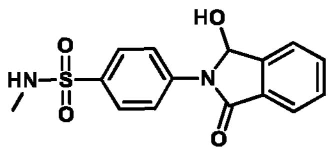
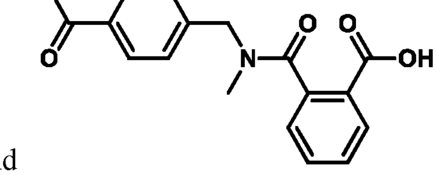
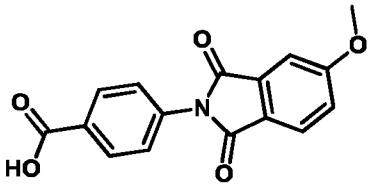
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 , and
 .

[00164] In another aspect, provided herein is a method of of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof, selected from: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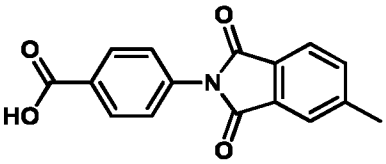
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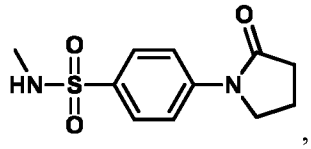
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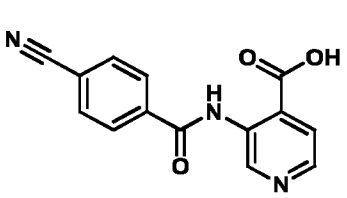
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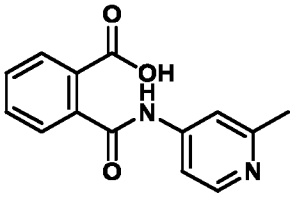
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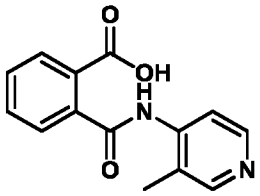
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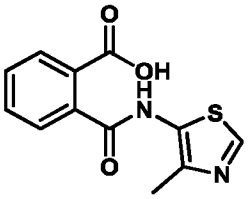
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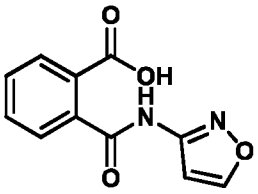
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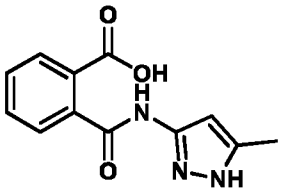
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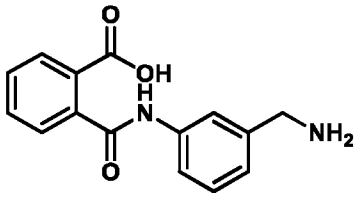
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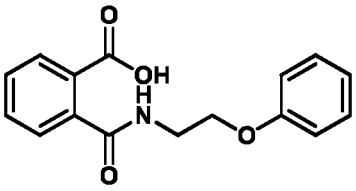
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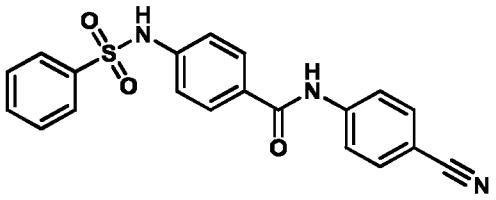
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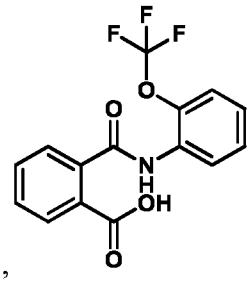
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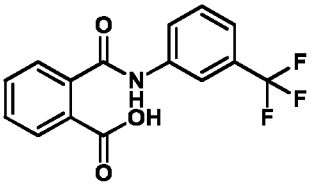
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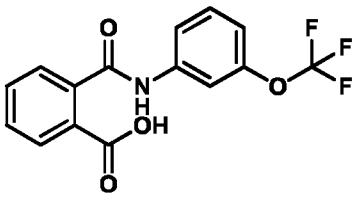
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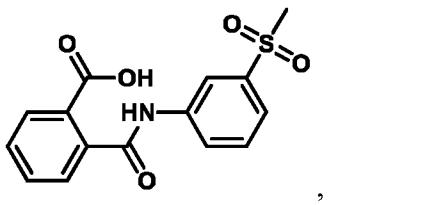
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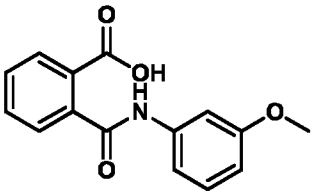
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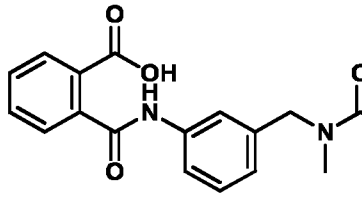
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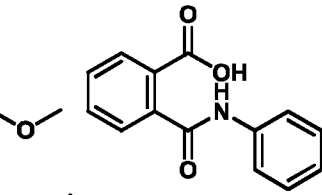
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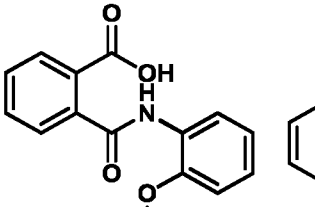
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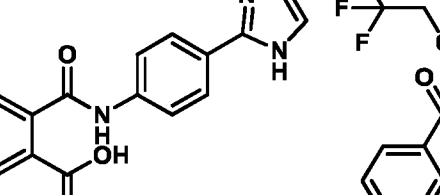
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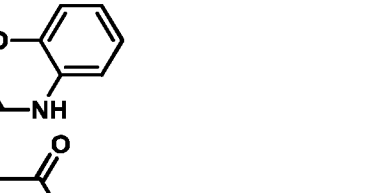
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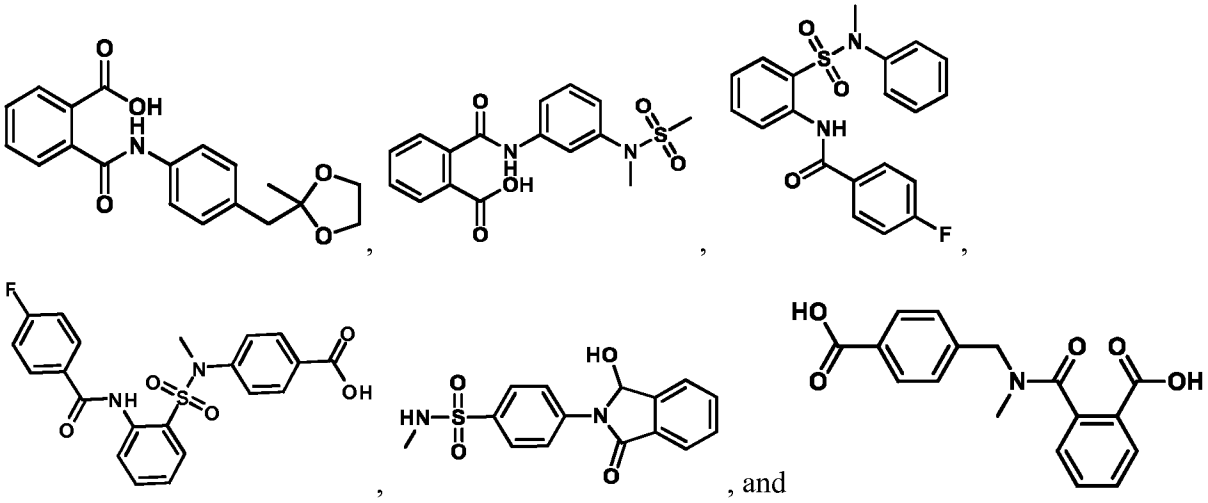


[00165] In some embodiments, the mammal does not have, but is at increased risk for, arthritis or joint injury.

[00166] It is contemplated that the compounds, compositions, and methods of the present invention may be used to ameliorate any type of arthritis or joint injury. It is further contemplated that the compounds, compositions, and methods of the present invention may be used to ameliorate various cartilagenous disorders. In some embodiments, the compounds and compositions of the present invention are administered to prevent arthritis or joint injury, for example where there is a genetic or family history of arthritis or joint injury or prior or during joint surgery or other circumstances where there is an increased risk of arthritis or joint injury. Exemplary conditions or disorders to be treated or prevented with the compounds, compositions, and methods of the invention, include, but are not limited to systemic rheumatoid arthritis, juvenile chronic arthritis, osteoarthritis, degenerative disc disease, spondyloarthropathies, and systemic sclerosis (scleroderma). In some embodiments of the invention, the compounds, compositions, and methods of the present invention may be used to treat osteoarthritis. In some embodiments, the arthritis can be osteoarthritis, trauma arthritis, degenerative disc disease, dupuytren disease, or tendon disease.

[00167] In some embodiments, the compounds, compositions, and methods of the present invention provide a method for stimulating chondrocyte proliferation and cartilage production in cartilagenous tissues that have been damaged due to traumatic injury or chondropathy. Traumatic injury can include, but is not limited to, blunt trauma to the joint, or damage to ligaments such as tearing the anterior cruciate ligament, medial collateral ligament, or a meniscal tear. Examples of tissues that exhibit articulated surfaces, and thus are particularly susceptible to treatment include, but are not limited to, spine, shoulder, elbow, wrist, joints of the fingers, hip, knee, ankle, and the joints of the feet. Examples of diseases that may benefit from treatment include osteoarthritis, rheumatoid arthritis, other autoimmune diseases, or osteochondritis dessicans. In addition, cartilage malformation is often seen in forms of dwarfism in humans suggesting that the compounds, compositions, and methods would be useful in these patients.

[00168] It is contemplated that the compounds, compositions, and methods of the present invention may be used to treat a mammal. As used herein a "mammal" refers to any mammal classified as a mammal, including humans, domestic and farm animals, and zoo, sports or pet animals, such as cattle (e.g. cows), horses, dogs, sheep, pigs, rabbits, goats, cats, etc. In some embodiments, the mammal can be a human, a dog, a cat, or a horse. In some embodiments of the invention, the mammal is a human. In some embodiments, the mammal is a dog, a cat, or a horse. In some embodiments, the mammal is cattle, sheep, pig, goat, or rabbit. In some embodiments, the mammal is a domesticated animal or livestock. In further embodiments, the domesticated animal or livestock is a dog, cat, or horse. In some embodiments, the mammal is a companion animal. As used herein, "companion animal" refers to dog, cat, rodent, and rabbit. In some embodiments, the mammal is a companion animal or livestock. In some embodiments, the mammal is livestock.

[00169] The compounds of the present invention are also useful for inducing differentiation of mesenchymal stem cells (MSCs) into chondrocytes. In some embodiments, the present invention provides a method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method including contacting mesenchymal stem cells with a sufficient amount of a compound of the present invention, thereby inducing differentiation of the stem cells into chondrocytes.

[00170] MSCs are multipotent stem cells that can differentiate into several different types of cells including, but not limited to, osteoblasts, chondrocytes and adipocytes. Differentiation is the process by which a specialized cell type is formed from a less specialized cell type, for example, a chondrocyte from a MSC. In some embodiments, the method is performed *in vitro*. In some embodiments, the method is performed *in vivo* in a mammal and the stem cells are present in the mammal. In certain embodiments, the mammal is a human, a dog, a cat, or a horse. In certain embodiments, the mammal is a human. In certain embodiments, the mammal is a dog, a cat, or a horse.

[00171] Inducing differentiation of MSCs into chondrocytes can be accomplished using any suitable amount of a compound of the present invention. In some embodiments, the compound of the present invention can be present in an amount from about 0.1 mg to about 10000 mg, e.g., 1.0 mg to 1000 mg, e.g., 10 mg to 500 mg, according to the particular application and potency of the active component. In some embodiments, the compound of the present invention can be present in a concentration of 0.1 μM – 100 μM in an intra-articular injection to the knee.

Assays for identifying compounds

[00172] The compounds of the present invention were identified using a variety of assays. The initial screen identified compounds that stimulated human mesenchymal stem cells (hMSCs) to develop into chondrocyte nodules. Additional assays were performed to determine toxicity and specificity of chondrocyte differentiation.

Compounds

[00173] Described herein are compounds that induce differentiation of mesenchymal stem cells into chondrocytes. In some embodiments, the compounds described herein ameliorate arthritis or joint injury in a mammal. In some embodiments, the compounds described herein treat arthritis or joint injury in a mammal.

[00174] In one aspect, provided herein are compounds of Formula I, or pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, esters, metabolites, N-oxides, stereoisomers, or isomers thereof.

[00175] In another aspect, provided herein are compounds of Formula Ia, or pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, esters, metabolites, N-oxides, stereoisomers, or isomers thereof.

[00176] In another aspect, provided herein are compounds of Formula Ib, or pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, esters, metabolites, N-oxides, stereoisomers, or isomers thereof.

[00177] In another aspect, provided herein are compounds of Formula Ic, or pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, esters, metabolites, N-oxides, stereoisomers, or isomers thereof.

[00178] In another aspect, provided herein are compounds of Formula II, or pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, esters, metabolites, N-oxides, stereoisomers, or isomers thereof.

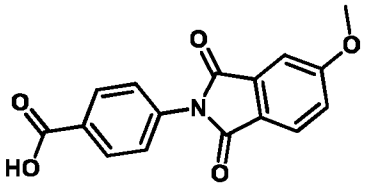
[00179] In another aspect, provided herein are compounds of Formula IIa, or pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, esters, metabolites, N-oxides, stereoisomers, or isomers thereof.

[00180] In another aspect, provided herein are compounds of Formula IIb, or pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, esters, metabolites, N-oxides, stereoisomers, or isomers thereof.

[00181] In another aspect, provided herein are compounds of Formula IIc, or pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, esters, metabolites, N-oxides, stereoisomers, or isomers thereof.

[00182] In another aspect, provided herein are compounds of Formula III, or pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, esters, metabolites, N-oxides, stereoisomers, or isomers thereof.

[00183] In another aspect, provided herein are compounds, or pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, esters, metabolites, N-oxides, stereoisomers, or isomers thereof, selected from: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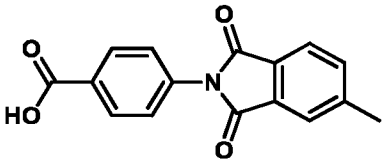
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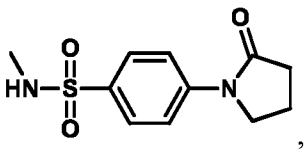
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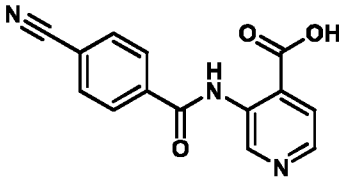
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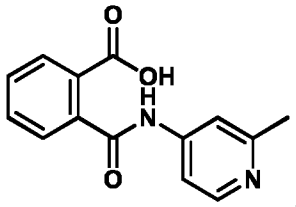
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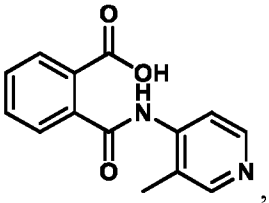
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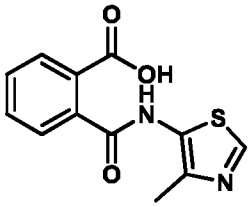
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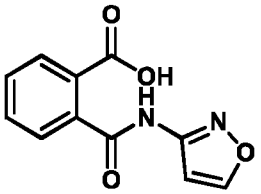
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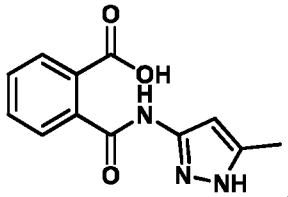
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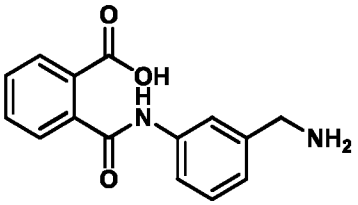
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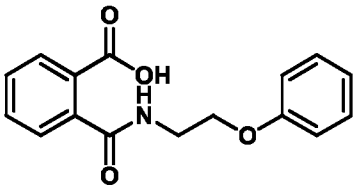
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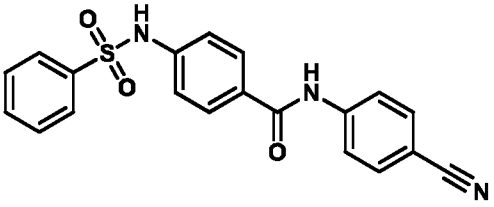
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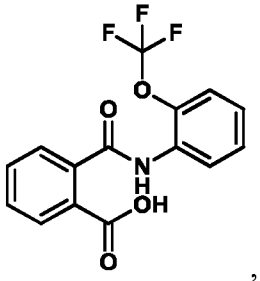
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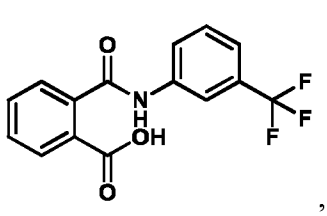
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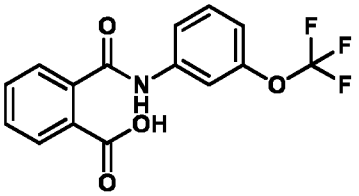
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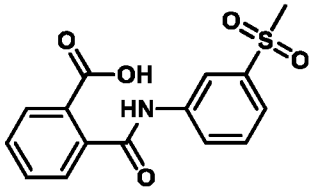
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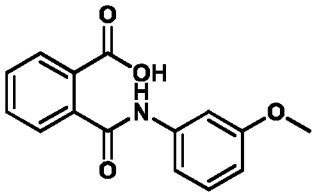
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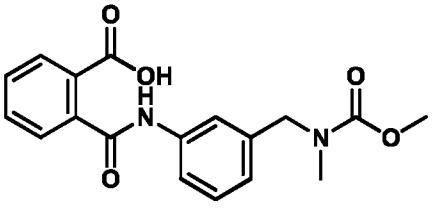
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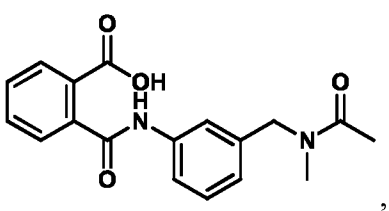
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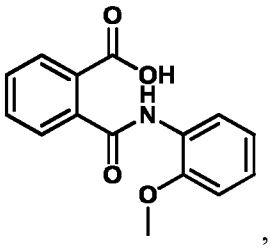

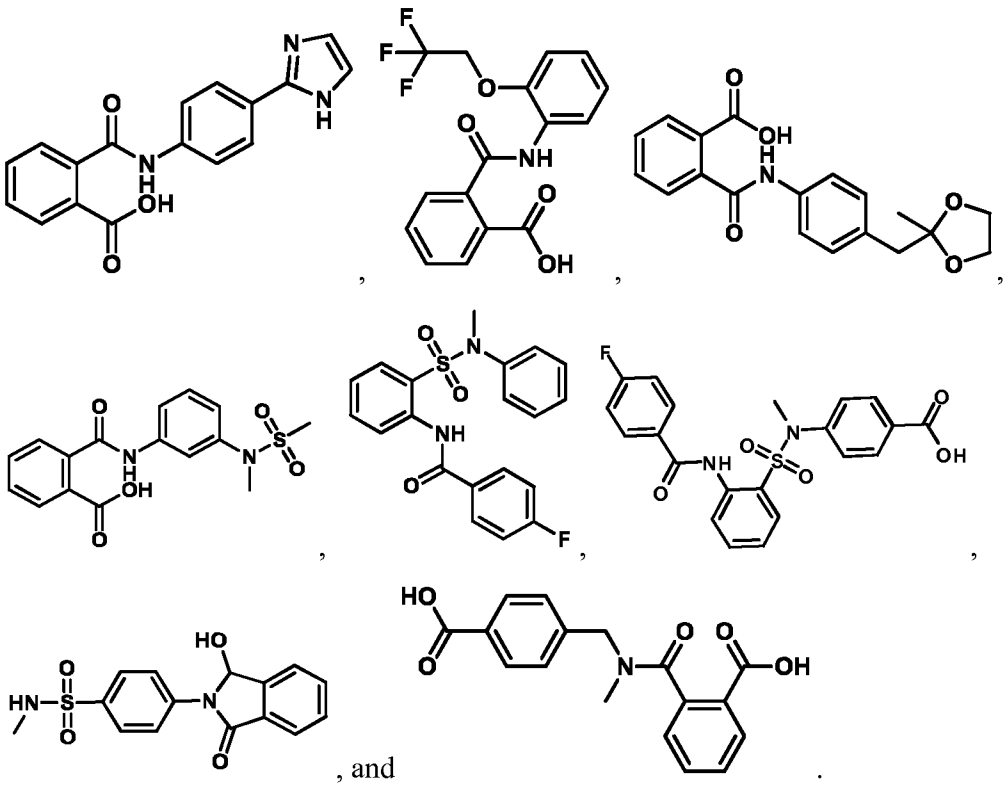

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Preparation of Compounds

[00184] Described herein are compounds for inducing differentiation of mesenchymal stem cells into chondrocytes and for ameliorating arthritis or joint injury in a mammal, and processes for the preparation of these compounds. Also described herein are pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically active metabolites, and pharmaceutically acceptable prodrugs of such compounds. Pharmaceutical compositions comprising at least one such compound or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, pharmaceutically active metabolite or pharmaceutically acceptable prodrug of such compound, and a pharmaceutically acceptable excipient are also provided.

[00185] Compounds described herein may be synthesized using standard synthetic reactions known to those of skill in the art or using methods known in the art. The reactions can be employed in a linear sequence to provide the compounds or they may be used to synthesize fragments which are subsequently joined by the methods known in the art.

[00186] The starting material used for the synthesis of the compounds described herein may be synthesized or can be obtained from commercial sources, such as, but not limited to, Aldrich Chemical Co. (Milwaukee, Wisconsin), Bachem (Torrance, California), or Sigma Chemical Co. (St. Louis, Mo.). The compounds described herein, and other related compounds having different substituents can be synthesized using techniques and materials known to those of skill in the art, such as described, for example, in March, ADVANCED ORGANIC CHEMISTRY 4th Ed., (Wiley 1992); Carey and Sundberg, ADVANCED ORGANIC CHEMISTRY 4th Ed., Vols. A and B (Plenum 2000, 2001); Green and Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 3rd Ed., (Wiley 1999); Fieser and

Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991); and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). (all of which are incorporated by reference in their entirety). Other methods for the synthesis of compounds described herein may be found in International Patent Publication No. WO 01/01982901, Arnold *et al.* *Bioorganic & Medicinal Chemistry Letters* 10 (2000) 2167-2170; Burchat *et al.* *Bioorganic & Medicinal Chemistry Letters* 12 (2002) 1687-1690. General methods for the preparation of compound as disclosed herein may be derived from known reactions in the field, and the reactions may be modified by the use of appropriate reagents and conditions, as would be recognized by the skilled person, for the introduction of the various moieties found in the formulae as provided herein.

[00187] The products of the reactions may be isolated and purified, if desired, using conventional techniques, including, but not limited to, filtration, distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

[00188] Compounds described herein may be prepared as a single isomer or a mixture of isomers.

Further Forms of Compounds Disclosed Herein

Isomers

[00189] In some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds presented herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the corresponding mixtures thereof. In some situations, compounds exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein. In some situations, the compounds described herein possess one or more chiral centers and each center exists in the R configuration, or S confirguration. The compounds described herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are useful for the applications described herein. In some embodiments, the compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. In some embodiments, dissociable complexes are preferred (e.g., crystalline diastereomeric salts). In some embodiments, the diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In some embodiments, the diastereomers are separated by chiral

chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In some embodiments, the optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization.

Labeled compounds

[00190] In some embodiments, the compounds described herein exist in their isotopically-labeled forms. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds as pharmaceutical compositions. Thus, in some embodiments, the compounds disclosed herein include isotopically-labeled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chloride, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, $^{18}0$, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds described herein, and the metabolites, pharmaceutically acceptable salts, esters, prodrugs, solvate, hydrates or derivatives thereof which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i. e., ^{3}H and carbon-14, i. e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavy isotopes such as deuterium, *i.e.*, ^{2}H, produces certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements. In some embodiments, the isotopically labeled compounds, pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof is prepared by any suitable method.

[00191] In some embodiments, the compounds described herein are labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

Pharmaceutically acceptable salts

[00192] In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

[00193] In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of a number of inorganic or organic bases, and inorganic and organic acids,

to form a pharmaceutically acceptable salt. In some embodiments, these salts are prepared *in situ* during the final isolation and purification of the compounds of the invention, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

[00194] Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with a mineral, organic acid or inorganic base, such salts including, acetate, acrylate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, bisulfite, bromide, butyrate, butyn-1,4-dioate, camphorate, camphorsulfonate, caproate, caprylate, chlorobenzoate, chloride, citrate, cyclopentanepropionate, decanoate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hexyne-1,6-dioate, hydroxybenzoate, γ-hydroxybutyrate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isobutyrate, lactate, maleate, malonate, methanesulfonate, mandelate metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, 1-napthalenesulfonate, 2-napthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, pyrosulfate, pyrophosphate, propiolate, phthalate, phenylacetate, phenylbutyrate, propanesulfonate, salicylate, succinate, sulfate, sulfite, succinate, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylate undeconate and xylenesulfonate.

[00195] Further, the compounds described herein can be prepared as pharmaceutically acceptable salts formed by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, including, but not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid metaphosphoric acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, p-toluenesulfonic acid, tartaric acid, trifluoroacetic acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, arylsulfonic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1 -carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid and muconic acid. In some embodiments, other acids, such as oxalic, while not in themselves pharmaceutically acceptable, are employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

[00196] In some embodiments, those compounds described herein which comprise a free acid group react with a suitable base, such as the hydroxide, carbonate, bicarbonate, sulfate, of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, tertiary, or quaternary amine. Representative salts include the alkali or alkaline earth salts, like lithium, sodium, potassium, calcium, and magnesium, and aluminum salts and the like. Illustrative examples of bases include sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, $N^+(C_{1-4}$ alkyl$)_4$, and the like.

[00197] Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. It should be understood that the compounds described herein also include the quaternization of any basic nitrogen-containing groups they contain. In some embodiments, water or oil-soluble or dispersible products are obtained by such quaternization.

Solvates

[00198] In some embodiments, the compounds described herein exist as solvates. The invention provides for methods of treating diseases by administering such solvates. The invention further provides for methods of treating diseases by administering such solvates as pharmaceutical compositions.

[00199] Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and, in some embodiments, are formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of the compounds described herein can be conveniently prepared or formed during the processes described herein. By way of example only, hydrates of the compounds described herein can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents including, but not limited to, dioxane, tetrahydrofuran or methanol. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

Polymorphs

[00200] In some embodiments, the compounds described herein exist as polymorphs. The invention provides for methods of treating diseases by administering such polymorphs. The invention further provides for methods of treating diseases by administering such polymorphs as pharmaceutical compositions.

[00201] Thus, the compounds described herein include all their crystalline forms, known as polymorphs. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. In certain instances, polymorphs have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical

properties, stability, and solubility. In certain instances, various factors such as the recrystallization solvent, rate of crystallization, and storage temperature cause a single crystal form to dominate.

Prodrugs

[00202] In some embodiments, the compounds described herein exist in prodrug form. The invention provides for methods of treating diseases by administering such prodrugs. The invention further provides for methods of treating diseases by administering such prodrugs as pharmaceutical compositions.

[00203] Prodrugs are generally drug precursors that, following administration to an individual and subsequent absorption, are converted to an active, or a more active species via some process, such as conversion by a metabolic pathway. Some prodrugs have a chemical group present on the prodrug that renders it less active and/or confers solubility or some other property to the drug. Once the chemical group has been cleaved and/or modified from the prodrug the active drug is generated. Prodrugs are often useful because, in some situations, they are easier to administer than the parent drug. They are, for instance, bioavailable by oral administration whereas the parent is not. In certain insatnces, the prodrug also has improved solubility in pharmaceutical compositions over the parent drug. An example, without limitation, of a prodrug would be a compound as described herein which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyamino acid) bonded to an acid group where the peptide is metabolized to reveal the active moiety. (See for example Bundgaard, "Design and Application of Prodrugs" in *A Textbook of Drug Design and Development*, Krosgaard-Larsen and Bundgaard, Ed., 1991, Chapter 5, 113-191, which is incorporated herein by reference).

[00204] In some embodiments, prodrugs are designed as reversible drug derivatives, for use as modifiers to enhance drug transport to site-specific tissues. The design of prodrugs to date has been to increase the effective water solubility of the therapeutic compound for targeting to regions where water is the principal solvent.

[00205] In some embodiments, prodrugs are C_1-C_6 alkyl esters of the compounds disclosed herein.

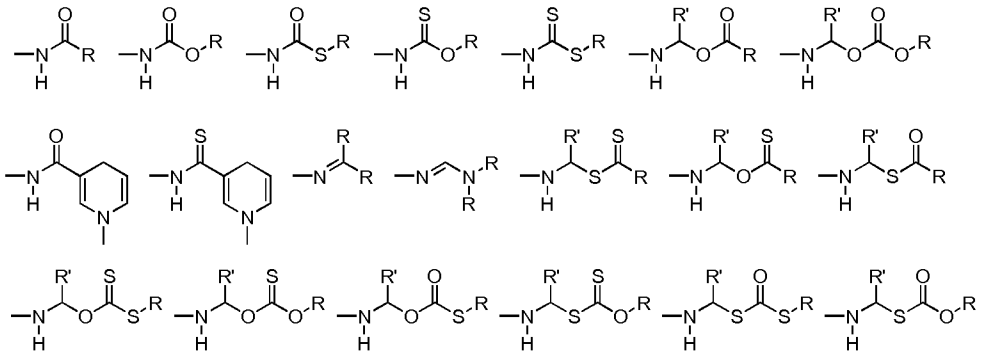
[00206] Additionally, prodrug derivatives of compounds described herein can be prepared by methods described herein are otherwise known in the art (for further details see Saulnier *et al.*, *Bioorganic and Medicinal Chemistry Letters*, **1994**, *4*, 1985). By way of example only, appropriate prodrugs can be prepared by reacting a non-derivatized compound with a suitable carbamylating agent, such as, but not limited to, 1,1-acyloxyalkylcarbanochloridate, *para*-nitrophenyl carbonate, or the like. Prodrug forms of the herein described compounds, wherein the prodrug is metabolized *in vivo* to produce a derivative as set forth herein are included within the scope of the claims. Indeed, some of the herein-described compounds are prodrugs for another derivative or active compound.

[00207] In some embodiments, prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e. g., two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of compounds of the present invention. The amino acid residues include but are not limited to the 20 naturally occurring amino acids and also includes 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvaline, beta-alanine, gamma-aminobutyric acid, cirtulline, homocysteine, homoserine, ornithine and methionine sulfone. In other embodiments, prodrugs include compounds wherein a nucleic acid residue, or an oligonucleotide of two or more (e. g., two, three or four) nucleic acid residues is covalently joined to a compound of the present invention.

[00208] Pharmaceutically acceptable prodrugs of the compounds described herein also include, but are not limited to, esters, carbonates, thiocarbonates, N-acyl derivatives, N-acyloxyalkyl derivatives, quaternary derivatives of tertiary amines, N-Mannich bases, Schiff bases, amino acid conjugates, phosphate esters, metal salts and sulfonate esters. Compounds having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. For instance, free carboxyl groups can be derivatized as amides or alkyl esters. In certain instances, all of these prodrug moieties incorporate groups including but not limited to ether, amine and carboxylic acid functionalities.

[00209] Hydroxy prodrugs include esters, such as though not limited to, acyloxyalkyl (e.g. acyloxymethyl, acyloxyethyl) esters, alkoxycarbonyloxyalkyl esters, alkyl esters, aryl esters, phosphate esters, sulfonate esters, sulfate esters and disulfide containing esters; ethers, amides, carbamates, hemisuccinates, dimethylaminoacetates and phosphoryloxymethyloxycarbonyls, as outlined in *Advanced Drug Delivery Reviews* **1996**, *19*, 115.

[00210] Amine derived prodrugs include, but are not limited to the following groups and combinations of groups:



as well as sulfonamides and phosphonamides.

[00211] In certain instances, sites on any aromatic ring portions are susceptible to various metabolic reactions, therefore incorporation of appropriate substituents on the aromatic ring structures, can reduce, minimize or eliminate this metabolic pathway.

Metabolites

[00212] In some embodiments, compounds described herein are susceptible to various metabolic reactions. Therefore, in some embodiments, incorporation of appropriate substituents into the structure will reduce, minimize, or eliminate a metabolic pathway. In specific embodiments, the appropriate substituent to decrease or eliminate the susceptibility of an aromatic ring to metabolic reactions is, by way of example only, a halogen, or an alkyl group.

[00213] In additional or further embodiments, the compounds described herein are metabolized upon administration to an organism in need to produce a metabolite that is then used to produce a desired effect, including a desired therapeutic effect.

Pharmaceutical Compositions/Formulations

[00214] In another aspect, provided herein are pharmaceutical compositions comprising a compound described herein, or a pharmaceutically acceptable salt, polymorph, solvate, prodrug, N-oxide, or isomer thereof, and a pharmaceutically acceptable excipient.

[00215] In some embodiments, the compounds described herein are formulated into pharmaceutical compositions. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable inactive ingredients that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999), herein incorporated by reference for such disclosure.

[00216] Provided herein are pharmaceutical compositions that include a compound as described herein and at least one pharmaceutically acceptable inactive ingredient. In some embodiments, the compounds described herein are administered as pharmaceutical compositions in which a compound described herein is mixed with other active ingredients, as in combination therapy. In other embodiments, the pharmaceutical compositions include other medicinal or pharmaceutical agents, carriers, adjuvants, preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, and/or buffers. In yet other embodiments, the pharmaceutical compositions include other therapeutically valuable substances.

[00217] A pharmaceutical composition, as used herein, refers to a mixture of a compound described herein with other chemical components (i.e. pharmaceutically acceptable inactive ingredients), such as carriers, excipients, binders, filling agents, suspending agents, flavoring agents, sweetening agents, disintegrating agents, dispersing agents, surfactants, lubricants, colorants, diluents, solubilizers, moistening agents, plasticizers, stabilizers, penetration enhancers, wetting

agents, anti-foaming agents, antioxidants, preservatives, or one or more combination thereof. The pharmaceutical composition facilitates administration of the compound to an organism. In practicing the methods of treatment or use provided herein, therapeutically effective amounts of compounds described herein are administered in a pharmaceutical composition to a mammal having a disease, disorder, or condition to be treated. In some embodiments, the mammal is a human, a dog, a cat, or a horse. In some embodiments, the mammal is a human. In some embodiments, the mammal is a dog, a cat, or a horse. A therapeutically effective amount can vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. The compounds can be used singly or in combination with one or more therapeutic agents as components of mixtures.

[00218] The pharmaceutical formulations described herein are administered to a subject by appropriate administration routes, including but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, intramuscular, intra-articular), intranasal, buccal, topical, rectal, or transdermal administration routes. The pharmaceutical formulations described herein include, but are not limited to, aqueous liquid dispersions, liquids, gels, syrups, elixirs, slurries, suspensions, self-emulsifying dispersions, solid solutions, liposomal dispersions, aerosols, solid oral dosage forms, powders, immediate release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, powders, dragees, effervescent formulations, lyophilized formulations, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

[00219] Pharmaceutical compositions including a compound described herein are manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[00220] The pharmaceutical compositions will include at least one compound described herein as an active ingredient in free-acid or free-base form, or in a pharmaceutically acceptable salt form. In addition, the methods and pharmaceutical compositions described herein include the use of *N*-oxides (if appropriate), crystalline forms, amorphous phases, as well as active metabolites of these compounds having the same type of activity. In some embodiments, compounds described herein exist in unsolvated form or in solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

[00221] Pharmaceutical preparations for oral use are obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, for example, fillers such as sugars, including

lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. If desired, disintegrating agents are added, such as the cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. In some embodiments, dyestuffs or pigments are added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[00222] Pharmaceutical preparations that are administered orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In some embodiments, stabilizers are added.

[00223] In certain embodiments, delivery systems for pharmaceutical compounds may be employed, such as, for example, liposomes and emulsions. In certain embodiments, compositions provided herein can also include an mucoadhesive polymer, selected from among, for example, carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate and dextran.

Combination Treatment

[00224] The compounds and compositions of the present invention can be used in combination with other components suitable for ameliorating arthritis or joint injury. In some embodiments, the composition can further comprise an additional compound which is therapeutically effective for the treatment of arthritis or joint injury and/or the symptoms associated with arthritis or joint injury in a mammal. In some embodiments, the composition can also include a non-steroidal anti-inflammatory drug (NSAID), an analgesic, a glucocorticoid, an angiopoietin-like 3 protein (ANGPTL3) or chondrogenic variant thereof, oral salmon calcitonin, SD-6010 (iNOS inhibitor), vitamin D3 (choliecalciferol), collagen hydrolyzate, FGF18, BMP7, avocado soy unsaponifiables (ASU) or hyaluronic acid. ANGPTL3 is described in more detail in WO201 1/008773 (incorporated herein in its entirety). In some embodiments, the composition includes an agent with anti-inflammatory activity. In some embodiments, the composition includes an apoptosis modulator. In certain embodiments, the apoptosis modulator is a caspase inhibitor. One non-limiting example of an apoptosis/caspase inhibitor is emricasan. In some embodiments, the composition includesan iNOS inhibitor. One non-limiting example of an iNOS inhibitor is SD-6010.

[00225] NSAIDS include, but are not limited to, aspirin, diflunisal, salsalate, ibuprofen, dexibuprofen, naproxen, fenoprofen, ketoprofen, dexketoprofen, flurbiprofen, oxaprozin,

loxoprofen, indomethacin, tolmetin, sulindac, etodolac, ketorolac, nabumetone, diclofenac, piroxicam, meloxicam, tenoxicam, droxicam, lornoxicam, isoxicam, mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid, celecoxib, parecoxib, etoricoxib, lumiracoxib, and firocoxib.

[00226] Analgesics include, but are not limited to, acetaminophen and opioids (narcotics). Opioids include, but are not limited to, dextropropoxyphene, codeine, tramadol, tapentadol, anileridine, alphaprodine, pethidine, hydocodone, morphine, oxycodone, methadone, diamorphine, hydromorphone, oxymorphone, levorphanol, 7-hydroxymitragynine, buprenorphine, fentanyl, sufentanil, bromadol, etorphine, dihydroetorphine, and carfentanil.

[00227] Glucocorticoids include, but are not limited to, hydrocortisone, cortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, beclometasone, or fludrocortisones.

[00228] The compounds described herein may be used in combination with one or more compounds which are therapeutically effective for the treatment of arthritis or joint injury and/or the symptoms associated with arthritis or joint injury. Such additional compounds may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with a compound disclosed herein. When a compound disclosed herein is used contemporaneously with one or more such additional compounds, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of the present invention is preferred. However, the combination therapy may also include therapies in which the compound disclosed herein and one or more additional compounds are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more additional compounds, the compounds may be used in lower doses than when each is used singly.

[00229] The above combinations include combinations of a compound disclosed herein not only with one compound which is therapeutically effective for the treatment of arthritis or joint injury and/or the symptoms associated with arthritis or joint injury, but also with two or more such compounds. Likewise, compounds disclosed herein, either in combination with a compound which is therapeutically effective for the treatment of arthritis or joint injury and/or the symptoms associated with arthritis or joint injury or by themselves, may be used in combination with other drugs that are used in the prevention, treatment, control, or amelioration of osteoarthritis or joint injury or conditions associated with osteoarthritis or joint injury. Such other drugs may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with a compound disclosed herein. When a compound disclosed herein is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention also include those that also contain one or more other active ingredients, in addition to a compound disclosed herein. The weight ratio of the

compound disclosed herein to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used.

Administration of Pharmaceutical Composition

[00230] Suitable routes of administration include, but are not limited to, oral, intravenous, intra-articular, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, intra-articular, and intranasal injections.

[00231] In some embodiments, compounds disclosed herein and compositions thereof are administered in any suitable manner. The manner of administration can be chosen based on, for example, whether local or systemic treatment is desired, and on the area to be treated. For example, the compositions can be administered orally, parenterally (e.g., intravenous, subcutaneous, intraperitoneal, intra-articular, or intramuscular injection), by inhalation, extracorporeally, topically (including transdermally, ophthalmically, vaginally, rectally, intranasally) or the like. In some embodiments, the compositions can be administered by microneedle. In some embodiments, the compositions can be administered by a microneedle array in the form of a patch which can perform intracutaneous drug delivery. In some embodiments, the compositions can be administered by transdermal microneedle patch delivery.

[00232] Parenteral administration of the composition, if used, is generally characterized by injection. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution of suspension in liquid prior to injection, or as emulsions. A more recently revised approach for parenteral administration involves use of a slow release or sustained release system such that a constant dosage is maintained.

EXAMPLES

List of abbreviations

[00233] As used above, and throughout the description of the invention, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

ACN	acetonitrile
Bn	benzyl
BOC or Boc	*tert*-butyl carbamate
BOP	benzotriazol-1-yl-oxytris (dimethylamino) phosphonium
t-Bu	tert-butyl
Cbz	benzyl carbamate
Cy	Cyclohexyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene

DCC	dicyclohexylcarbodiimide
DCM	dichloromethane (CH_2CI_2)
DIC	1,3-diisopropylcarbodiimide
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIPEA	diisopropylethylamine
DMAP	4-(N,N-dimethylamino)pyridine
DMP reagent	Dess-Martin Periodinane reagent
DMF	dimethylformamide
DMA	N,N-Dimethylacetamide
DME	1,2-Dimethoxy-ethane
DMSO	dimethylsulfoxide
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
EDCI	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide HCl
eq	equivalent(s)
Et	ethyl
Et_2O	diethyl ether
EtOH	ethanol
EtOAc	ethyl acetate
HOAt	1-hydroxy-7-azabenzotriazole
HOBT	1-hydroxybenztriazole
HOSu	N-hydroxysuccinamide
HPLC	high performance liquid chromatography
LAH	lithium aluminum anhydride
Me	methyl
MeI	methyliodide
MeOH	methanol
MOMCl	methoxymethylchloride
MOM	methoxymethyl
MS	mass spectroscopy
NMP	*N*-methyl-pyrrolidin-2-one
NMR	nuclear magnetic resonance
PyBOP	benzotriazole-1-yl-oxytris-pyrrolidino-phosphonium Hexafluorophosphate
SPHOS	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl

TBD	1,5,7-triazabicyclo[4.4.0]-dec-5-ene
RP-HPLC	reverse phase-high pressure liquid chromatography
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
TBTU	O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium
TEOC	2-Trimethylsilylethyl Carbamate
TFA	trifluoroacetic acid
Tf_2O	triflate anhydride
TMG	1,1,3,3-Tetramethylguanidine
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
XPHOS	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

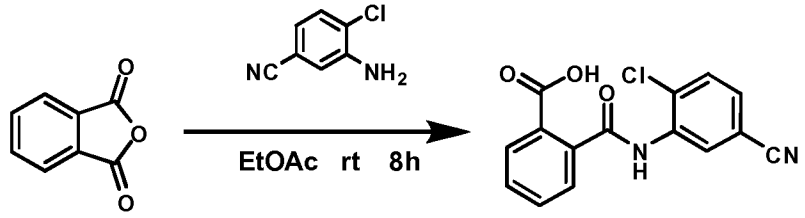
General Examples for the Preparation of Compounds of the Invention

[00234] The starting materials and intermediates for the compounds of this invention may be prepared by the application or adaptation of the methods described below, their obvious chemical equivalents, or, for example, as described in literature such as The Science of Synthesis, Volumes 1-8. Editors E. M. Carreira et al. Thieme publishers (2001-2008). Details of reagent and reaction options are also available by structure and reaction searches using commercial computer search engines such as Scifinder (www.cas.org) or Reaxys (www.reaxys.com).

Synthetic Examples

[00235] The following preparations of compounds disclosed herein and intermediates are given to enable those of skill in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as illustrative and representative thereof.

Synthetic Scheme A: ***Sample Experimental for compound # 1***



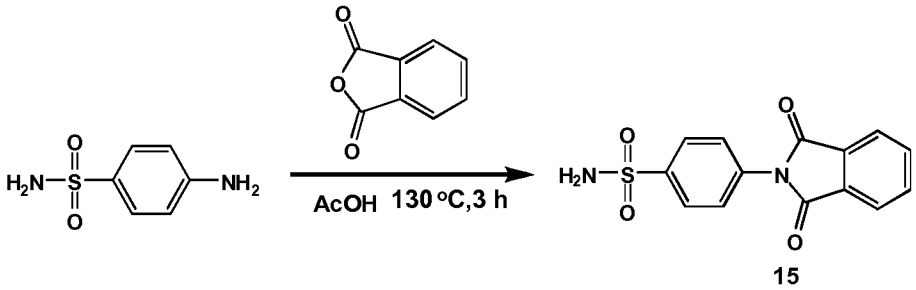
1

[00236] To a solution of phthalic anhydride (1.0 eq) in EtOAc was added 3-amino-4-chlorobenzonitrile (1 eq), then was stirred for 1-8h at 20-30 °C. TLC indicated starting material had

disappeared. The reaction mixture was filtered and the solid was purified by recrystallization in EtOAc to afford compound **1** (12 mg). Final product **1** was confirmed by ^{1}H NMR and LCMS. LCMS: Found 301.0 [M+H]. ^{1}H NMR (400 MHz, MeOD-d_4): 8.35 (s, 1H), 8.09 (d, J = 7.7 Hz, 1H), 7.71 (dd, J = 8.0, 4.1 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.61 (t, J = 7.4 Hz. 2H), 7.57 (dd, J = 8.4, 2.0 Hz, 1H).

[00237] Select compounds in Table 1 were obtained using analogous conditions as the reaction scheme given above, substituting 3-amino-4-chlorobenzonitrile with the appropriate aniline or amine. Reaction yields based on isolated products ranged from 20% to 80%.

Synthetic Scheme B-1: ***Sample Experimental for compound # 15***

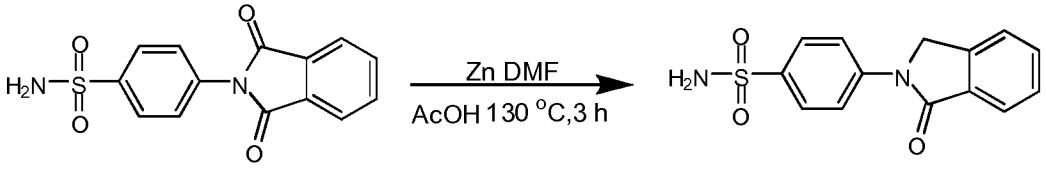


15

[00238] To a solution of 4-aminobenzenesulfonamide (100 mg, 0.58 mmol) in AcOH (20 mL), phthalic anhydride (82 mg, 0.55 mmol) was added. The mixture was stirred at 130 °C for 3 h. The mixture was diluted with H_2O (30 mL) and stirred for 2 h. After filtration to get compound **15** (44 mg, yield: 26%) as a white solid. Final product **15** was confirmed by ^{1}H NMR and LCMS. LCMS: Found 303.0 [M+H]. ^{1}H NMR (400 MHz, DMSO-d_6): 7.10-7.36 (m, 6H), 6.56-6.70 (m, 2H), 6.62 (br s, 2H).

[00239] Select compounds in Table 1 were obtained using analogous conditions as the reaction scheme given above, substituting 4-aminobenzenesulfonamide with the appropriate aniline. In the case of compound **33**, reaction time was 3 h and the reaction mixture was diluted with H_2O and stirred for 12 h for crystallization.

Synthetic Scheme B-2: ***Sample Experimental for compound # 26***



15 26

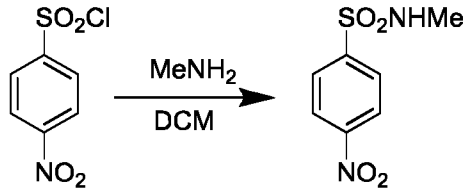
[00240] To a solution of compound **15** (276 mg, 0.913 mmol) in AcOH (5 mL), Zn (596.91 mg, 9.13 mmol) and DMF (0.1 mL) were added. The mixture was stirred at 130 °C for 3 h, then cooled to room temperature and concentrated to get the crude products as colorless oil. The residue was purified by prep-HPLC (0.1% TFA as additive), most CH_3CN was removed by evaporation under

reduced pressure, and the remaining solvent was removed by lyophilization to afford compound **26** (80 mg, yield: 30%) as a white solid. LCMS: Found 289.1 [M+H].

[00241] Compound **27** (Table 1) was obtained using analogous conditions as the reaction scheme given above. In the preparation of compound **27**, DMF was not used.

[00242] The starting material of product **27** was made by the following procedure.

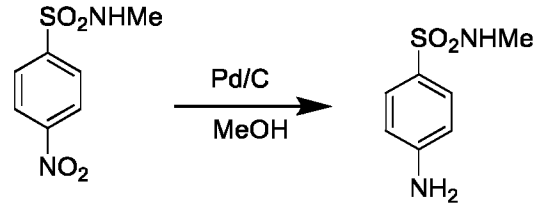
Preparation of compound 27-2



27-1 **27-2**

[00243] To a solution of compound **27-1** (3.8 g, 17 mmol) in DCM (50 ml), $MeNH_2$ (5.3 g, 51 mmol) in alcohol was added. The mixture was stirred at room temperature for 2 h. The mixture was diluted by DCM (30 ml) and washed with H_2O (30 ml).The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to afford compound **27-2** (3.3 g, yield: 90%).

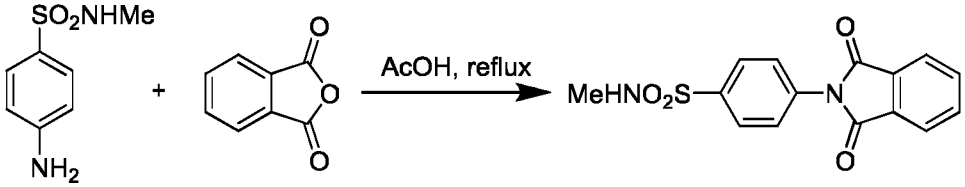
Preparation of compound 27-3



27-2 **27-3**

[00244] To a solution of compound **27-2** (3.3 g, 15.3 mol) in CH_3OH (50 mL) was added Pd/C (0.16 g) at room temperature. The mixture was stirred under H_2 (30 psi) at room temperature for 12 h. The mixture was filtered and the solvent was removed to give the compound **27-3** (2.3 g, yield: 80%) as a gray solid.

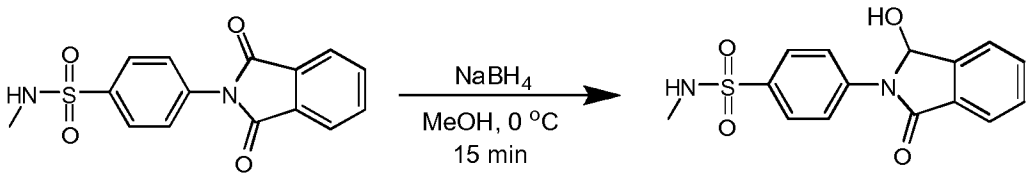
Preparation of starting material of compound 27



27-3 **27-4** **Starting material of 27**

[00245] To a solution of **27-3** (0.5 g, 2.68 mmol) in AcOH (40 mL) was added **27-4** (0.433 g, 2.92 mmol). The reaction mixture was stirred at 130 °C for 3 h. The reaction mixture was cooled down, and the solvent was removed to afford crude product which was used directly in the next step.

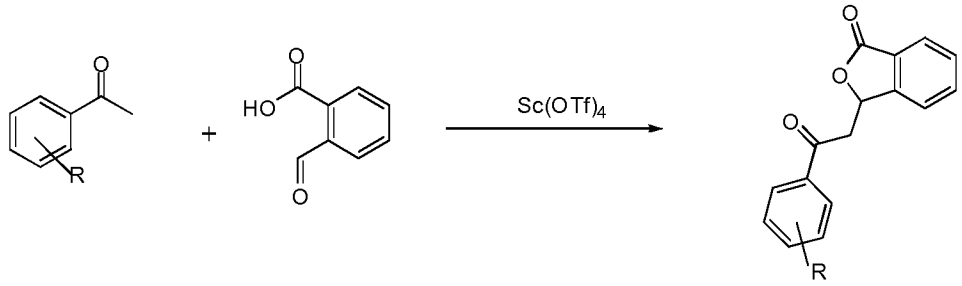
Synthetic Scheme B-3: ***Sample Experimental for compound # 177***



Starting material of 27 177

[00246] To a solution of the starting material for compound **27** (1.0 g, 3.16 mmol) in CH_3OH (20 mL) at 0 °C was added $NaBH_4$ (239 mg, 6.32 mmol). The mixture was stirred at 0 °C for 15 min before the solvent was removed under reduced pressure. Water (20 mL) and sat'd. aq. NH_4Cl (20 mL) was added to the crude residue. The mixture was stirred for 30 min at room temperature. Filtration provided compound **177** (840 mg, yield: 83%) as an off-white solid.

Synthetic Scheme C: ***General procedure for compounds C***

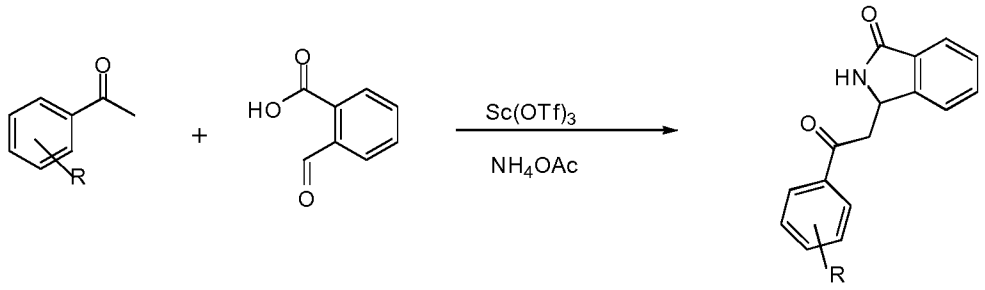


sm-1 sm-2 C

[00247] To a solution of ketone **sm-1** (1.0 eq) in dioxane (V/M=10:1) was added carboxybenzaldehyde **sm-2** (1.2 eq), followed by $Sc(OTf)_4$. The mixture heated to reflux for 12 h. Upon cooling to room temperature, the mixture was concentrated and purified by prep-HPLC to afford compound **C**.

[00248] Select compounds in Table 1 were obtained using Synthetic Scheme C. Reaction yields based on isolated products ranged from 5% to 50%.

Synthetic Scheme D: ***General procedure for compounds D***

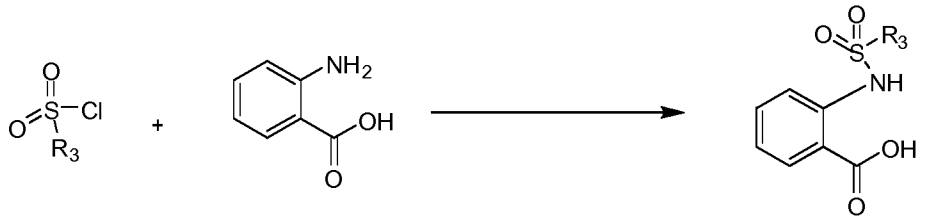


sm-1 sm-2 D

[00249] To a solution of ketone **sm-1** (1.0 eq) in dioxane (V/M=15:1) was added carboxybenzaldehyde **sm-2** (1.2 eq), followed by $Sc(OTf)_4$ (2 eq). The mixture was heated to reflux for 12 h. NH_4OAc (5 eq) was added, and the reaction mixture was heated to reflux for an additional 12 h. Upon cooling to room temperature, the mixture was concentrated and purified by prep-HPLC to afford compound **D**.

[00250] Select compounds in Table 1 were obtained using Synthetic Scheme D. Reaction yields based on isolated products ranged from 3% to 20%.

Synthetic Scheme E: ***General procedure for compounds E***

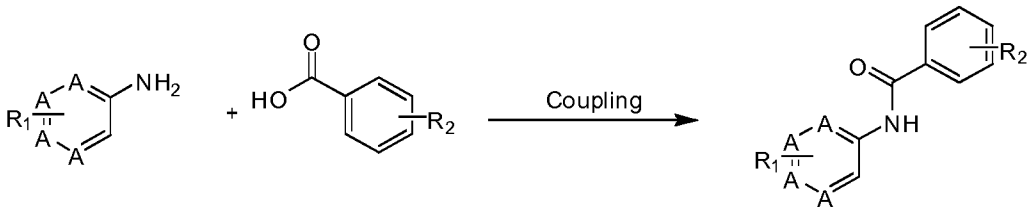


sm-3 **sm-4** **E**

[00251] To a solution of 2-aminobenzoic acid **sm-4** (1 eq) in 2 M $NaHCO_3$ (V=10eq) was added sulfonyl chloride **sm-3** (1.0 eq), and the mixture was stirred at room temperature for 2 h. TLC indicated starting material had disappeared. The mixture was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, concentrated and purified by pre-HPLC to afford pure product **E**.

[00252] Compound **53** (Table 1) was obtained using Synthetic Scheme E. Reaction yields based on isolated product ranged from 60% to 80%.

Synthetic Scheme F: ***General procedure for compounds F***

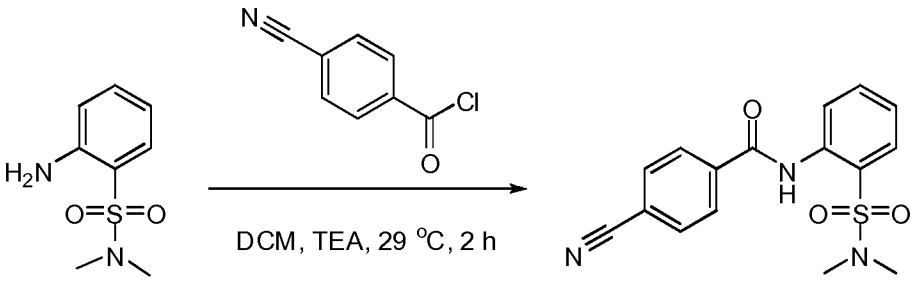


sm-5 **sm-6** **F**

[00253] To a solution of benzoic acid **sm-6** (1 eq) in DMF (10eq) was added EDCI (1.5 eq) and HOBT (1.5 eq) at 0 ℃ prior to stirring at room temperature for about 2 h. Amine **sm-5** (1.5 eq) was added to the reaction mixture, which was stirred at room termperature for an additional 12 h. Water was added, and the mixture was extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography to give the product **F**.

[00254] Select compounds in Table 1 were obtained using Synthetic Scheme F. Reaction yields based on isolated products ranged from 20% to 40%.

Synthetic Scheme G: ***Sample Experimental for compound # 56***



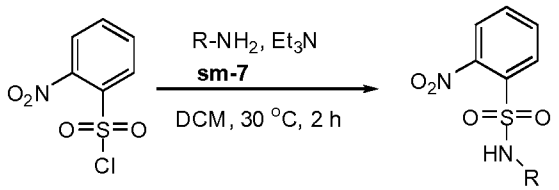
56

[00255] 4-Cyanobenzoyl chloride (1.0 eq) was added to a solution of 2-amino-*N,N*-dimethylbenzenesulfonamide (1.0 eq) and TEA (1.5 eq) in DCM. The reaction mixture was stirred at 29 °C for about 2 h. TLC indicated starting material had disappeared. The reaction mixture was quenched with sat'd. aq. $NaHCO_3$, extracted with DCM, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by prep-HPLC to afford compound **56** (yield: 70%). LCMS: Found 330.1 [M+H].

[00256] Compound **62** (Table 1) was obtained using analogous conditions as the reaction scheme given above. Reaction yields based on isolated products ranged from 70% to 80%.

[00257] The requisite aniline starting material **I** of compounds **56** and **62** were made by the following procedure.

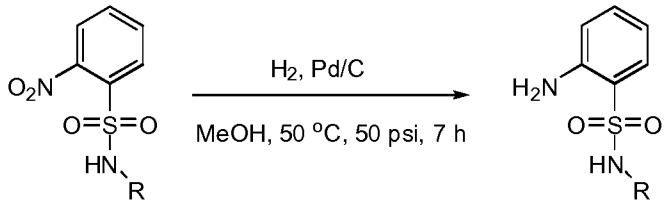
Preparation of intermediates sm-8



sm-8

[00258] A solution of 2-nitrobenzene-1-sulfonyl chloride (1.0 eq) and amine **sm-7** (1.0 eq) in DCM was stirred at 30 °C for about 2 h. TLC indicated starting material had disappeared. The reaction mixture was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to afford intermediate **sm-8** (yield: 72-91%).

Preparation of aniline starting materials I

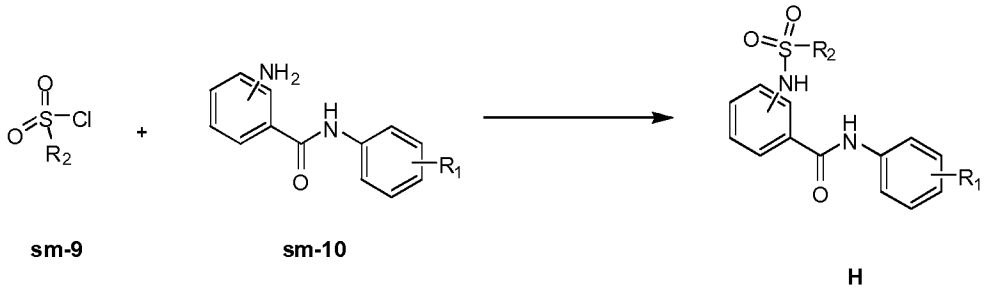


sm-8 **I**

[00259] To a solution of intermediate **sm-8** (1.0 eq) in MeOH was added Pd/C. The reaction mixture was stirred at 50 °C under 50 psi of H_2 for 7 h. TLC indicated starting material had

disappeared. The mixture was filtered, and the filtrate was concentrated to afford compound **I** (yield: 89~91%).

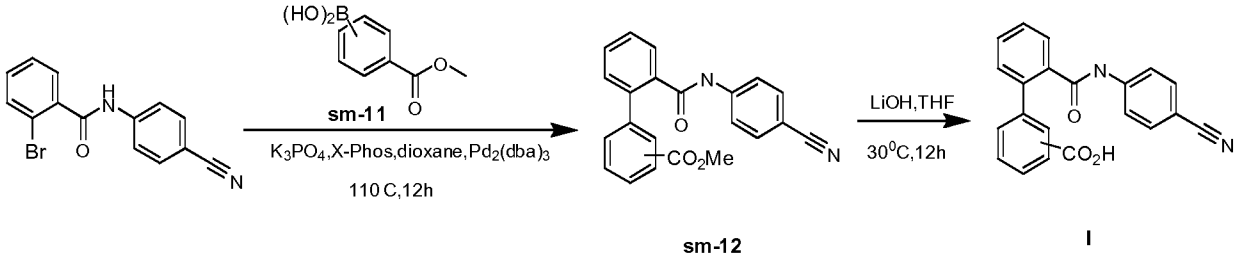
Synthetic Scheme H: ***General procedure for compounds H***



[00260] To a solution of amide **sm-10** (1 eq) in THF (V=10 eq) was added dropwise LiHMDS(1eq) at 0 °C. After 30 min, sulfonyl chloride **sm-9** (1.0 eq) was added, and the mixture was stirred at room temperature for 2 h. TLC indicated starting material had disappeared. The mixture was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, concentrated and purified by pre-HPLC to afford compound **H**.

[00261] Select compounds in Table 1 were obtained using Synthetic Scheme H. Reaction yields based on isolated products ranged from 50% to 80%.

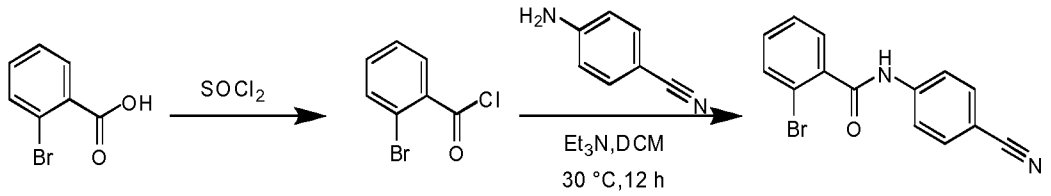
Synthetic Scheme I: ***General procedure for compounds I***



[00262] To a stirring mixture of 2-bromo-N-(4-cyanophenyl)benzamide (1.66 mmol) and boronic acid **sm-11** (3.32 mmol) in dioxane (10 mL) was added K_3PO_4 (1.06 g, 4.98 mmol). $Pd_2(dba)_3$ (45.61 mg, 49.81 umol) and X-Phos (39.58 mg, 83.02 umol) were added under N_2. Finally the mixture was heated to 110 °C and stirred for 12 h. After filtration, the mixture was concentrated to give intermediate **sm-12** as a brown oil. To a solution of **sm-12** (770 mg, 2.16 mmol) in THF (30 mL) was added LiOH (4.32 mL, 4.32 mmol) drop-wise and stirred for 12 h. The solution was acidified to pH 4 at 10 °C, extracted with EtOAc (30 mL), washed with H_2O (50 mL) and brine (50 mL), concentrated and purified by prep-HPLC (0.1% TFA as additive). Solvents were removed by evaporation under reduced pressure and lyophilization to afford compound **I** as a white solid.

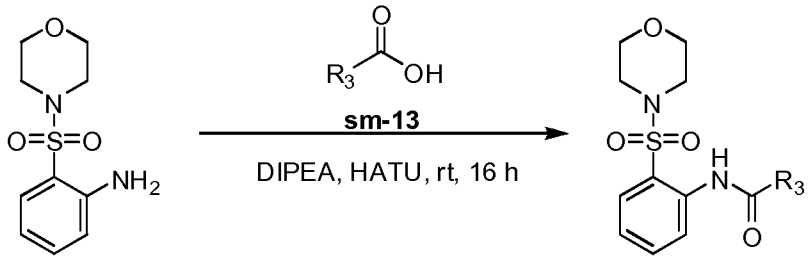
[00263] Select compounds in Table 1 were obtained using Synthetic Scheme I. Reaction yields based on isolated products ranged from 15% to 30%.

[00264] 2-Bromo-N-(4-cyanophenyl)benzamide was prepared by the following procedure.



[00265] A solution of 2-bromobenzoic acid (4.4 g, 21.89 mmol) in $SOCl_2$ (45 mL) was heated to 70 °C for 2 h. It was evaporated to obtain 2-bromobenzoyl chloride as a yellow oil, which was diluted with DCM (90 mL). The resultant mixture was added drop-wise to a solution of 4-aminobenzonitrile (2.59 g, 21.92 mmol) in DCM (10 mL) and Et_3N (4.43 g, 43.78 mmol) at 10 °C. Finally the mixture was warmed to 30 °C and stirred for 12 h. The mixture was diluted with DCM (100 mL), and washed with HCl (100 mL), $NaHCO_3$ (50 mL), H_2O (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4, concentrated, and purified by silica gel column chromatography (PE:EtOAc =5: 1) to provide 2-bromo-N-(4-cyanophenyl)benzamide (4.7 g, yield: 72%) as a white solid.

Synthetic Scheme J: ***General procedure for compounds J***

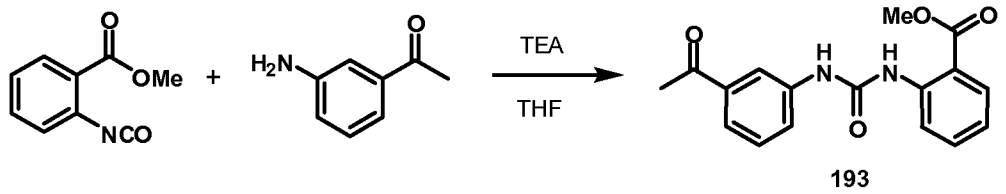


J

[00266] To a solution of 2-(morpholinosulfonyl)aniline (1.0 eq) in DMF was added carboxylic acid **sm-13** (1.0 eq), DIPEA (1.5 eq) and HATU (1.3 eq). The resultant mixture was stirred at 10-15 °C for 16-24 h. TLC indicated starting material had disappeared. The reaction mixture was concentrated and the solid was purified by silica gel column chromatography to afford compound **J**.

[00267] Select compounds in Table 1 were obtained using Synthetic Scheme J.

Synthetic Scheme K-1: ***Sample Experimental for compound # 193***



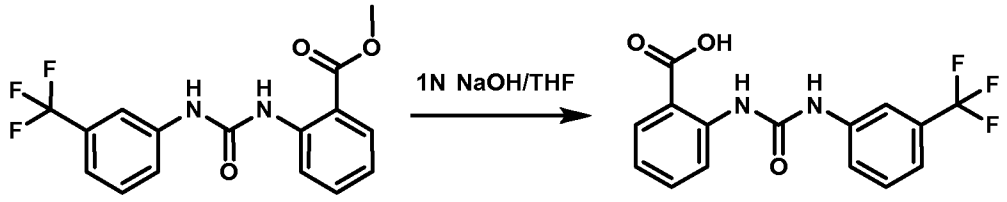
193

[00268] Methyl 2-isocyanatobenzoate (200 mg 1.13 mmol) and 1-(3-aminophenyl)ethanone (167 mg, 1.24 mmol) were dissolved in THF (2.5 ml) and heated using microwave heating at 100 °C for 15 min. The reaction mixture was washed with sat'd. aq. $NaHCO_3$ and purified via column

chromatography (EtOAc:hexanes) to provide the final product **193** (262 mg, yield: 75%), which was confirmed by ^{1}H NMR and LCMS.

[00269] Select compounds in Table 1 were obtained using analogous conditions as the reaction scheme given above. In these reactions, DIPEA was used instead of TEA and the temperature was increased to 120 °C. Reaction yields based on isolated products ranged from 47-90%.

Synthetic Scheme K-2: ***Sample Experimental compound # 196***

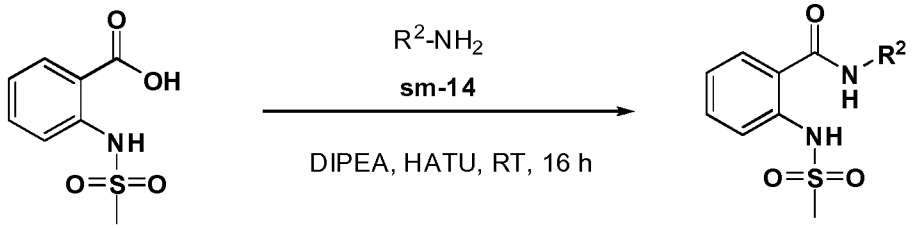


195 196

[00270] Compound **195** was dissolved in THF (2 mL) and 1 N NaOH (1 mL). The reaction mixture was stirred at room temperature for 15 h. The mixture was diluted with EtOAc (20 mL) prior to the drop-wise addition of 1 N HCl (3 mL) with constant stirring. The organic layer was extracted, dried, and concentrated. The crude product was recrystallized from EtOAc to provide compound **196** (25 mg).

[00271] Select compounds in Table 1 were obtained using analogous conditions as the reaction scheme given above. Reaction yields based on isolated products ranged from 80-90%.

Synthetic Scheme L: ***General procedure for compounds L***

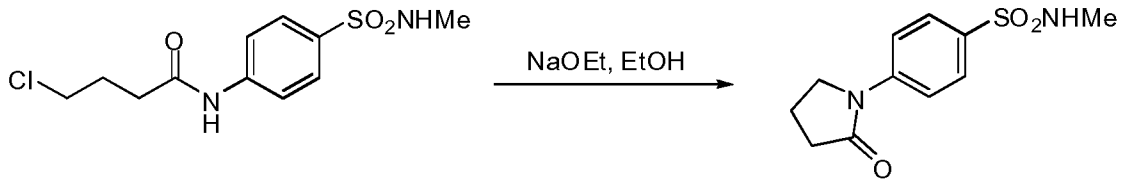


L

[00272] To a solution of 2-(methylsulfonamido)benzoic acid (1.0 eq) in DMF was added **sm-14** (1.0 eq), DIPEA (1.5 eq) and HATU (1.3 eq). The mixture was stirred at 10-15 °C for 16-24 h. Upon reaction completion as indicated by TLC, the reaction mixture was concentrated, and the solid was purified by silica gel chromatography to afford compound **L**.

[00273] Select compounds in Table 1 were obtained using Synthetic Scheme L.

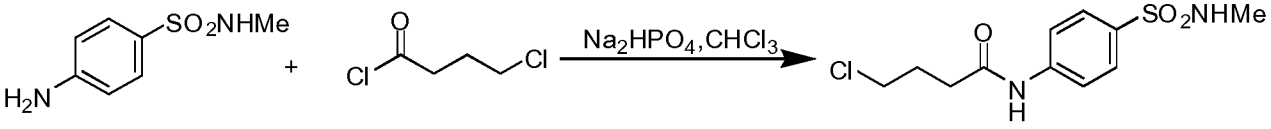
Synthetic Scheme for Compound 28:



sm-15 **28**

[00274] A solution of compound **I** (320 g, 1.1 mmol) in EtOH (10 mL) was added dropwisely NaOEt (571.6 mg, 8.4 mmol) at 0 °C for 3 h. The reaction was acidific with 1N HCl and removed the solvent to get the crude product. The residue was purified by pre-HPLC (0.1% TFA as additive), most CH_3CN was removed by evaporation under reduced pressure, and the remained solvent was removed by hyophilization to afford the compound **28** (17 mg, 6% yield) as white solid. LCMS: Found 255.0 [M+H]. ^{1}H NMR (400 MHz, $CDCl_3$): 7.50-7.72 (m, 4H), 4.85 (br s, 1H), 3.90 (t, 2H, *J* = 7.2 Hz), 2.53-2.72 (m, 5H), 2.14-2.28 (m, 2H).

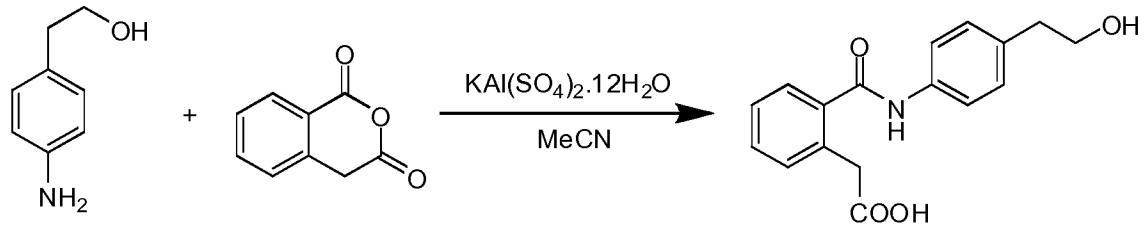
[00275] The intermediate **sm-15** was made by the following procedure.



sm-15

[00276] To a solution of 4-amino-*N*-methylbenzenesulfonamide (200 mg, 1.1 mmol) and Na_2HPO_4 (300 mg, 2.2 mmol) in $CHCl_3$ (10 mL) was added 4-chlorobutanoyl chloride (151 mg, 1.1 mol) drop-wise at 0 °C. After reagent addition, the mixture was allowed to stir at room temperature. The mixture was concentrated to give crude **sm-15**, which was used directly in the next step without further purification.

Synthetic Scheme for Compound 47:



47

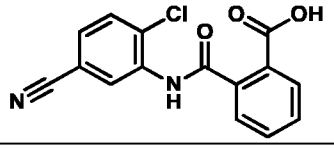
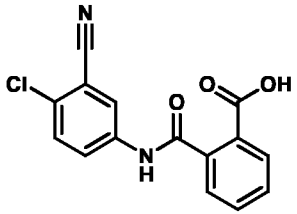
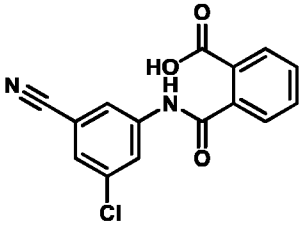
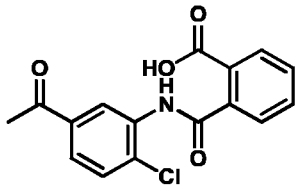
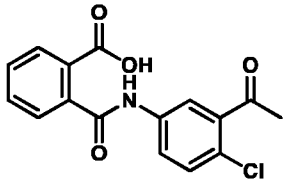
[00277] A solution of 2-(4-aminophenyl)ethanol (300 mg, 2.2 mmol), isochroman-1,3-dione (355 mg, 2.2 mmol) and $KAl(SO_4)_2$-$12H_2O$ (522 mg, 11 mmol) in MeCN (10 mL) was stirred at room temperature for 1-1.5 h. The solvent was removed to obtain crude product. The residue was purified by prep-HPLC (0.1% TFA as additive). Solvents were removed by evaporation under reduced pressure and lyophilization to afford compound **47** (25 mg, 5.5% yield) as a white solid. LCMS: Found 300.1 [M+H].

Biological Examples

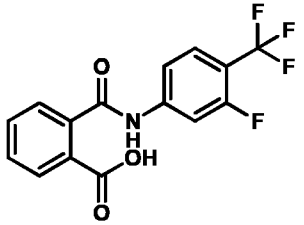
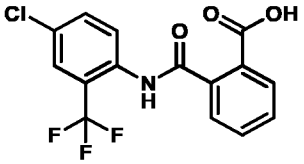
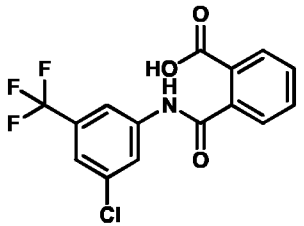
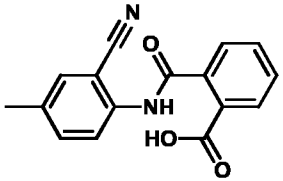
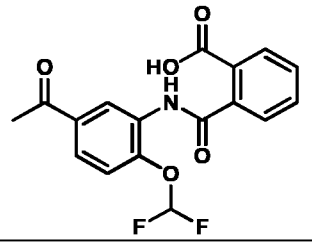
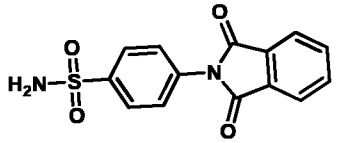
EXAMPLE 1: Human chondrocyte differentiation assay

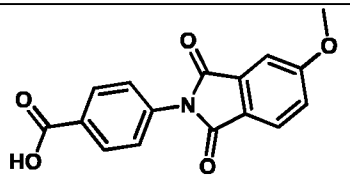
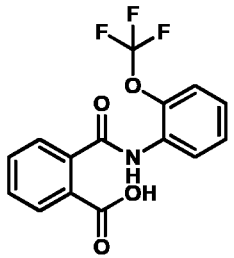
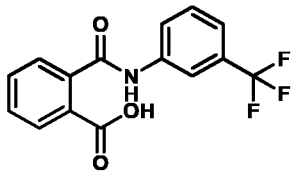
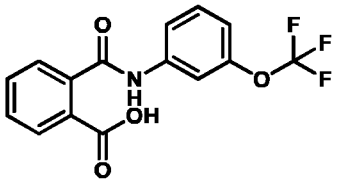
[00278] Human MSCs (50,000) were plated into each well of a 96-well plate and cultured overnight. Compounds (in DMSO solution) were added to the cells at a final concentration of 1 μM, and the cells were cultured for 7 days at 5% CO_2, 37°C. The cells were fixed with 10% formalin solution at room temperature for 10 min, and immunostained using antibodies specific for type II collagen (Abcam), Sox9 (Santa Cruz) and cartilage oligomeric matrix protein (COMP, Santa Cruz), and fluorescently labeled secondary antibodies (Li-Cor). The total intensity of the staining was measured using Oddyssey CLx imaging system (Li-Cor). Vehicle (DMSO) was used as control to determine the basal level of chondrocyte differentiation. Compounds exhibiting 30% or higher increase in staining intensity compared to vehicle control were selected as active hits. Representative data are shown in Table 1 [A: >50% increase in staining intensity compared to vehicle control; B: 30-50% increase in staining intensity compared to vehicle control].

TABLE 1

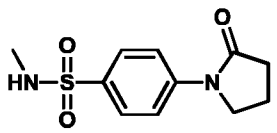
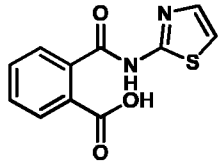
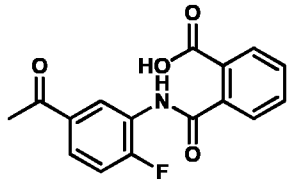
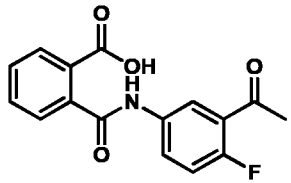
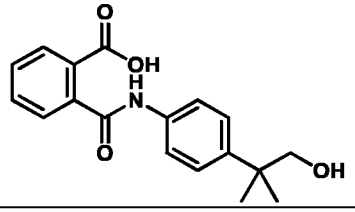
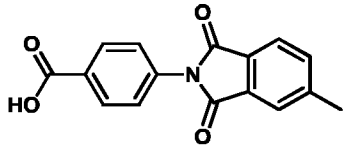
Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
1		A	LCMS: Found 301.0 [M-H]	B
2		A	LCMS: Found 301.0 [M-H] LCMS: Found 323.0 [M+Na]	B
3		A	LCMS: Found 301.0 [M-H]	A
4		A	LCMS: Found 318.0 [M-H] LCMS: Found 340.0 [M+Na]	A
5		A	LCMS: Found 318.0 [M-H] LCMS: Found 340.0 [M+Na]	B

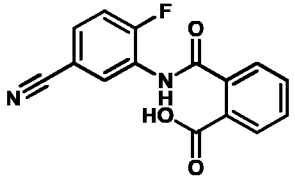
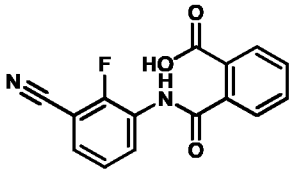
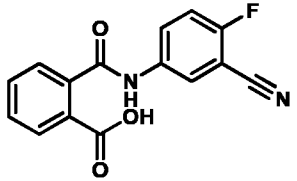
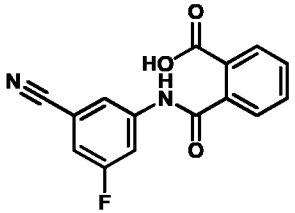
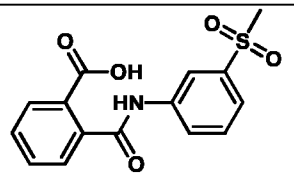
Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
6		A	LCMS: Found 297.0 [M·H] LCMS: Found 615.2 [2M+Na]	A
7		A	LCMS: Found 297.0 [M−H] LCMS: Found 615.2 [2M+Na]	A
8		A	LCMS: Found 301.1 [M·H] LCMS: Found 322.9 [M+Na] ^{1}H NMR (400 MHz, DMSO-d_6): 13.19 (S, 1H), 10.72 (S, 1H), 8.05 (D, J 2.5Hz, 1H), 7.94 (DD, J 7.7, 1.3Hz, 1H), 7.84 (DD, J 8.8, 2.5Hz, 1H), 7.72-7.55 (M, 4H)	B
9		A	LCMS: Found 335.0 [M+H] LCMS: Found 691.0 [2M·Na] LCMS: Found 357.0 [M+Na]	A

Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
10		A	LCMS: Found 328 [M−H] LCMS: Found 350 [M−Na] LCMS: Found 677 [2M · Na]	B
11		A	LCMS: Found 344 [M · H] LCMS: Found 366 [M · Na] ^{1}H NMR (400 MHz, DMSO-d_6): 13.19 (S, 1H), 10.19 (S, 1H), 7.93-7.86 (M, 3H), 7.71- 7.58(M, 4H)	B
12		A	LCMS: Found 344 [M+H]	B
13		A	LCMS: Found 281.0 [M+H]	B
14		A	LCMS: Found 350 [M · H] LCMS: Found 372 [M · Na]	B
15		B-1	LCMS: Found 303.0 [M · H] ^{1}H NMR (400 MHz, DMSO-d_6): 7.10-7.36 (M, 6H),	B

Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
			6.56-6.70 (M, 2H), 6.62 (br s, 2H)	
16		B-1	LCMS: Found 298.0 [M·H]	A
17		A	LCMS: Found 326 [M+H] LCMS: Found 348 [M·Na]	B
18		A	LCMS: Found 308.0 [M-H] NEG ^{1}H NMR (400 MHz, DMSO-d_6): 13.12 (S, 1H), 10.69 (S, 1H), 8.21 (S, 1H), 7.93-7.85 (M, 2H), 7.71-7.67 (M, 1H), 7.63-7.61 (M 3H), 7.46-7.44 (M, 1H)	A
19		A	LCMS: Found 326 [M+H] LCMS: Found 348 [M·Na] LCMS: Found 673 [2M·Na] ^{1}H NMR (400 MHz, DMSO-d_6): 13.05 (S, 1H), 10.65 (S, 1H), 7.92-7.87 (M, 2H), 7.69-7.45 (M, 5H), 7.09-7.07 (D, J=8 Hz, 1H)	A

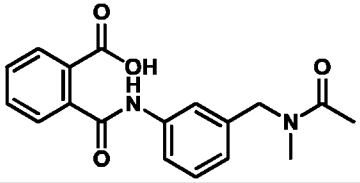
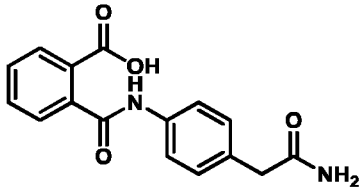
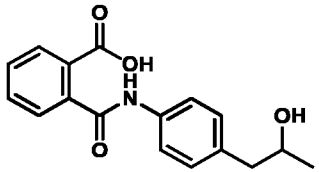
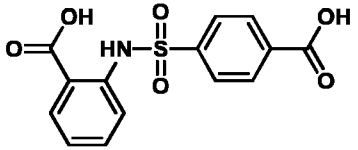
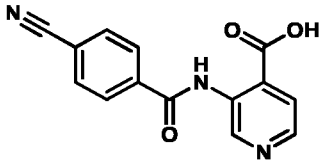
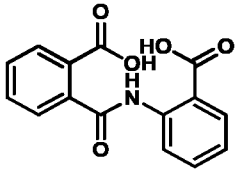
Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
21		A	LCMS: Found 300 [M+H] LCMS: Found 322 [M·Na] LCMS: Found 622 [2M−Na]	A
22		A	LCMS: Found 263.1 [M+H] LCMS: Found 571.1 [2M·Na]	B
23		C	LCMS: Found 314.0 [M·Na] LCMS: Found 292.0 [M·H]	A
24		D	LCMS: Found 277.2 [M·H] LCMS: Found 299.1 [M·Na]	A
25		C	LCMS: Found 278.0 [M·H] LCMS: Found 300.0 [M·Na]	B
26		B-2	LCMS: Found 289.1 [M·H]	B
27		B-2	LCMS: Found 303.1 [M·H]	A

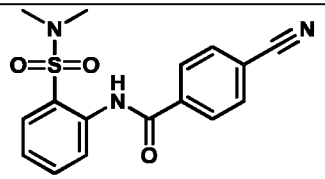
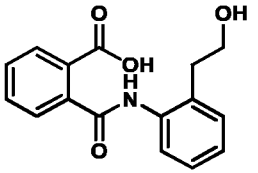
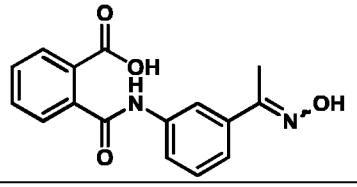
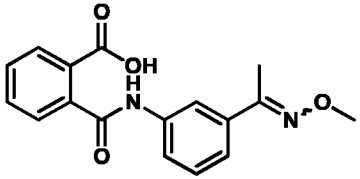
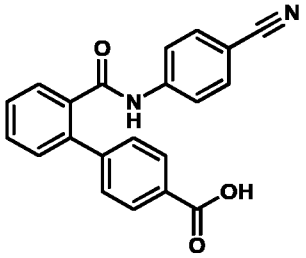
Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
28		28	LCMS: Found 255.0 [M+H] ^{1}H NMR (400 MHz, $CDCl_3$): 7.50-7.72 (M, 4H), 4.85 (br s, 1H), 3.90 (T, 2H, J 7.2 Hz), 2.53-2.72 (M, 5H), 2.14-2.28 (M, 2H)	B
29		A	LCMS: Found 249 [M+H] LCMS: Found 271 [M−Na]	B
30		A	LCMS: Found 302 [M+H] LCMS: Found 324 [M·Na] LCMS: Found 625 [2M·Na]	B
31		A	LCMS: Found 302 [M+H] LCMS: Found 324 [M·Na] LCMS: Found 625 [2M·Na]	B
32		A	LCMS: Found 314 [M+H]	B
33		B-1	LCMS: Found 282.2 [M·H]	B

Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
34		A	LCMS: Found 307 [M−Na] LCMS: Found 591 [2M · Na]	B
35		A	LCMS: Found 307 [M · Na] LCMS: Found 591 [2M · Na] ^{1}H NMR (400 MHz, DMSO-d_6): 13.15 (S, 1H), 10.54 (S, 1H), 8.21-8.19 (D, J 7.6 Hz, 1H), 7.92-7.90 (D, J=7.6 Hz, 1H), 7.72-7.44 (M, 5H)	B
36		A	LCMS: Found 284 [M+H] LCMS: Found 307 [M · Na] LCMS: Found 591 [2M · Na]	B
37		A	LCMS: Found 284 [M+H] LCMS: Found 307 [M · Na] LCMS: Found 591 [2M · Na] ^{1}H NMR (400 MHz, DMSO-d_6): 13.23 (S, 1H), 10.91 (S, 1H), 7.95-7.88 (S, 3H), 7.71-7.69 (M, 1H), 7.65-7.58 (M, 3H)	A
38		A	LCMS: Found 320.0 [M · H] LCMS: Found 342.0 [M · Na] LCMS: Found 661.0 [2M · Na]	B

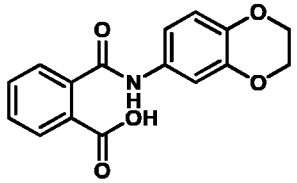
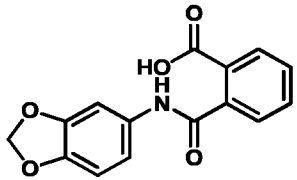
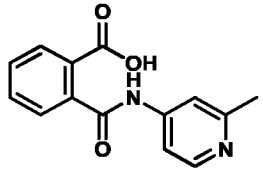
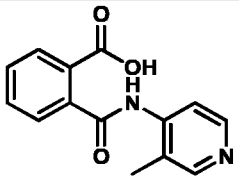
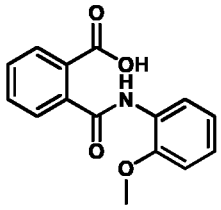
Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
39		D	LCMS: Found 277.1 [M+H] LCMS: Found 299.1 [M+Na] ^{1}H NMR (400 MHz, DMSO-d_6): 8.60 (S, 1H), 8.47 (S, 1H), 8.29 (D, 1H), 8.13 (D, 1H), 7.78-7.49 (M, 5H), 5.13-5.10 (M, 1H), 3.80 (DD, 1H), 3.41 (DD, 1H)	B
40		C	LCMS: Found 278.1 [M+H]	B
41		C	LCMS: Found 287.1 [M+H] LCMS: Found 309.0 [M+Na] ^{1}H NMR (400 MHz, DMSO-d_6): 7.87-7.75 (M, 4H), 7.64-7.45 (M, 4H), 6.09 (M, 1H), 3.86 (DD, 1H), 3.62 (DD, 1H)	A
42		D	LCMS: Found 320.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 8.61 (S, 1H), 8.20 (D, J 8.1Hz, 2H), 7.92 (D, J 8.2Hz, 2H), 7.69-7.59 (M, 3H), 7.50 (TD, J 7.3, 1.3Hz, 1H), 5.13(DD, J 8.0, 4.4Hz, 1H), 3.80(DD, J 18.1, 4.4Hz, 1H), 3.43(DD, J=18.1, 8.1Hz, 1H)	B
43		C	LCMS: Found 311.0 [M+H] LCMS: Found 333.0 [M+Na]	B

Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
44		C	LCMS: Found 331.0 [M+H] LCMS: Found 353.0 [M·Na]	B
45		H	LCMS: Found 330.0 [M·H] LCMS: Found 352.0 [M−Na]	B
46		H	LCMS: Found 369.0 [M·H] LCMS: Found 391.0 [M·Na]	B
47		47	LCMS: Found 300.1 [M·H]	B
48		A	LCMS: Found 272.0 [M·H] LCMS: Found 294.0 [M·Na] LCMS: Found 565.1 [2M·Na]	B
49		A	LCMS: Found 365.0 [M·Na] LCMS: Found 707.2 [2M+Na]	B

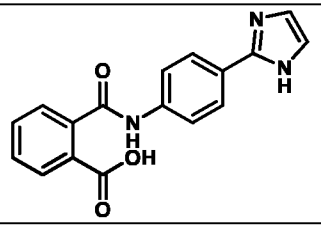
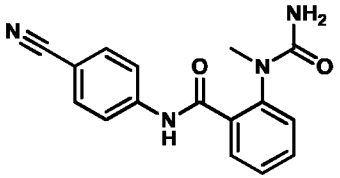
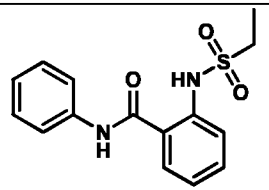
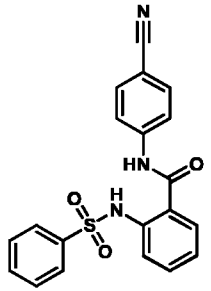
Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
50		A	LCMS: Found 349.1 [M·Na]	B
51		A	LCMS: Found 299.1 [M·H] LCMS: Found 321.0 [M−Na] ^{1}H NMR (400 MHz, DMSO-d_6): 13.03 (S, 1H), 10.29 (S, 1H), 7.88 (T, 1H), 7.62 (M, 5 H), 7.43 (S, 1H), 7.22 (D, J 8.4 Hz, 1H), 6.86 (S, 1H), 3.17 (S, 2H)	B
52		A	LCMS: Found 300.1 [M·H] LCMS: Found 322.0 [M·Na]	B
53		E	LCMS: Found 322.0 [M·H] LCMS: Found 344.0 [M·Na]	B
54		F	LCMS: Found 268.1 [M·H]	B
55		A	LCMS: Found 289.0 [M·H] LCMS: Found 308.0 [M·Na] LCMS: Found 593.0 [2M·Na] ^{1}H NMR (400 MHz, MeOD): 8.71 (D, J 8 Hz, 1H),	A

Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
			8.13 (M, 1H), 8.01 (D, J 8 Hz, 1H), 7.65 (M, 4H), 7.20 (M, 1H)	
56		G	LCMS: Found 330.1 [M·H]	A
57		A	LCMS: Found 286.2 [M·H] LCMS: Found 308.1 [M·Na] LCMS: Found 593.3 [2M·Na]	B
58		A	LCMS: Found 299.2 [M·H] LCMS: Found 321.2 [M·Na] LCMS: Found 619.1 [2M·Na]	B
59		A	LCMS: Found 313.1 [M·H] LCMS: Found 335.0 [M·Na] LCMS: Found 647.1 [2M·Na]	B
60		I	LCMS: Found 343.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.00 (br s, 1H), 10.72 (br s, 1H), 8.03 (S, 1H), 7.82-7.91 (M, 1H), 7.58-7.80 (M, 7H), 7.42-7.58 (M, 3H)	A

Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
61		I	LCMS: Found 343.1 [M−H]	A
62		G	LCMS: Found 372.2 [M·H] LCMS: Found 394.1 [M·Na]	A
63		A	LCMS: Found 249 [M+H] LCMS: Found 271 [M·Na]	A

Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
64		A	LCMS: Found 300.2 [M·H] LCMS: Found 621.2 [2M−Na] ^{1}H NMR (400 MHz, DMSO-d_6): 12.99 (S, 1H), 10.13 (S, 1H), 7.86 (M, 1H), 7.63 (M, 1H), 7.51 (M, 2H), 7.31 (S, 1H), 7.07 (M, 1H), 6.80 (D, J = 8.4 Hz, 1H), 4.23 (M, 4H)	B
65		A	LCMS: Found 286.2 [M·H] LCMS: Found 593.2 [2M·Na]	A
66		A	LCMS: Found 257.0 [M·H]	B
67		A	LCMS: Found 257.0 [M·H]	A
68		A	LCMS: Found 272.0 [M·H] LCMS: Found 294.0 [M·Na] LCMS: Found 565.1 [2M·Na] ^{1}H NMR (400 MHz, DMSO-d_6): 9.37 (S, 1H), 7.98 (D, J 7.6 Hz, 1H), 7.85 (D, J 7.6 Hz, 1H), 7.65 (M, 1H), 7.58 (M, 2H), 7.15 (M, 1H), 7.07 (M, 1H), 6.98 (M,	A

Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
			1H)	
69		A	LCMS: Found 392.1 [M−H] LCMS: Found 414.1 [M·Na]	B
70		A	LCMS: Found 267.1 [M·H]	A
71		A	LCMS: Found 271.0 [M·H]	A
72		A	LCMS: Found 349.0 [M·H] LCMS: Found 371.0 [M·Na] ^{1}H NMR (400 MHz, DMSO-d_6): 10.38 (S, 1H), 7.89 (T, 1H), 7.23 (S, 1H), 7.66 (M, 1H), 7.58 (M, 4H), 7.07 (D, J 7.6 Hz, 1H), 4.15 (D, J 6 Hz, 2H), 2.89 (S, 3H)	A
73		A	LCMS: Found 363.0 [M·H] LCMS: Found 385.0 [M·Na] LCMS: Found 747.0 [2M·Na] ^{1}H NMR (400 MHz, DMSO-d_6): 13.02 (S, 1H), 10.41	A

Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
			(S, 1H), 7.87 (D, J 7.2 Hz, 1H), 7.65 (M, 3H), 7.35 (T, 1H), 7.04 (D, J = 7.6 Hz, 1H), 4.21 (S, 1H), 2.96 (S, 1H), 2.67 (S, 1H)	
74		A	LCMS: Found 308.2 [M·H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.53 (S, 1H), 7.88 (D, J 8.4 Hz, 3H), 7.56 (D, J 8.8 Hz, 2H), 7.65 (M, 1H), 7.59 (M, 2H), 7.10 (S, 1H)	B
75		F	LCMS: Found 295.1 [M·H] LCMS: Found 317.1 [M·Na] ^{1}H NMR (400 MHz, $CDCl_3$):) 9.47 (br s, 1 H), 7.86 (D, 1H), 7.79 (D, 2H), 7.57 - 7.66 (M, 3H), 7.48 - 7.54 (M, 1H), 7.31 (D, 1H), 4.74 (br s, 2H), 3.25 (S, 3H)	B
76		H	LCMS: Found 330.1 [M·H]	B
77		H	LCMS: Found 378.1 [M·H]	A

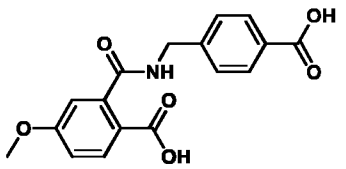
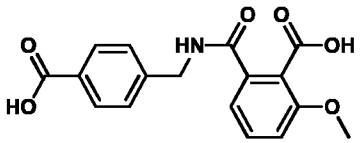
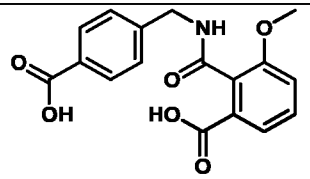
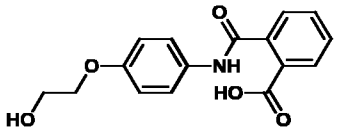
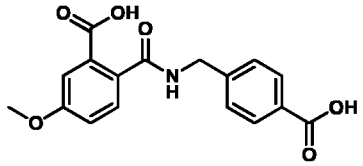
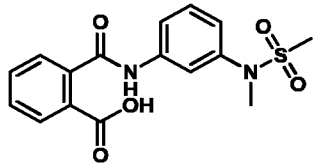
Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
78		H	LCMS: Found 330.1 [M·H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.70 (S, 1H), 7.90 (D, 2H), 7.82 (D, 2H), 7.64-7.49 (M, 4H), 3.26 (S, 3H), 3.00 (S, 3H)	B
79		H	LCMS: Found 360.1 [M−H] ^{1}H NMR (400 MHz, CDCl3) 10.85 (S, 1H), 9.97 (S, 1H), 7.94 (D, 2H), 7.84 (D, 2H), 7.59 – 7.63 (M, 2H), 7.30 - 7.32 (M, 1H), 3.61 - 3.64 (M, 2H), 3.44 - 3.47 (M, 2H), 3.06 (S, 3H)	B
80		A	LCMS: Found 233.1 [M·H] LCMS: Found 255.1 [M·Na] LCMS: Found 487.0 [2M·Na]	B
81		A	LCMS: Found 286.0 [M·H] LCMS: Found 308.0 [M·Na]	B
82		A	LCMS: Found 246.2 [M·H] LCMS: Found 513.2 [2M·Na]	A

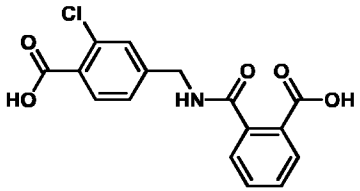
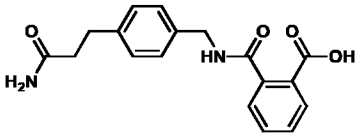
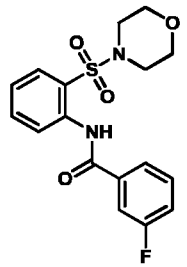
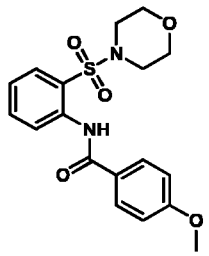
Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
83		A	LCMS: Found 340.0 [M−H] LCMS: Found 362.0 [M−Na] LCMS: Found 701.1 [2M·Na]	A
84		A	LCMS: Found 300.2 [M−H] LCMS: Found 322.1 [M·Na] ^{1}H NMR (400 MHz, DMSO-d_6): 10.24 (S, 1H), 7.84 (D, J 6.8 Hz, 1H), 7.56 (M, 4H), 7.15 (D, J = 8.8 Hz, 1H), 4.61 (T, 1H), 3.47 (M, 1H), 2.75 (M, 1H), 1.14 (D, J = 6.8 Hz, 3H)	A
85		A	LCMS: Found 274.2 [M·H] LCMS: Found 296.1 [M·Na]	B
86		A	LCMS: Found 322.1 [M·H] LCMS: Found 344.0 [M+Na]	B
87		A	LCMS: Found 302.0 [M·H] LCMS: Found 625.1 [2M·Na]	B

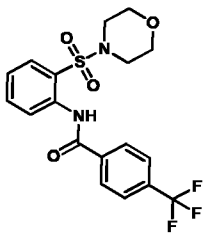
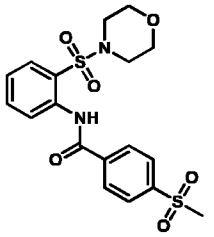
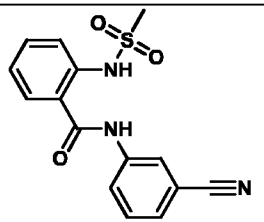
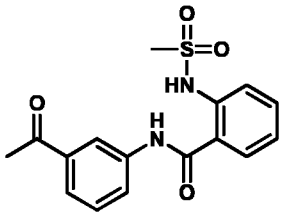
Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
88		A	LCMS: Found 297.1 [M·H] LCMS: Found 316.0 [M–Na] ^{1}H NMR (400 MHz, CD_3OD): 8.06-8.04 (D, 1H), 7.75-7.65 (M, 2H), 7.61-7.53 (M, 3H), 7.24-7.24 (D, 2H), 3.95 (S, 3H)	-
89		A	LCMS: Found 461.0 [M·Na] ^{1}H NMR (400 MHz, CD_3OD): 8.05 (D,1H), 7.69-7.57 (M, 5H), 7.46-7.35 (M, 6H), 7.20 (D, 1H), 4.45 (S, 2H), 4.16 (S, 2H), 2.69 (S, 3H).	-
90		A	LCMS: Found 377.0 [M·H], LCMS: Found 399.0 [M·Na] ^{1}H NMR (400 MHz, CD_3OD): 8.05 (D,1H), 7.72-7.57 (M, 5H), 7.37 (T, 1H), 7.18 (D, 1H), 4.39 (S, 2H), 3.15 (Q, 2H), 2.81 (S, 3H), 1.38 (T, 3H).	-
91		A	LCMS: Found 335.1 [M·H]	-

Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
92		A	LCMS: Found 318.1 [M·H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.05 (br s, 2H), 9.04-8.98 (M, 1H), 7.92-7.88 (D, 2H), 7.58-7.45 (M, 3H), 7.37-7.33 (M, 1H), 4.50(D, 2H)	-
93		A	LCMS: Found 318.1 [M−H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.20 (br s, 2H), 9.03 (S, 1H), 7.90 (D, 2H), 7.74 (D, 1H), 7.55-7.50 (M, 4H), 4.52(D, 2H)	B
94		A	LCMS: Found 318.1 [M·H]	B
95		A	LCMS: Found 318.1 [M·H]	-
96		A	LCMS: Found 334.0 [M·H]	B

Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
97		A	LCMS: Found 334.0 [M·H] ^{1}H NMR (400 MHz, DMSO-d_6): 9.74 (br s, 1H), 9.39 (br s, 1H), 7.90 (D, 2H), 7.59-7.56(M, 3H), 7.51-7.47 (M, 2H), 4.50(D, 2H)	-
98		A	LCMS: Found 377.0 [M·H], LCMS: Found 399.0 [M−Na] ^{1}H NMR (400 MHz, CD_3OD): 8.05 (D,1H), 7.76-7.57 (M, 5H), 7.37 (T, 1H), 7.20 (D, 1H), 4.43 (S, 2H), 3.32-3.27 (M, 2H), 2.96 (S, 3H), 1.15 (T, 3H).	-
99		A	LCMS: Found 334.0 [M·H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.10 (br s, 2H), 8.93-8.90(M, 1H), 7.90 (D, 2H), 7.74 (D, 1H), 7.56-7.51 (M, 3H), 4.51(D, 2H)	B
100		A	LCMS: Found 334.0 [M·H]	B
101		A	LCMS: Found 334.1 [M·H]	-

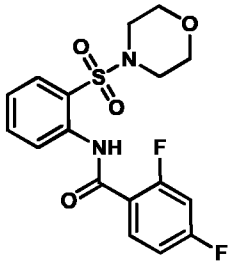
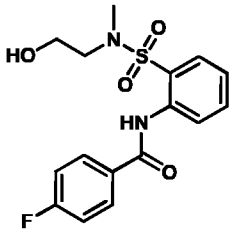
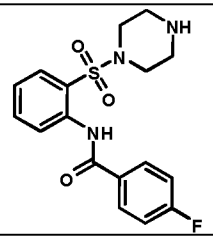
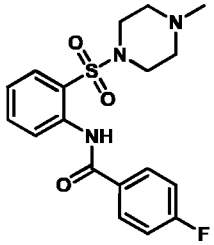
Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
102		A	LCMS: Found 330.1 [M-H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.96 (br s, 2H), 7.90 (D, 2H), 7.51-7.47 (M, 3H), 7.19 (D, 1H), 7.10 (DD, 1H), 4.49 (D, 2H), 3.82 (S,3H)	-
103		A	LCMS: Found 330.0 [M-H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.90 (br s, 2H), 8.65(T, 1H), 7.91 (D, 2H), 7.54 (D, 2H), 7.45 (D, 2H), 7.32 (DD, 1H), 4.48 (D, 1H), 3.83 (S,3H)	A
104		A	LCMS: Found 330.0 [M-H]	A
105		A	LCMS: Found 302.1 [M-H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.98 (br s, 1H), 10.19 (S, 1H), 7.86 (D, 1H), 7.67-7.52 (M, 5H), 6.91 (D, 2H), 4.87(br s, 1H), 3.96 (T, 2H), 3.71 (Q, 2H)	B
106		A	LCMS: Found 330.1 [M-H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.80 (br s, 2H), 7.90 (D, 2H), 7.81 (D, 1H), 7.52 (D, 2H), 7.05 (DD, 1H), 6.95(D, 1H), 4.49(D, 2H), 3.85(S,3H)	B
107		A	LCMS: Found 349.0 [M-H], LCMS: Found 371.0 [M-Na] ^{1}H NMR (400 MHz, CD_3OD): 8.06 (D,1H), 7.83 (S,	B

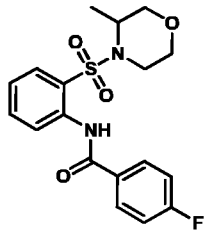
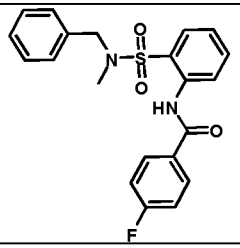
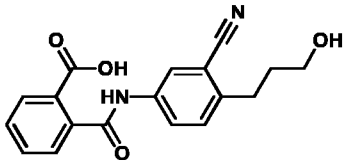
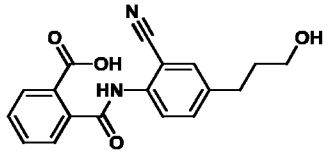
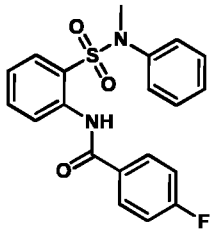
Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
			1H), 7.69-7.56 (M, 4H), 7.39 (T, 1H), 7.23 (D, 1H), 3.32 (S, 3H), 2.95 (S, 3H).	
108		A	LCMS: Found 334.1 [M·H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.18 (br s, 2H), 9.01 (S, 1H), 7.92 (D, 1H), 7.88 (DD, 1H), 7.80 (DD, 1H), 7.71 (D,1H), 7.63-7.53(M, 3H), 4.53(D, 2H)	-
109		A	LCMS: Found 327.2 [M·H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.98 (br s, 1H), 8.81 (S, 1H), 7.76 (D, 2H), 7.58-7.44 (M, 3H), 7.28 (D, 2H), 7.15 (D, 2H), 4.40(D, 2H), 2.77(Q, 2H), 2.34(Q,2H)	-
110		G	LCMS: Found 365.2 [M·H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.50 (S, 1H), 8.76 (D, 1H), 7.82-7.70 (M, 4H), 7.54-7.53 (M, 1H), 7.34 - 7.30 (m, 2H), 3.71 - 3.69 (m, 4H), 3.05-3.03 (m, 4H).	B
111		G	LCMS: Found 377.2 [M·H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.38 (S, 1H), 8.74 (D, 1H), 7.94-8.07 (M, 2H), 7.80 (D, 1H), 7.68 (D, 1H), 7.25 - 7.31 (M, 1H), 6.95-7.14 (M, 2H), 3.91 (S, 3H), 3.62 - 3.72 (M, 4H), 2.96-3.11 (M, 4H).	-

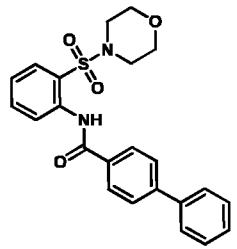
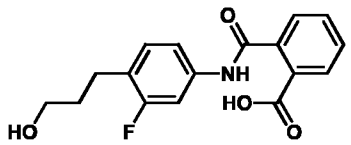
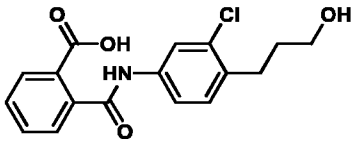
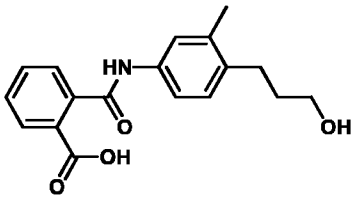
Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
112		G	LCMS: Found 415.1 [M-H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.62 (S, 1H), 8.78 (D, 1H), 8.14 (D, 2H), 7.84-7.82 (M, 3H), 7.51-7.46 (M, 1H), 7.36-7.32 (M, 1H), 3.72 - 3.69 (M, 4H), 3.05-3.03 (M, 4H).	-
113		G	LCMS: Found 425.1 [M-H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.68 (S, 1H), 8.78 (D, 1H), 8.22 (D, 2H), 8.14 (D, 2H), 7.81 (D, 1H), 7.76-7.68 (M, 1H), 7.37-7.33 (M, 1H), 3.73 - 3.70 (M, 4H), 3.05-3.03 (M, 4H).	A
114		L	LCMS: Found 316.1 [M-H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.76 (S, 1H), 9.98 (S, 1H), 8.21 (S, 1H), 7.98 (T, 1H), 7.83 (D, 1H), 7.62-7.57 (M,4H), 7.32(T, 1H), 3.12(S, 3H)	-
115		L	LCMS: Found 333.1 [M-H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.70 (br s, 1H), 10.18 (br s, 1H), 8.33 (S, 1H), 7.99 (D, 1H), 7.89 (D, 1H), 7.76 (D, 1H), 7.58-7.52 (M, 3H), 7.30(T, 1H), 3.13(S, 3H), 2.60(S, 3H)	-

Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
116		L	LCMS: Found 346.1 [M−H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.60 (S, 1H), 10.16 (S, 1H), 8.07 (S, 1H), 7.90 (DD, 2H), 7.59-7.57 (M, 2H), 7.31-7.29 (M, 2H), 3.92(S, 3H), 3.12(S, 3H)	-
117		L	LCMS: Found 349.2 [M·H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.44 (S, 1H), 10.29 (S, 1H), 7.88 (D, 1H), 7.64-7.55 (M, 4H), 7.31-7.22 (M, 3H), 3.52 (Q, 2H), 3.25 (S, 3H), 3.13 (S, 3H), 2.79 (Q,2H)	A
118		G	LCMS: Found 365.1 [M·H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.40 (D, 1H), 8.67 (D, 1H), 8.14-8.10 (M, 2H), 7.87 (D, 1H), 7.72-7.68 (M, 1H), 7.61-7.55 (M, 1H), 7.36-7.30 (M, 4H), 3.71 - 3.68 (M, 4H), 3.10-3.07 (M, 4H).	B
119		L	LCMS: Found 349.1 [M·H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.31 (br s, 2H), 7.90 (D, 1H), 7.62 (D, 2H), 7.53 (S, 2H), 7.20-7.18 (M, 3H), 4.49-4.46 (M, 1H), 3.43-3.39(M, 2H), 3.08(S, 3H), 2.65-2.55(M, 2H), 1.74-1.67 (M, 2H)	-

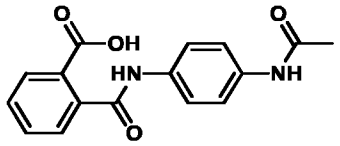
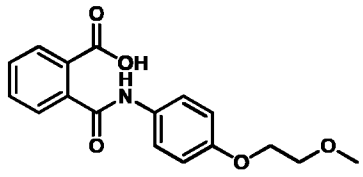
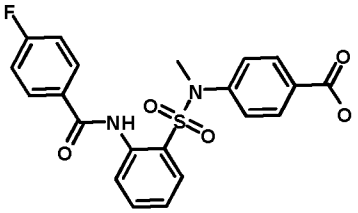
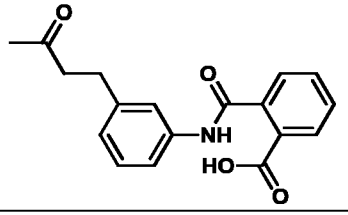
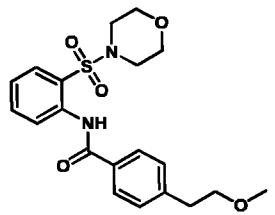
Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
120		L	LCMS: Found 349.1 [M·H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.91 (br s, 1H), 11.13 (br s, 1H), 9.51 (T, 1H), 7.94-7.91 (M, 3H), 7.57 (S, 2H), 7.46 (D, 2H), 7.24-7.21 (M, 1H), 4.56(D, 2H), 3.12(S, 3H)	B
121		J	LCMS: Found 372.1 [M·H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.37 (S, 1H), 8.37 (S, 1H), 8.26 (M, 1H), 8.14-8.12 (M, 2H), 7.86-7.79 (M, 3H), 7.52 (M, 1H), 3.56-3.54 (T, 4H), 2.83-2.86 (T, 4H)	-
122		J	LCMS: Found 389.1 [M·H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.42 (S, 1H), 8.51 (S, 1H), 8.30 (D, 1H), 8.23-8.19 (M, 2H), 7.87-7.74 (M, 3H), 7.50 (T, 1H), 3.57-3.55 (M, 4H), 2.92-2.89 (M, 4H), 2.67 (S,3H)	A
123		J	LCMS: Found 365.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.27 (S, 1H), 8.30 (D, 1H), 8.05-8.01 (M, 2H), 7.84-7.80 (M, 2H), 7.47-7.41 (M, 3H), 3.62-3.55 (M, 4H), 2.95-2.88 (M, 4H)	A

Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
124		G	LCMS: Found 383.1 [M-H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.36 (D, 1H), 8.64 (D, 1H), 8.20-8.14 (M, 1H), 7.85 (D, 1H), 7.69 (T, 1H), 7.35-7.29 (M, 2H), 7.10-6.95 (M, 2H), 3.71 - 3.69 (M, 4H), 3.09-3.06 (M, 4H).	-
125		G	LCMS: Found 353.1 [M-H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.40 (S, 1H), 8.66 (D, 1H), 8.07-8.04 (M, 2H), 7.85 (D, 1H), 7.60 (T, 1H), 7.32-7.20 (M, 3H), 3.73 - 3.71 (M, 2H), 3.25-3.23 (M, 2H), 2.86 (S, 3H).	B
126		G	LCMS: Found 364.2 [M-H] ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD): 8.60 (D, 1H), 7.97-7.94 (M, 2H), 7.80 (D, 1H), 7.70 (T, 1H), 7.32-7.16 (M, 3H), 3.37 - 3.33 (M, 4H), 3.18-3.15 (M, 4H).	-
127		G	LCMS: Found 378.2 [M-H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.17 (S,1H), 8.73 (D, 1H), 8.03-8.00 (M, 2H), 7.80 (D, 1H), 7.74 (T, 1H), 7.35-7.22 (M, 3H), 3.81 (br s, 2H), 3.56 (br s, 2H), 3.29 (br s, 2H), 2.90 (br s, 2H), 2.81 (S, 3H).	-

Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
128		G	LCMS: Found 379.2 [M-H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.28 (S,1H), 8.64 (D, 1H), 8.06-8.03 (M, 2H), 7.89 (D, 1H), 7.65 (T, 1H), 7.30-7.21 (M, 3H), 3.87-3.85 (M, 1H), 3.75 (D, 1H), 3.55-3.26 (M, 5H), 1.19 (D, 3H).	A
129		G	LCMS: Found 399.2 [M-H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.55 (S,1H), 8.76 (D, 1H), 8.05-8.02 (M, 2H), 7.90 (D, 1H), 7.69 (T, 1H), 7.33-7.17 (M, 8H), 4.19 (S, 2H), 2.63 (S, 3H).	-
130		A	LCMS: Found 325.1 [M-H]	-
131		A	LCMS: Found 325.1 [M-H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.15 (br s, 1H), 10.58 (S, 1H), 7.92 (D, 1H), 7.72-7.53 (M, 6H), 4.54 (T,1H), 4.42-4.39 (M, 2H), 2.68-2.65 (M, 2H), 1.76-1.69 (M, 2H)	-
132		G	LCMS: Found 385.1 [M-H] ^{1}H NMR (400 MHz, $CDCl_3$): 9.84 (S,1H), 8.63 (D, 1H), 7.89 (D, 1H), 7.67-7.59 (M, 3H), 7.30-7.28 (M, 1H), 7.11-7.05 (M, 6H), 6.95-6.93 (M, 1H), 3.19 (S, 3H).	-

Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
133		G	LCMS: Found 423.1 [M+H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.54 (S,1H), 8.79 (D, 1H), 8.10 (D, 2H), 7.83-7.66 (M, 6H), 7.54-7.42 (M, 3H), 7.33-7.29 (M, 1H), 3.71-3.69 (M, 4H), 3.07-3.05 (M, 4H).	B
134		A	LCMS: Found 318.2 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.10 (br s, 1H), 10.49 (S, 1H), 7.89 (D, 1H), 7.63-7.53 (M, 4H), 7.31(D, 2H), 7.23 (T, 1H), 4.51 (T, 1H), 3.45-3.42 (M, 2H), 2.62-2.58 (M, 2H), 1.71-1.65 (M, 2H)	-
135		A	LCMS: Found 334.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.09 (br s, 1H), 10.44 (S, 1H), 7.90-7.84 (M, 2H), 7.67-7.49 (M, 4H), 7.28(D, 2H), 4.53 (T, 1H), 3.46-3.42 (M, 2H), 2.70-2.66 (M, 2H), 1.73-1.66 (M, 2H)	-
136		A	LCMS: Found 314.1 [M+H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.17 (S, 1H), 7.86-7.84 (D, 1H), 7.63-7.62 (D, 1H), 7.55-7.47 (M, 3H), 7.40-7.35 (D, 1H), 7.06-7.04 (D, 1H), 4.49-4.47 (T, 1H), 3.45-3.41 (M, 2H), 2.57-2.53 (M, 2H), 2.24 (S, 3H), 1.67-1.60 (M, 2H)	-

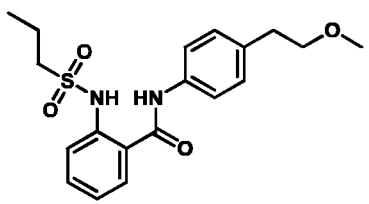
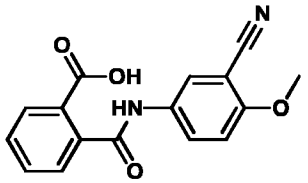
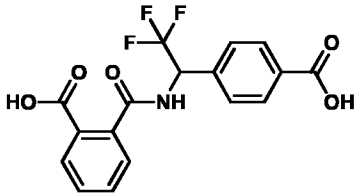
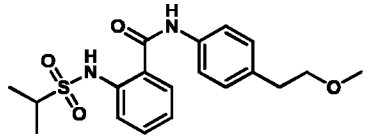
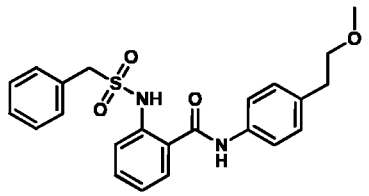
Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
137		A	LCMS: Found 343.0 [M−H]	-
138		A	LCMS: Found 344.1 [M·H]	-
139		G	LCMS: Found 383.2 [M·H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.50 (S,1H), 8.73 (D, 1H), 7.92 (T, 1H), 7.82-7.70 (M, 3H), 7.40-7.29 (M, 2H), 3.72-3.70 (M, 4H), 3.05-3.02 (M, 4H).	-
140		A	LCMS: Found 311.2 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.10 (br s, 1H), 10.51 (S, 1H), 8.02 (S, 1H), 7.90-7.82 (M, 2H), 7.67-7.55(M, 3H), 7.26 (D, 1H), 4.18 (Q, 2H),1.37 (T, 3H)	-
141		G	LCMS: Found 412.9 [M·H] ^{1}H NMR (400 MHz, CD_3OD): 8.33 (D,1H), 8.11-8.08 (M, 2H), 7.98 (D, 1H), 7.79 (T,1H), 7.49 (T, 1H), 7.36-7.31 (M, 2H), 3.68-3.66 (M, 4H), 3.28-3.16 (M, 4H).	B

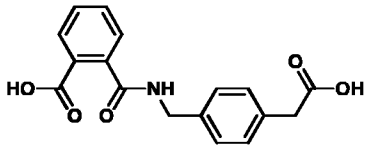
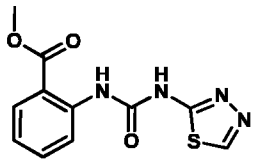
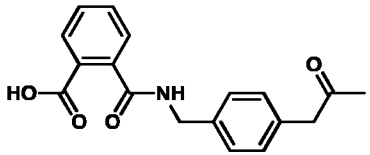
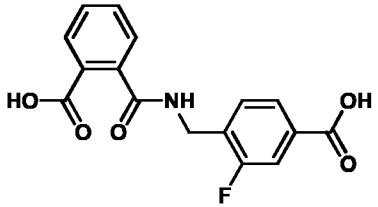
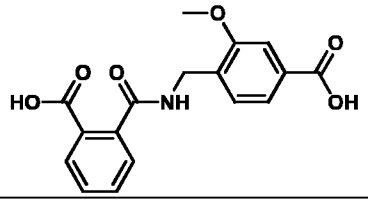
Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
142		A	LCMS: Found 299.1 [M-H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.99 (br s, 1H), 10.27 (S, 1H), 9.89(S,1H), 7.87 (D, 1H), 7.67-7.50 (M, 7H), 2.03(S, 3H)	B
143		A	LCMS: Found 316.1 [M−H] ^{1}H NMR (400 MHz, CD_3OD): 8.03-8.01 (T, 1H), 7.66-7.63 (T, 1H), 7.58-7.52 (M, 4H), 6.94-6.92 (M, 2H), 4.12-4.10 (M, 2H), 3.75-3.73 (M, 2H), 3.42 (S, 3H)	-
144		G	LCMS: Found 429.0 [M-H] ^{1}H NMR (400 MHz, CD_3OD): 8.40 (D,1H), 7.99 (D, 1H), 7.74 (T, 1H), 7.65-7.57 (M, 4H), 7.42 (T, 1H), 7.20-7.11 (M, 4H), 3.19 (S, 3H).	-
145		A	LCMS: Found 312.1 [M-H] ^{1}H NMR (400 MHz, DMSO-d_6): 11.18 (br s, 1H), 7.80 (D, 1H), 7.62-7.50 (M, 5H), 7.22(T, 1H), 6.91 (D, 1H), 2.75 (S, 3H),2.12-2.09 (M, 2H)	B
146		G	LCMS: Found 405.0 [M-H], LCMS: Found 427.0 [M+Na] ^{1}H NMR (400 MHz, CD_3OD): 8.53 (D,1H), 7.93 (D, 2H), 7.88 (D, 1H), 7.76 (T, 1H), 7.47 (D, 2H), 7.42 (D, 1H), 3.68 (T, 2H), 3.64-3.62 (M, 4H), 3.36 (S, 3H), 3.01-2.96 (M, 6H).	-

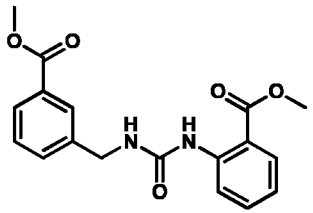
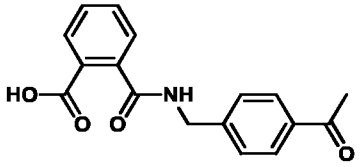
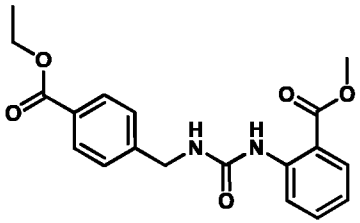
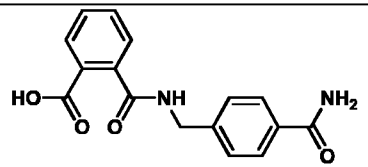
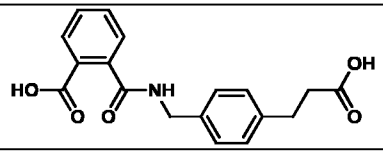
Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
147		G	LCMS: Found 391.0 [M+H] ^{1}H NMR (400 MHz, CD_3OD): 8.53 (D,1H), 8.22 (D, 2H), 8.12 (D, 2H), 7.92 (D, 1H), 7.80 (T, 1H), 7.44 (T, 1H), 3.65-3.63 (M, 4H), 3.02-3.00 (M, 4H).	B
148		A	LCMS: 384.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 11.18 (br s, 1H), 7.80 (D, 1H), 7.62-7.50 (M, 5H), 7.22(T, 1H), 6.91 (D, 1H), 2.75 (S, 3H),2.12-2.09 (M, 2H)	B
149		A	LCMS: Found 325.2 [M·H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.09 (S, 1H), 10.48 (S, 1H), 8.01-8.01 (D, 1H), 7.90-7.88 (D, 1H), 7.81-7.80 (D, 1H), 7.67 (S,1H), 7.59-7.56 (D, 2H), 7.31-7.28 (D, 2H), 4.77-4.72 (M, 1H), 1.32-1.31 (D, 6H)	-
150		A	LCMS: Found 318.1 [M·H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.03 (S, 1H), 10.05 (S, 1H), 7.88-7.86 (D, 2H), 7.07-7.65 (M, 2H), 7.57-5.52 (M, 2H), 7.11-7.03 (M, 2H), 4.50 (S, 1H), 3.42-3.41 (D, 2H), 2.64-2.60 (T, 2H), 1.76-1.69 (M, 2H)	-
151		A	LCMS: Found 334.1 [M·H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.13 (S, 1H), 9.93 (S, 1H), 7.88-7.86 (D, 1H), 7.66-7.65 (M, 1H), 7.59-7.54 (M, 3H), 7.35 (S, 1H), 7.22-7.20 (D, 1H), 4.50 (S, 1H),	-

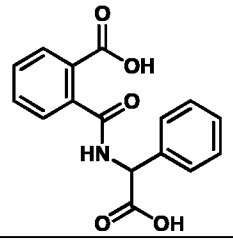
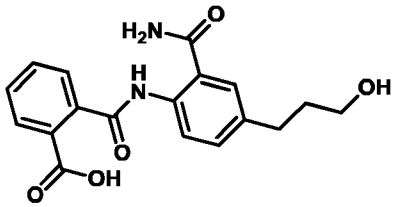
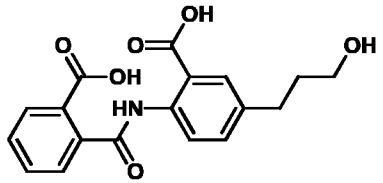
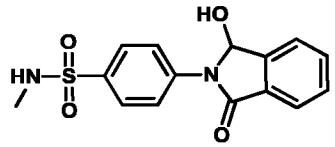
Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
			3.43-3.39 (M, 2H), 2.64-2.60 (T, 2H), 1.74-1.68 (M, 2H)	
152		G	LCMS: Found 405.0 [M·H] ^{1}H NMR (400 MHz, CD_3OD): 8.36 (D,1H), 8.05 (D, 2H), 7.76 (D, 1H), 7.67 (T, 1H), 7.53 (D, 2H), 7.35 (T, 1H), 3.88 (S, 2H), 3.51-3.48 (M, 4H), 2.64-2.62 (M, 4H).	-
153		A	LCMS: Found 314.1 [M·H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.91 (br s, 2H), 8.98 (S, 1H), 7.80-7.75 (M, 2H), 7.58-7.50(M, 3H), 7.31-7.28 (M, 2H), 4.46-4.04 (M, 2H)	-
154		A	LCMS: Found 330.0 [M·H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.95 (br s, 1H), 12.55(br s, 1H), 8.93 (S, 1H), 7.78 (D, 1H), 7.62-7.49(M, 4H), 7.16 (D, 1H), 4.47 (D, 2H), 3.84 (S, 3H)	B
155		A	LCMS: Found 325.0 [M·H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.37 (br s, 1H), 8.99(T, 1H), 8.07 (D, 1H), 7.97 (S, 1H), 7.83-7.80(M, 2H), 7.62-7.51 (M, 3H), 4.54 (D, 2H)	A

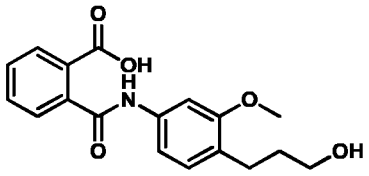
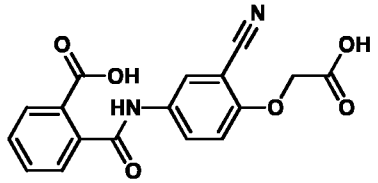
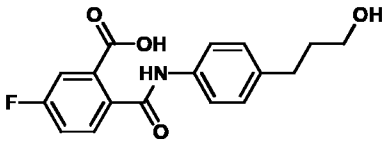
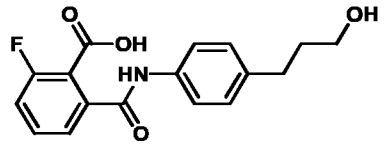
Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
156		H	LCMS: Found 455.1 [M·2Na-H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.36 (S,1H), 7.82-7.75 (M, 3H), 7.51-7.43 (M, 5H), 7.37-7.33 (M, 2H), 7.29-7.27 (M, 2H), 7.16 (T, 1H), 4.38 (T, 2H), 3.81 (S, 3H), 3.02 (T, 2H).	A
157		A	LCMS: Found 314.1 [M·H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.92 (br s, 2H), 8.86 (T, 1H), 7.79-7.73 (M, 3H), 7.60-7.48(M, 4H), 4.45 (D, 2H), 2.38 (S, 3H)	-
158		A	LCMS: 314.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.97 (br s, 2H), 8.83(D, 1H), 8.02 (D, 1H), 7.91 (D, 1H), 7.79 (D,1H), 7.61-7.55(M, 3H), 7.44 (D, 1H), 5.18-5.11 (M,1H), 1.44 (D, 3H)	-

Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
159		H	LCMS: Found 421.2 [M·2Na-H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.36 (S,1H), 7.96 (S, 1H), 7.79 (D, 1H), 7.67 (D, 1H), 7.56-7.51 (M, 3H), 7.29-7.27 (M, 1H), 7.19 (T, 1H), 4.36 (T, 2H), 3.80 (S, 3H), 3.14 (T, 2H), 3.01 (T, 2H), 1.91-1.85 (M, 2H), 1.02 (T, 3H).	B
160		A	LCMS: Found 297.1 [M·H]	-
161		A	LCMS: Found 368.1 [M·H] ^{1}H NMR (400 MHz, CD_3OD): 8.08-8.06 (D, 2H), 8.01-7.99 (D, 1H), 7.68-7.64 (M, 3H), 7.56-7.56 (D, 1H), 7.42-7.40 (D, 1H), 6.03-5.97 (M, 1H)	-
162		H	LCMS: Found 421.2 [M+2Na-H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.35 (S,1H), 7.95 (S, 1H), 7.85 (D, 1H), 7.65 (D, 1H), 7.56-7.48 (M, 3H), 7.31-7.27 (M, 1H), 7.16 (T, 1H), 4.36 (T, 2H), 3.80 (S, 3H), 3.37-3.32 (M, 1H), 3.01 (T, 2H), 1.41 (S, 6H).	B
163		H	LCMS: Found 469.2 [M·2Na-H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.42 (S,1H), 7.80 (S, 1H), 7.67 (D, 1H), 7.61 (D, 1H), 7.50-7.44 (M, 3H), 7.29-7.24 (M, 6H), 7.16 (T, 1H), 4.42 (S, 2H), 4.37 (T,	-

Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
			2H), 3.80 (S, 3H), 3.01 (T, 2H).	
164		A	LCMS: Found 314.1 [M−H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.70 (br s, 2H), 8.83 (T, 1H), 7.76 (D, 1H), 7.59-7.45(M, 3H), 7.32 (D, 2H), 7.20 (D, 2H), 4.41 (D, 2H), 3.55 (S,2H)	A
165		K-1	LCMS: Found 279.0 [M+H] ^{1}H NMR (400MHz,$CDCl_3$): 10.98 (S, 1H), 8.80 (S, 1H), 8.46 (D, 1H), 8.03 (D, 1H), 7.61-7.56 (M, 1H), 7.28 – 7.11 (M, 1H), 3.92 (S, 3H)	-
166		A	LCMS: Found 312.1 [M·H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.99 (br s, 1H), 8.84 (T, 1H), 7.76 (D, 1H), 7.59-7.47(M, 3H), 7.33 (D, 2H), 7.14 (D, 2H), 4.41 (D, 2H), 3.74 (S,2H), 2.12 (S,3H)	B
167		A	LCMS: Found 318.1 [M·H]	-
168		A	LCMS: Found 330.1 [M·H] ^{1}H NMR (400 MHz, DMSO-d_6): 9.39 (br s, 2H), 7.71 (D, 1H), 7.59-7.47(M, 6H), 4.43 (D, 2H), 3.55 (S,2H)	-

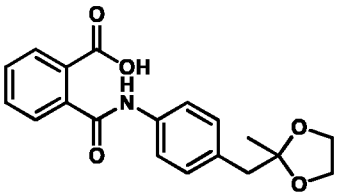
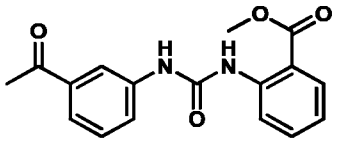
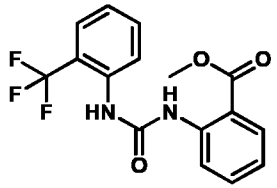
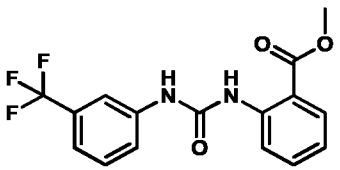
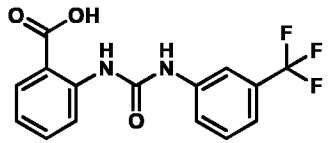
Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
169		K-1	LCMS: Found 343.0 [M+H] LCMS: Found 365.0 [M+Na] ^{1}H NMR (400MHz,$CDCl_3$): 10.48 (S, 1H), 8.56 (D, 1H), 8.04-7.79 (M, 3H), 7.60 (D, 1H), 7.53 (T, 1H), 7.45 (T, 1H), 7.02-6.98 (M,1H), 5.11 (br s, 1H), 4.56 (D, 2H), 3.94 (S, 3H), 3.91 (S, 3H)	-
170		A	LCMS: Found 298.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.03 (br s, 1H), 8.94 (T, 1H), 7.92(D, 2H), 7.78 (D, 2H), 7.61-7.49 (M, 5H), 4.50 (D,2H), 2.58 (S, 3H)	-
171		K-1	LCMS: Found 357.0 [M+H] LCMS: Found 379.0 [M+Na] ^{1}H NMR (400MHz,$CDCl_3$): 10.50 (S, 1H), 8.56 (D, 1H), 8.05-8.01 (M, 3H), 7.53 (T, 1H), 7.44 (D, 1H), 7.00 (T,1H), 5.10 (br s, 1H), 4.57 (D, 2H), 4.38 (Q, 2H), 3.91 (S, 3H), 1.41 (T, 3H)	-
172		A	LCMS: Found 299.1 [M+H]	B
173		A	LCMS: Found 328.2 [M+H]	-

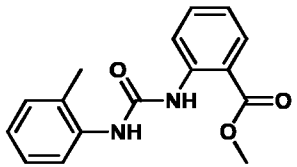
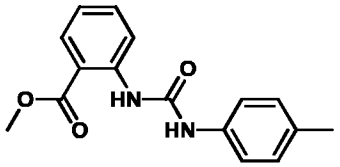
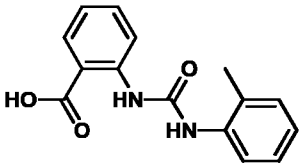
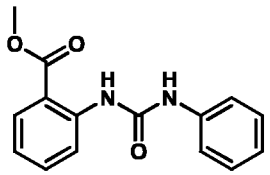
Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
174		A	LCMS: Found 300.1 [M−H] ^{1}H NMR (400 MHz, CD_3OD): 7.98-7.97 (D, 1H), 7.63-7.51 (M, 5H), 7.39-7.36 (T, 3H), 5.68 (S, 1H)	-
175		A	LCMS: Found 365.1 [M−Na] ^{1}H NMR (400 MHz, DMSO-d_6): 13.09 (br s, 1H), 12.09 (S, 1H), 8.49(D, 1H), 8.30 (S, 1H), 7.82 (D, 1H), 7.7-7.61 (M, 4H), 7.36 (D, 1H), 4.52 (T,1H), 3.44-3.41 (M, 2H), 2.63-2.60 (M,2H), 1.78-1.71 (M, 2H)	-
176		A	LCMS: Found 344.1 [M−H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.12 (S, 1H), 11.42 (S, 1H), 8.52-8.50 (D, 1H), 7.86-7.83 (M, 2H), 7.70-7.64 (M, 3H), 7.62 (D, 1H), 4.49 (S, 1H), 3.41 (M, 2H), 2.65-2.62 (T, 2H), 1.75-1.68 (M, 2H)	B
177		B-3	LCMS: Found 318.9 [M−H] LCMS: Found 301.0 [M-H_2O] ^{1}H NMR (400 MHz, DMSO-d_6): 8.07 (D,2H), 7.84 (D, 2H), 7.83-7.71 (M, 3H), 7.64 (T, 1H), 7.42 (br s, 1H), 7.03 (br s, 1H), 6.66 (S, 1H), 2.44 (S, 3H).	-

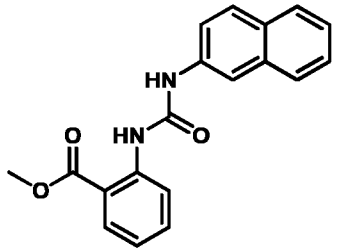
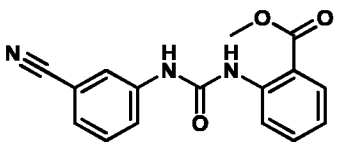
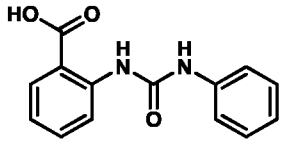
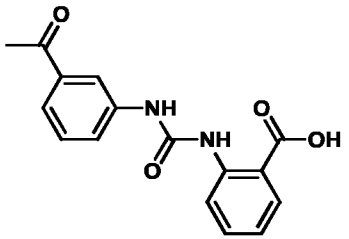
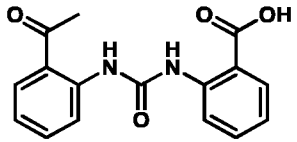
Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
178		A	LCMS: Found 330.2 [M-H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.03 (S, 1H), 10.26 (S, 1H), 7.88 (D, 1H), 7.64 (D, 1H), 7.59-7.52 (M, 2H), 7.41 (S, 1H), 7.17 (D, 1H), 7.06 (D, 1H), 4.43 (T, 1H), 3.75 (S, 3H), 3.43-3.38 (M, 2H), 2.51-2.50 (M, 2H), 1.67-1.65 (M, 2H)	B
179		A	LCMS: Found 341.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.21 (br s, 1H), 10.56 (S, 1H), 8.03(D, 1H), 7.90 (D, 1H), 7.80(D, 1H), 7.69-7.55 (M, 3H),7.17 (D, 1H), 4.87 (S, 2H)	-
180		A	LCMS: Found 318.1 [M-H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.13 (br s, 1H), 10.31 (S, 1H), 7.96 (D, 1H), 7.63-7.39(M, 5H), 7.15 (D, 2H), 4.47 (T, 1H), 3.42-3.40 (M, 2H), 2.59-2.53 (M, 2H), 1.73-1.66 (M, 2H)	B
181		A	LCMS: Found 318.1 [M-H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.25 (br s, 1H), 10.46 (S, 1H), 7.64-7.45(M, 6H), 7.15 (D, 2H), 4.47 (T, 1H), 3.43-3.37 (M, 2H), 2.60-2.56 (M, 2H), 1.74-1.66 (M, 2H)	B

Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
182		A	LCMS: Found 318.1 [M·H]	B
183		A	LCMS: Found 318.1 [M+H]	B
184		A	LCMS: Found 334.1 [M·H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.30 (br s, 1H), 10.31 (S, 1H), 7.90-7.55(M, 6H), 7.15 (D, 2H), 4.47 (br s, 1H), 3.43-3.38 (M, 2H), 2.60-2.55 (M, 2H), 1.73-1.68 (M, 2H)	B
185		A	LCMS: Found 334.1 [M·H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.46 (S, 1H), 7.727.68 (M, 2H), 7.61-7.54 (M, 3H), 7.16 (D, 2H), 4.47 (S, 1H), 3.43-3.39 (M, 2H), 2.60-2.50 (M, 2H), 1.74-1.66 (M, 2H)	B
186		A	LCMS: Found 334.1 [M·H]	B

Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
187		A	LCMS: Found 334.1 [M·H]	B
188		A	LCMS: Found 314.2 [M·H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.85 (br s, 1H), 10.19 (S, 1H), 7.79-7.56 (M, 3H), 7.44-7.33(M, 2H), 7.13 (D, 2H), 4.47 (T, 1H), 3.42-3.39 (M, 2H), 2.59-2.51 (M, 2H), 1.73-1.66 (M, 2H)	-
189		A	LCMS: Found 314.2 [M·H] ^{1}H NMR (400 MHz, MeOD): 7.59-7.53 (M, 3H), 7.48-7.41 (M, 2H), 7.18-7.14 (M, 2H), 3.60-3.57 (T, 2H), 2.72-2.67 (M, 2H), 2.47 (S, 3H), 1.88-1.81 (M, 2H)	A
190		A	LCMS: Found 314.2 [M·H]	A
191		A	LCMS: Found 314.2 [M·H]	-

Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
192		A	LCMS: Found 342.2 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.04 (br s, 1H), 10.28 (S, 1H), 7.86 (D, 1H), 7.65-7.53 (M, 5H), 7.19 (D, 2H), 3.86-3.77 (M, 4H), 2.81 (S, 2H), 1.19 (S, 3H)	-
193		K-1	LCMS: Found 313.2 [M−H] ^{1}H NMR (400 MHz, DMSO-d_6):10.63 (S, 1H), 8.53 (D, 1H), 8.03 (M, 2H), 7.75 (D, 1H), 7.68 (D, 1H), 7.53 (T, 1H), 7.42 (T, 1H), 7.04 (M, 1H), 3.90 (S, 3H), 2.30 (S, 3H)	B
194		K-1	LCMS: Found 339.2 [M−H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.70 (S, 1H), 8.50 (D, 1H), 8.00 (T, 2H), 7.65 (D, 1H), 7.55 (M, 2H), 7.26 (M, 1H), 6.67 (S, 1H), 3.88 (S, 3H)	B
195		K-1	LCMS: Found 339.2 [M−H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.65 (S, 1H), 8.55 (D, 1H), 8.02 (D, 1H), 7.81 (S, 1H), 7.62 (D, 1H), 7.55 (T, 1H), 7.45 (T, 1H), 7.26 (D, 1H), 7.05 (T, 1H), 6.95 (S, 1H), 3.91 (S, 3H)	B
196		K-2	LCMS: Found 307.1 [M-H_2O+H] ^{1}H NMR (400 MHz, DMSO-d_6): 11.63 (S, 1H), 7.95 (D, 1H), 7.82 (M, 1H), 7.81 (S, 1H), 7.73 (M, 2H), 7.68 (M, 1H), 7.24 (M, 2H)	B

Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
197		K-1	LCMS: Found 285.2 [M-H] ^{1}H NMR (400 MHz, DMSO-d_6): 9.96 (S, 1H), 9.01 (S, 1H), 8.29 (D, 1H), 7.92 (DD, 1H), 7.55 (T, 1H),7.46 (DD, 1H), 7.22-7.16 (M, 2H), 7.07-7.04 (M, 2H), 3.87 (S, 3H), 2.25 (S, 3H)	B
198		K-1	LCMS: Found 285.2 [M-H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.47 (S, 1H), 8.55 (D, 1H), 7.99 (D, 1H), 7.51 (T, 1H), 7.30 (D, 2H),7.16 (D, 2H), 7.0 (T, 1H), 6.68 (S,1H), 3.87 (S, 3H), 2.33 (S, 3H)	B
199		K-2	LCMS: Found 253.2 [M-H_2O+H] ^{1}H NMR (400 MHz, DMSO-d_6): 11.60 (S, 1H), 7.96 (D, 1H), 7.72 (T, 1H), 7.35 (M, 2H), 7.30 (M, 1H), 7.22 (M, 3H), 3.32 (S, 3H)	B
200		K-1	LCMS: Found 271.2 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.50 (S, 1H), 8.55 (D, 1H, J 6Hz), 7.97 (D, 1H, J 7.8Hz), 7.52 (M, 1H), 7.44 (M, 1H), 7.34 (M, 2H), 7.11 (M, 1H), 7.00 (M, 1H), 6.84 (S, 1H), 3.88 (S, 3H)	B

Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
201		K-1	LCMS: Found 321.2 [M+H] ^{1}H NMR (400 MHz,$CDCl_3$): 10.64 (S, 1H), 8.60 (DD, 1H), 8.08 – 7.98 (M, 2H), 7.83 – 7.74 (M, 3H), 7.55 (DD, 1H), 7.49 – 7.34 (M, 3H), 7.06 – 6.97 (M, 1H), 6.95 (S, 1H), 3.89 (S, 3H)	B
202		K-1	LCMS: Found 296.2 [M+H] ^{1}H NMR (400 MHz,$CDCl_3$): 10.70 (S, 1H), 8.52 (DD, 1H), 8.02 (DD, 1H), 7.89 (T, 1H), 7.64 (DD, 1H), 7.56 (DD, 1H), 7.45 – 7.33 (M, 2H), 7.05 (DD, 1H), 6.92 (S, 1H), 3.93 (S, 3H)	A
203		K-2	LCMS: Found 238.07 [M-H_2O+H] ^{1}H NMR (400 MHz, DMSO-d_6): 11.56 (S, 2H), 7.94 (D, 1H, J 8Hz), 7.70 (T, 1H, J 6Hz), 7.48 (M, 2H), 7.42 (M, 1H), 7.32 (M, 2H), 7.22 (M, 2H)	B
204		K-2	LCMS: Found 280.08 [M-H_2O+H] ^{1}H NMR (400 MHz, DMSO-d_6): 11.60 (S, 2H), 8.03 (D, 2H, J 6Hz), 7.95 (M, 2H), 7.72 (T, 2H, J 6Hz), 7.25 (D, 2H, J 6.4Hz), 3.32 (S, 3H)	B
205		K-2	LCMS: Found 281.2 [M-H_2O+H] ^{1}H NMR (400 MHz, DMSO-d_6): 11.55 (S, 1H), 8.05 (D, 1H), 7.90 (D, 1H), 7.70 (M, 2H), 7.61 (M, 1H), 7.42 (D, 1H), 7.23 (M, 2H), 2.46 (S, 3H)	B

Cmpd #	Structure	Synthetic Scheme	Characterization Data (NMR and/or LCMS)	Biological Activity
206		K-1	LCMS: Found 313.2 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.67 (S, 2H), 8.52 (D, 1H, J 7.8Hz), 8.00 (D, 1H), 7.94 (D, 2H, J 8Hz), 7.55 (M, 3H), 7.03 (T, 1H, J 6Hz), 3.88 (S, 3H), 2.58 (S, 3H)	B

EXAMPLE 2: Cell viability assay

[00279] Human MSCs, chondrocytes, osteoblasts and synoviocytes are plated into 384-well plates at 10,000 cells per well. Compounds are added at a final concentration of 100μM. The cells are cultured for 48 h. Cell viability is analyzed by Cell Titer-Glo (Promega) assay using EnVision plate reader (PerkinElmer). Apoptosis activity is analyzed by Caspase 3/7-Glo (Promega) assay using EnVision plate reader (PerkinElmer).

EXAMPLE 3: PK study via intra-articular injection in rats

[00280] A 30μl-compound solution (100 μM in PBS containing 0.1% DMSO) is injected into the articular space of the right knee of each rat. The animals are bled at 1, 3, 4, 6, 7, 8, 9, and 10 hours post-injection. The animals are terminated at 2 or 12 hours post-dose. Plasma and joint lavage of the injected knees are collected. The quantities of the injected compounds are analyzed using LCMS.

EXAMPLE 4: Rat medial meniscal tear (MMT) osteoarthritis (OA) model

[00281] The medial meniscus of the right knee of each animal is surgically torn to induce OA. Dosing of the compound solutions (30 μl of 100 μM in PBS containing 0.1% DMSO) is begun 7 days post-surgery at one dose per week for three weeks. Body weights and gait deficits are monitored weekly right before dosing. Animals are terminated at day 28 post-surgery. The joints of the operated knees are processed and histochemically stained for cartilage, and the cartilage is evaluated.

[00282] Following 4-6 days in 5% formic acid decalcifier, the operated joints are cut into two approximately equal halves in the frontal plane and embedded in paraffin. Three sections are cut from each operated right knee (g1-8) at approximately 200 μm steps and stained with toluidine blue. Left knees of group 1 and right knees from group 9 have a single section prepared and stained with toluidine blue.

[00283] All three sections of each operated knee are analyzed microscopically. The worst-case scenario for the two halves on each slide is determined for general cartilage degeneration, proteoglycan loss, collagen damage, and osteophyte formation. The values for each parameter are then averaged across the three sections to determine overall subjective scores.

[00284] In addition, for some parameters (noted below), regional differences across the tibial plateau are taken into consideration by dividing each section into three zones (1-outside, 2-middle, 3-inside). In the surgical OA model, the outside (z1) and middle (z2) thirds are most severely affected, and milder changes are present on the inside third (z3). When zones are scored individually, scores are assigned based on percent area of the zone affected. Zone areas are delineated using an ocular micrometer.

[00285] The following parameters are measured and/or scored:

[00286] General cartilage degeneration includes the important parameters of chondrocyte death/loss, proteoglycan loss, and collagen loss or fibrillation. Cartilage degeneration in the tibia is scored none to severe (numerical values 0-5) for each zone using the following criteria:

- 0 = no degeneration
- 1 = minimal degeneration, within the zone 5-10% of the matrix appears non viable as a result of significant chondrocyte loss (greater than 50% of normal cell density). PG loss is usually present in these areas of cell loss and collagen matrix loss may be present.
- 2 = mild degeneration, within the zone 11-25% of the matrix appears non viable as a result of significant chondrocyte loss (greater than 50% of normal cell density). PG loss is usually present in these areas of cell loss and collagen matrix loss may be present.
- 3 = moderate degeneration, within the zone 26-50% of the matrix appears non viable as a result of significant chondrocyte loss (greater than 50% of normal cell density). PG loss is usually present in these areas of cell loss and collagen matrix loss may be present.
- 4 = marked degeneration, within the zone 51-75% of the matrix appears non viable as a result of significant chondrocyte loss (greater than 50% of normal cell density). PG loss is usually present in these areas of cell loss and collagen matrix loss may be present.
- 5 = severe degeneration, within the zone 76-100% of the matrix appears non viable as a result of significant chondrocyte loss (greater than 50% of normal cell density). PG loss is usually present in these areas of cell loss and collagen matrix loss may be present.

In some cases, image analysis may be used to determine the exact % of matrix viability and/or loss in each zone or in selected zones so that absolute % rather than scores (0-5) can be compared. A 3-zone sum for cartilage degeneration is calculated in addition to expressing the data for each zone.

[00287] The same process is applied to evaluation of the femoral cartilage with the exception that lesions are not analyzed based on zones since the lesions are not generally distributed over the surface in a zonal pattern. The total width of the load-bearing surface (approximately 2000 μm for the femur) is determined and the above criteria is applied to the most severely affected 1/3, 2/3 or 3/3. For example, if 1/3 of the total area (lesion may be in the center of the plateau covering about 667 μm) has minimal degeneration (5-10% of total area has loss of chondrocytes and/or matrix), a score of 1 is assigned. If that minimal degeneration extends over the entire surface (3/3) then the score is 3. If the entire femoral cartilage is absent as a result of severe diffuse degeneration, then the score is 15.

[00288] In addition to this overall cartilage degeneration score, collagen matrix damage is scored separately in order to identify more specific effects of agents. Collagen damage across the medial tibial plateau (most severely affected section of the two halves) is quantified by measuring the total width of the following:

- Any damage (fibrillation ranging from superficial to full thickness loss).

- Severe damage (total or near total loss of collagen to tidemark, >90% thickness)
- Marked damage (extends through 61-90% of the cartilage thickness)
- Moderate damage (extends thru 31-60% of the cartilage thickness)
- Mild damage (extends through 11-30% of the cartilage thickness)
- Minimal damage (very superficial, affecting upper 10% only)

[00289] In addition to the above subjective general cartilage scoring, two cartilage degeneration width measurements are taken:

- Total Tibial Cartilage Degeneration Width (μm) is a micrometer measurement of total extent of tibial plateau affected by any type of degeneration (cell loss, proteoglycan loss or collagen damage). This measurement extends from the origination of the osteophyte with adjacent cartilage degeneration (outside 1/3) across the surface to the point where tangential layer and underlying cartilage appear histologically normal.
- Substantial Cartilage Degeneration Width (μm) reflects areas of tibial cartilage degeneration in which both chondrocyte and proteoglycan loss extend through greater than 50% of the cartilage thickness. In general, the collagen damage is mild (25% depth) or greater for this parameter but chondrocyte and proteoglycan loss extend to at least 50% or greater of the cartilage depth.

[00290] A micrometer depth of any type of lesion (both chondrocyte and proteoglycan loss, but may have good retention of collagenous matrix and no fibrillation), expressed as a ratio of depth of changed area vs. depth to tidemark, is taken in the area of greatest lesion severity in each of the three zones across the tibial surface at the midpoint of the zone. This measurement is the most critical analysis of any type of microscopic change present. The denominator can serve as an average measure of cartilage thickness in each of the three zones for comparison of anabolics when measures are taken at the midpoint of the zone.

[00291] Scoring of the osteophytes and categorization into small, medium and large is done with an ocular micrometer. Marginal zone proliferative changes have to be >200 μm in order to be measured and designated as osteophytes. Scores are assigned to the largest osteophyte in each section (typically found in the tibia) according to the following criteria:

- 1 = small up to 299 μm
- 2 = moderate 300-399 μm
- 3 = large 400-499 μm
- 4 = very large 500-599
- 5 = very large ≥600

The actual osteophyte measurement (tidemark to furthest distance point extending toward synovium) is also recorded.

[00292] The femoral cartilage degeneration score and the three-zone sum of the tibial cartilage degeneration scores (mean of three levels) are summed to create a total cartilage degeneration score. The mean osteophyte score for each joint is added to this value to produce a total joint score.

Image analysis

[00293] In order to quantify and compare the cartilage matrix preservation, cartilage area measurements are taken from the most severely affected section of each animal. Photomicrographs are taken with a CoolSNAP-Pro microscope camera and loaded into ImagePro Plus software. The following measurements are taken from tracings of these photomicrographs, four per page, which are included in the report:

- Total area from the tidemark to the surface (or projected surface in degenerated areas) over 9 cm (photomicrograph) of the tibial plateau, measured from the inner edge of the osteophyte
- Area of non-viable matrix (cartilage with less than 50% chondrocytes, proteoglycan, and intact collagen) and no matrix within the total area
- Area of no matrix within the total area

The area of non-viable matrix is subtracted from the total area to get the area of viable matrix, and the area of no matrix is subtracted from the total area to get the area of any matrix (collagen matrix with or without chondrocytes and proteoglycan). These two values are then compared back to the total area to derive the percent viable matrix area and the percent any matrix area, which are compared between groups. Five left knees from the vehicle group are included in this process as normal controls. This process may be used to analyze the entire surface or selected zones depending on lesion severity and apparent treatment effects.

[00294] Synovial reaction, if abnormal, is described (should be mainly fibrosis) and characterized with respect to inflammation type and degree but is not included in the OA score.

[00295] Damage to the calcified cartilage layer and subchondral bone (worst case scenario for all sections) is scored using the following criteria:

- 0 = No changes
- 1 = Increased basophilia at tidemark, no fragmentation of tidemark, no marrow changes or if present minimal and focal
- 2 = Increased basophilia at tidemark, minimal to mild focal fragmentation of calcified cartilage of tidemark, mesenchymal change in marrow involves 1/4 of total area but generally is restricted to subchondral region under lesion
- 3 = Increased basophilia at tidemark, mild to marked focal or multifocal fragmentation of calcified cartilage (multifocal), mesenchymal change in marrow is up to 3/4 of total area, areas of marrow chondrogenesis may be evident but no major collapse of articular cartilage into epiphyseal bone (definite depression in surface)

- 4 = Increased basophilia at tidemark, marked to severe fragmentation of calcified cartilage, marrow mesenchymal change involves up to 3/4 of area and articular cartilage has collapsed into the epiphysis to a depth of 250 μm or less from tidemark (see definite depression in surface cartilage)
- 5 = Increased basophilia at tidemark, marked to severe fragmentation of calcified cartilage, marrow mesenchymal change involves up to 3/4 of area and articular cartilage has collapsed into the epiphysis to a depth of greater than 250 μm from tidemark

In addition, measurements are made of the thickness of the medial synovial/collateral ligament repair in a non-tangential area of the section.

[00296] Growth plate thickness is measured in all knees on medial and lateral sides (2 measures/joint) at the approximate midpoint of the medial and lateral physis (assuming a non tangential area of the section).

EXAMPLE 5: Extraction and Quantitation of Chondrogenesis Compounds in Joint and Plasma Rat Samples

[00297] LC-MS/MS analysis for Chondrogenesis compounds were performed using an API 3000 equipped with an Agilent 1100 HPLC and a Leap Technologies autosampler. A HPLC Phenomenex 5 micron, 100 A Luna C18 (2) analytical column with dimensions of 2.0 x 50 mm (Part No. 00B-4252-B0) at a temperature of 30 C, flow rate of 0.6 mL/min, injection volume of 10 uL, and a 6.0 min run time was used. Mobile phase A1 was 0.1% formic acid in water and Mobile phase B1 was 0.1% formic acid in acetonitrile. The gradient was 90% A1/10% B1 at time 0; 90% A1/10% B1 at time 1.0 min; 10% A1/90% B1 at time 2.0 min; 10% A1/90% B1 at time 4.0 min; 90% A1/10% B1 at time 4.10 min; 90% A1/10% B1 at time 6.0 min. Analytes and internal standard quantitation were performed using Multiple Reaction Monitoring (MRM) quantitation method. Listed below are specific methods used to dose and measure exposure in plasma and the observed concentration in joint extract.

[00298] **Rat Plasma Samples**: Calibration standard curve was prepared by serial dilution of a concentrated, spike solution of the compound in control rat plasma. Calibration standards and rat plasma samples were prepared via protein precipitation by adding aliquots of Acetonitrile and internal standard to each aliquot of standards and samples. Following vortex mixing and centrifugation, aliquots of the supernatants from each standards and samples were diluted with formic acid in water, mixed and injected. All plasma samples collected after IA dosing (starting at t = 0, 0.5, 1, 2, 4, and 6h) indicated no systemic exposure for any of the compounds listed in Table 2.

[00299] **Rat Knee Joint Samples**: Calibration standard curve was prepared by serial dilution of a concentrated, spike solution of the compound in internal standard diluents. Internal standard diluent was prepared by dissolving the internal standard compound at a certain concentration in acetonitrile. Rat knee joint samples for each time points were individually crushed and transferred into each

centrifuge tube and added 1.0-mL of internal standard diluent. Each centrifuge tube was vortexed and centrifuged for 30 minutes. From each tube, supernatant was removed and injected onto the column for analysis. In addition, plasma samples were obtained by retro-orbital bleeds into heparin coated tubes and stored at -80C and later processed by analogy to the protocol described above for rat plasma samples.

[00300] Compound administration and tissue processing: 30 μL of 100 μM compound solution (PBS with 0.1% DMSO) was injected into the intra-articular space of the right hinder knee of each animal. The animals were euthanized at indicated time points (0 hr, 0.5 hr, 1 hr, 2 hr, 4 hr and 6hr). Four animals were used for each timepoint. The injected knee joints were harvested, flash freeze in liquid nitrogen. The whole joints were grounded into powder while frozen, mixed with 1 mL internal standard-containing acetonitrile, incubated at 4 °C overnight, vortexed and centrifuged for 30 min. The supernatant from each sample was analyzed using LC-MS/MS. Data shown in Table 2 indicates the observed concentration in knee extract. ND = Not determined.

TABLE 2

Compound #	Concentration observed in extract (ng/mL)					
	T = 0 h	T = 0.5 h	T = 1 h	T=2 h	T = 4 h	T = 6 h
21	433.5	9.1	4.9	0	ND	ND
27	592	35.4	6.3	2.5	ND	ND
62	411	108.75	52.6	15.7	ND	ND
73	587	28.5	9.41	2.6	ND	ND
113	565.5	25.3	4.2	0	ND	ND
117	925.5	50.6	4.4	0	ND	ND
123	4430	1102	741.25	337.5	38	0
128	7280	2942.5	1365	546	ND	ND
156	108.8	3.5	0	0	ND	ND

EXAMPLE 6: Parenteral Composition of a Compound Presented Herein

[00301] To prepare a parenteral pharmaceutical composition suitable for administration by injection, 100 mg of a compound presented herein, or a water soluble pharmaceutically acceptable salt thereof, is dissolved in DMSO and then mixed with 10 ml of 0.9% sterile saline solution. The mixture is incorporated into a dosage unit suitable for administration by injection.

EXAMPLE 7: Oral Composition of a Compound Presented Herein

[00302] To prepare a pharmaceutical composition for oral delivery, 400 mg of a compound presented herein, and the following ingredients are mixed intimately and pressed into single scored tablets.

Tablet Formulation

Ingredient	Quantity per tablet mg
compound	400
cornstarch	50
croscarmellose sodium	25
lactose	120
magnesium stearate	5

[00303] The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

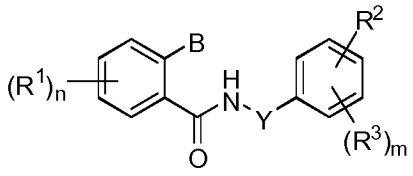
Capsule Formulation

Ingredient	Quantity per capsule mg
compound	200
lactose spray dried	148
magnesium stearate	2

CLAIMS

WHAT IS CLAIMED IS:

1. A method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula I)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NR^4R^{11}, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

m is 1, 2, 3, or 4;

B is CO_2R^4, CH_2CO_2H, $CH_2CO_2R^4$, or optionally substituted phenyl;

Y is a bond, $-(CR^5R^6)-$, $-(CR^7R^8)(CR^9R^{10})-$, or $-(CR^7R^8)(CR^9R^{10})X-$;

X is O or CR^5R^6;

R^2 is halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$;

each R^3 is independently selected from H, CN, halo, $C(O)R^4$, CO_2H, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$;

each R^4 is independently selected from H and optionally substituted alkyl;

each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, optionally substituted alkyl, OH, CO_2R^4, NR^4R^{11}, and optionally substituted alkoxy; and

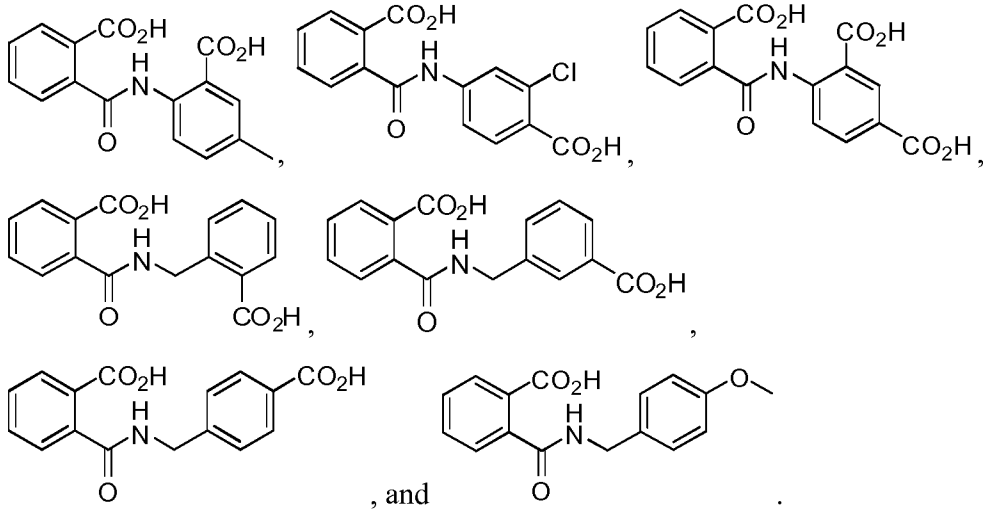
R^{11} is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

provided that

a) if Y is a bond and m is 0, then R^2 is selected from $C(O)NR^4R^{11}$, $(CR^7R^8)OR^4$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$; and

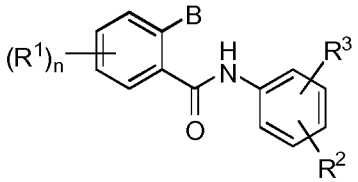
R^2 is not $C(O)NH_2$, p-CH_2OR^4, p-$CH(OH)CH_2OH$, p-CH_2CH_2OH, or p-$CH_2CH_2CH_2OH$; and

b) the compound is not selected from



, and .

2. A method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula Ia, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula Ia)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NR^4R^{11}, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

B is CO_2R^4;

R^2 is halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$;

each R^3 is independently selected from CN, halo, $C(O)R^4$, CO_2H, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$;

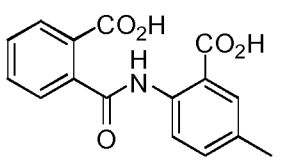
X is O or CR^5R^6;

each R^4 is independently selected from H and optionally substituted alkyl;

each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, optionally substituted alkyl, OH, NR^4R^{11}, and optionally substituted alkoxy; and

R^{11} is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

provided that the compound is not selected from



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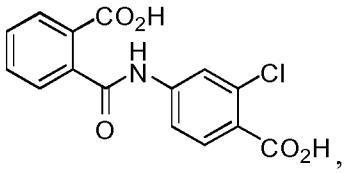

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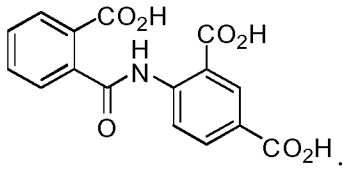

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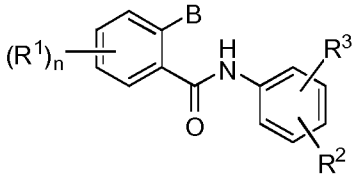
3. A method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula Ib, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula Ib)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NR^4R^{11}, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

B is CO_2R^4;

R^2 is $C(O)NR^4R^{11}$, $(CR^7R^8)OR^4$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$;

R^3 is H;

X is O or CR^5R^6;

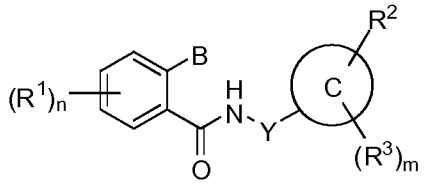
each R^4 is independently selected from H and optionally substituted alkyl;

each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, optionally substituted alkyl, OH, NR^4R^{11}, and optionally substituted alkoxy; and

R^{11} is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

provided that if n is 0, then R^2 is not $C(O)NH_2$, p-CH_2OR^4, p-$CH(OH)CH_2OH$, p-CH_2CH_2OH, or p-$CH_2CH_2CH_2OH$.

4. A method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula Ic, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula Ic)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NR^4R^{11}, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

m is 1, 2, 3, or 4;

B is CO_2R^4;

Y is -(CR^5R^6)-;

C is aryl or heteroaryl;

X is O or CR^5R^6;

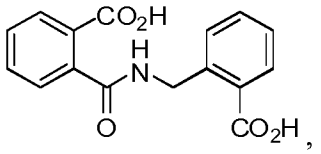
R^2 is halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, SO_2NH_2, SO_3H, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$;

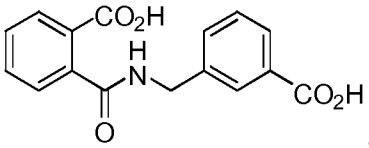
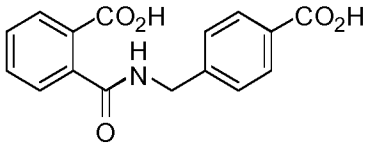
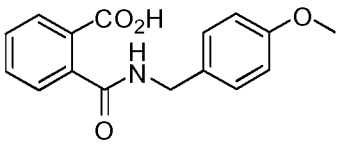
each R^3 is independently selected from H, CN, halo, $C(O)R^4$, CO_2H, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$;

each R^4 is independently selected from H and optionally substituted alkyl;

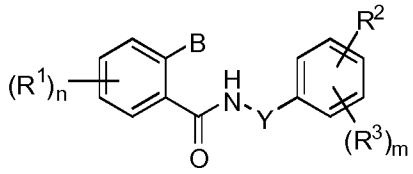
each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, optionally substituted alkyl, OH, CO_2R^4, NR^4R^{11}, and optionally substituted alkoxy; and

R^{11} is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

provided that the compound is not selected from  ,

 ,  , and  .

5. A method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula I, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula I)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NR^4R^{11}, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

m is 1, 2, 3, or 4;

B is CO_2R^4, CH_2CO_2H, $CH_2CO_2R^3$, or optionally substituted phenyl;

Y is a bond, $-(CR^5R^6)-$, $-(CR^7R^8)(CR^9R^{10})-$, or $-(CR^7R^8)(CR^9R^{10})X-$;

X is O or CR^5R^6;

R^2 is halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$;

each R^3 is independently selected from H, CN, halo, $C(O)R^4$, CO_2H, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$;

each R^4 is independently selected from H and optionally substituted alkyl;

each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, optionally substituted alkyl, OH, CO_2R^4, NR^4R^{11}, and optionally substituted alkoxy; and

R^{11} is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

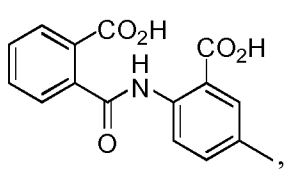
provided that

a) if Y is a bond and m is 0, then R^2 is selected from $C(O)NR^4R^{11}$, $(CR^7R^8)OR^4$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$,

$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$; and

R^2 is not $C(O)NH_2$, p-CH_2OR^4, p-$CH(OH)CH_2OH$, p-CH_2CH_2OH, or p-$CH_2CH_2CH_2OH$; and

b) the compound is not selected from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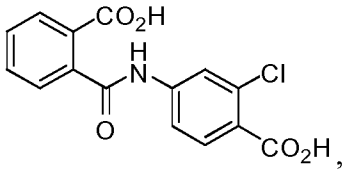
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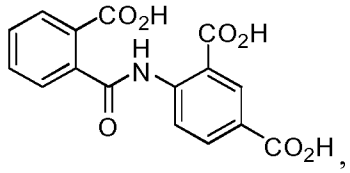
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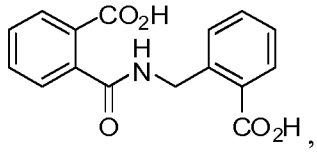
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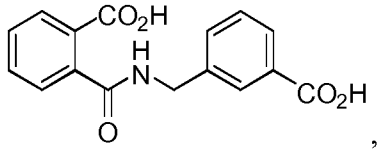
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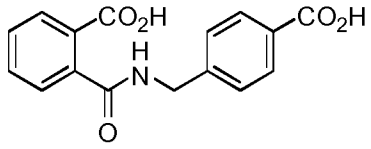
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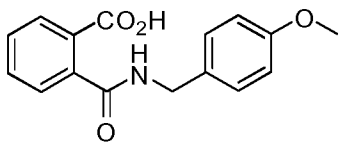
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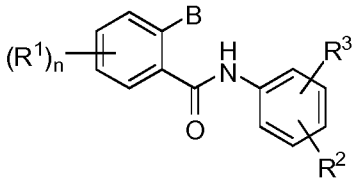
6. A method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula Ia, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula Ia)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NR^4R^{11}, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

B is CO_2R^4;

R^2 is halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$;

each R^3 is independently selected from CN, halo, $C(O)R^4$, CO_2H, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$;

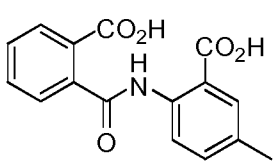
X is O or CR^5R^6;

each R^4 is independently selected from H and optionally substituted alkyl;

each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, optionally substituted alkyl, OH, NR^4R^{11}, and optionally substituted alkoxy; and

R^{11} is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

provided that the compound is not selected from



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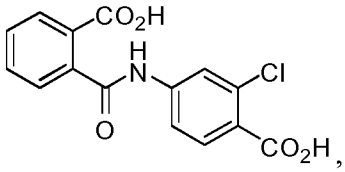

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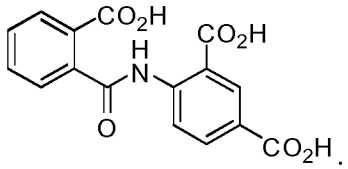

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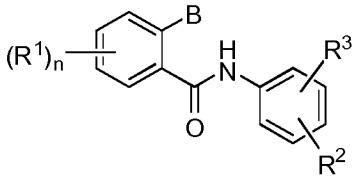
7. A method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula Ib, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula Ib)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NR^4R^{11}, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

B is CO_2R^4;

R^2 is $C(O)NR^4R^{11}$, $(CR^7R^8)OR^4$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$;

R^3 is H;

X is O or CR^5R^6;

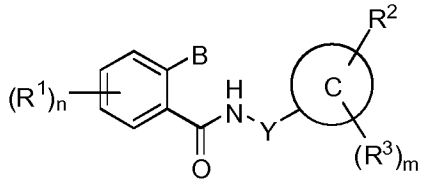
each R^4 is independently selected from H and optionally substituted alkyl;

each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, optionally substituted alkyl, OH, NR^4R^{11}, and optionally substituted alkoxy; and

R^{11} is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

provided that if n is 4 and R^1 is H, then R^2 is not $C(O)NH_2$, p-CH_2OR^4, p-$CH(OH)CH_2OH$, p-CH_2CH_2OH, or p-$CH_2CH_2CH_2OH$.

8. A method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula Ic, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula Ic)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NR^4R^{11}, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

m is 1, 2, 3, or 4;

B is CO_2R^4;

Y is -(CR^5R^6)-;

C is aryl or heteroaryl;

X is O or CR^5R^6;

R^2 is halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, SO_2NH_2, SO_3H, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$,

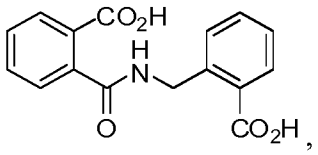
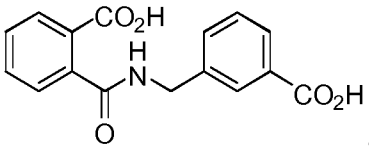
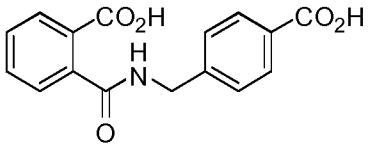
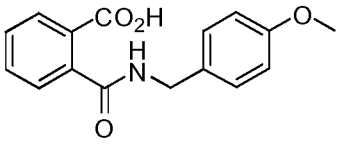
$X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$;

each R^3 is independently selected from H, CN, halo, $C(O)R^4$, CO_2H, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2R^4, $(CR^7R^8)OR^4$, $(CR^7R^8)NR^4R^{11}$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)OR^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)(CR^9R^{10})C(O)R^4$, $X(CR^7R^8)(CR^9R^{10})C(O)OR^4$, $X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, and $C(=NOR^4)R^4$;

each R^4 is independently selected from H and optionally substituted alkyl;

each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, optionally substituted alkyl, OH, CO_2R^4, NR^4R^{11}, and optionally substituted alkoxy; and

R^{11} is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

provided that the compound is not selected from  ,  ,  , and  .

9. The method of any one of claims 1, 2, 5, or 6 wherein:

R^2 is halo, $C(O)R^4$, alkyl, optionally substituted alkoxy, haloalkyl, $(CR^7R^8)OR^4$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)C(O)OR^4$, or $X(CR^7R^8)C(O)NR^4R^{11}$; and

each R^3 is independently selected from CN, halo, $C(O)R^4$, CO_2H, $C(O)NR^4R^{11}$, alkyl, or optionally substituted alkoxy;

or R^3 together with an adjacent R^3 or with R^2 form a ring.

10. The method of claim 9 wherein:

R^2 is F, Cl, $C(O)CH_3$, CH_3, CF_3, OCH_3, OEt, OPr, OCF_3, $OCHF_2$, $(CR^7R^8)OR^4$, $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)C(O)OR^4$, or $X(CR^7R^8)C(O)NR^4R^{11}$; and

each R^3 is independently selected from CN, F, Cl, $C(O)CH_3$, CO_2H, $C(O)NH_2$, CH_3, OCF_3, or OCH_3;

or R^3 together with an adjacent R^3 or with R^2 form a ring.

11. The method of claim 10 wherein R^2 is F, Cl, $C(O)CH_3$, CH_3, CF_3, OCH_3, OEt, OPr, OCF_3, $OCHF_2$, CH_2OCH_3, CH_2OH, CH_2CH_2OH, $CHOHCH_2OH$, $CH_2CH_2CH_2OH$, $CH_2CHOHCH_2OH$, $OCH_2C(O)OH$, or $OCH_2C(O)NH_2$.

12. The method of claim 11 wherein each R^3 is independently selected from CN, F, Cl, $C(O)CH_3$, or CO_2H.

13. The method of claim 12 wherein R^2 is F, Cl, $C(O)CH_3$, CH_3, CF_3, OCH_3, OEt, OPr, OCF_3, or $CH_2CH_2CH_2OH$.

14. The method of any one of claims 1, 3, 5, or 7 wherein:

R^2 is $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, $X(CR^7R^8)C(O)NR^4R^{11}$, $(CR^7R^8)NR^4SO_2R^4$, or $C(=NOR^4)R^4$; and

R^3 is H.

15. The method of claim 14 wherein R^2 is $(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})OR^4$, $X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$, or $(CR^7R^8)NR^4SO_2R^4$.

16. The method of claim 15 wherein R^2 is CH_2CH_2OH, $CH_2CH_2OCH_3$, CH_2CHCH_3OH, $CHCH_3CH_2OH$, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2NH_2$, $CH_2CH_2CHCH_3OH$, $C(CH_3)_2CH_2CH_2OH$, $CH_2CH_2C(CH_3)_2OH$, OCH_2CH_2OH, $OCH_2CH_2OCH_3$, or $OCH_2CH_2NH_2$.

17. The method of claim 14 wherein R^2 is $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)R^4$, or $X(CR^7R^8)C(O)NR^4R^{11}$.

18. The method of claim 17 wherein R^2 is $CH_2C(O)CH_3$, $CH_2C(O)NH_2$, $CH_2CH_2C(O)CH_3$, or $CH_2CH_2C(O)NH_2$.

19. The method of any one of claims 1, 4, 5, or 8 wherein C is aryl.

20. The method of claim 19 wherein C is phenyl.

21. The method of any one of claims 1, 4, 5, or 8 wherein C is heteroaryl.

22. The method of claim 21 wherein C is pyridinyl, pyrimidinyl, pyridazinyl, or pyrazinyl.

23. The method of any one of claims 1, 4, 5, 8, or 19-22 wherein:

R^2 is halo, $C(O)R^4$, CO_2R^4, $C(O)NR^4R^{11}$, alkyl, optionally substituted alkoxy, haloalkyl, SO_2NH_2, SO_3H, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)OR^4$, or $X(CR^7R^8)C(O)NR^4R^{11}$; and

each R^3 is independently selected from H, CN, halo, CO_2H, or haloalkyl.

24. The method of claim 23 wherein:

R^2 is Cl, F, $C(O)CH_3$, CO_2H, $C(O)NR^4R^{11}$, CH_3, optionally substituted alkoxy, CF_3, SO_2NH_2, SO_3H, $(CR^7R^8)C(O)R^4$, $(CR^7R^8)C(O)OR^4$, $(CR^7R^8)C(O)NR^4R^{11}$, $X(CR^7R^8)C(O)OR^4$, or $X(CR^7R^8)C(O)NR^4R^{11}$; and

each R^3 is independently selected from H, CN, Cl, F, CO_2H, or CF_3.

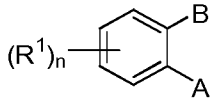
25. The method of claim 24 wherein:

R^2 is Cl, F, $C(O)CH_3$, CO_2H, CH_3, OCH_3, CF_3; and

each R^3 is independently selected from H, CN, or CO_2H.

26. The method of claim 24 wherein R^2 is $CH_2C(O)NH_2$, $CH_2C(O)CH_3$, $CH_2C(O)OH$, $CH_2CH_2C(O)OH$, or $CH_2CH_2C(O)NH_2$.

27. A method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula II, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula II)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

B is $NHC(O)R^2$, $NR^3C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NHR^2$, $NHC(O)NR^2R^4$, $NR^3C(O)NH_2$, $NR^3C(O)NHR^2$, $NR^3C(O)NR^2R^4$, $NHC(O)OR^2$, $NR^3C(O)OR^2$, $NHSO_2R^3$, $NR^3SO_2R^3$, $NHSO_2R^4$, $NR^3SO_2R^4$, $NHSO_2NH_2$, $NHSO_2NHR^2$, $NHSO_2NR^2R^4$, $NR^3SO_2NH_2$, $NR^3SO_2NHR^2$, or $NR^3SO_2NR^2R^4$;

each R^2 and R^4 is independently optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted alkyl;

R^3 is optionally substituted alkyl or optionally substituted aralkyl;

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

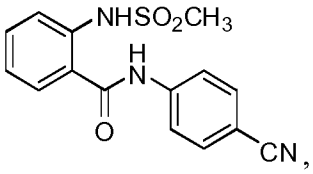
A is CO_2H, CO_2R^3, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^4$, or $SO_2NR^aR^b$; and

each R^a and R^b is independently optionally substituted alkyl or together with the N to which they are attached make a ring;

provided that

a) if B is $NHC(O)R^2$ or $NR^3C(O)R^2$, then A is not CO_2H; and

b) the compound is not selected from



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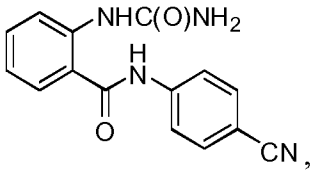

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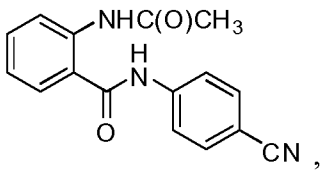

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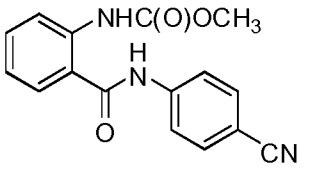

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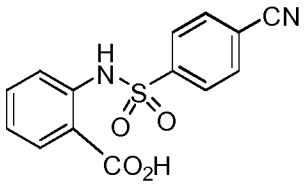

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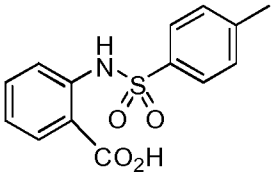
and



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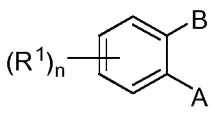
28. A method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula IIa, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula IIa)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

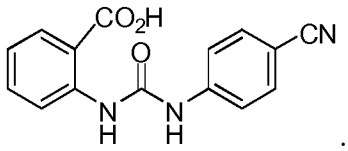
B is $NHC(O)NH_2$, $NHC(O)NHR^2$, $NHC(O)NR^2R^4$, $NR^3C(O)NH_2$, $NR^3C(O)NHR^2$, or $NR^3C(O)NR^2R^4$;

each R^2 and R^4 is independently optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted alkyl;

R^3 is optionally substituted alkyl or optionally substituted aralkyl;

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4; and

A is CO_2H or CO_2R^3;

provided that the compound is not 

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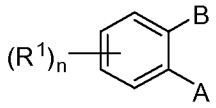
29. A method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula IIb, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula IIb)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

B is $NHC(O)R^2$ or $NR^3C(O)R^2$;

R^2 is optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted alkyl;

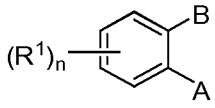
R^3 is optionally substituted alkyl or optionally substituted aralkyl;

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

A is $SO_2NR^aR^b$; and

each R^a and R^b is independently optionally substituted alkyl or together with the N to which they are attached make a ring.

30. A method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula IIc, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula IIc)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

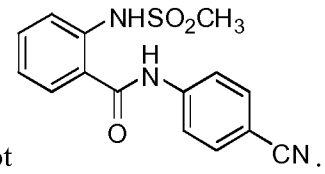
B is $NHSO_2R^3$, $NR^3SO_2R^3$, $NHSO_2R^4$, $NR^3SO_2R^4$, $NHSO_2NH_2$, $NHSO_2NHR^2$, $NHSO_2NR^2R^4$, $NR^3SO_2NH_2$, $NR^3SO_2NHR^2$, or $NR^3SO_2NR^2R^4$;

each R^2 and R^4 is independently optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted alkyl;

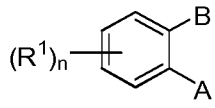
each R^3 is independently optionally substituted alkyl or optionally substituted aralkyl;

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4; and

A is $C(O)NHR^2$ or $C(O)NR^2R^4$;

provided that the compound is not  .

31. A method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula II, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula II)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

B is $NHC(O)R^2$, $NR^3C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NHR^2$, $NHC(O)NR^2R^4$, $NR^3C(O)NH_2$, $NR^3C(O)NHR^2$, $NR^3C(O)NR^2R^4$, $NHC(O)OR^2$, $NR^3C(O)OR^2$, $NHSO_2R^3$, $NR^3SO_2R^3$, $NHSO_2R^4$, $NR^3SO_2R^4$, $NHSO_2NH_2$, $NHSO_2NHR^2$, $NHSO_2NR^2R^4$, $NR^3SO_2NH_2$, $NR^3SO_2NHR^2$, or $NR^3SO_2NR^2R^4$;

each R^2 and R^4 is independently optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted alkyl;

R^3 is optionally substituted alkyl or optionally substituted aralkyl;

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

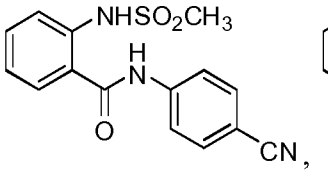
A is CO_2H, CO_2R^3, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^4$, or $SO_2NR^aR^b$; and

each R^a and R^b is independently optionally substituted alkyl or together with the N to which they are attached make a ring;

provided that

a) if B is $NHC(O)R^2$ or $NR^3C(O)R^2$, then A is not CO_2H; and

b) the compound is not selected from



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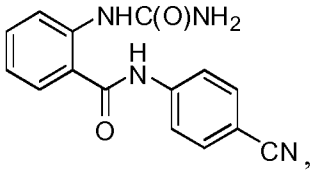

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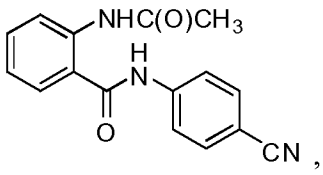

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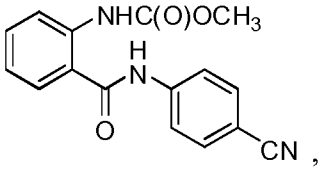

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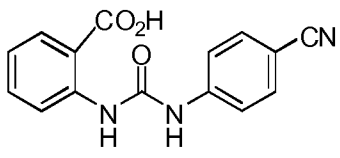

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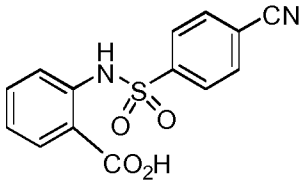

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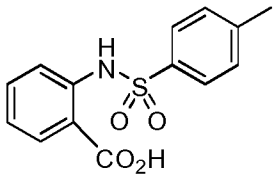
and


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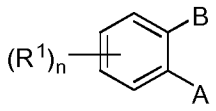
32. A method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula IIa, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula IIa)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

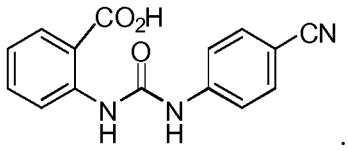
B is $NHC(O)NH_2$, $NHC(O)NHR^2$, $NHC(O)NR^2R^4$, $NR^3C(O)NH_2$, $NR^3C(O)NHR^2$, or $NR^3C(O)NR^2R^4$;

each R^2 and R^4 is independently optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted alkyl;

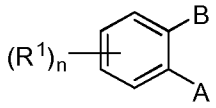
R^3 is optionally substituted alkyl or optionally substituted aralkyl;

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4; and

A is CO_2H or CO_2R^3;

provided that the compound is not  .

33. A method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula IIb, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula IIb)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

B is $NHC(O)R^2$ or $NR^3C(O)R^2$;

R^2 is optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted alkyl;

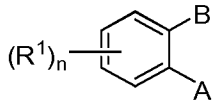
R^3 is optionally substituted alkyl or optionally substituted aralkyl;

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4;

A is $SO_2NR^aR^b$; and

each R^a and R^b is independently optionally substituted alkyl or together with the N to which they are attached make a ring.

34. A method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula IIc, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula IIc)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

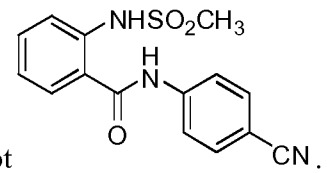
B is $NHSO_2R^3$, $NR^3SO_2R^3$, $NHSO_2R^4$, $NR^3SO_2R^4$, $NHSO_2NH_2$, $NHSO_2NHR^2$, $NHSO_2NR^2R^4$, $NR^3SO_2NH_2$, $NR^3SO_2NHR^2$, or $NR^3SO_2NR^2R^4$;

each R^2 and R^4 is independently optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted alkyl;

each R^3 is independently optionally substituted alkyl or optionally substituted aralkyl;

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4; and

A is $C(O)NHR^2$ or $C(O)NR^2R^4$;

provided that the compound is not 

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35. The method of any one of claims 27, 28, 31, or 32 wherein B is $NHC(O)NHR^2$, $NHC(O)NR^2R^4$, $NR^3C(O)NHR^2$, or $NR^3C(O)NR^2R^4$.

36. The method of claims 35 wherein B is $NHC(O)NHR^2$ or $NR^3C(O)NHR^2$.

37. The method of claims 35 wherein B is $NHC(O)NR^2R^4$ or $NR^3C(O)NR^2R^4$.

38. The method of claims 36 wherein B is $NHC(O)NHR^2$.

39. The method of any one of claims 36-38 wherein R^2 is optionally substituted phenyl.

40. The method of claim 39 wherein the phenyl of R^2 is bisubstituted.

41. The method of claim 39 wherein the phenyl of R^2 is monosubstituted.

42. The method of either claim 40 or 41 wherein substitution on the phenyl of R^2 is independently selected from F, Cl, CO_2H, CN, OCH_3, $C(O)CH_3$, CF_3, CH_3, CH_2OH, CH_2CH_2OH, and $CH_2CH_2CH_2OH$.

43. The method of any one of claims 27, 29, 31, or 33 wherein B is $NHC(O)R^2$.

44. The method of any one of claims 27, 29, 31, or 33 wherein B is $NR^3C(O)R^2$.

45. The method of claims 44 wherein R^3 is optionally substituted alkyl.

46. The method of any one of claims 43-45 wherein each R^a and R^b is independently optionally substituted alkyl.

47. The method of any one of claims 43-45 wherein R^a and R^b together with the N to which they are attached make a ring.

48. The method of any one of claims 43-47 wherein R^2 is optionally substituted phenyl.

49. The method of claim 48 wherein the phenyl of R^2 is bisubstituted.

50. The method of claim 48 wherein the phenyl of R^2 is monosubstituted.

51. The method of either claim 49 or 50 wherein substitution on the phenyl of R^2 is independently selected from F, Cl, CO_2H, CN, OCH_3, $C(O)CH_3$, CF_3, CH_3, CH_2OH, CH_2CH_2OH, and $CH_2CH_2CH_2OH$.

52. The method of any one of claims 27, 30, 31, or 34 wherein B is $NHSO_2R^3$, $NR^3SO_2R^3$, $NHSO_2R^4$, or $NR^3SO_2R^4$.

53. The method of any one of claims 27, 30, 31, or 34 wherein B is $NHSO_2NH_2$, $NHSO_2NHR^2$, $NHSO_2NR^2R^4$, $NR^3SO_2NH_2$, $NR^3SO_2NHR^2$, or $NR^3SO_2NR^2R^4$.

54. The method of claim 52 wherein B is $NHSO_2R^3$ or $NR^3SO_2R^3$.

55. The method of claim 54 wherein B is $NHSO_2R^3$.

56. The method of either claim 54 or 55 wherein R^3 is optionally substituted alkyl.

57. The method of claim 56 wherein R^3 is CH_3.

58. The method of claim 52 wherein B is $NHSO_2R^4$ or $NR^3SO_2R^4$.

59. The method of claim 58 wherein R^4 is optionally substituted phenyl.

60. The method of any one of claims 52-59 wherein A is $C(O)NHR^2$.

61. The method of any one of claims 52-59 wherein A is $C(O)NR^2R^4$.

62. The method of either claim 60 or 61 wherein R^2 is optionally substituted phenyl.

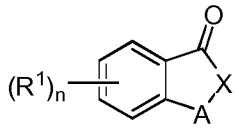
63. The method of claim 62 wherein the phenyl of R^2 is bisubstituted.

64. The method of claim 62 wherein the phenyl of R^2 is monosubstituted.

65. The method of either claim 63 or 64 wherein substitution on the phenyl of R^2 is independently selected from F, Cl, CO_2H, CN, OCH_3, $C(O)CH_3$, CF_3, CH_3, CH_2OH, CH_2CH_2OH, and $CH_2CH_2CH_2OH$.

66. A method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective

amount of a compound of Formula III, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula III)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

X is O, NH, or NR^6;

A is C(O), CH_2, or $CH\text{-}CR^3R^4\text{-}C(O)R^2$;

R^2 is optionally substituted aryl or optionally substituted heteroaryl;

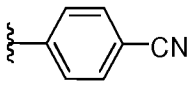
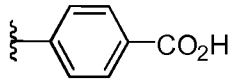
each R^3 and R^4 is independently H or optionally substituted alkyl;

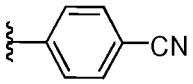
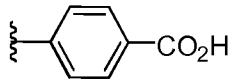
R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4; and

R^6 is optionally substituted phenyl;

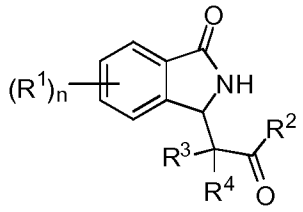
provided that

a) if A is $CH\text{-}CR^3R^4\text{-}C(O)R^2$, then X is O or NH;

b) if n is 0, A is $CHCH_2C(O)R^2$ and X is O, then R^2 is not  or  ; and

c) if A is C(O) or CH_2, then X is NR^6 and R^6 is not  or  .

67. A method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound of Formula IIIa, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula IIIa)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

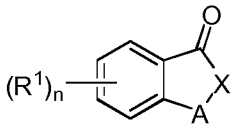
n is 0, 1, 2, 3, or 4;

R^2 is optionally substituted aryl or optionally substituted heteroaryl;

each R^3 and R^4 is independently H or optionally substituted alkyl; and

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4.

68. A method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula III, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula III)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

X is O, NH, or NR^6;

A is C(O), CH_2, or $CH\text{-}CR^3R^4\text{-}C(O)R^2$;

R^2 is optionally substituted aryl or optionally substituted heteroaryl;

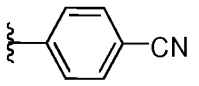
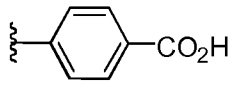
each R^3 and R^4 is independently H or optionally substituted alkyl;

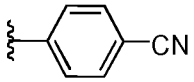
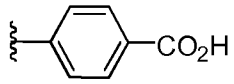
R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4; and

R^6 is optionally substituted phenyl;

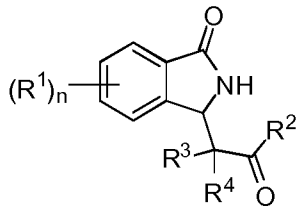
provided that

a) if A is $CH\text{-}CR^3R^4\text{-}C(O)R^2$, then X is O or NH;

b) if n is 0, A is $CHCH_2C(O)R^2$ and X is O, then R^2 is not  or  ; and

c) if A is C(O) or CH_2, then X is NR^6 and R^6 is not  or  .

69. A method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound of Formula IIIa, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof:



(Formula IIIa)

wherein

each R^1 is independently halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, CN, NO_2, SR^4, $S(O)R^4$, SO_2R^4, NHR^5, NR^4R^5, CO_2H, or CO_2R^4;

n is 0, 1, 2, 3, or 4;

R^2 is optionally substituted aryl or optionally substituted heteroaryl;

each R^3 and R^4 is independently H or optionally substituted alkyl; and

R^5 is H, optionally substituted alkyl, $C(O)R^4$, $C(O)OR^4$, $C(O)NR^4R^4$, or SO_2R^4.

70. The method of either claim 66 or 68 wherein X is NR^6 and A is C(O).

71. The method of either claim 66 or 68 wherein X is NR^6 and A is CH_2.

72. The method of either claim 66 or 68 wherein X is O and A is $CH\text{-}CR^3R^4\text{-}C(O)R^2$.

73. The method of either claim 66 or 68 wherein X is NH and A is $CH\text{-}CR^3R^4\text{-}C(O)R^2$.

74. The method of any one of claims 67, 69, 72, or 73 wherein R^3 and R^4 are both hydrogen.

75. The method of any one of claims 67, 69, 72, or 73 wherein R^3 is optionally substituted alkyl and R^4 is hydrogen.

76. The method of any one of claims 67, 69, 72, or 73 wherein R^3 and R^4 are independently optionally substituted alkyl.

77. The method of any one of claims 74-76 wherein R^2 is optionally substituted heteroaryl.

78. The method of any one of claims 74-76 wherein R^2 is optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted pyridazinyl, or optionally substituted pyrazinyl.

79. The method of any one of claims 74-76 wherein R^2 is optionally substituted phenyl.

80. The method of any one of claims 79 wherein the phenyl of R^2 is bisubstituted.

81. The method of any one of claims 79 wherein the phenyl of R^2 is monosubstituted.

82. The method of either claim 80 or 81 wherein substitution on the phenyl is independently selected from F, Cl, CO_2H, CN, OCH_3, $C(O)CH_3$, CF_3, CH_3, CH_2OH, CH_2CH_2OH, and $CH_2CH_2CH_2OH$.

83. The method of any one of claims 1-65 wherein B is CO_2R^4 and R^4 is optionally substituted alkyl.

84. The method of any one of claims 1-65 wherein B is CO_2R^4 and R^4 is hydrogen.

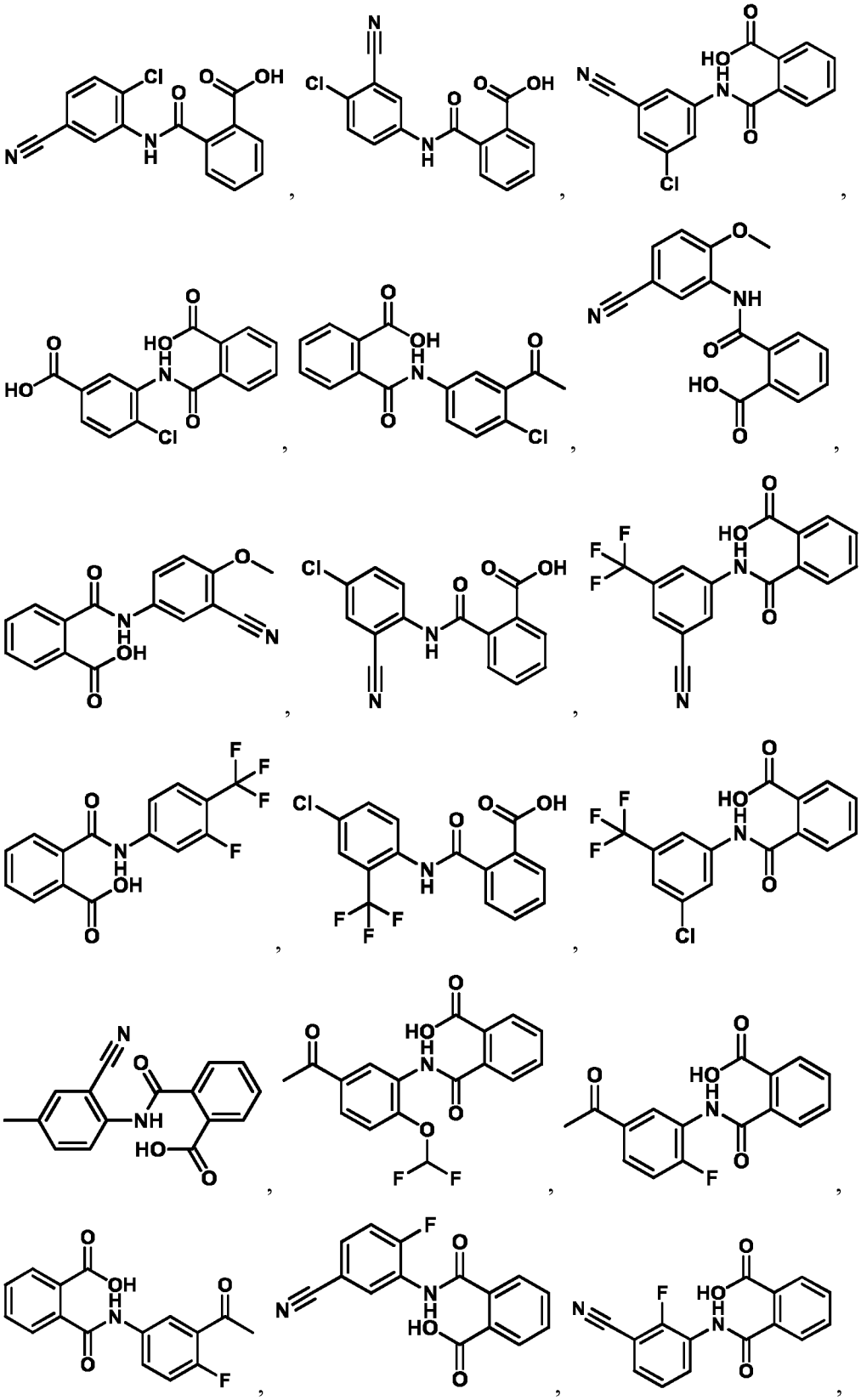
85. The method of any one of claims 1-84 wherein n is 0, 1, or 2.

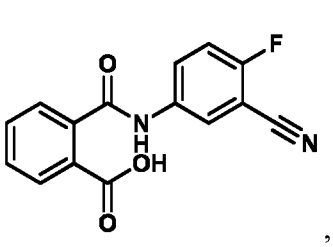
86. The method of claim 84 wherein n is 0.

87. The method of claim 84 wherein n is 1.

88. The method of claim 85 wherein R^1 is independently selected from Cl, F, CH_2OH, CH_2NH_2, OCH_3, OCF_3, $OCHF_2$, CN, NO_2, CO_2H, and CO_2CH_3.

89. The method of either claim 1 or 5, wherein the compound is selected from

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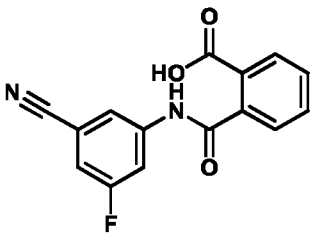
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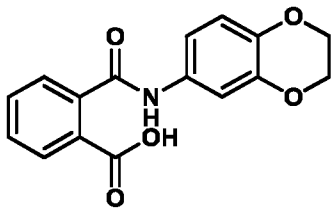
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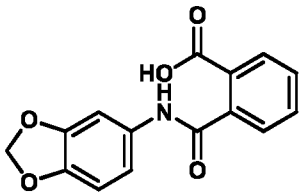
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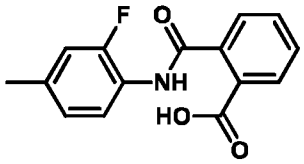
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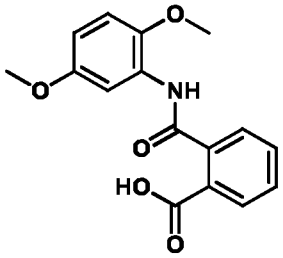
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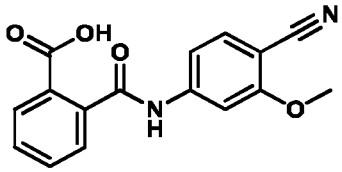
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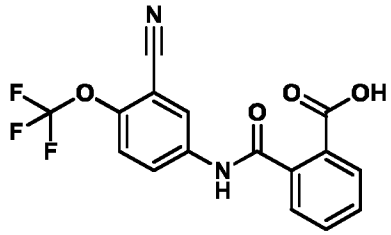
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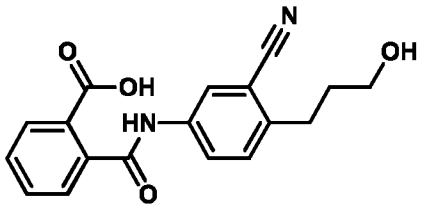
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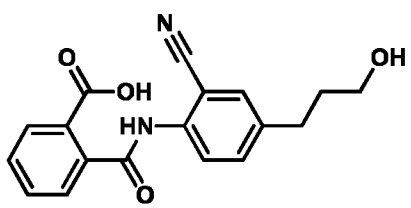
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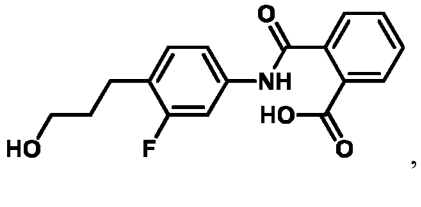
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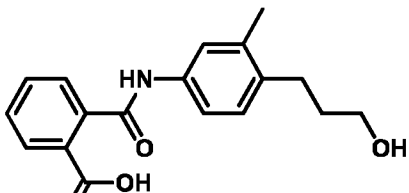
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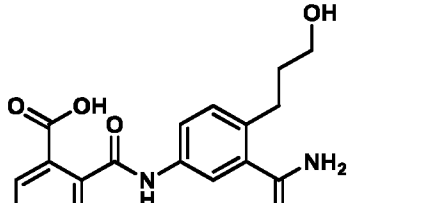
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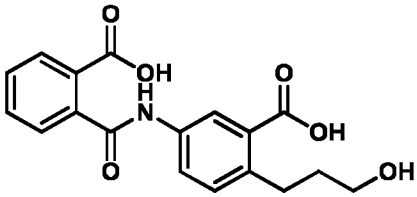
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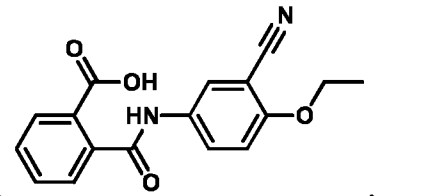
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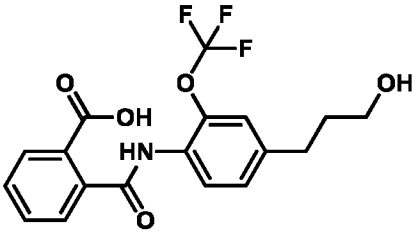
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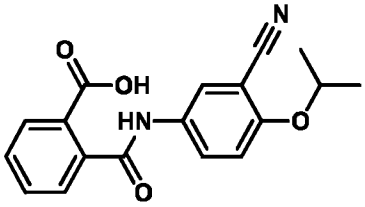
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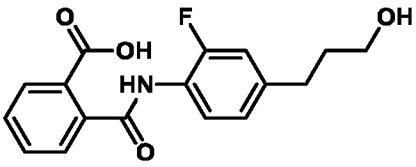
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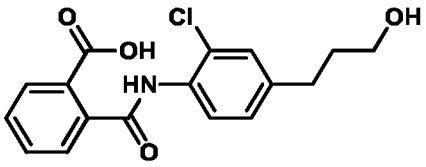
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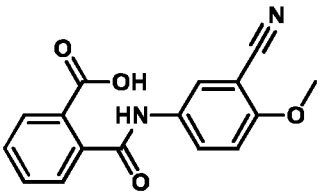
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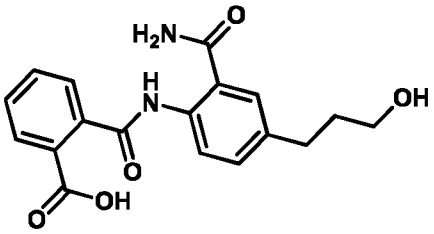
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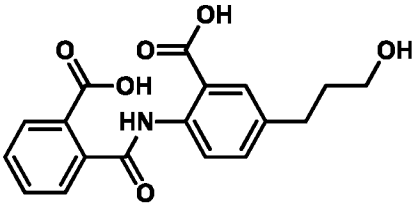
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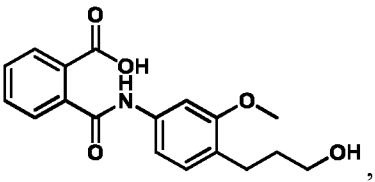
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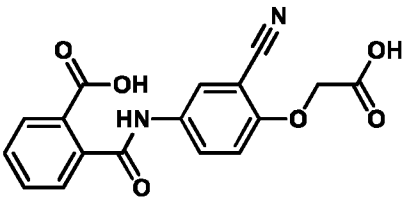
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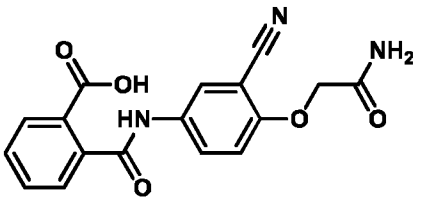
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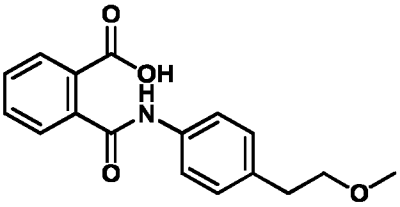
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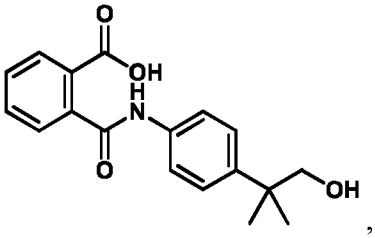
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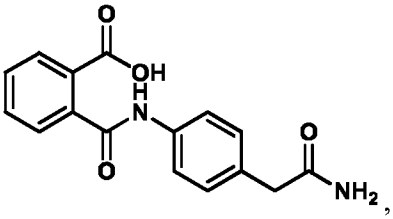
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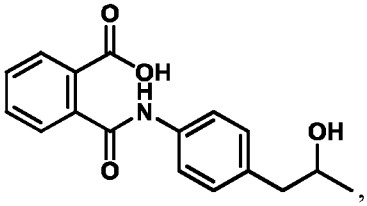
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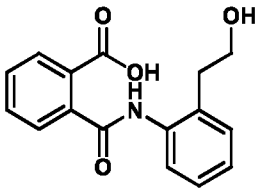
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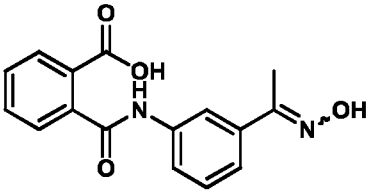
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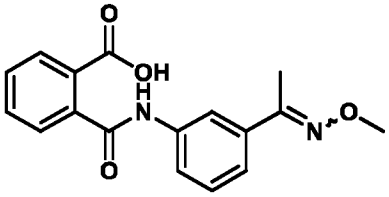
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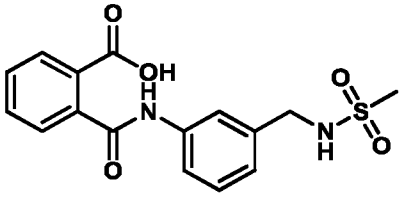
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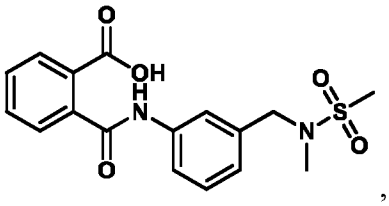
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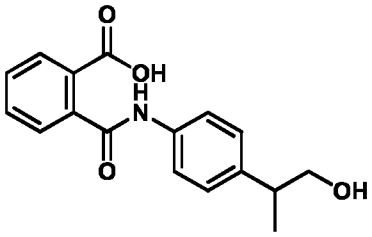
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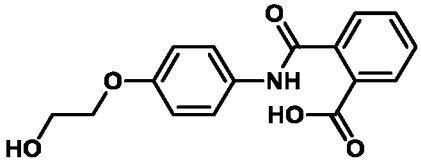
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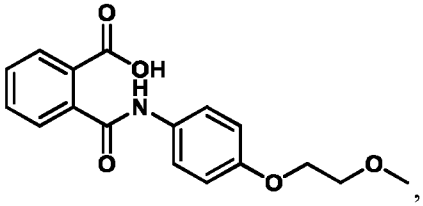
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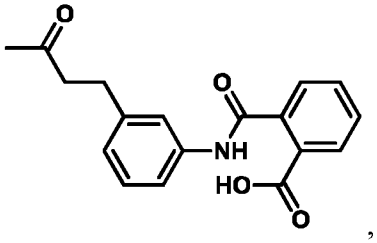
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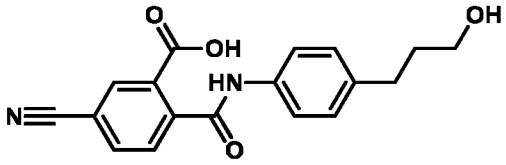
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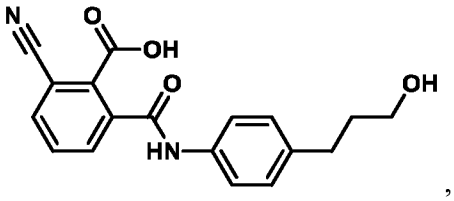
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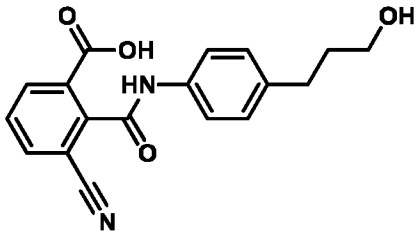
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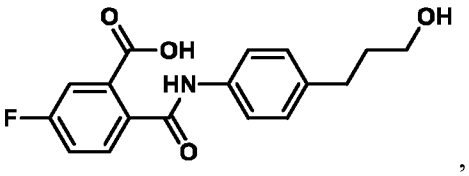
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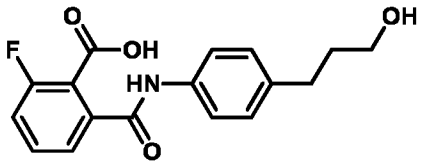
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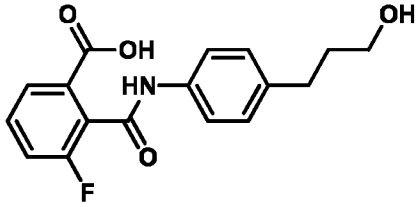
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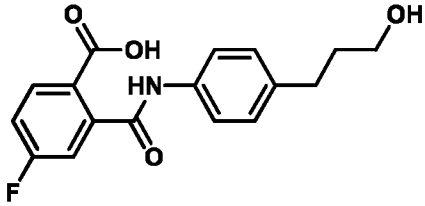
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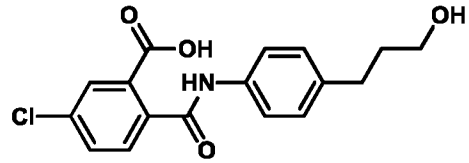
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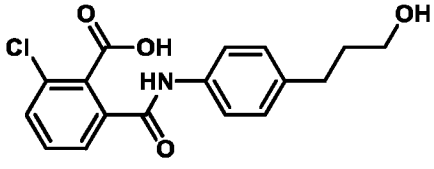
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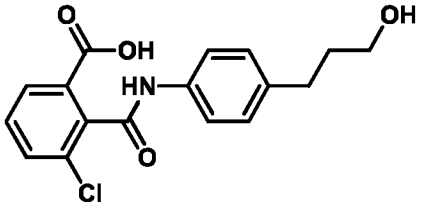
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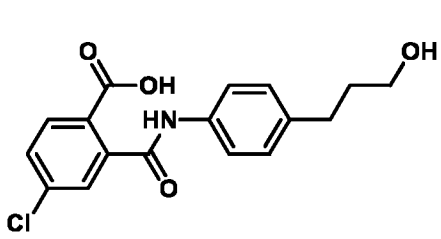
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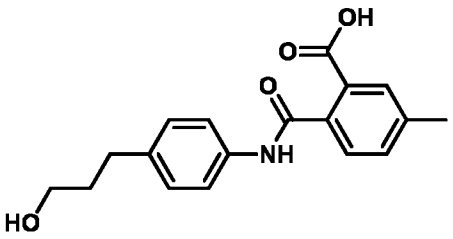
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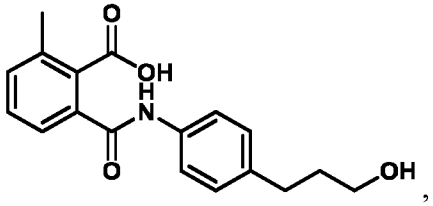
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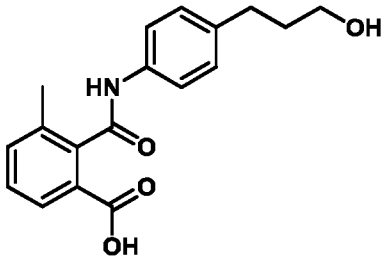
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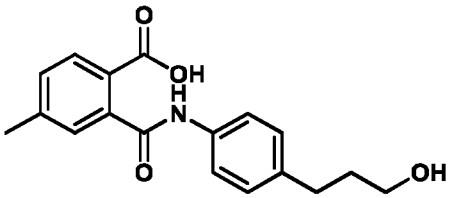
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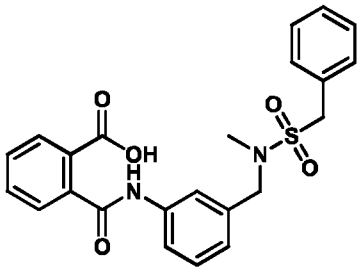
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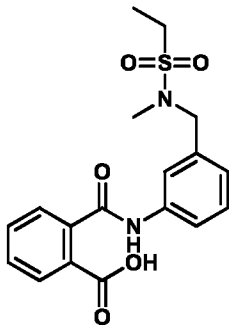
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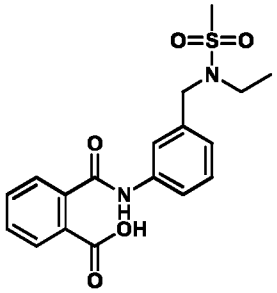
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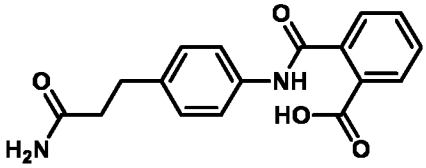
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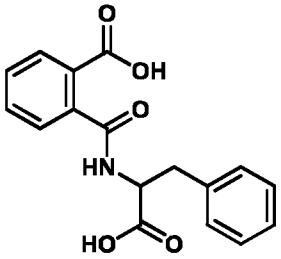
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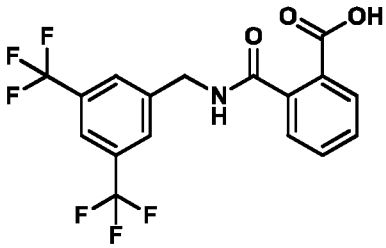
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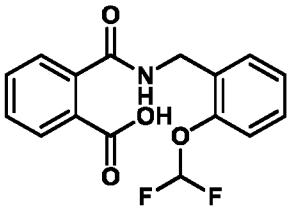
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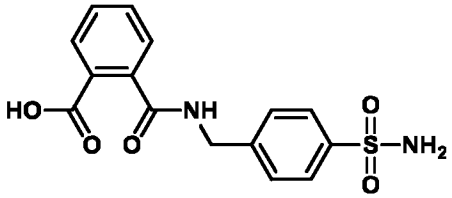
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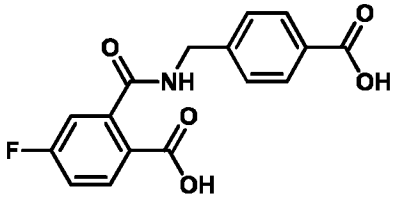
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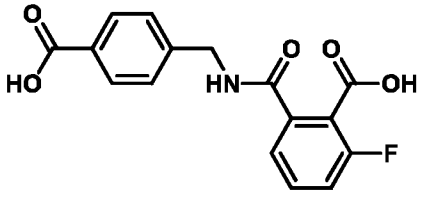
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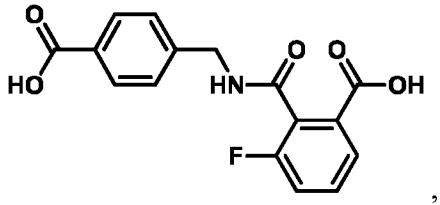
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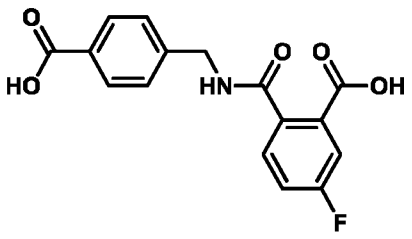
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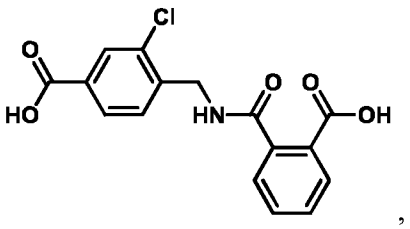
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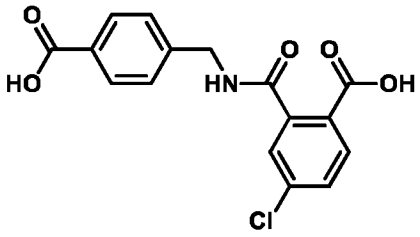
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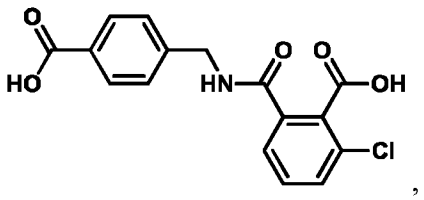
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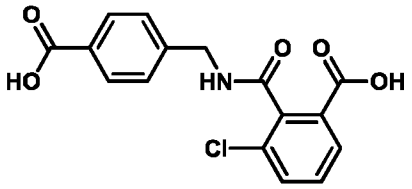
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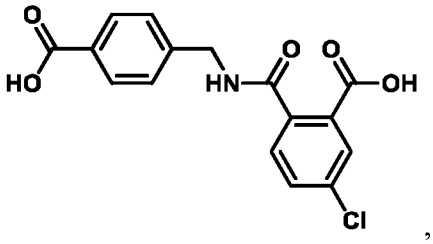
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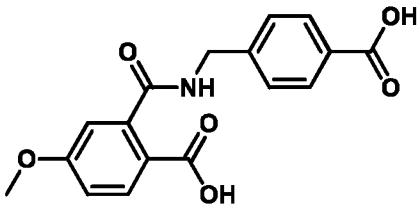
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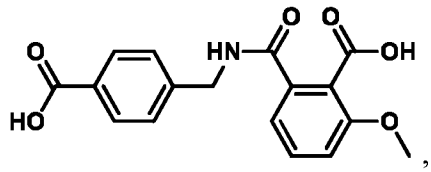
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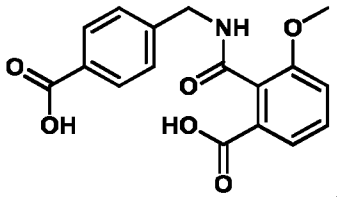
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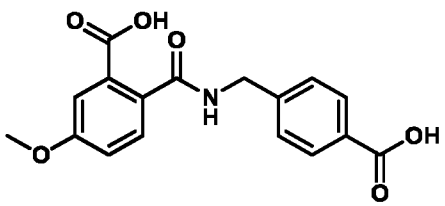
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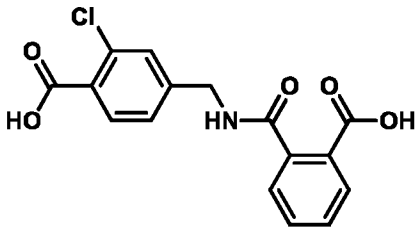
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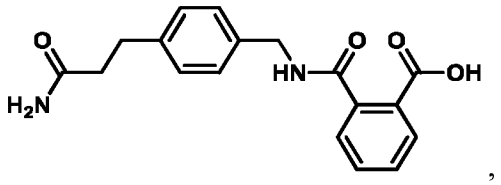
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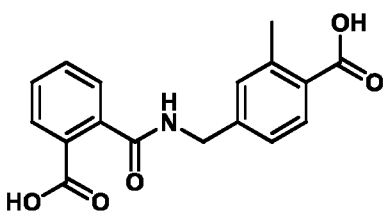
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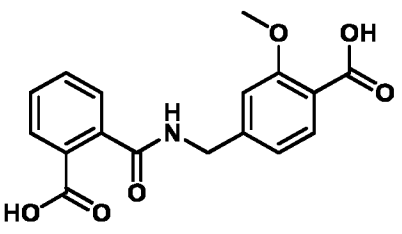
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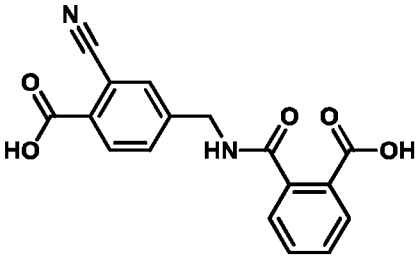
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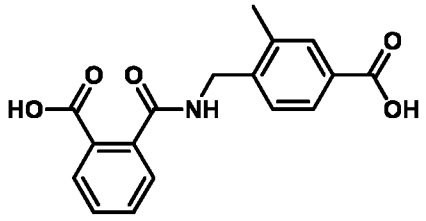
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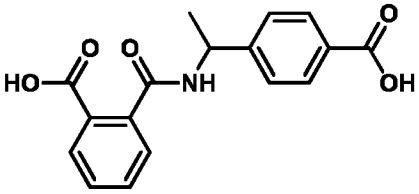
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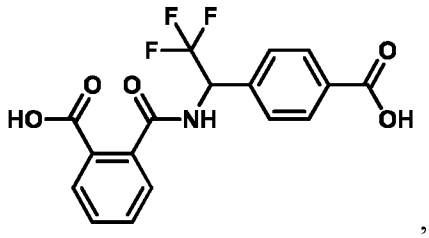
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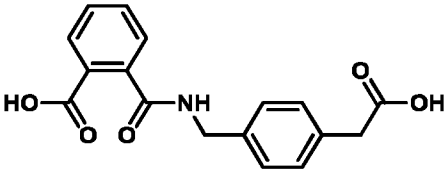
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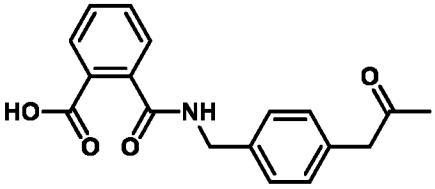
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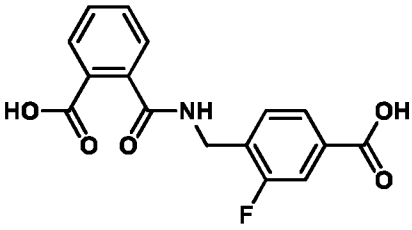
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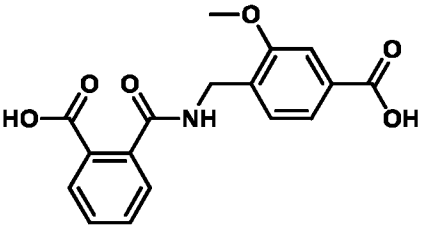
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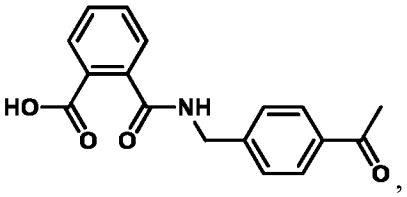
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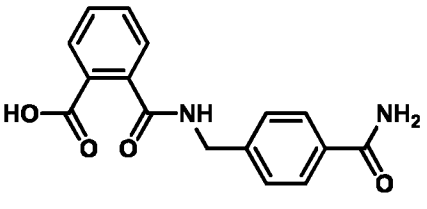
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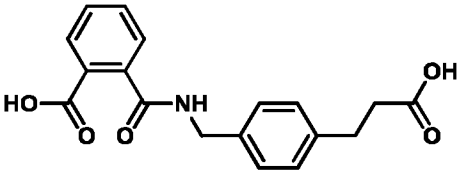
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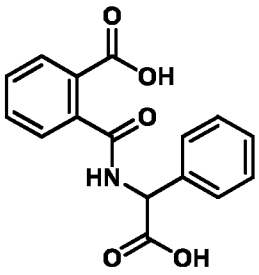
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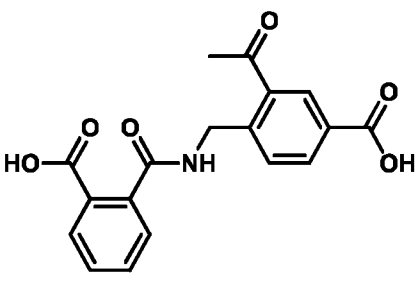
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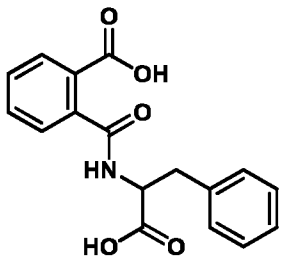
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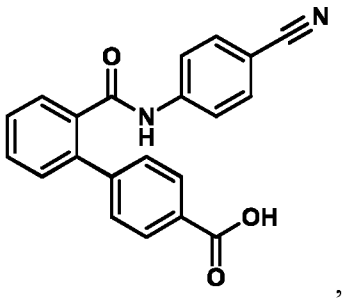
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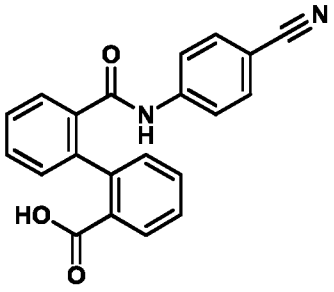
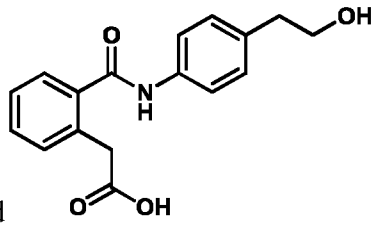

, and 
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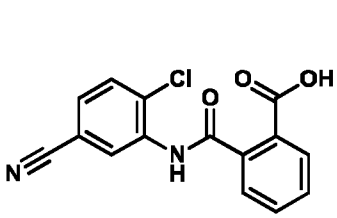
90. The method of either claim 2 or 6, wherein the compound is selected from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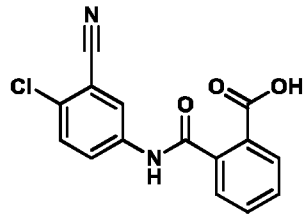
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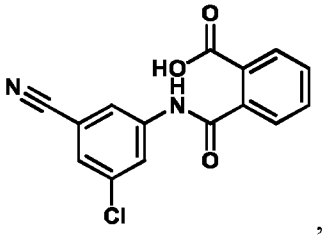
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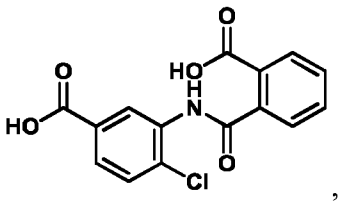
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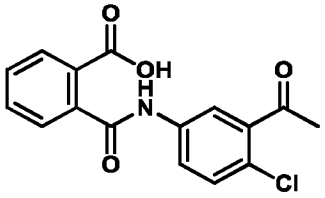
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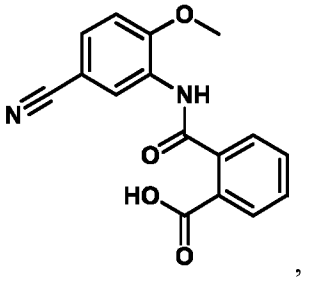
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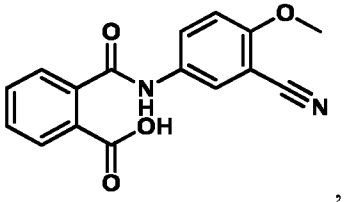
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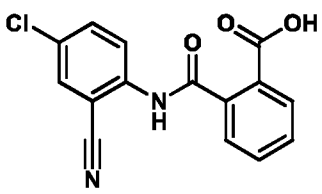
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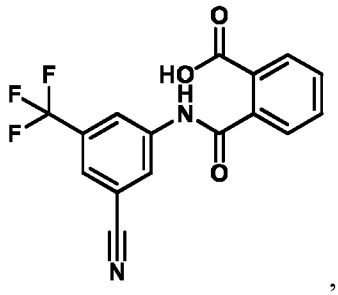
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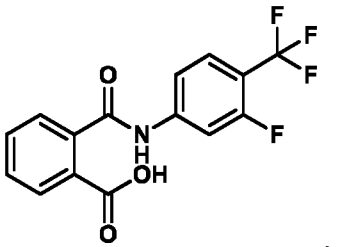
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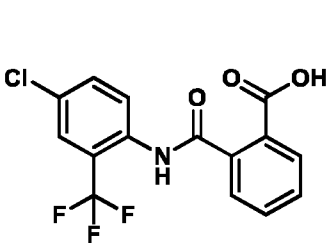
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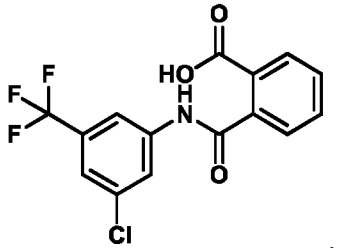
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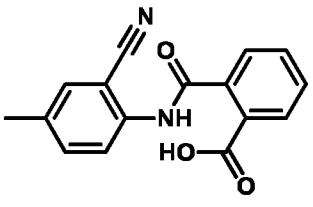
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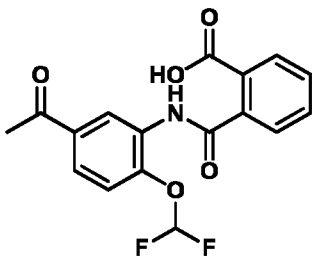
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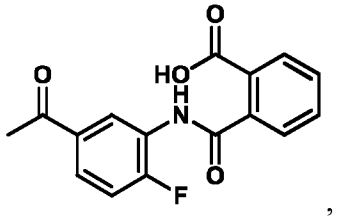
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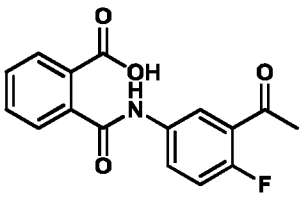
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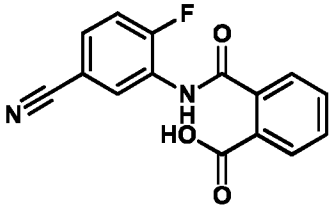
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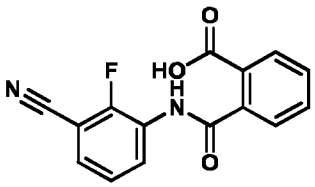
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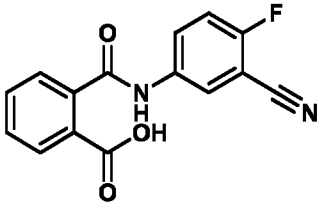
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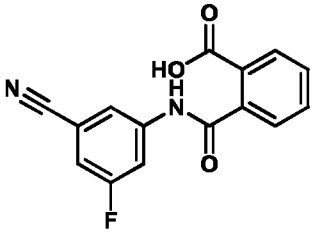
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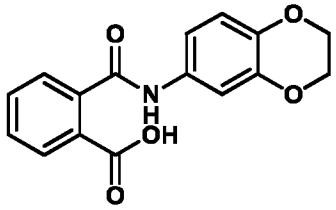
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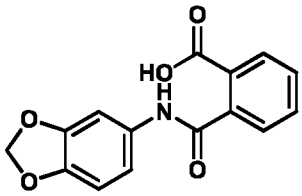
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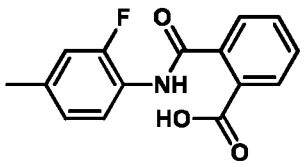
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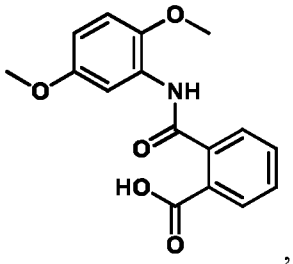
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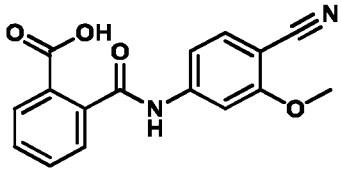
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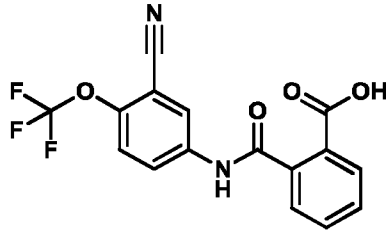
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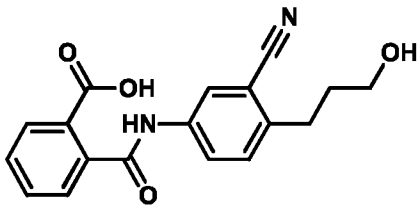
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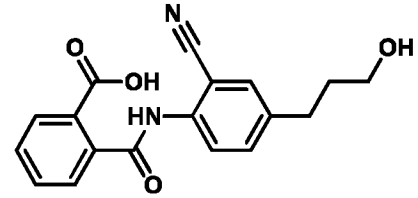
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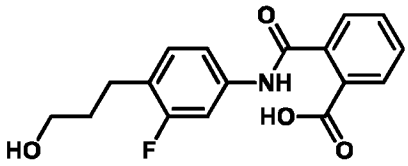
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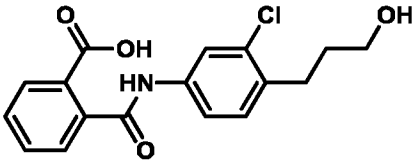
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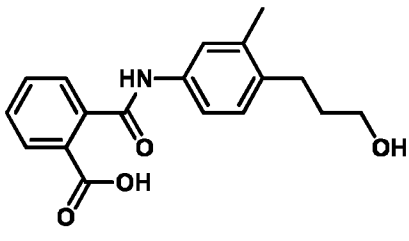
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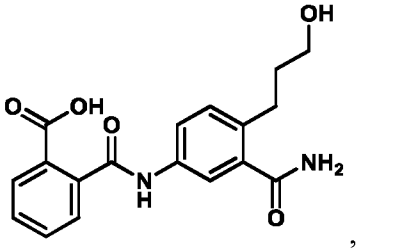
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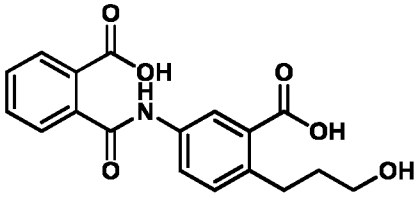
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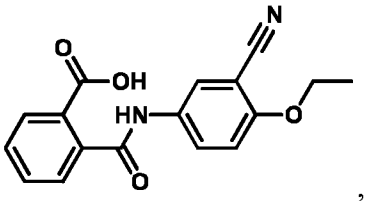
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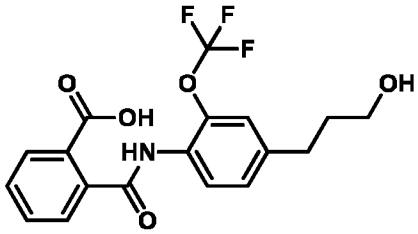
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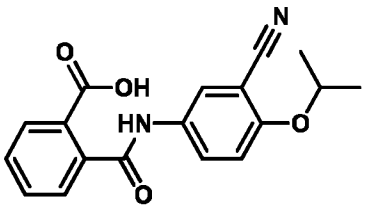
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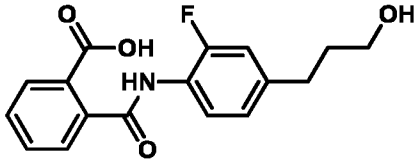
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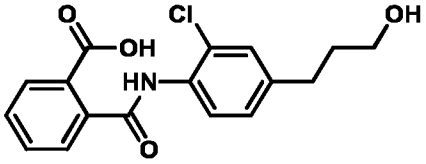
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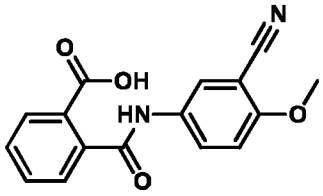
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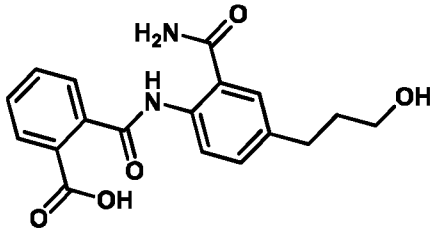
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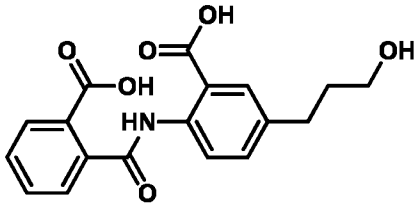
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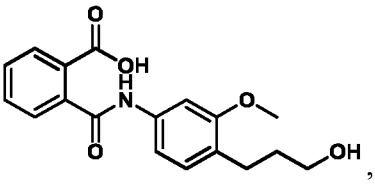
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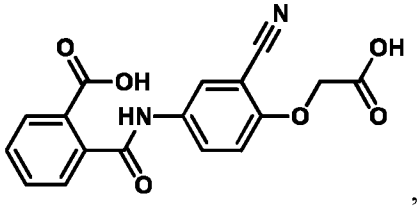
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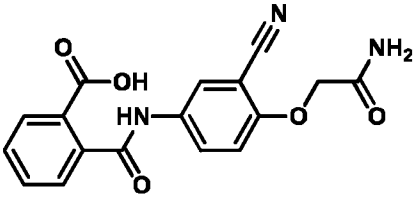
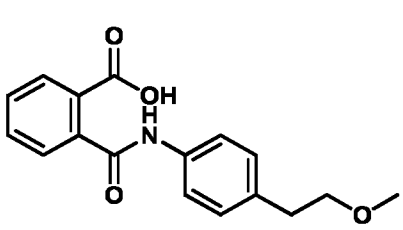

; or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

91. The method of either claim 3 or 7, wherein the compound is selected from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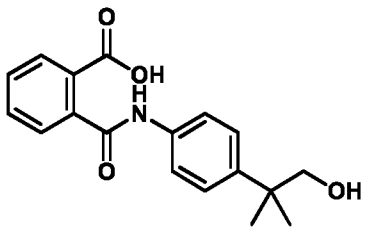
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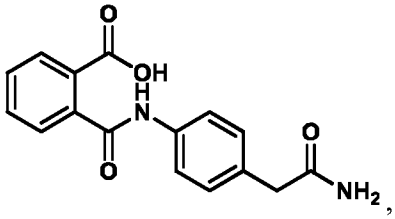
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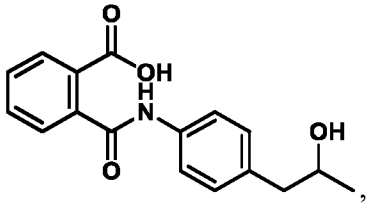
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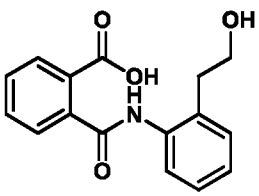
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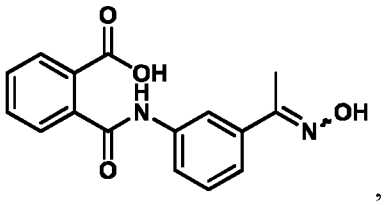
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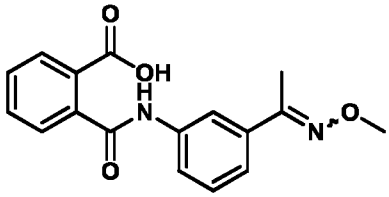
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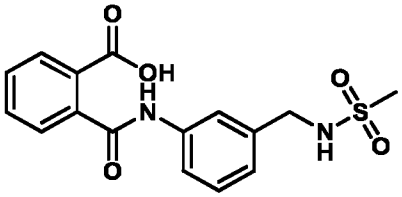
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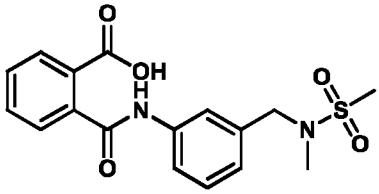
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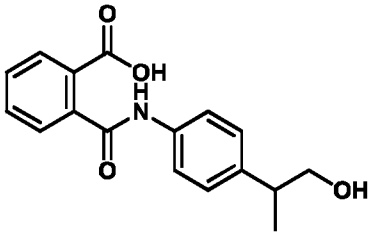
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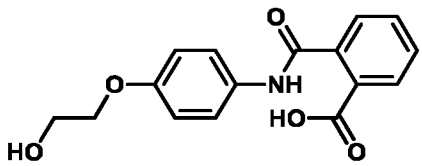
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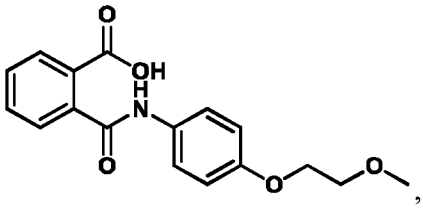
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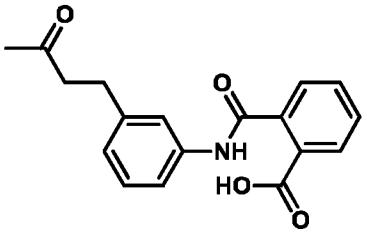
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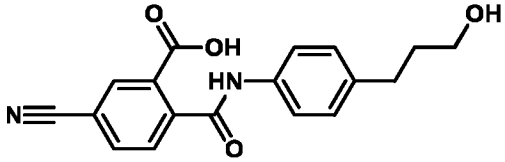
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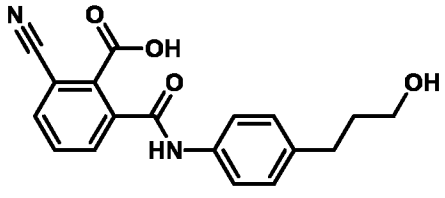
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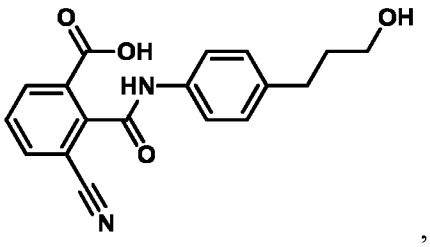
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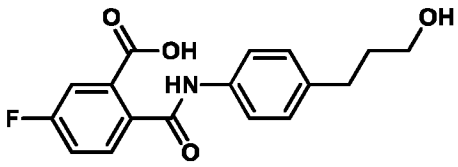
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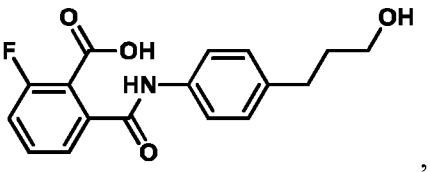
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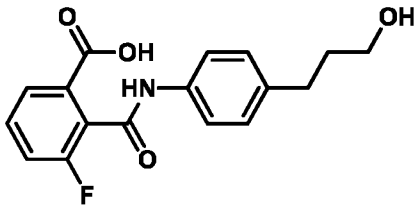
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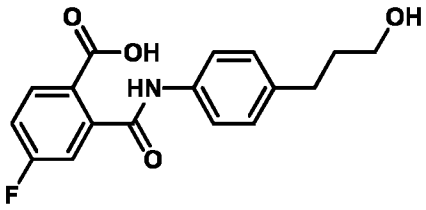
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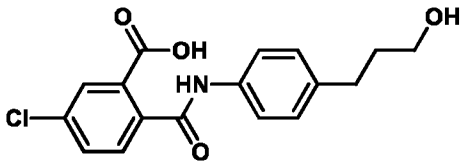
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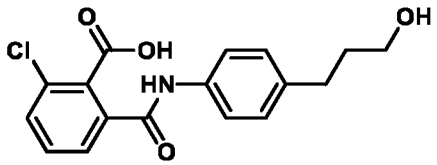
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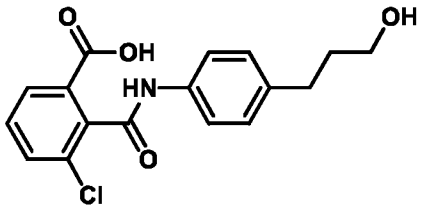
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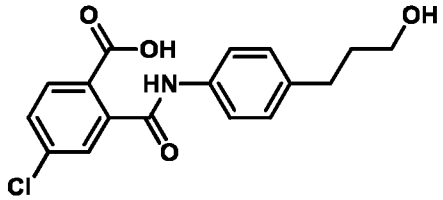
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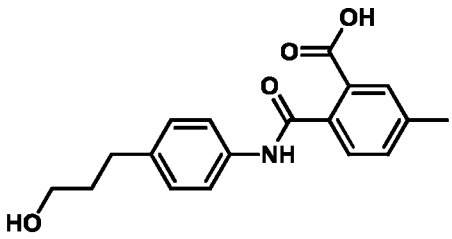
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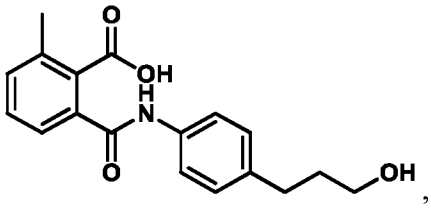
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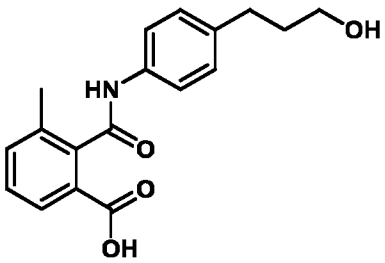
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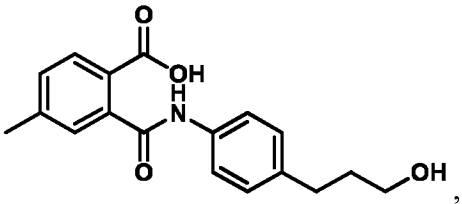
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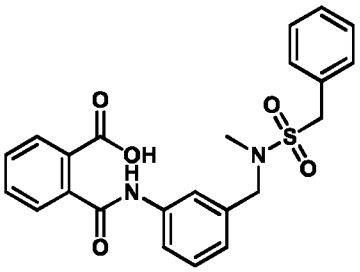
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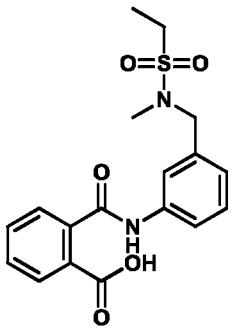
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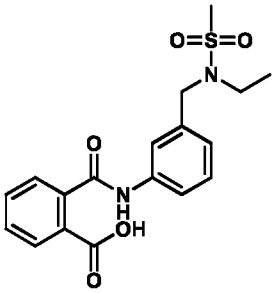
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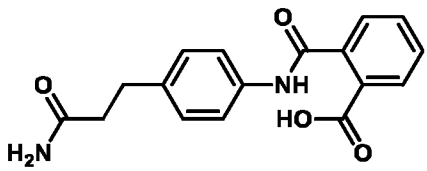
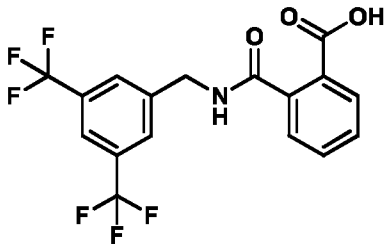


; or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

92. The method of either claim 4 or 8, wherein the compound is selected from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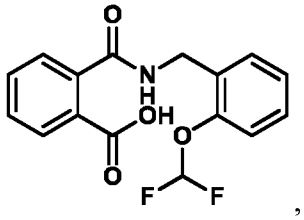
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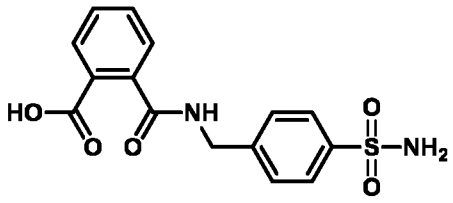
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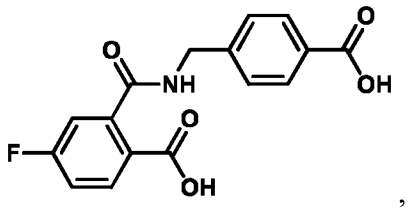
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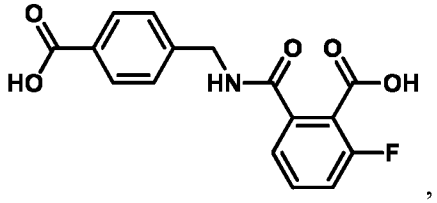
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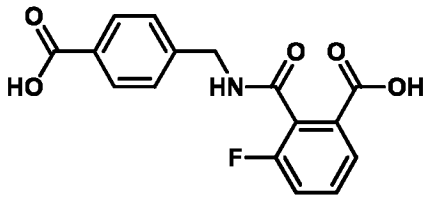
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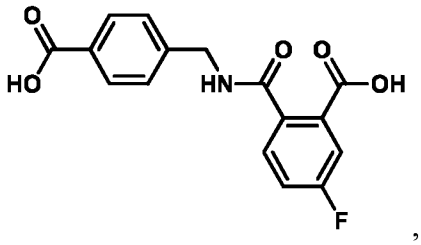
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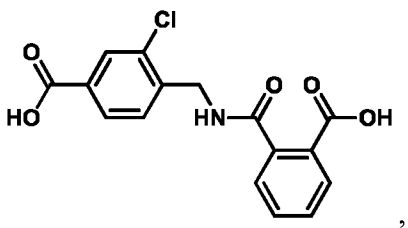
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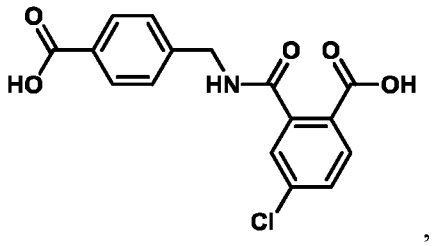
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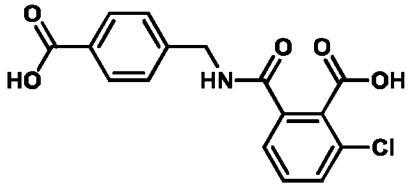
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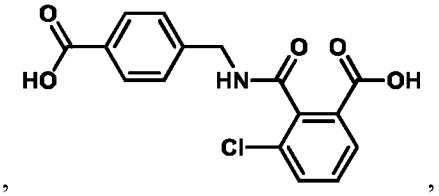
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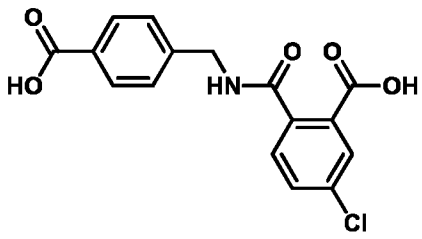
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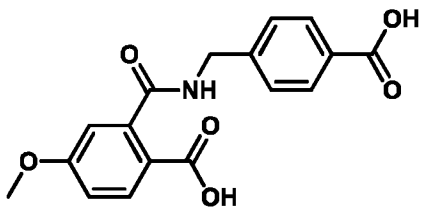
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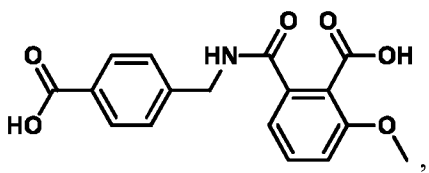
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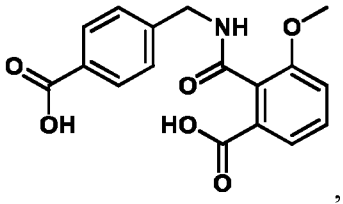
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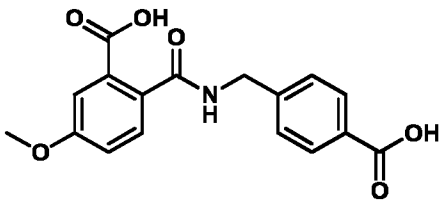
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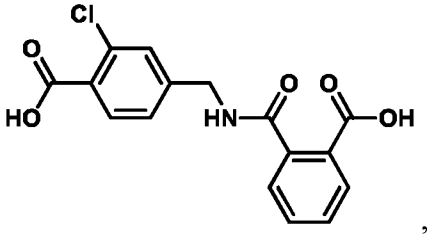
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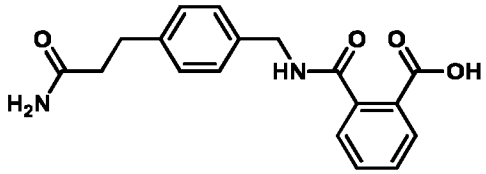
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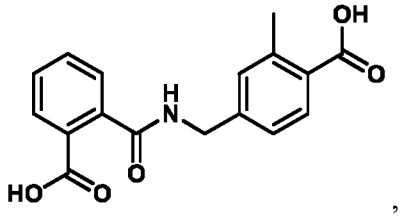
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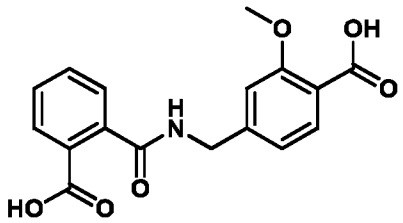
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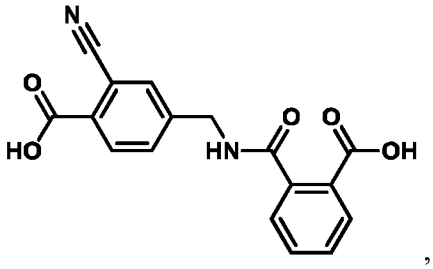
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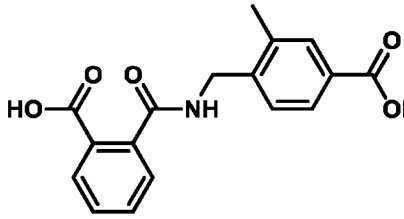
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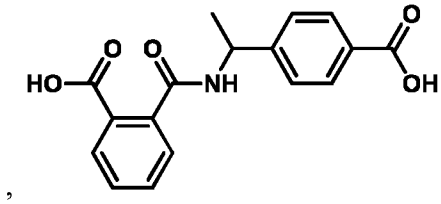
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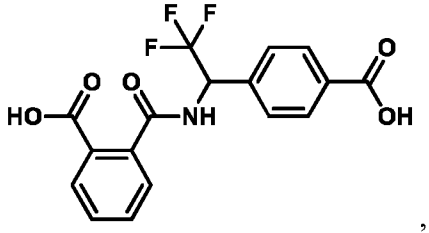
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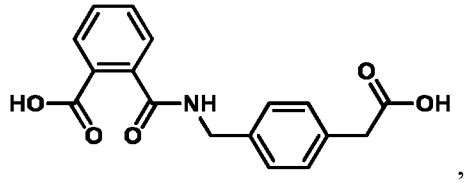
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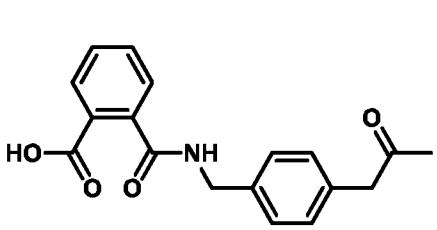
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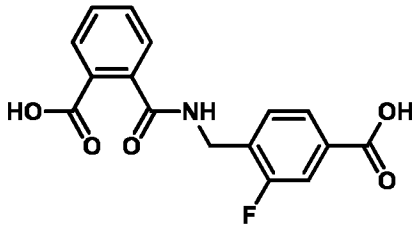
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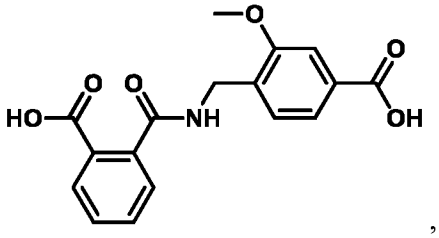
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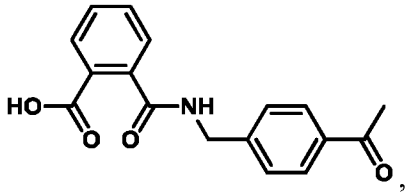
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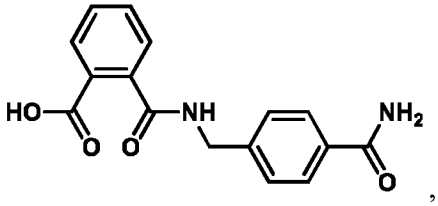
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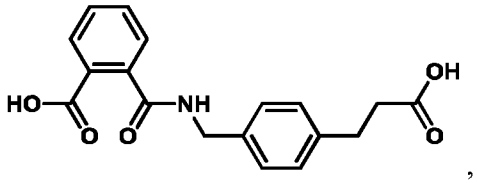
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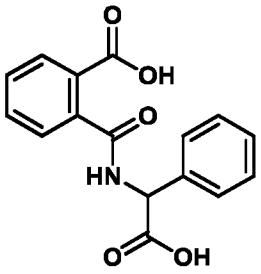
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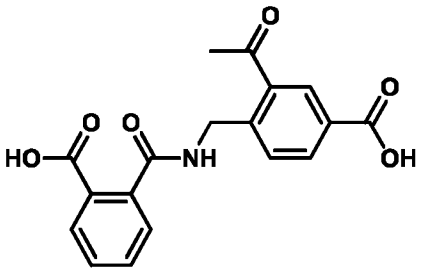
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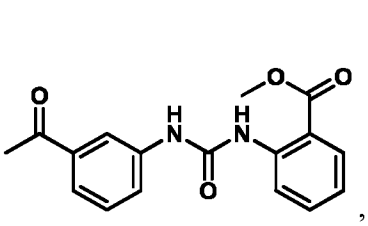
93. The method of either claim 27 or 31, wherein the compound is selected from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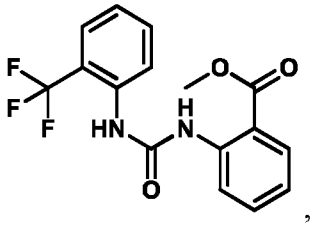
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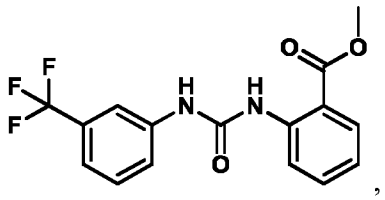
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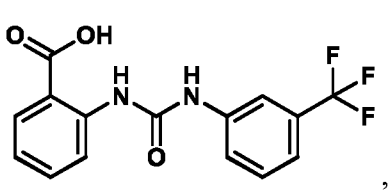
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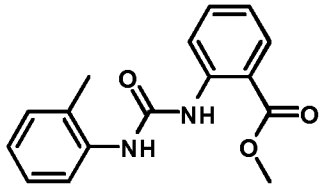
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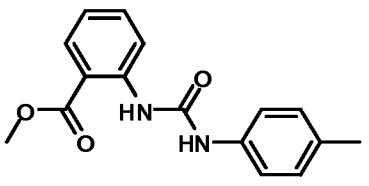
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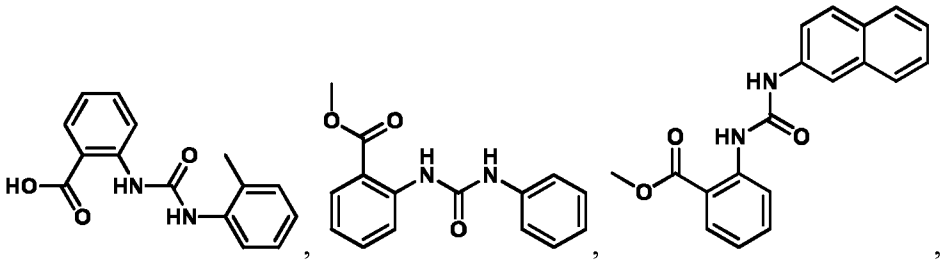

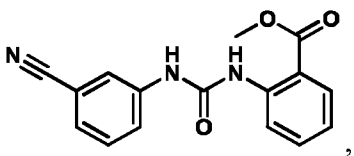
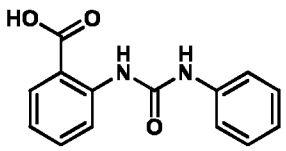
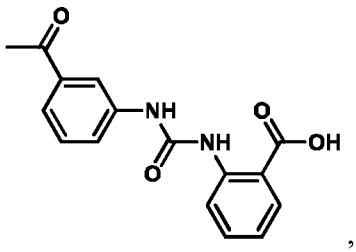
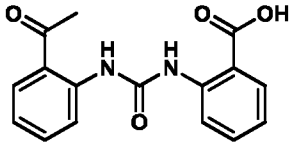
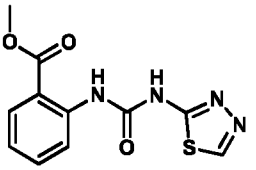
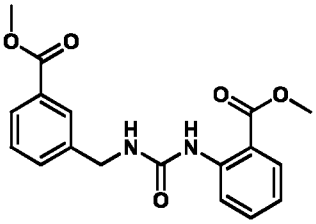
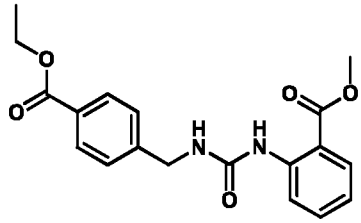
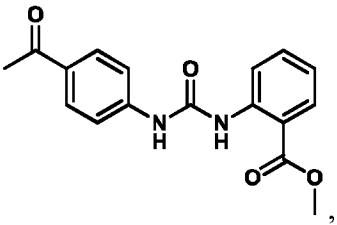
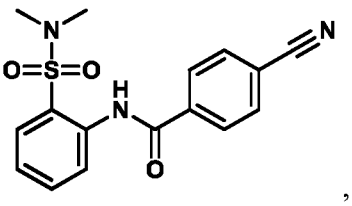
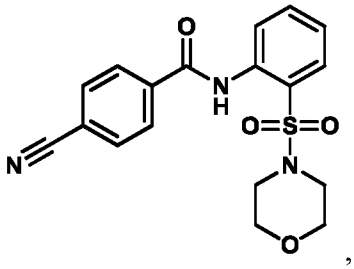

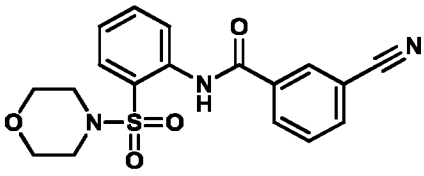
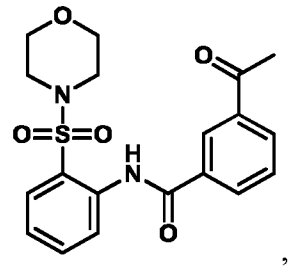
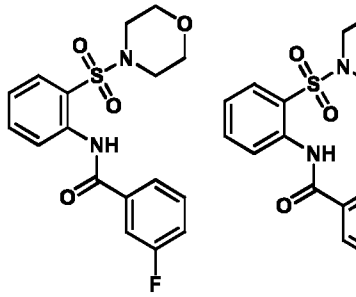

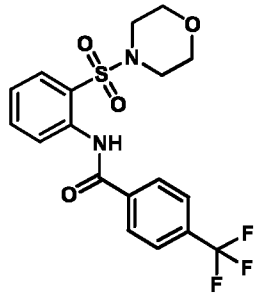
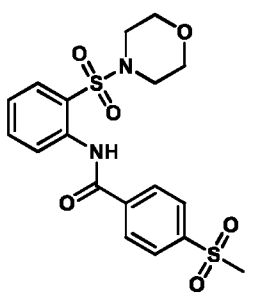

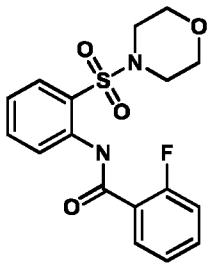
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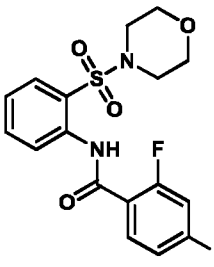
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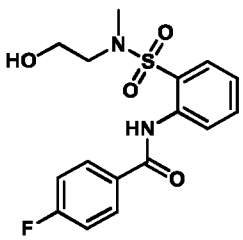
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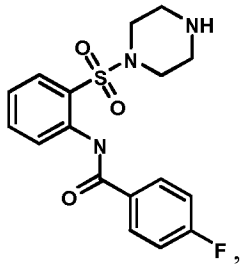
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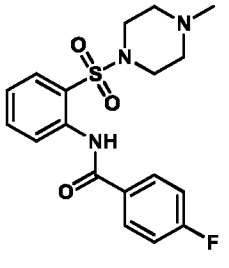
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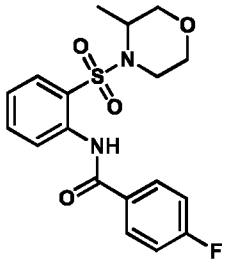
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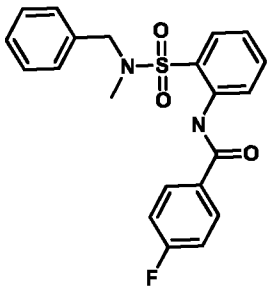
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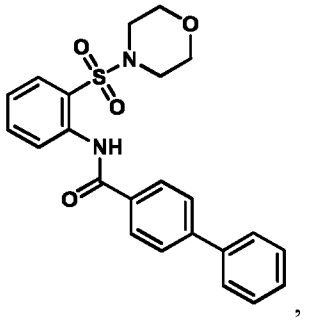
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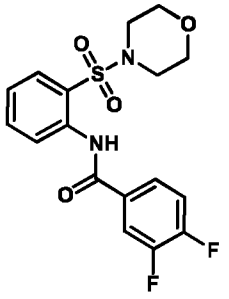
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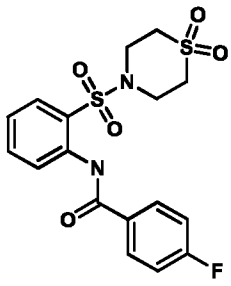
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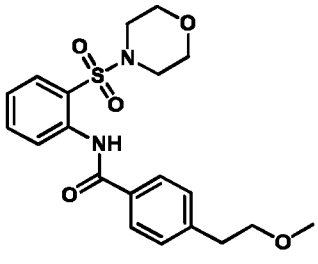
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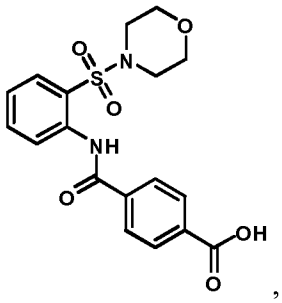
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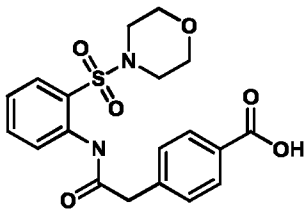
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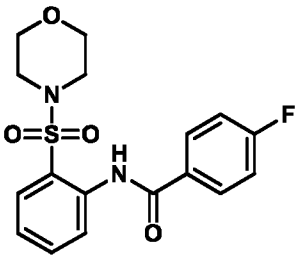
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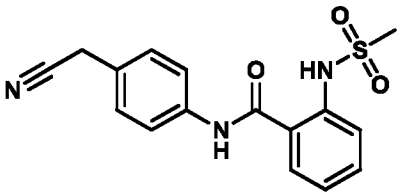
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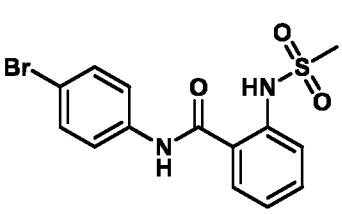
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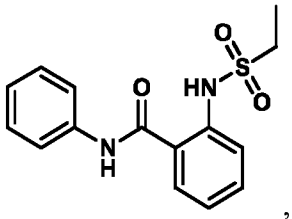
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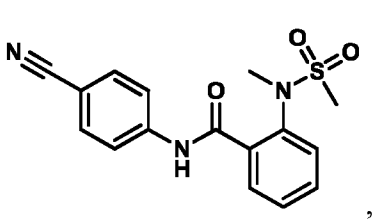
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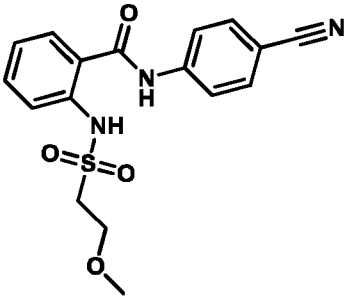
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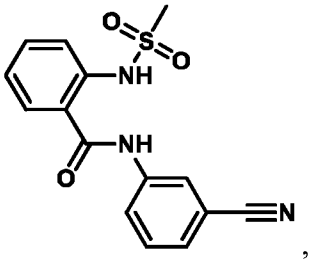
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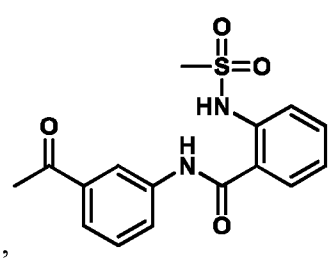
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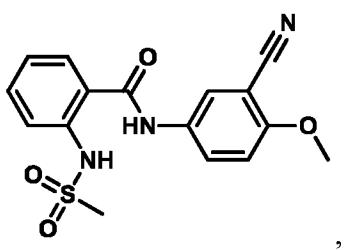
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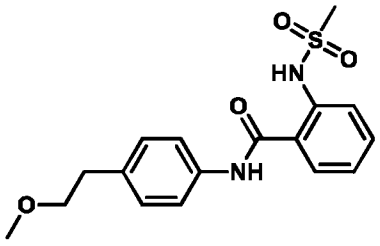
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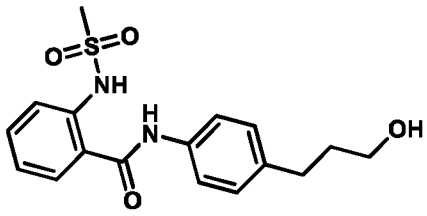
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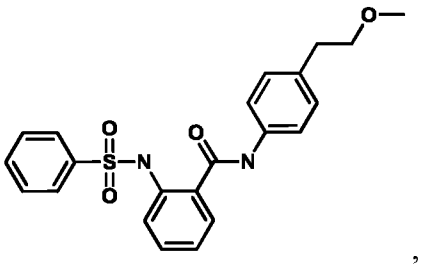
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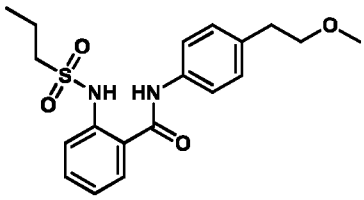
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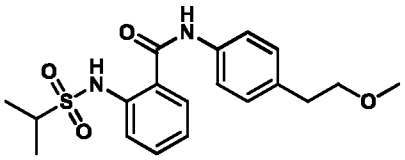
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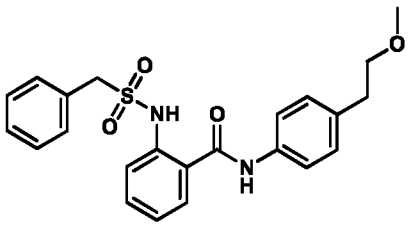
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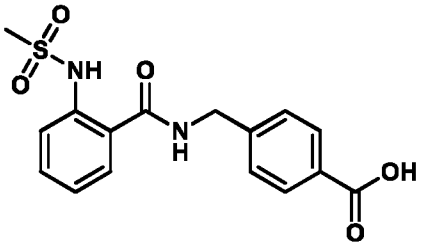
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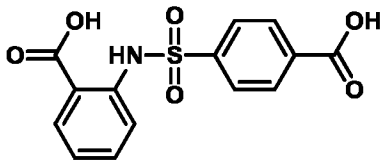
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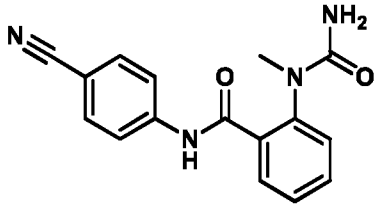
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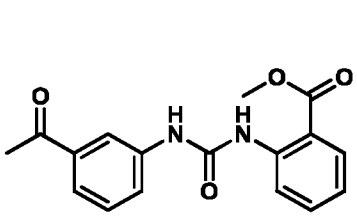
94. The method of either claim 28 or 32, wherein the compound is selected from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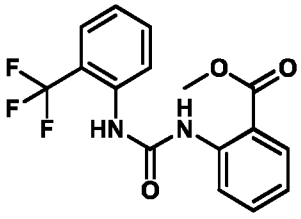
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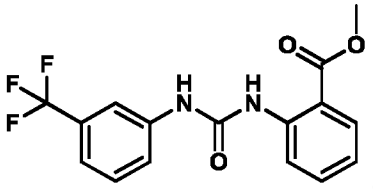
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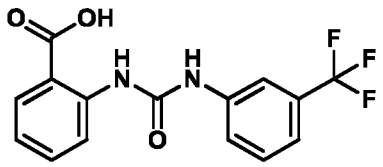
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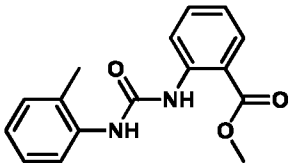
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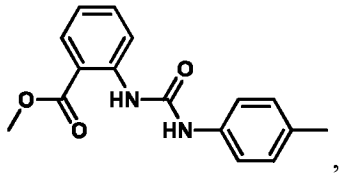
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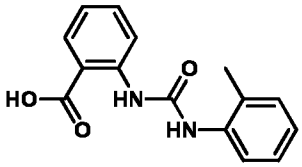
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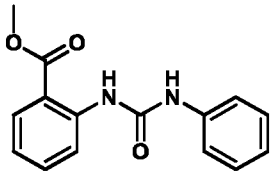
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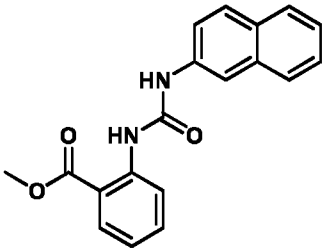
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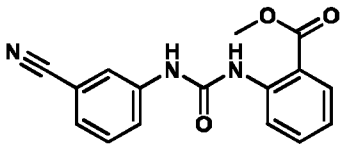
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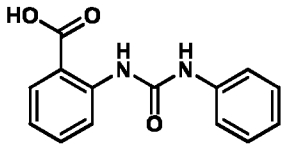
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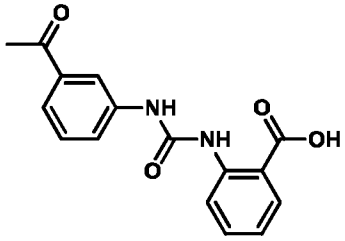
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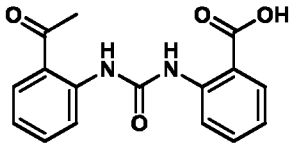
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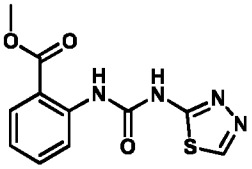
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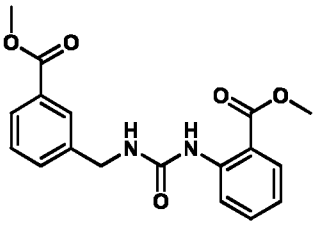
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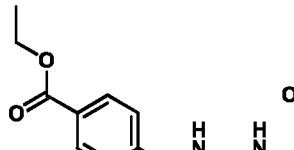
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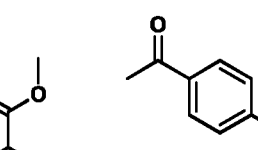
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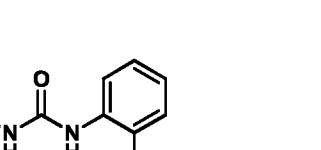
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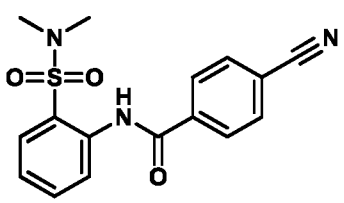
; or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

95. The method of either claim 29 or 33, wherein the compound is selected from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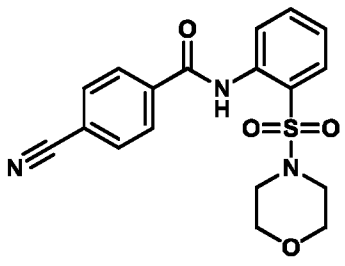
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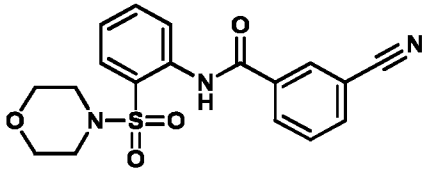
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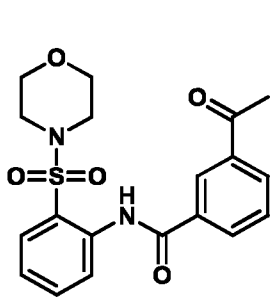

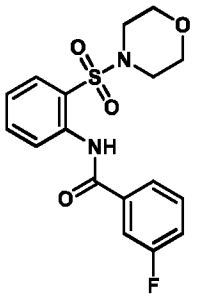

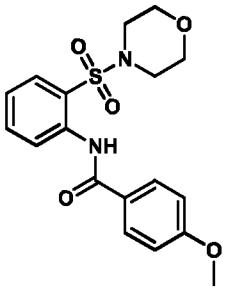

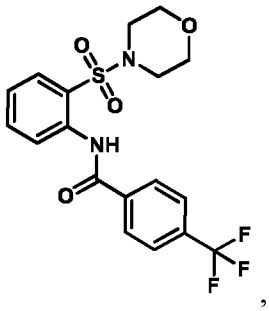

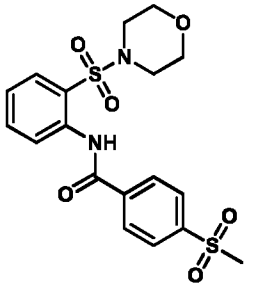

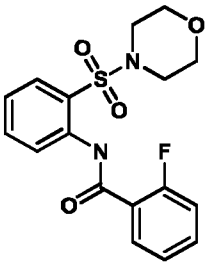

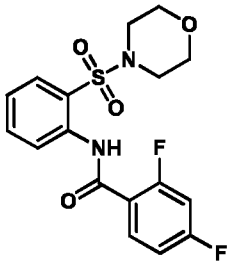

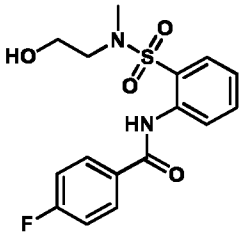

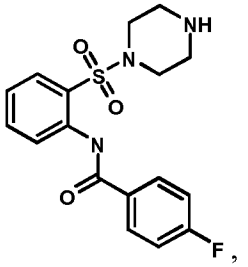

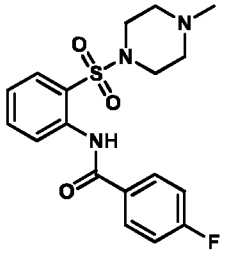

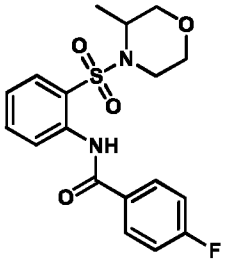

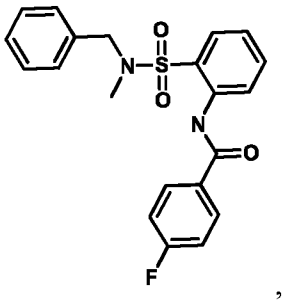

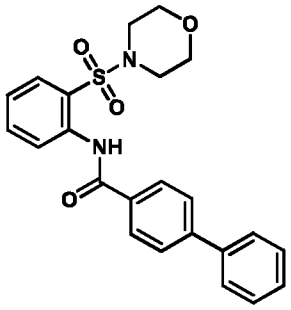

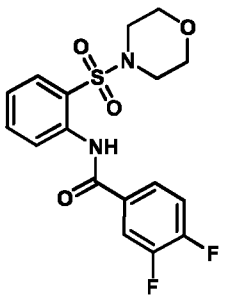

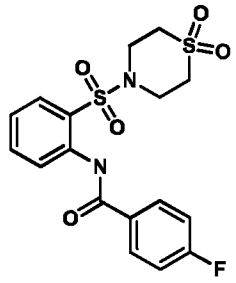

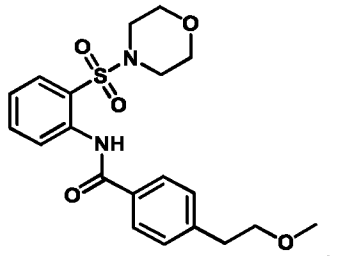

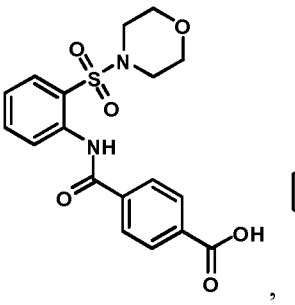

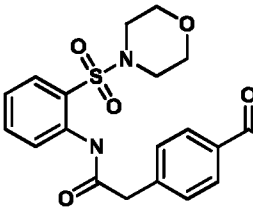

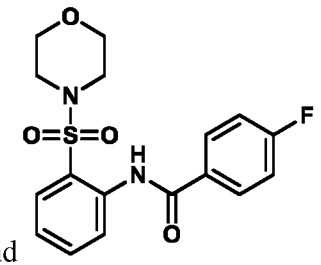

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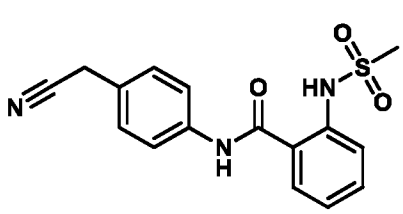
, , and ; or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

96. The method of either claim 30 or 34, wherein the compound is selected from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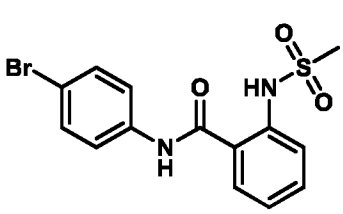
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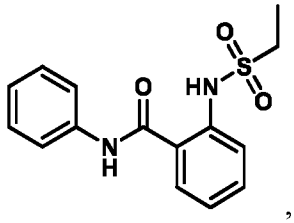
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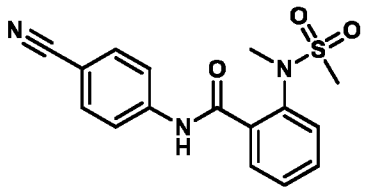
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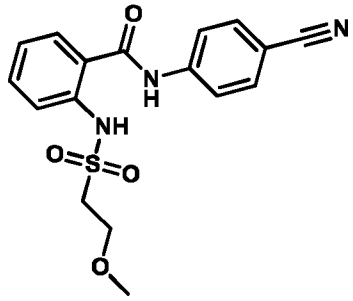
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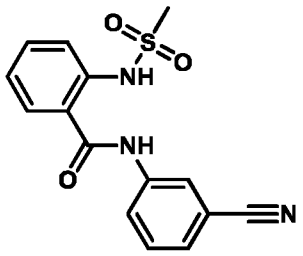
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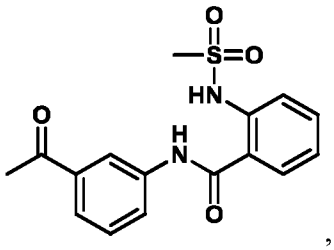
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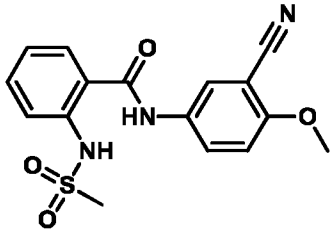
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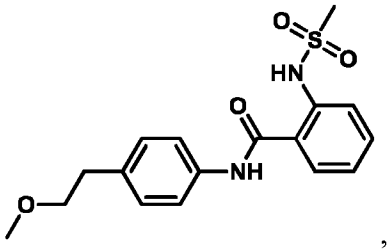
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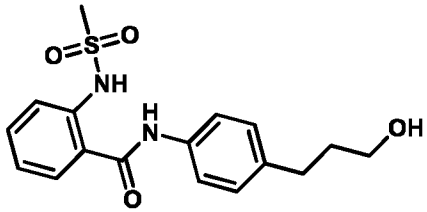
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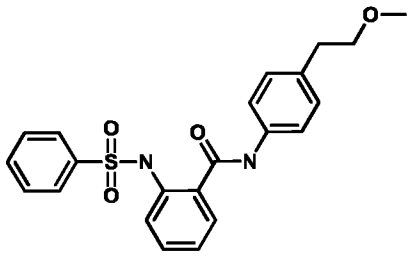
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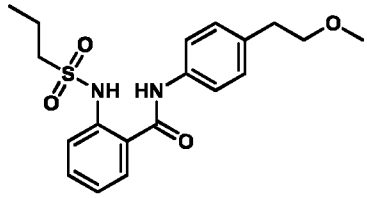
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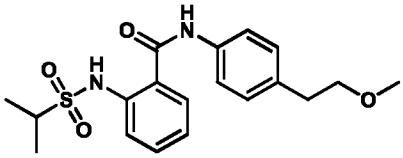
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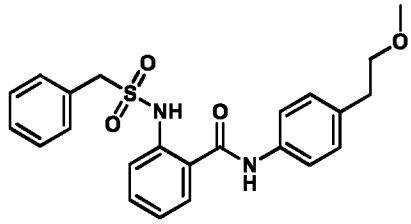
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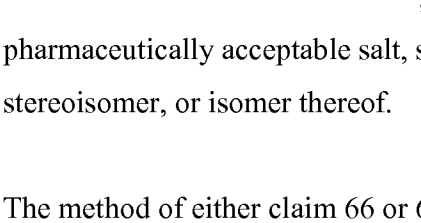
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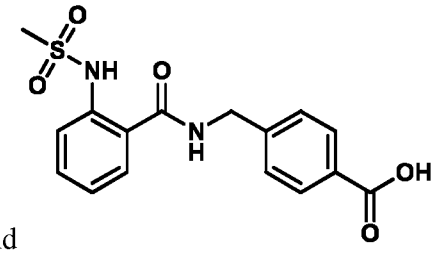
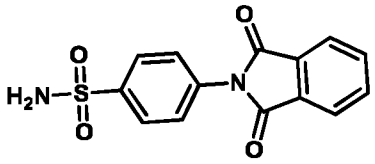

; or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

97. The method of either claim 66 or 68, wherein the compound is selected from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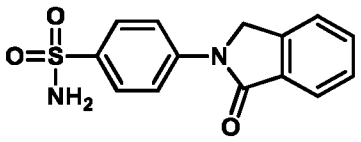
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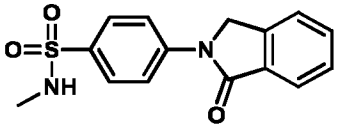
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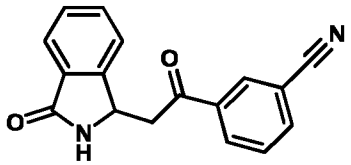
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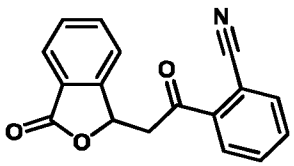
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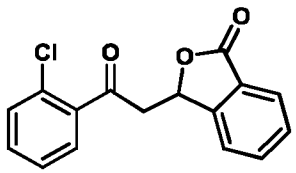
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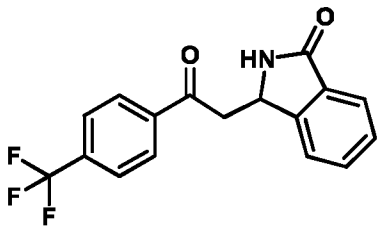
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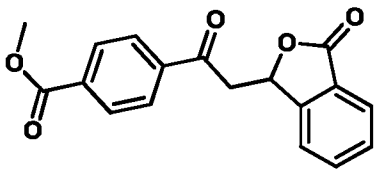
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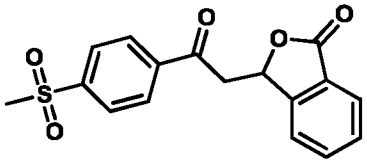
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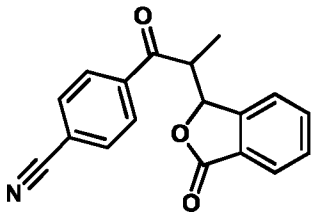
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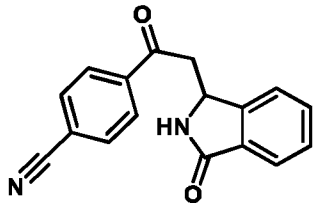
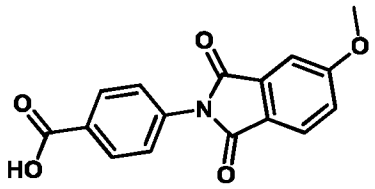

; or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

98. A method of ameliorating arthritis or joint injury in a mammal, the method comprising administering to a joint of the mammal a composition comprising a therapeutically effective amount of a compound selected from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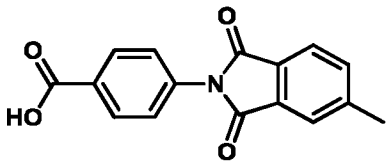
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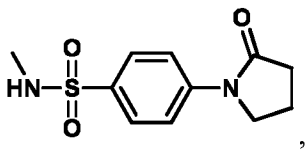
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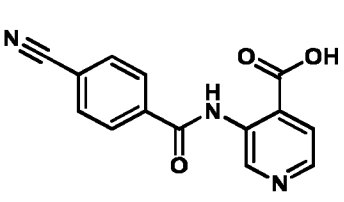
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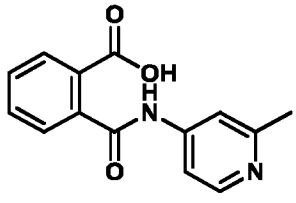
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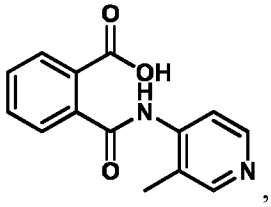
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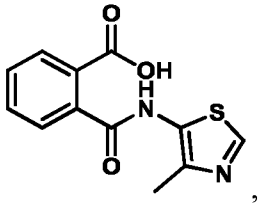
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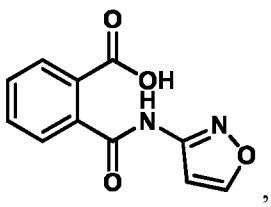
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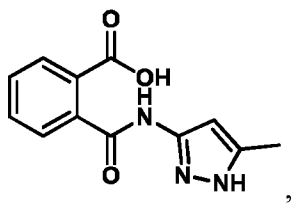
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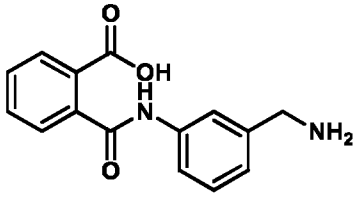
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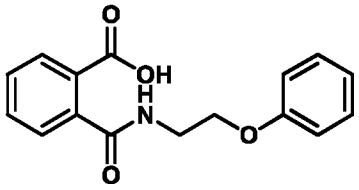
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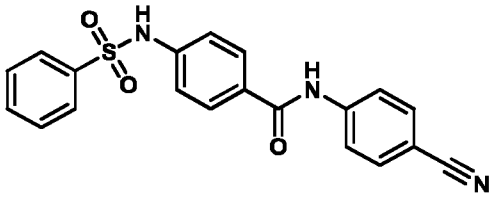
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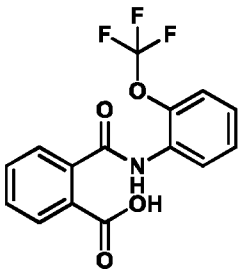
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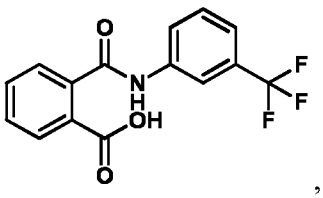
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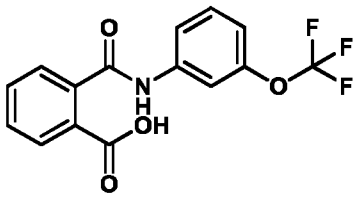
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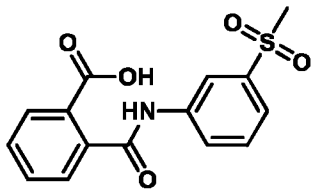
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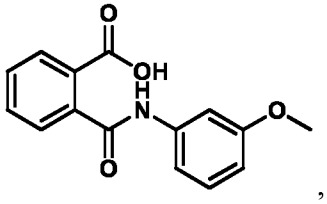
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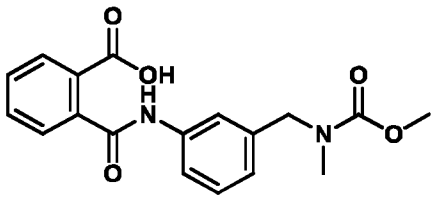
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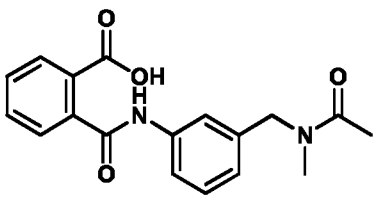
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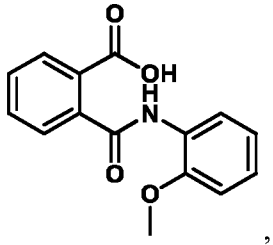
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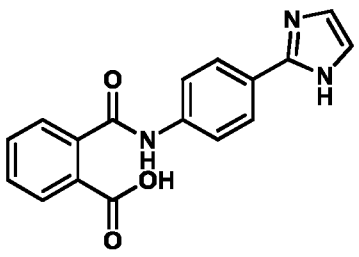
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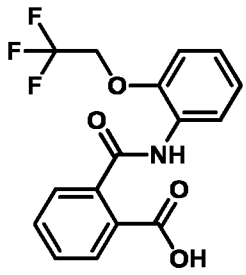
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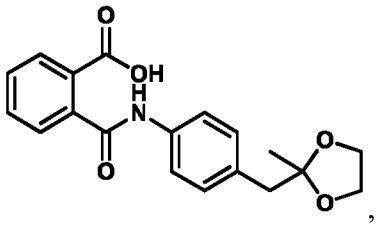
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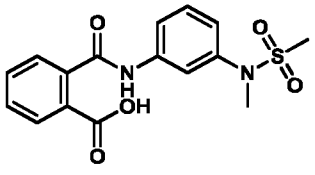
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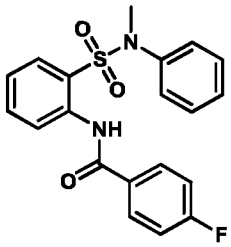
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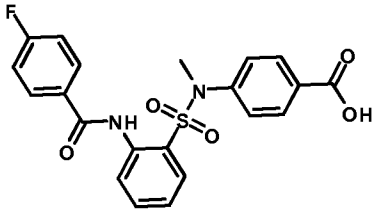
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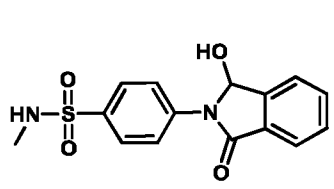
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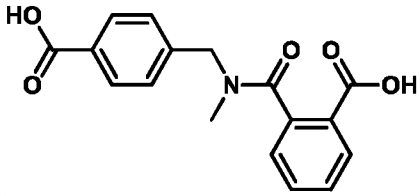
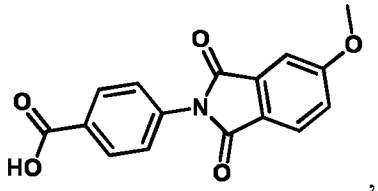

; or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

99. A method of inducing differentiation of mesenchymal stem cells into chondrocytes, the method comprising contacting mesenchymal stem cells with a sufficient amount of a compound selected from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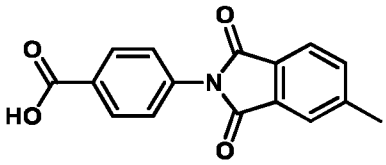
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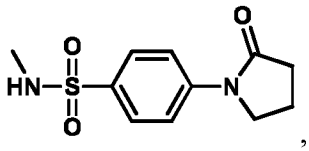
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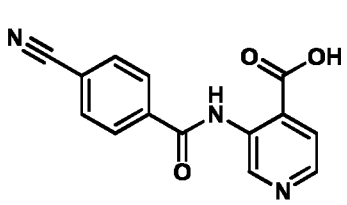
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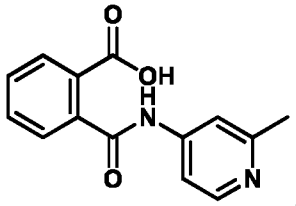
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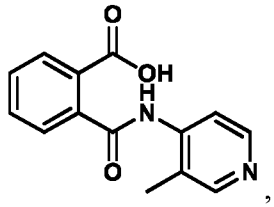
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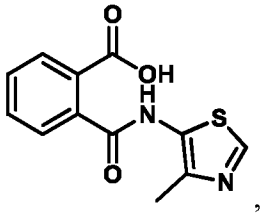
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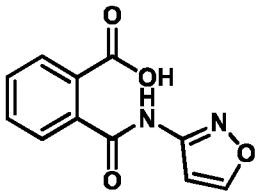
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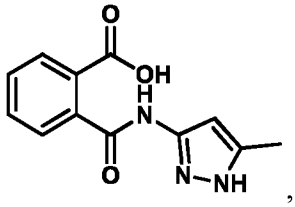
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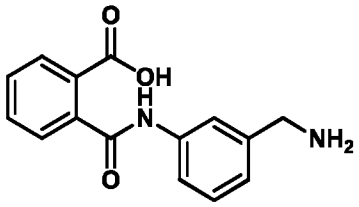
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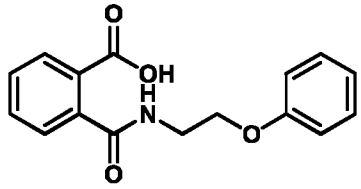
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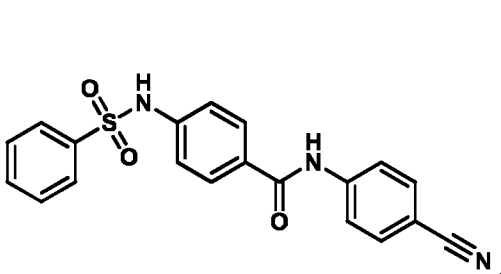
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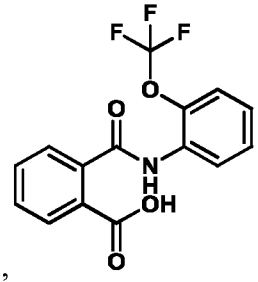
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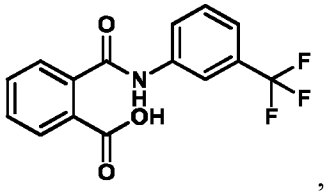
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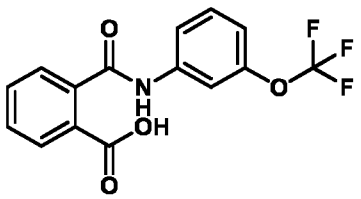
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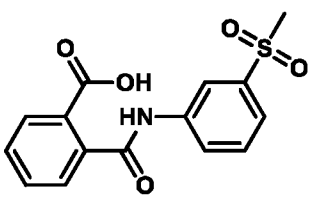
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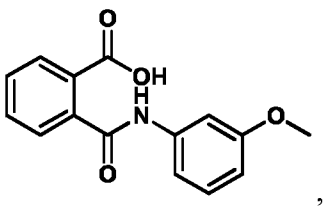
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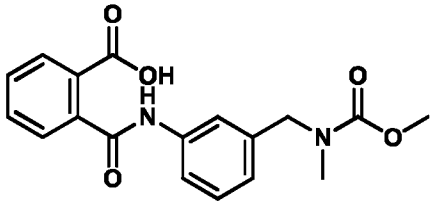
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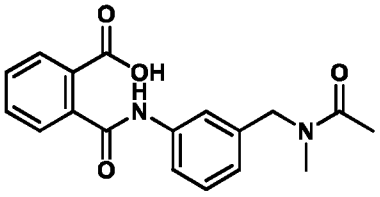
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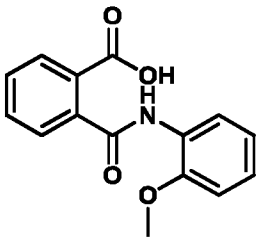
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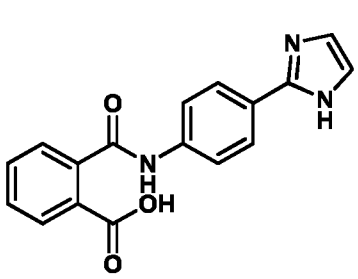
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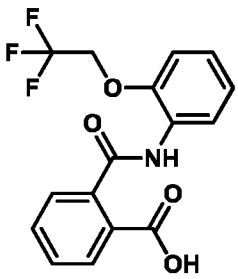
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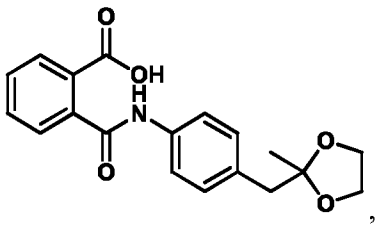
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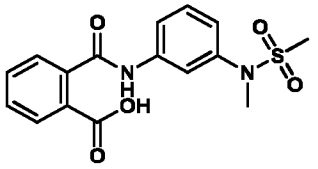
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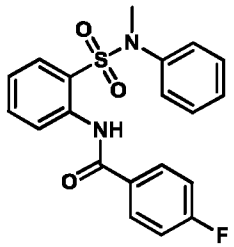
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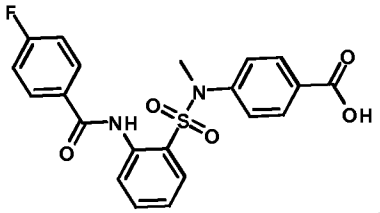
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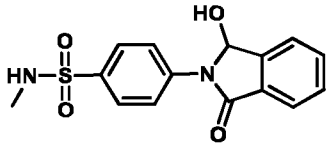
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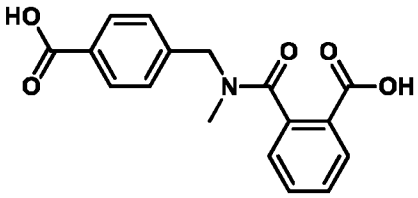
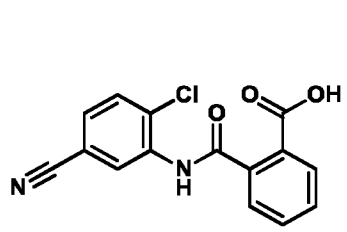

; or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

100. The method of any one of claims 5-8, 31-34, 68, 69, or 99 wherein the method is performed *in vitro*.

101. The method of any one of claims 5-8, 31-34, 68, 69, or 99 wherein the method is performed *in vivo* in a mammal and the stem cells are present in the mammal.

102. The method of claim 101 wherein the mammal is a human, a dog, a cat, or a horse.

103. A compound of Formula I selected from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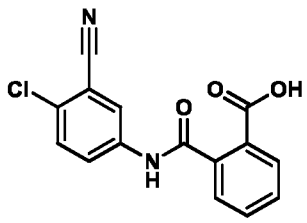
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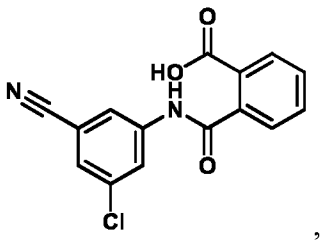
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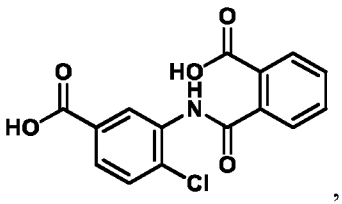
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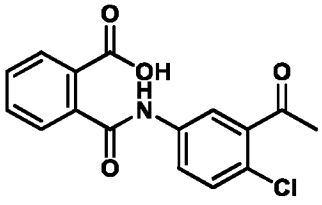
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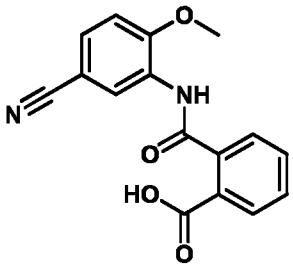
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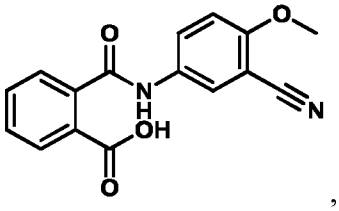
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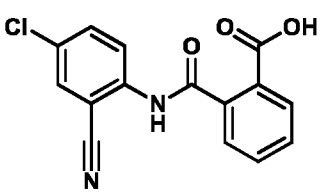
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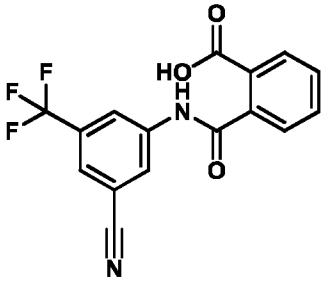
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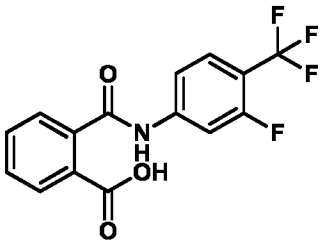
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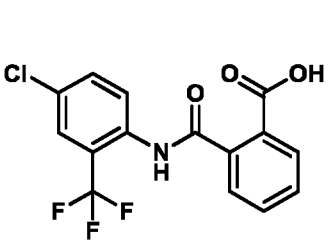
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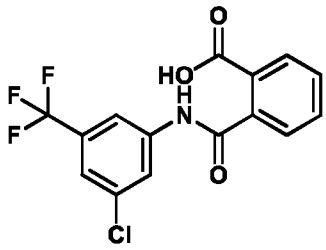
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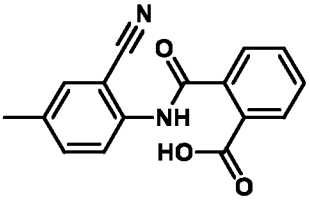
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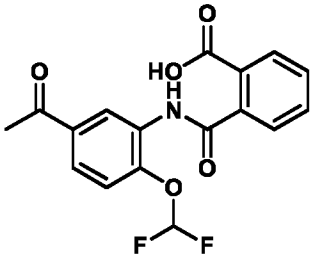
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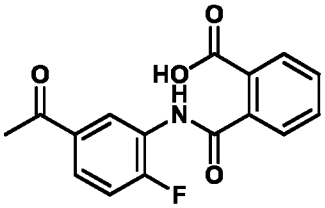
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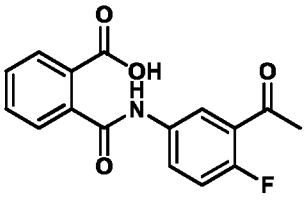
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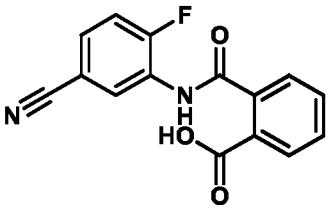
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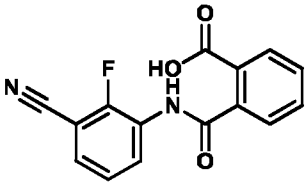
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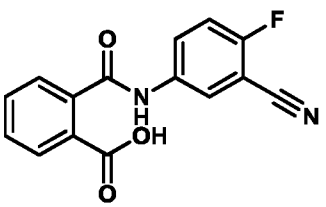
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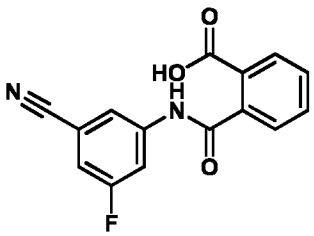
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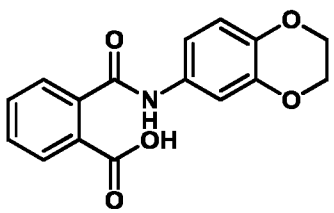
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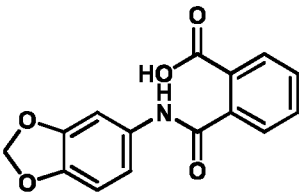
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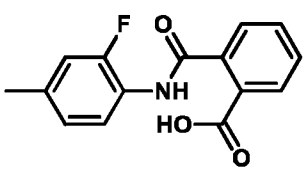
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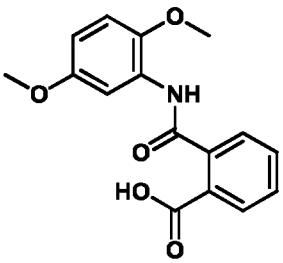
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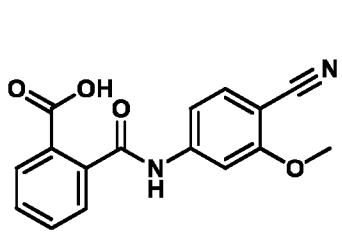
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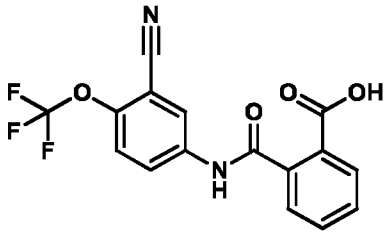
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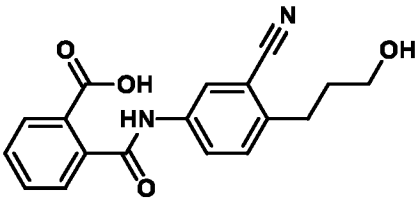
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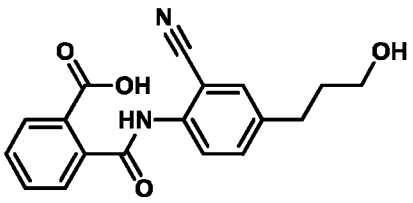
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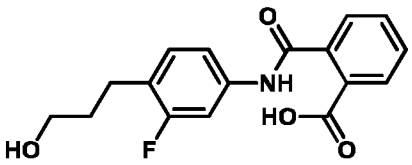
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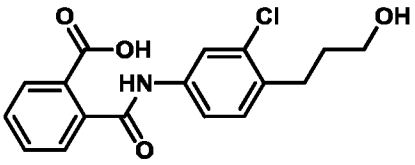
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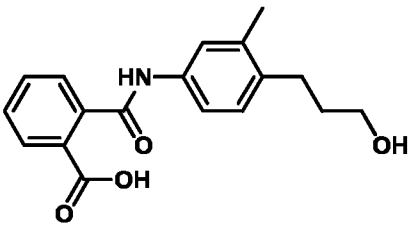
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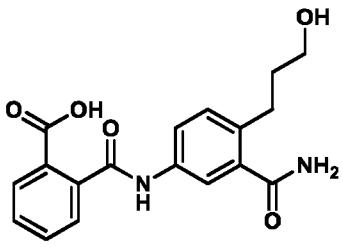
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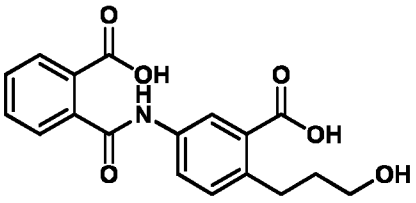
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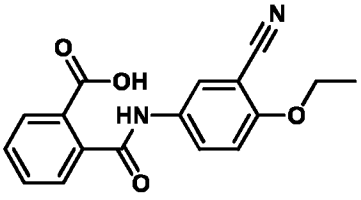
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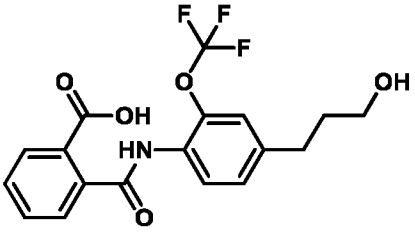
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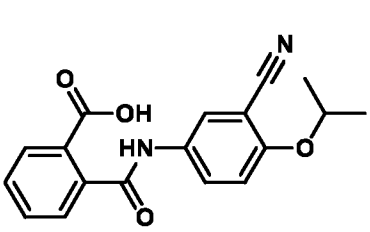
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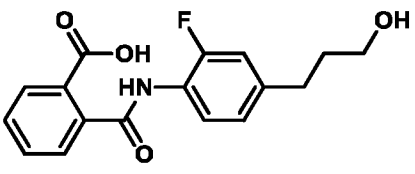
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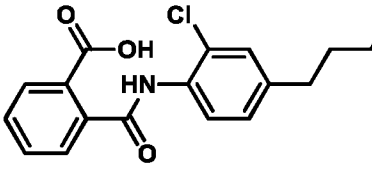
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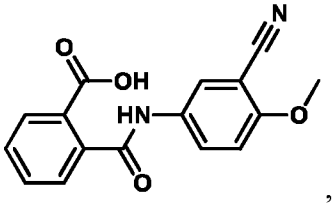
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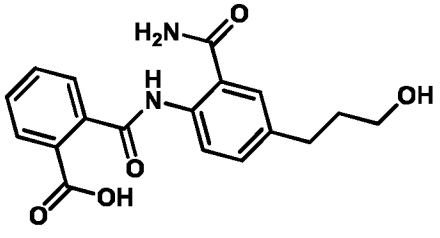
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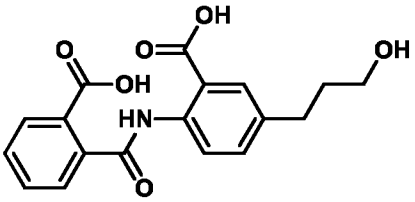
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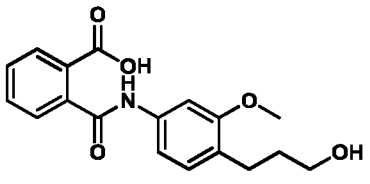
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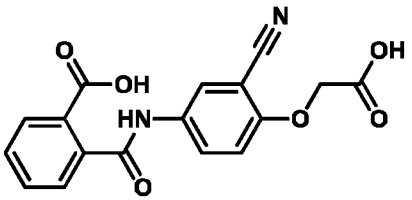
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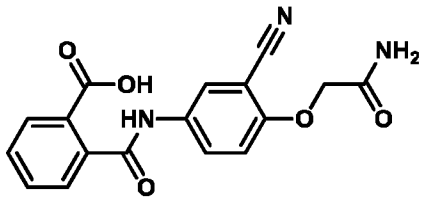
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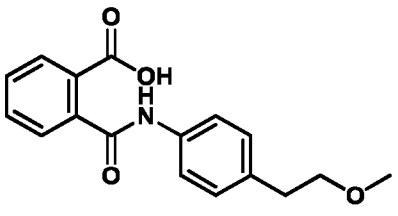
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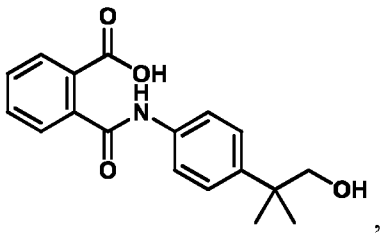
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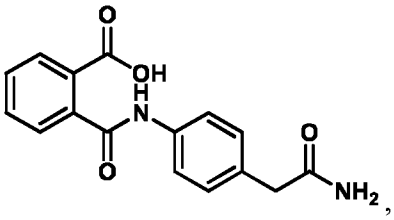
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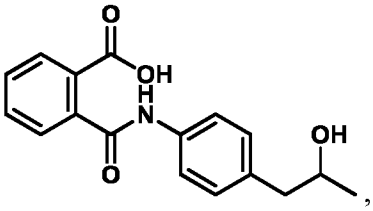
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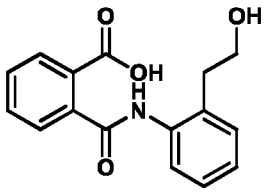
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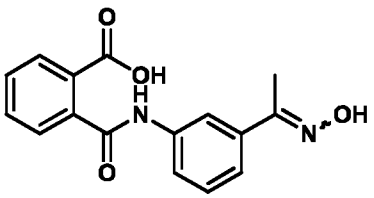
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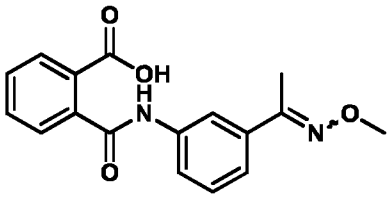
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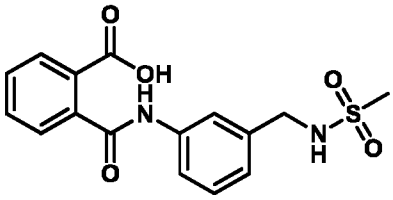
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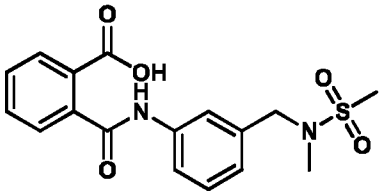
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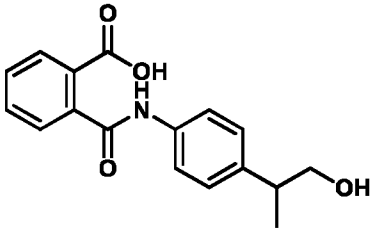
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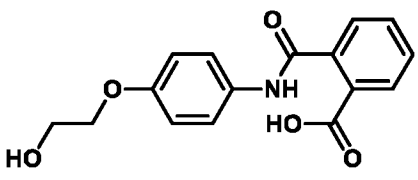
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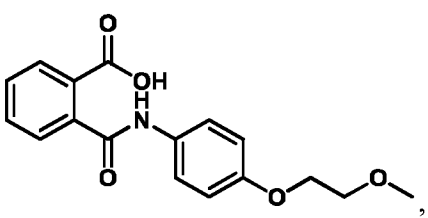
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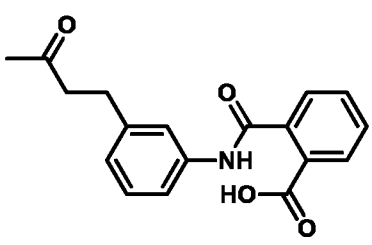
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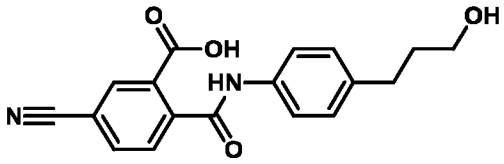
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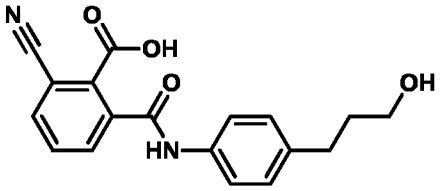
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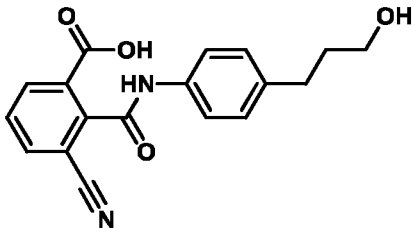
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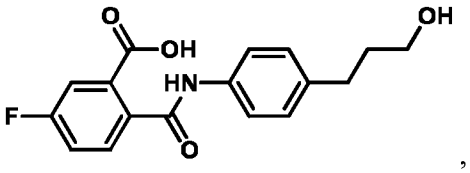
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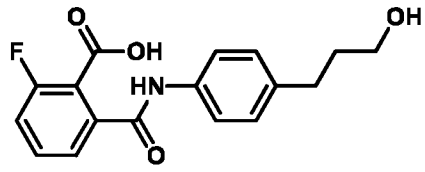
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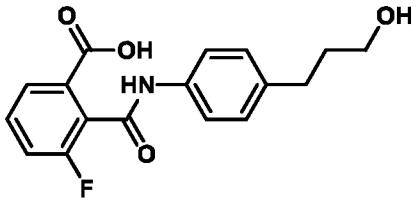
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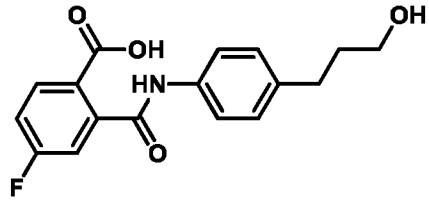
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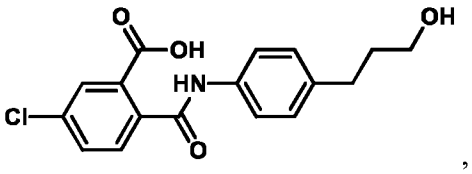
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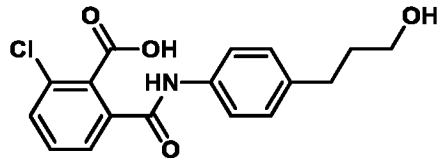
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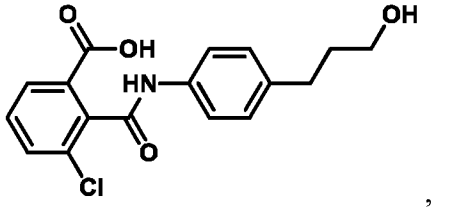
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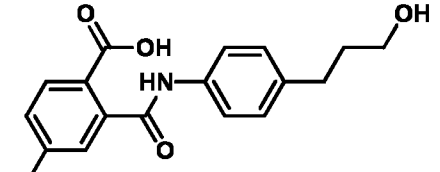
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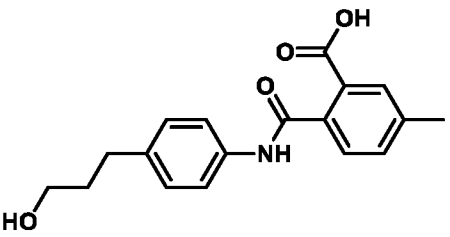
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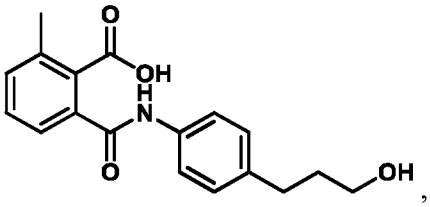
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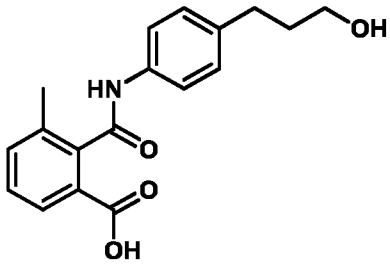
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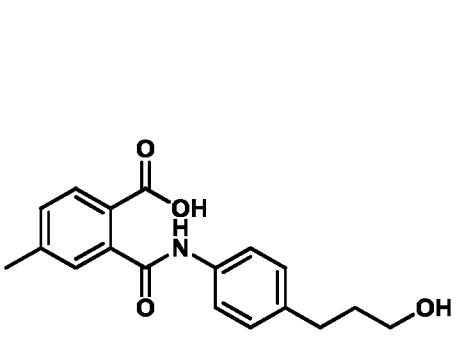
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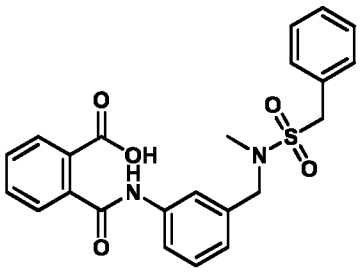
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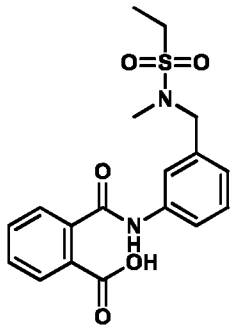
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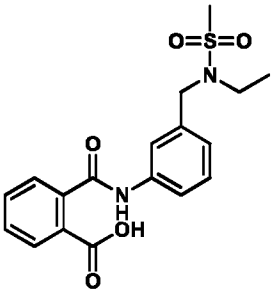
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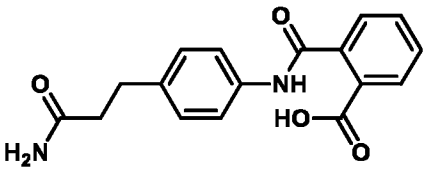
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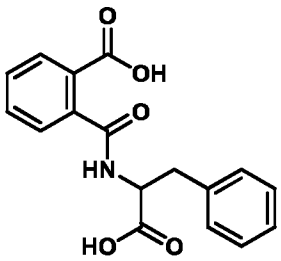
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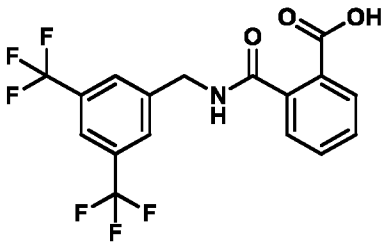
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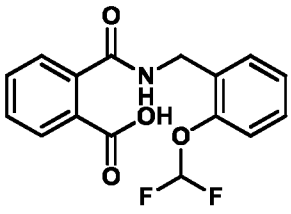
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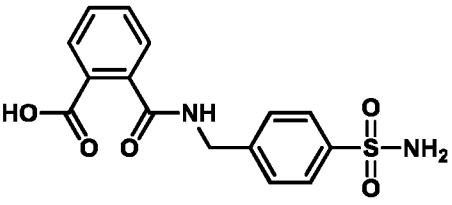
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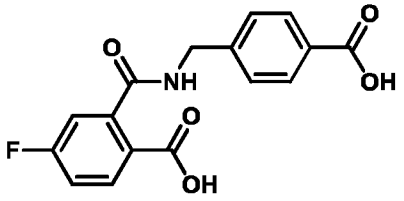
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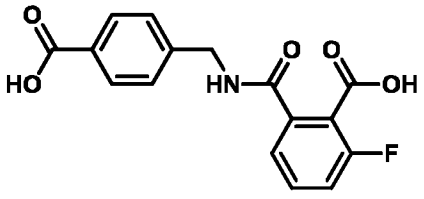
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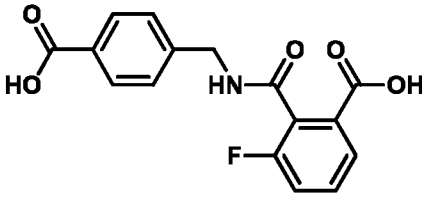
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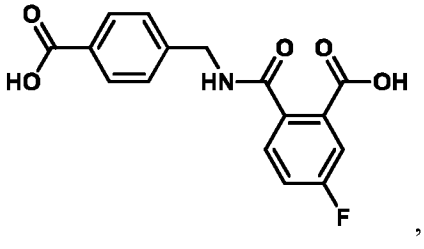
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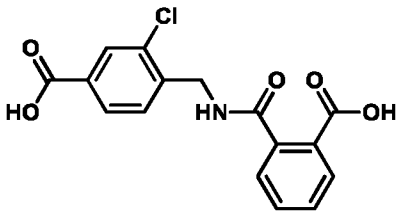
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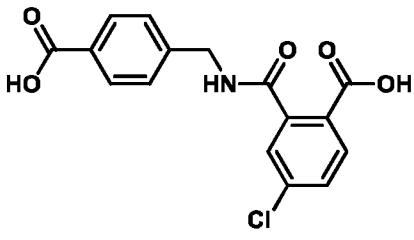
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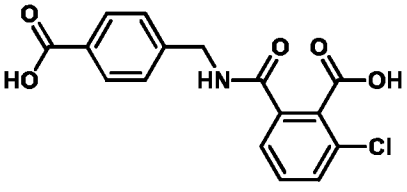
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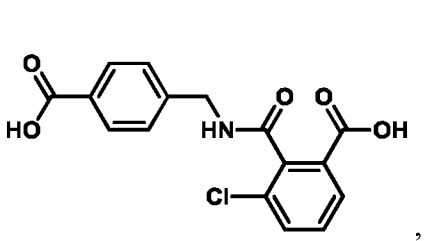
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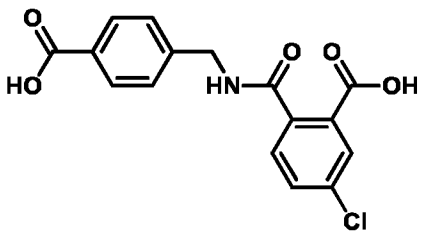
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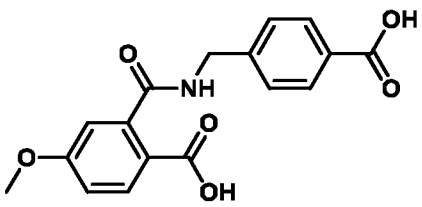
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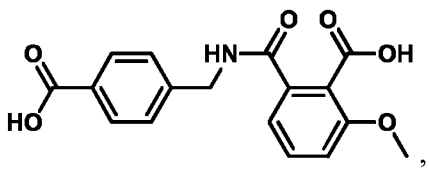
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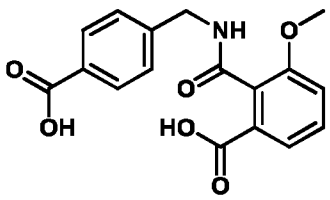
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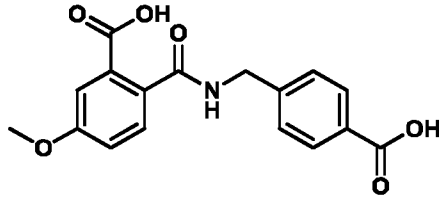
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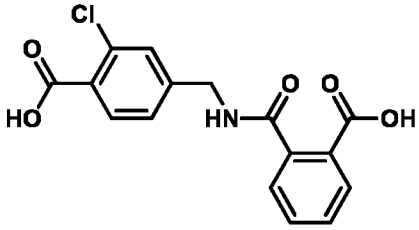
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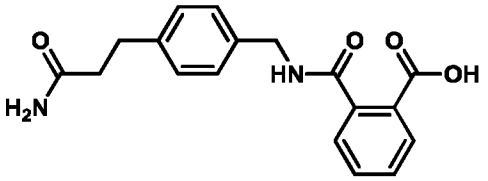
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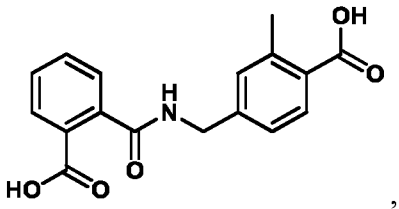
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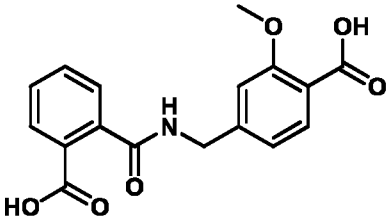
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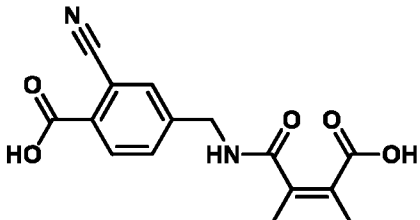
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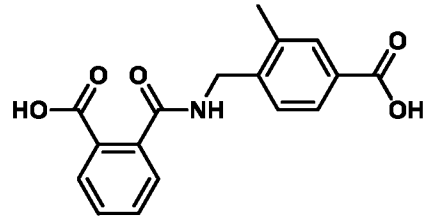
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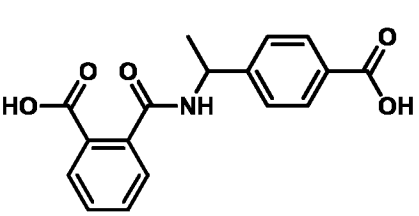
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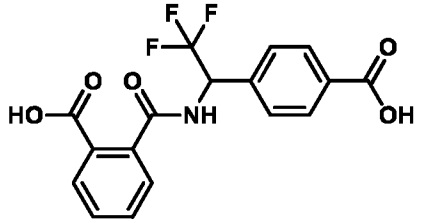
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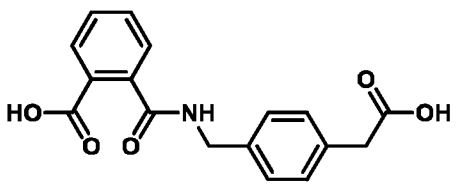
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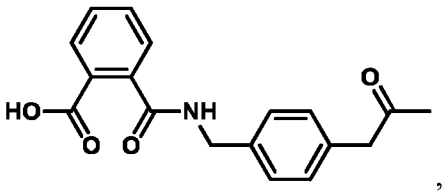
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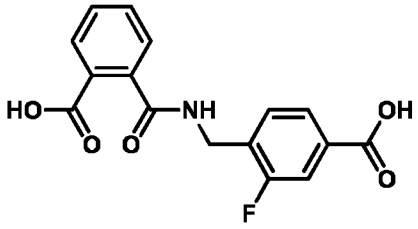
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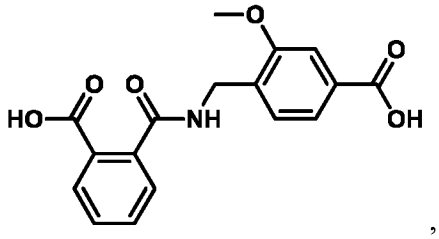
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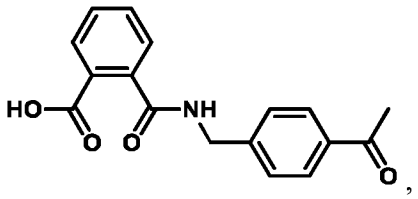
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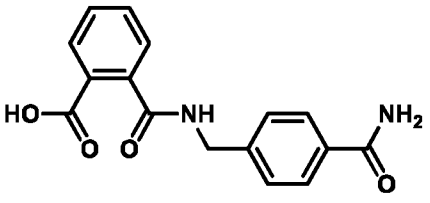
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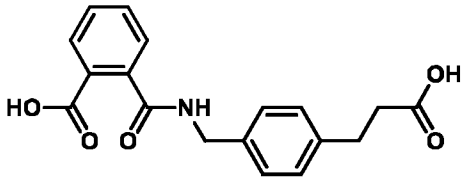
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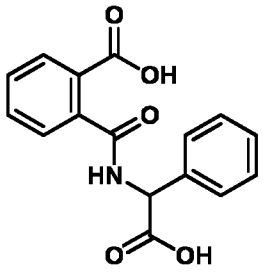
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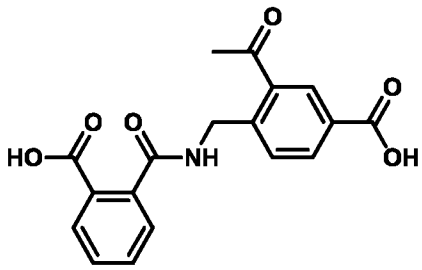
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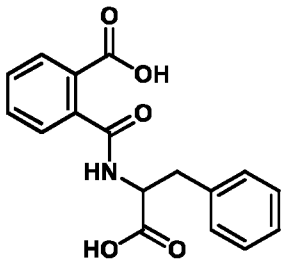
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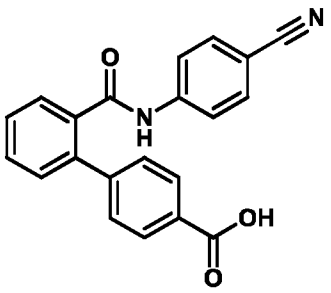
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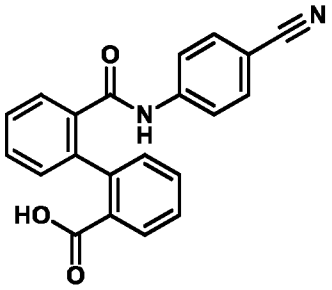
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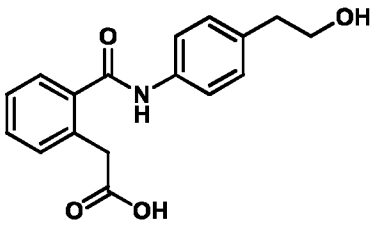
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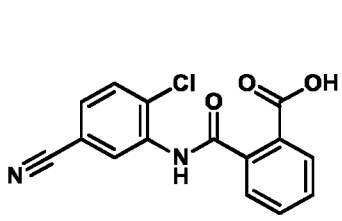
104. A compound of Formula Ia selected from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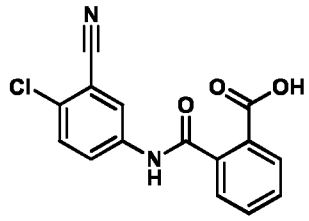
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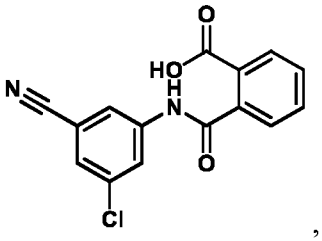
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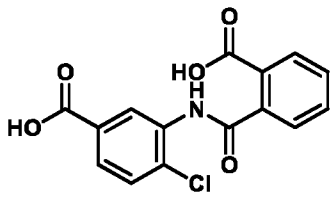
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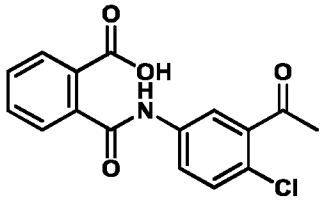
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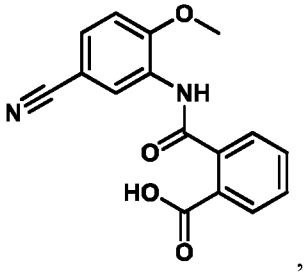
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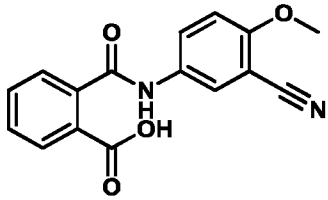
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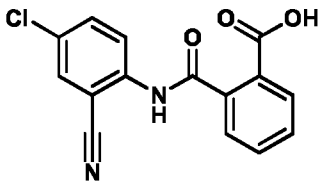
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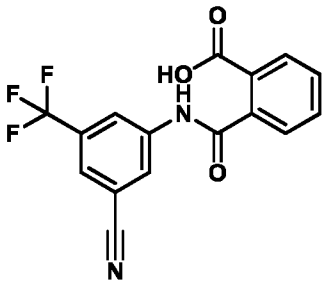
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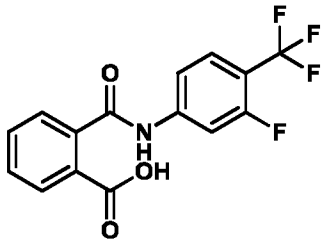
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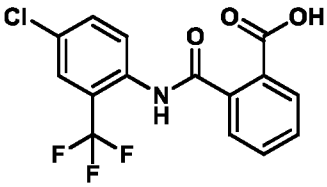
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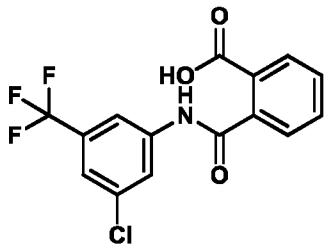
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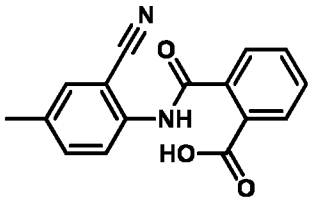
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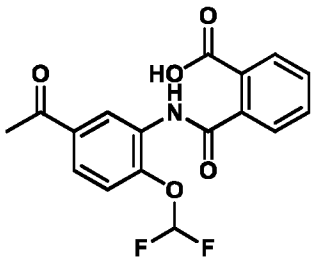
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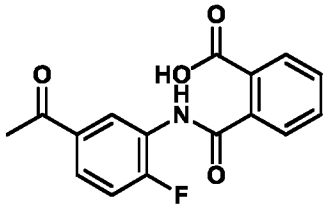
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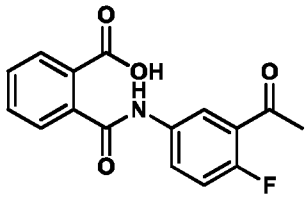
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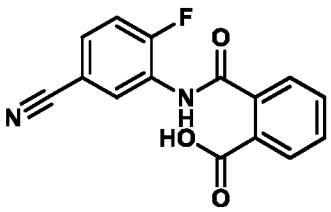
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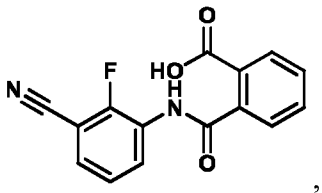
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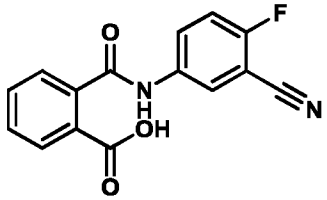
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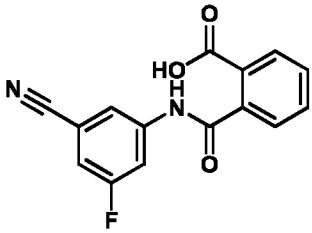
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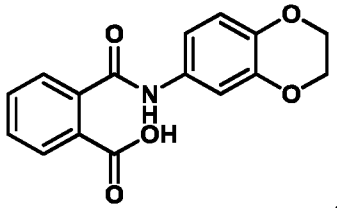
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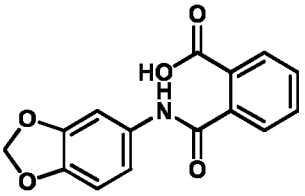
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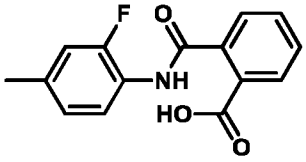
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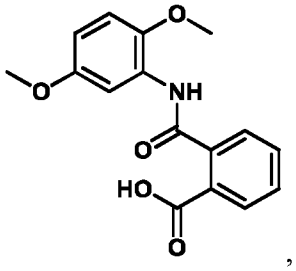
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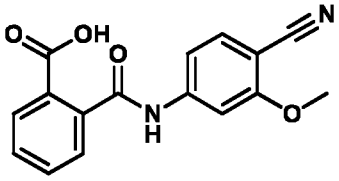
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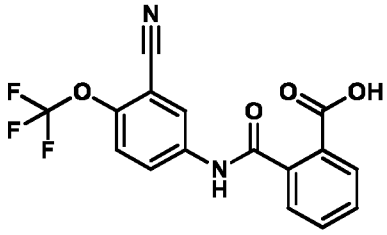
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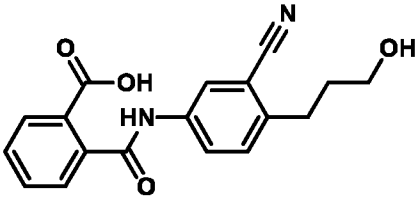
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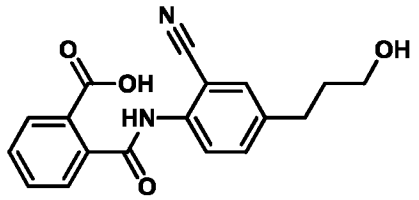
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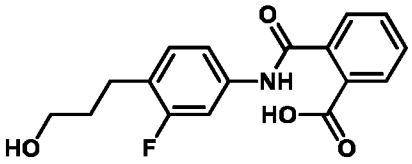
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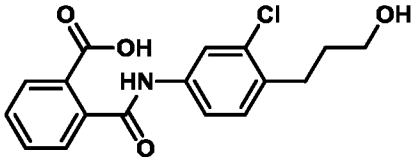
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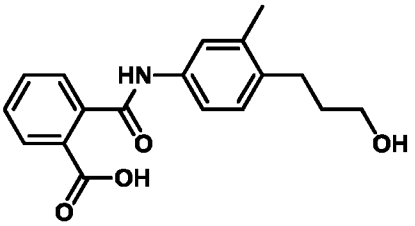
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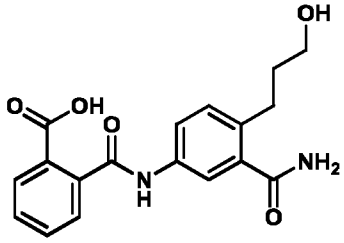
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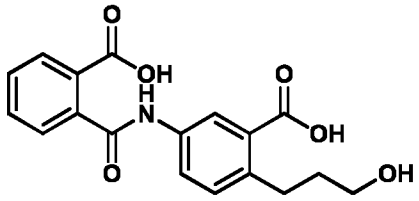
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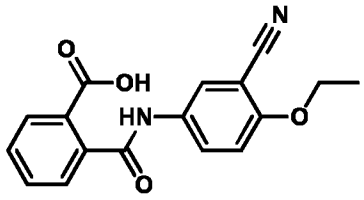
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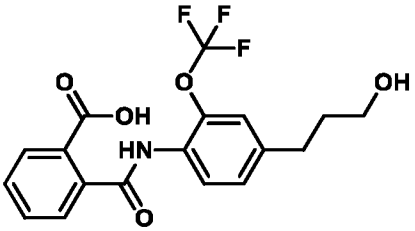
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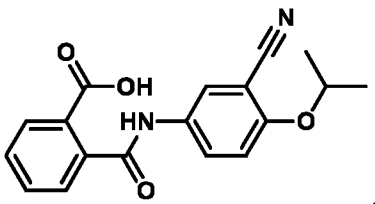
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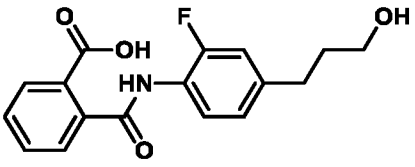
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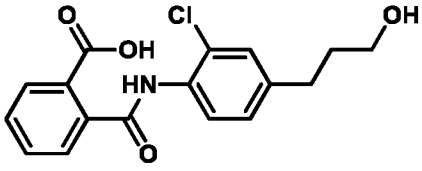
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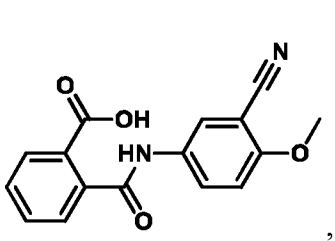
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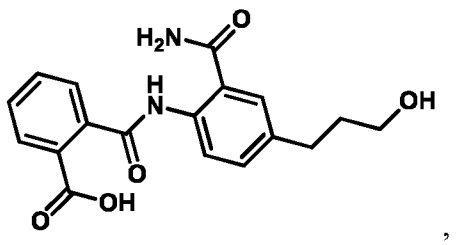
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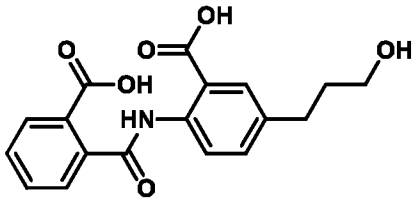
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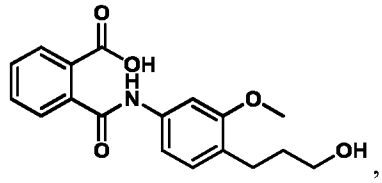
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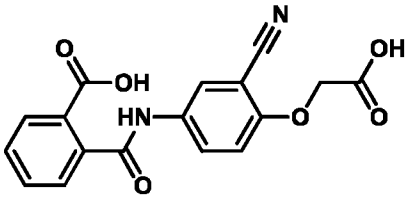
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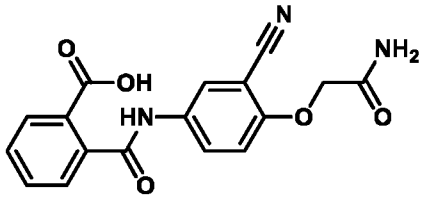
; or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

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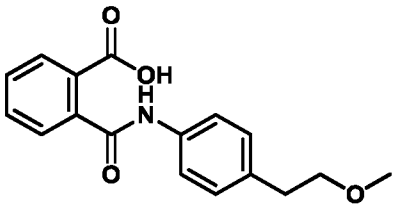
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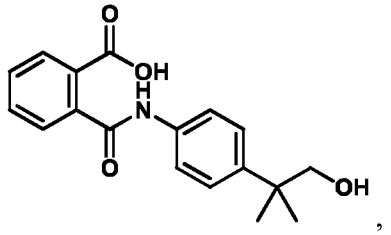
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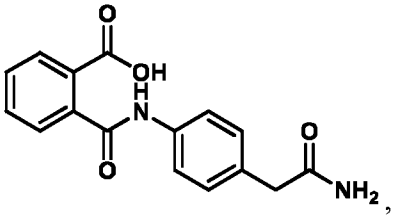
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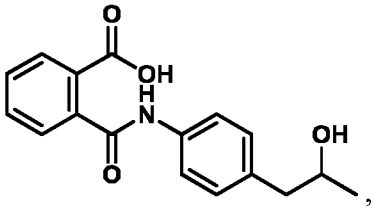
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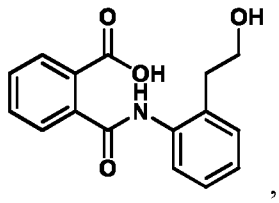
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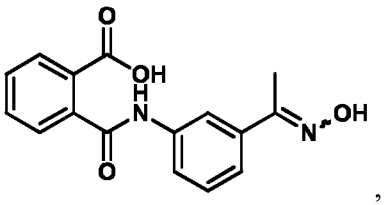
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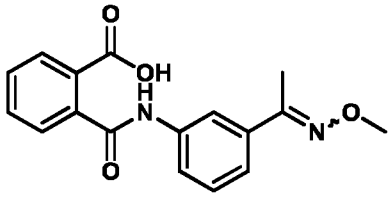
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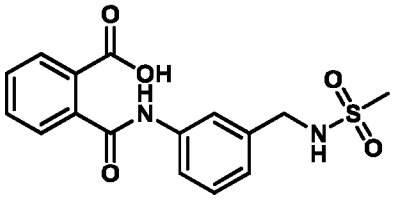
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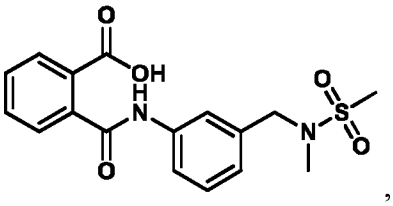
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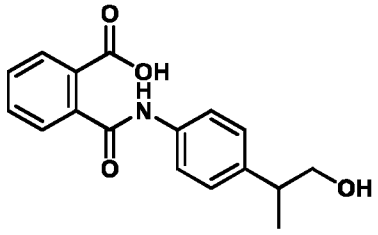
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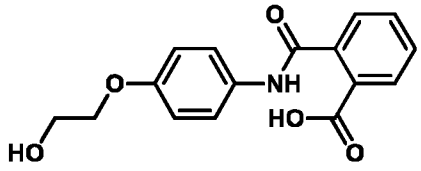
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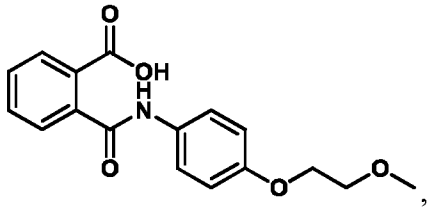
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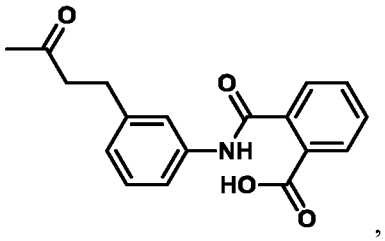
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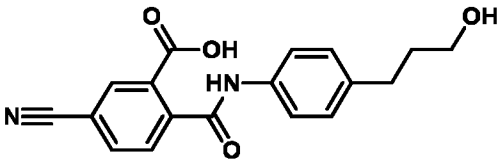
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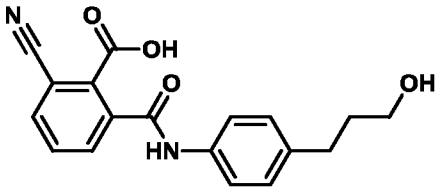
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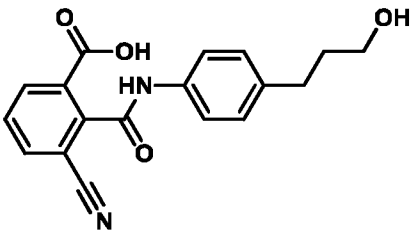
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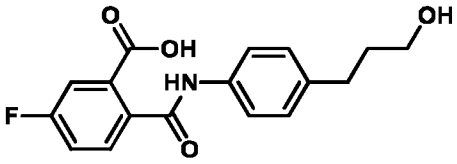
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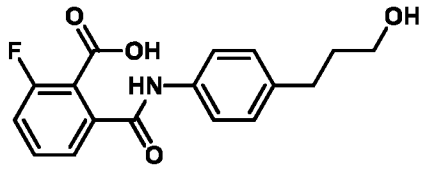
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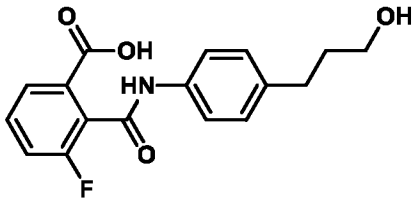
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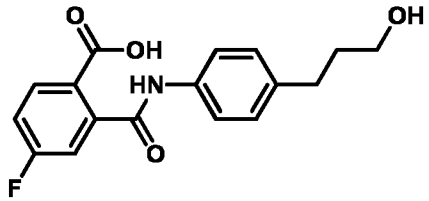
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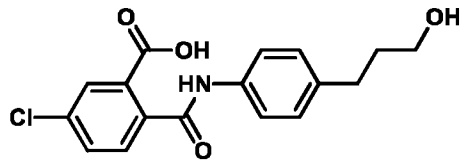
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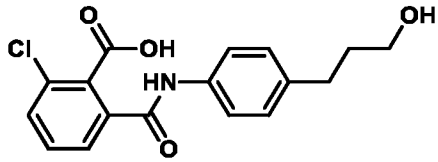
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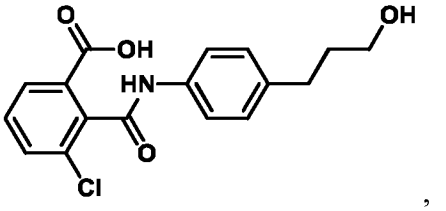
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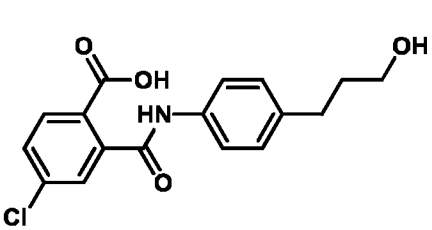
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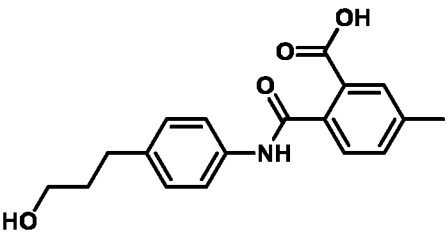
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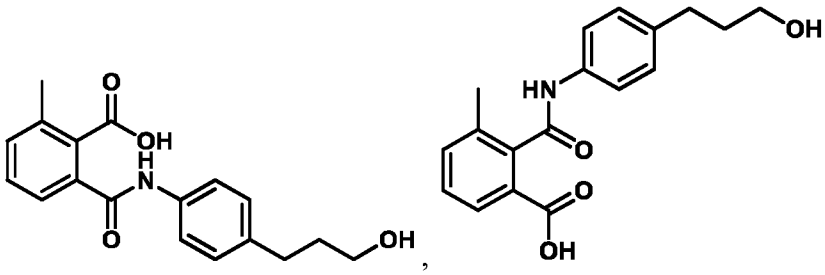
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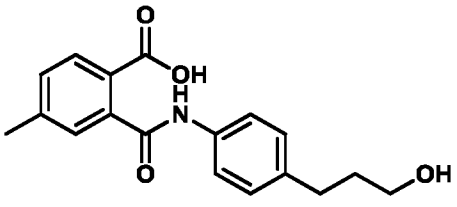
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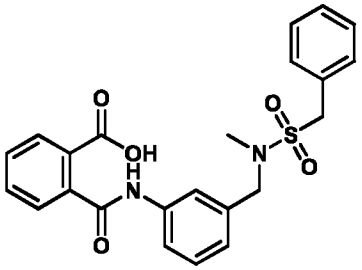
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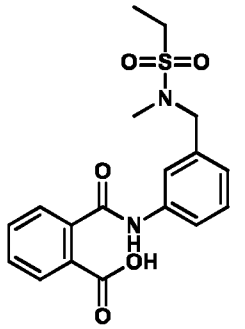
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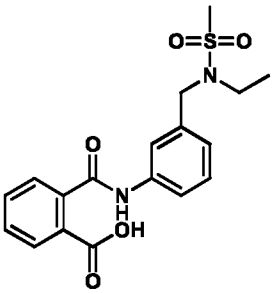
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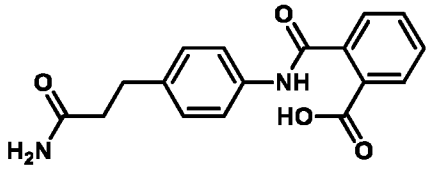
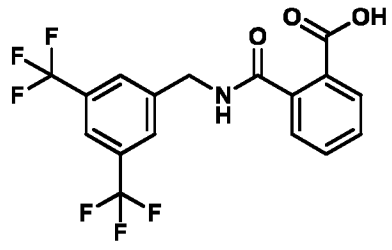

; or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

106. A compound of Formula Ic selected from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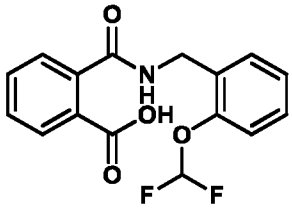
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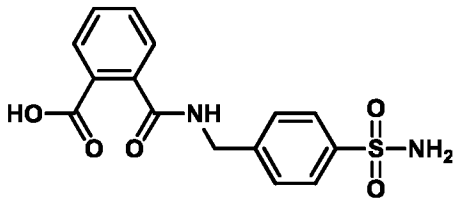
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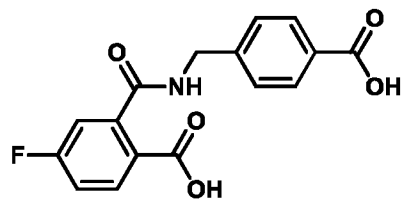
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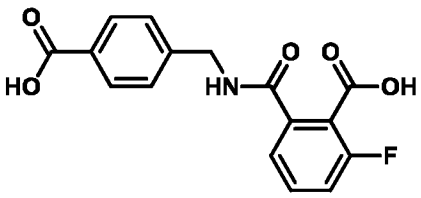
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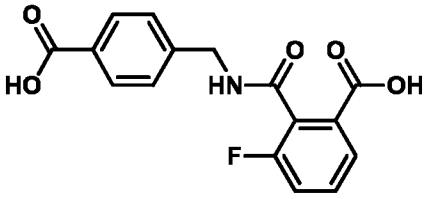
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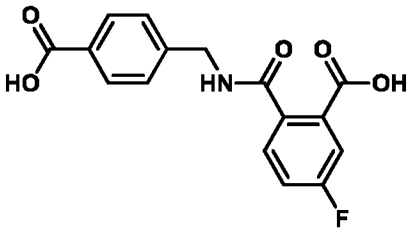
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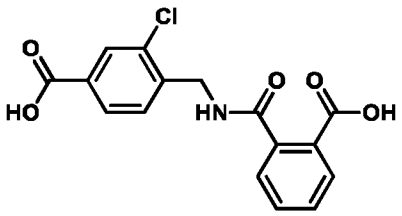
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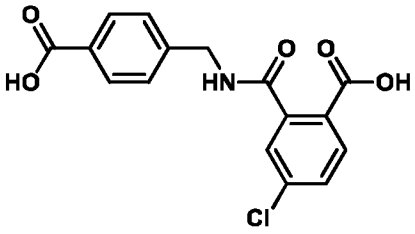
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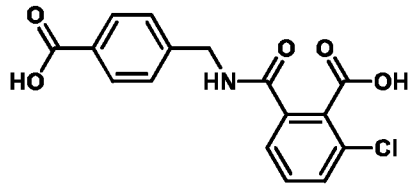
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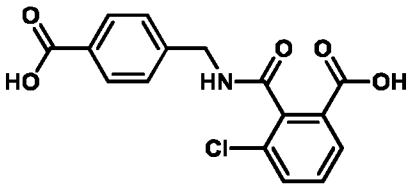
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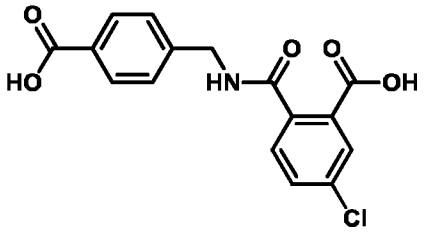
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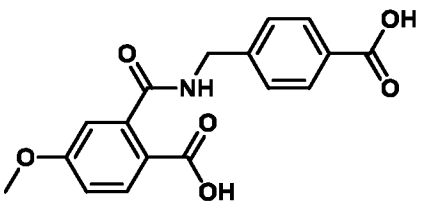
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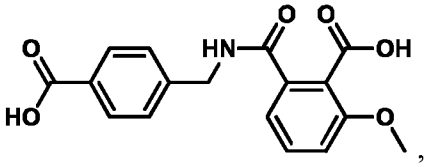
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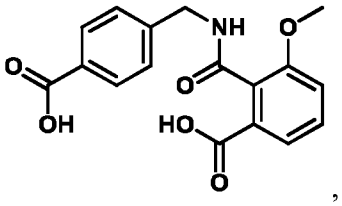
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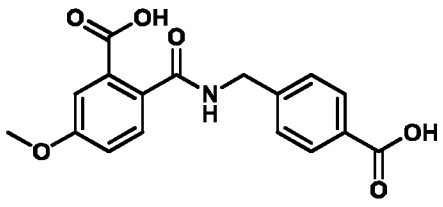
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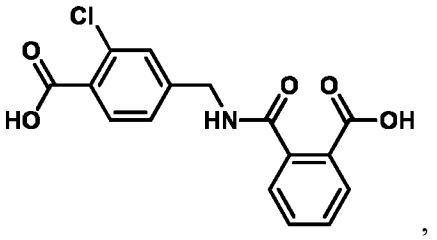
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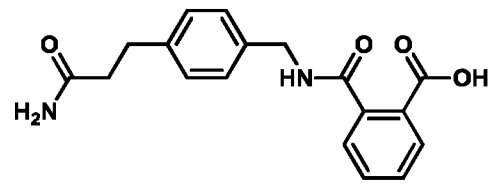
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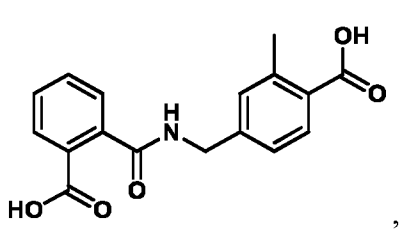
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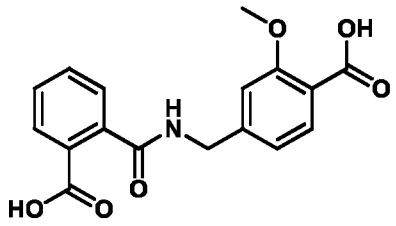
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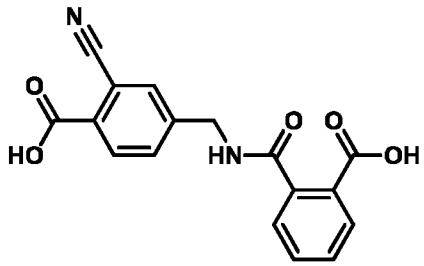
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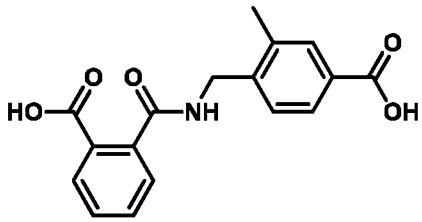
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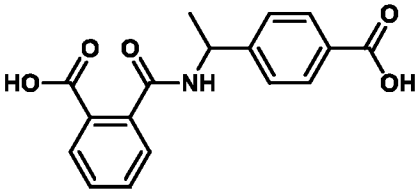
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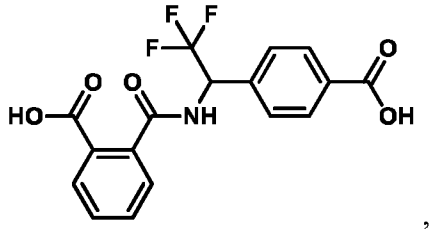
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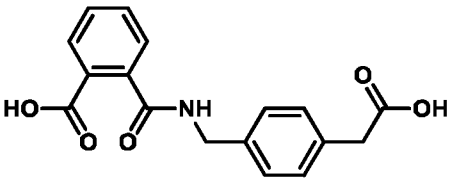
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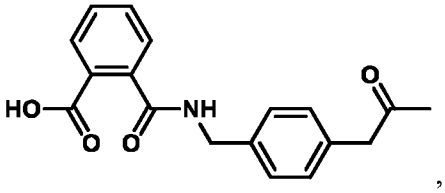
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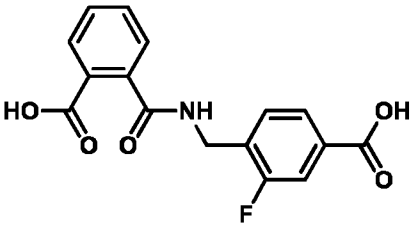
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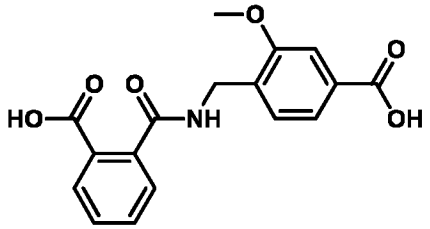
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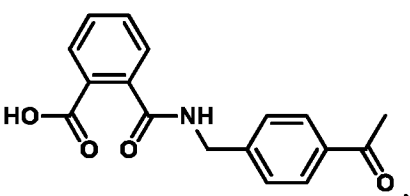
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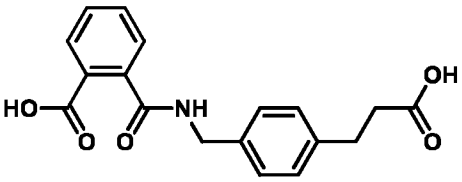
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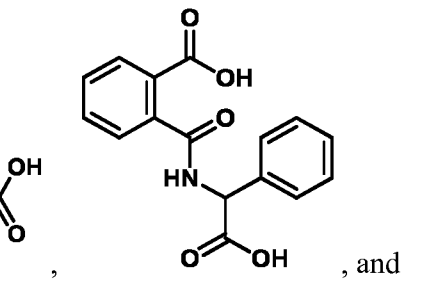
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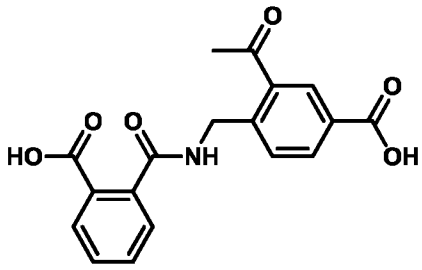
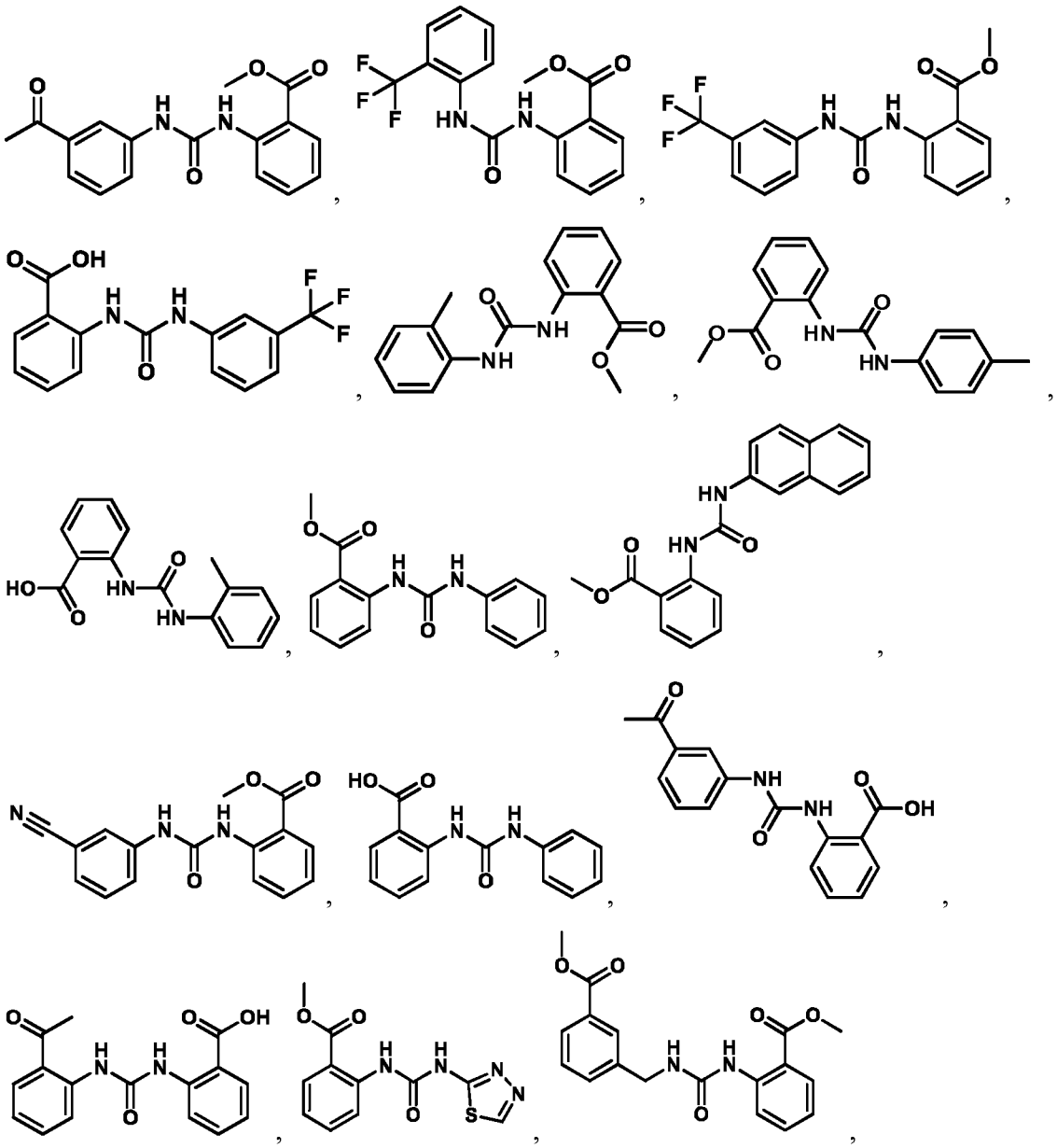
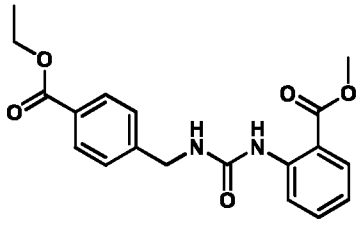


; or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

107. A compound of Formula II selected from

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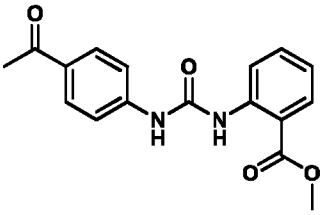
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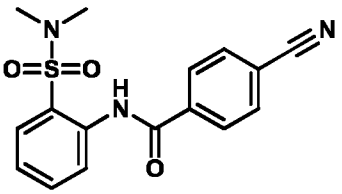
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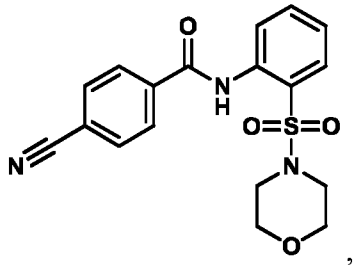
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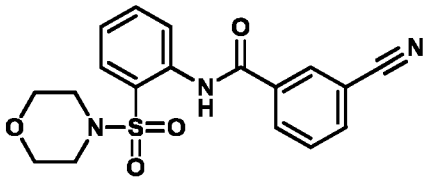
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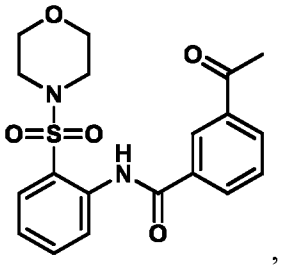
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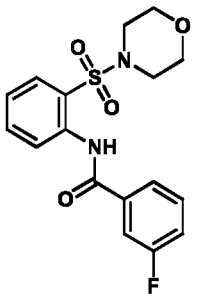
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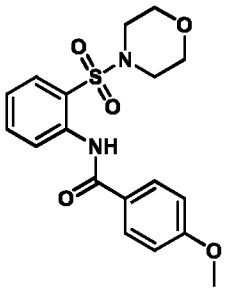
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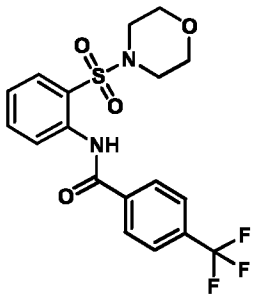
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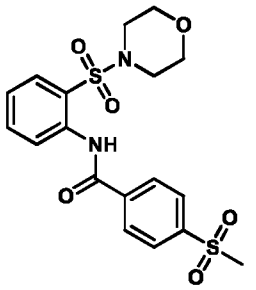
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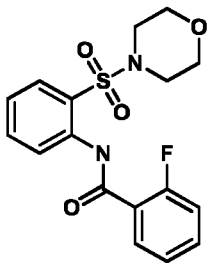
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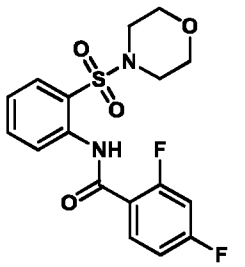
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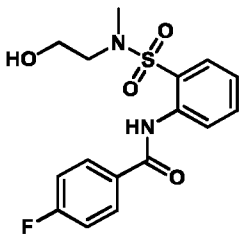
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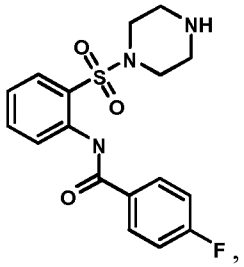
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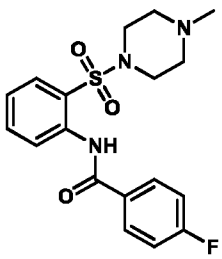
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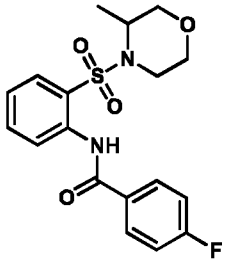
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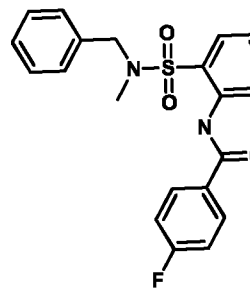
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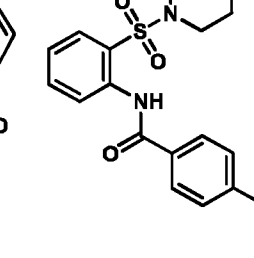
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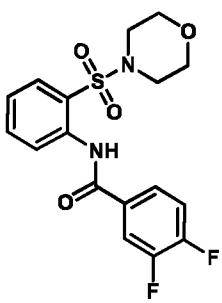
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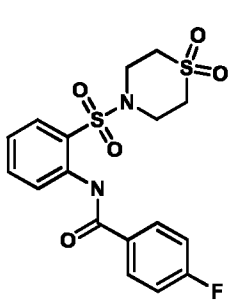
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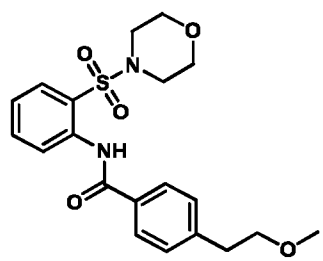
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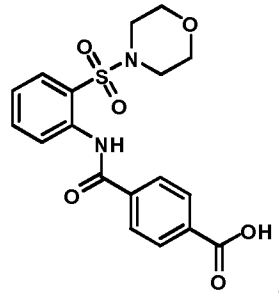
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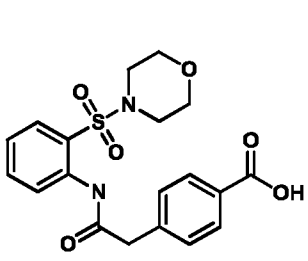
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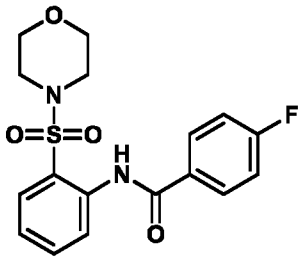
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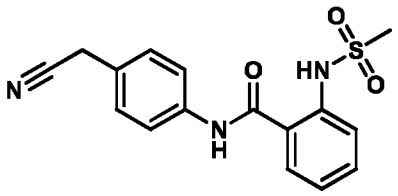
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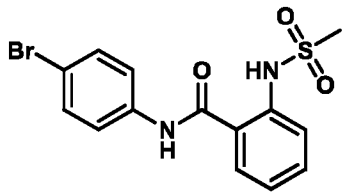
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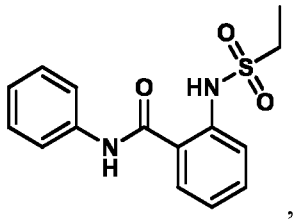
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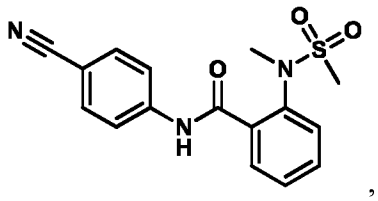
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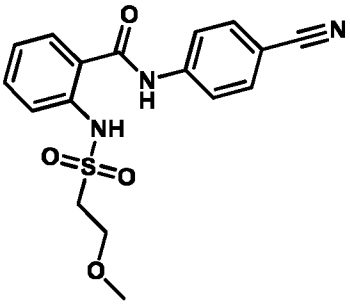
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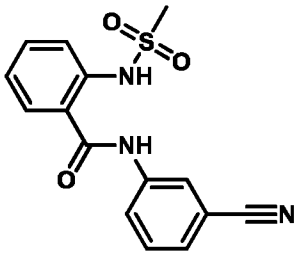
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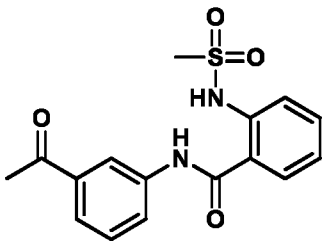
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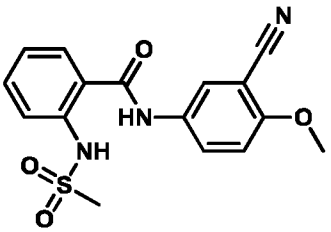
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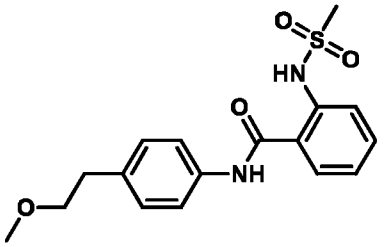
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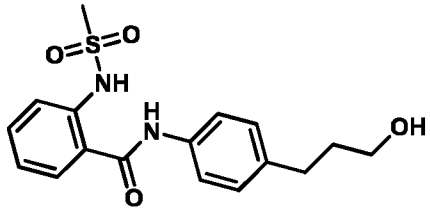
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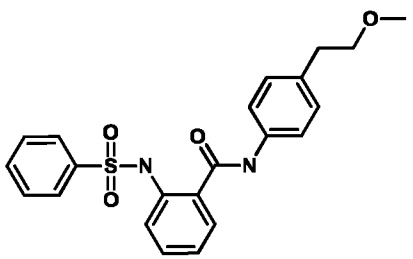
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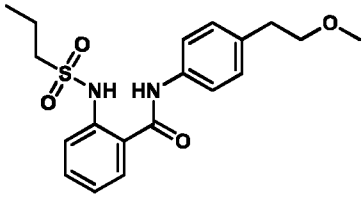
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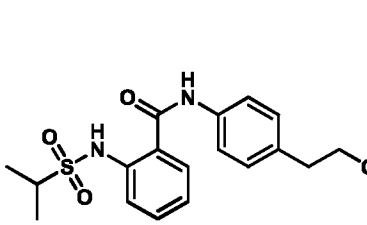
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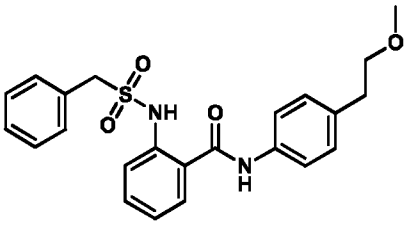
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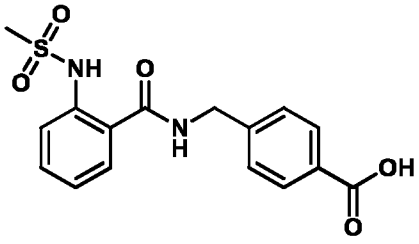
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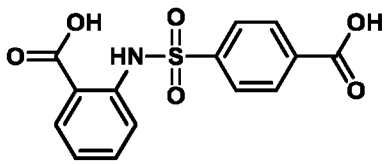
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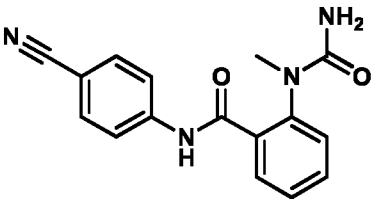
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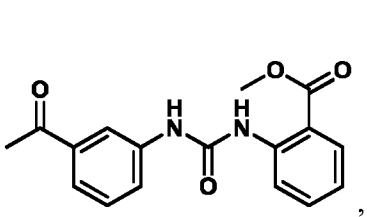
108. A compound of Formula IIa selected from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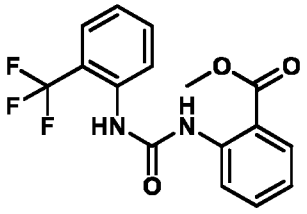
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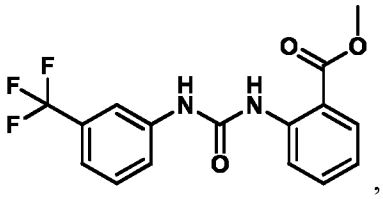
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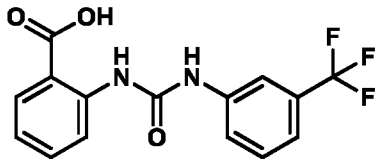
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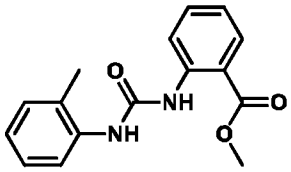
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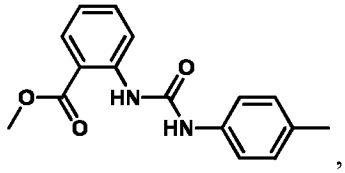
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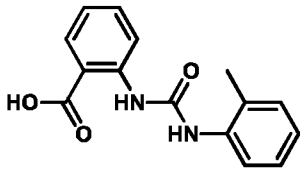
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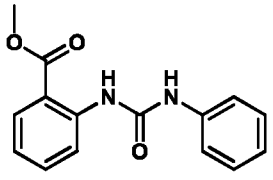
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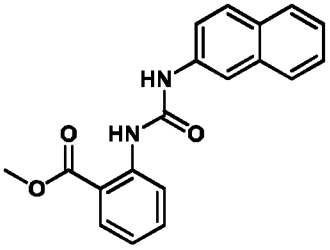
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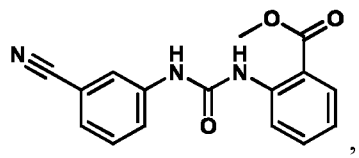
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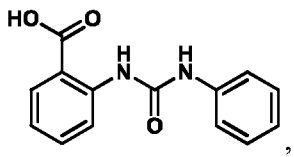
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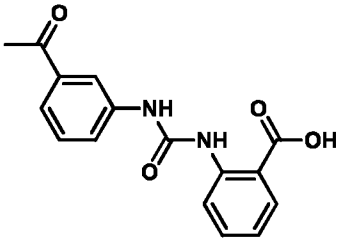
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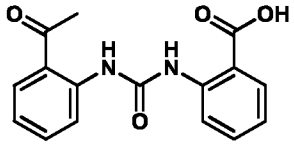
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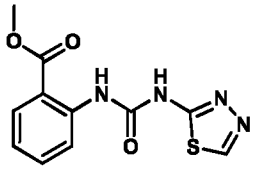
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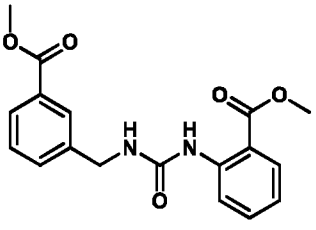
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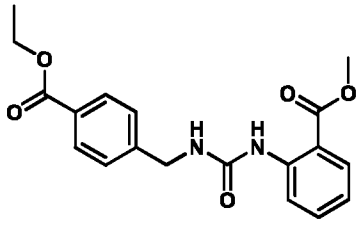
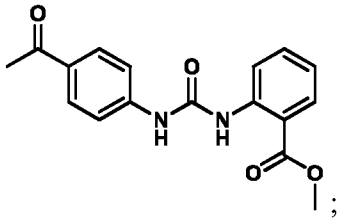
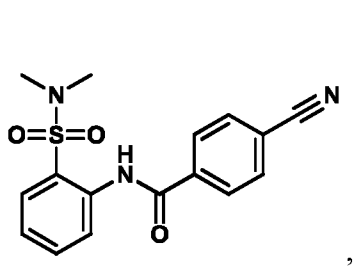

, and  ; or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

109. A compound of Formula IIb selected from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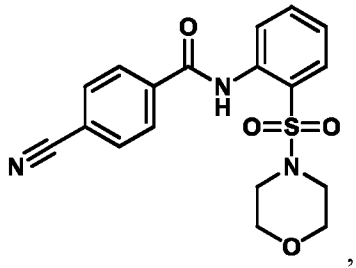
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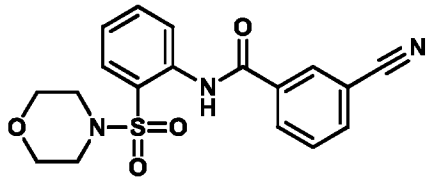
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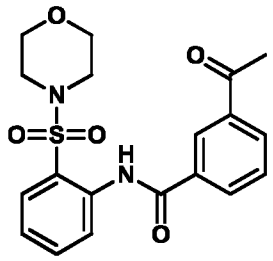
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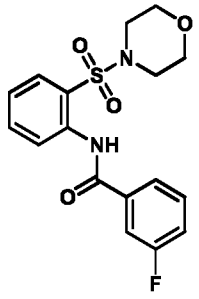
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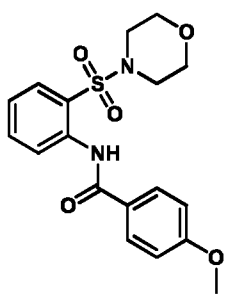
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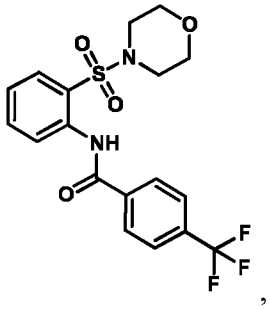
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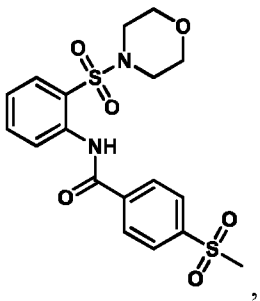
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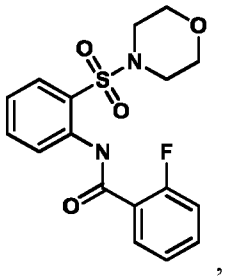
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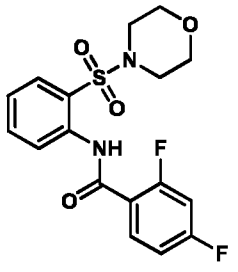
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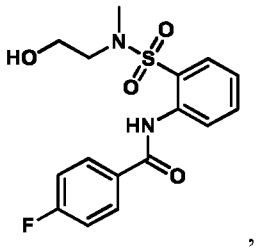
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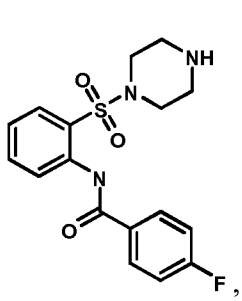
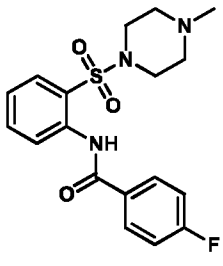
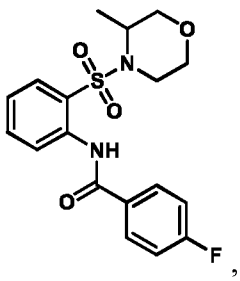
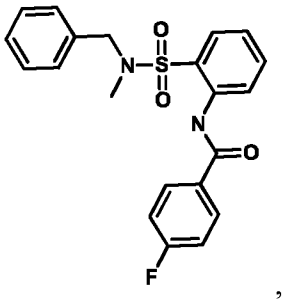
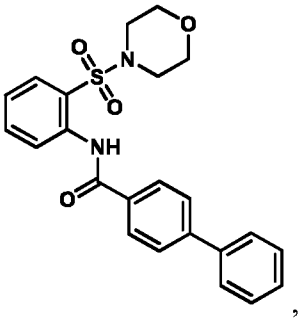
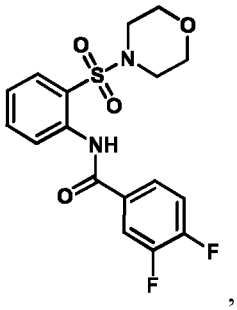
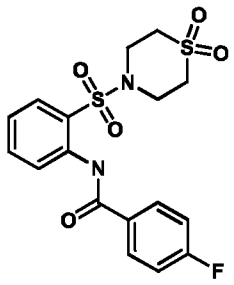
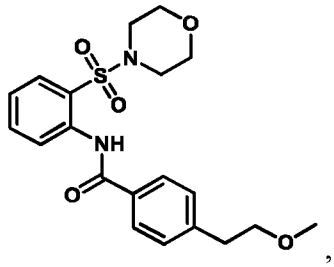
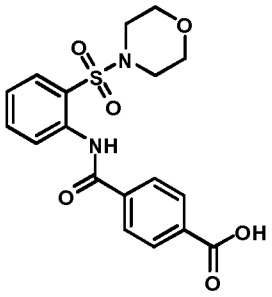
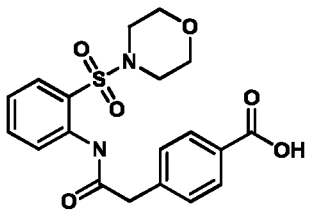
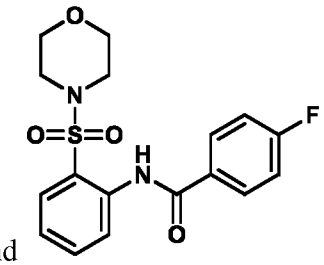
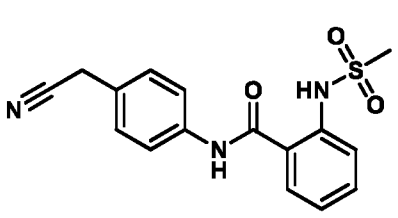
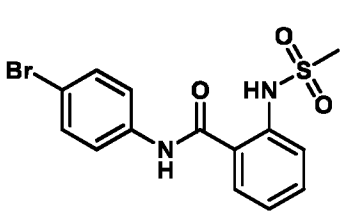
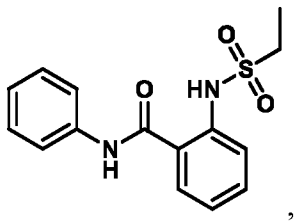
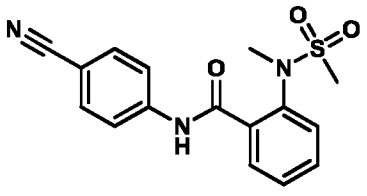
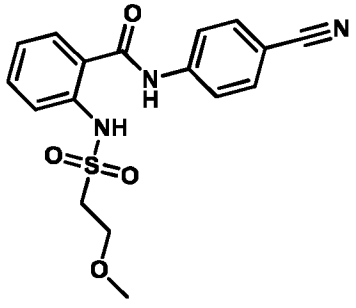
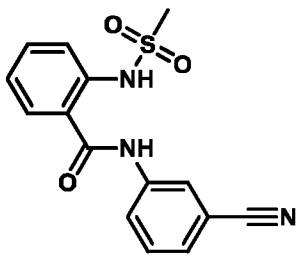
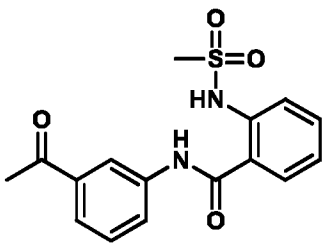












pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

110. A compound of Formula IIc selected from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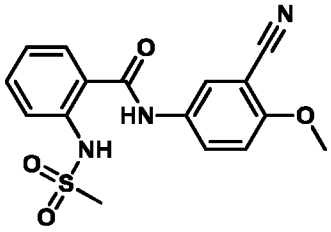
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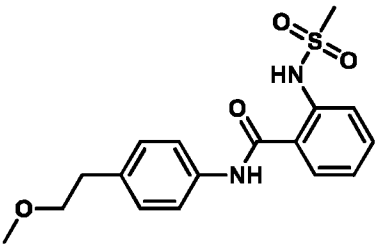
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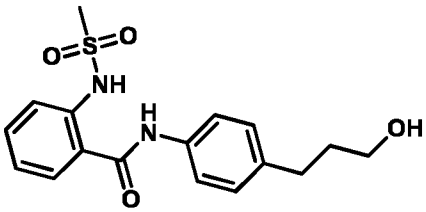
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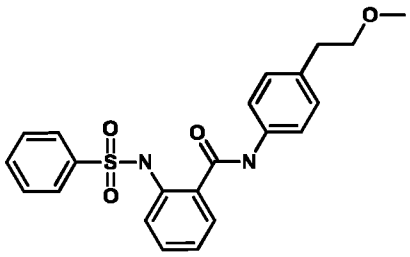
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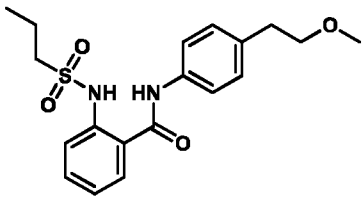
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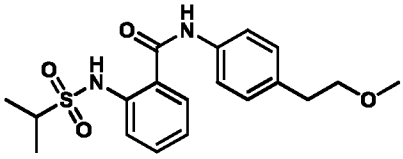
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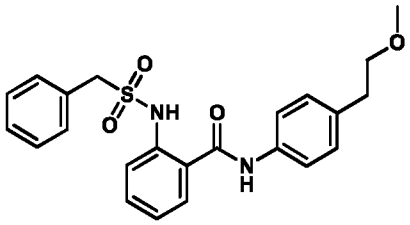
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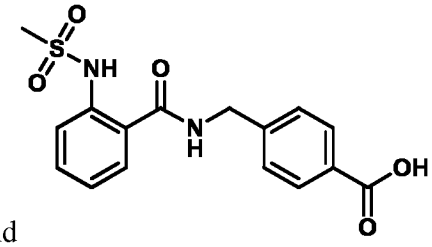
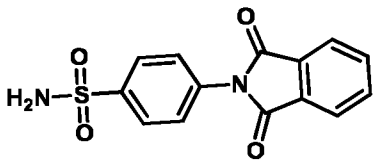

; or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

111. A compound of Formula III selected from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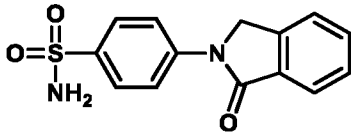
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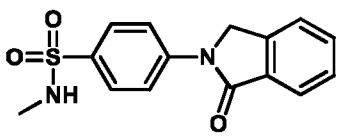
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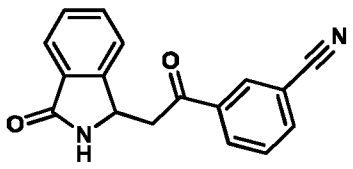
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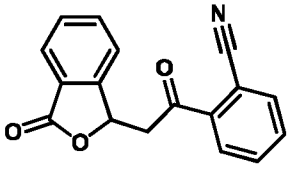
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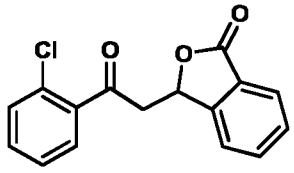
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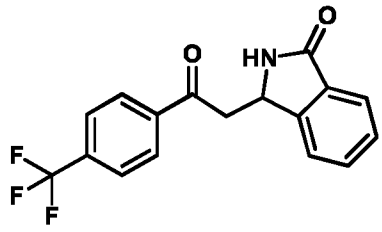
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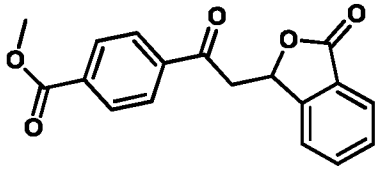
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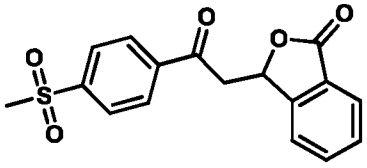
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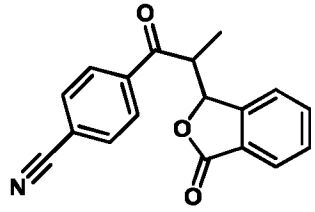
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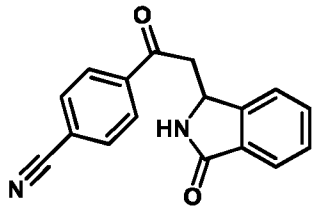
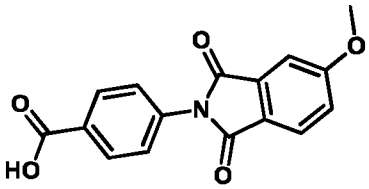

; or

a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

112. A compound selected from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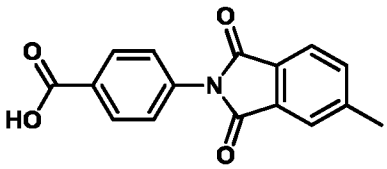
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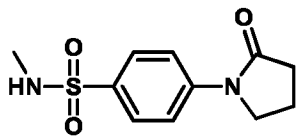
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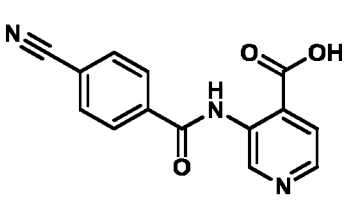
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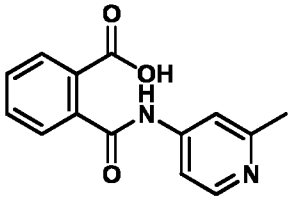
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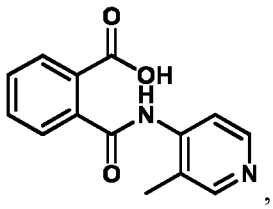
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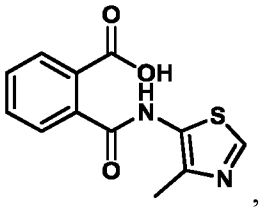
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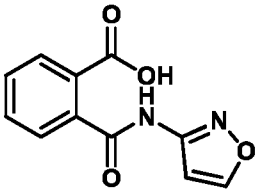
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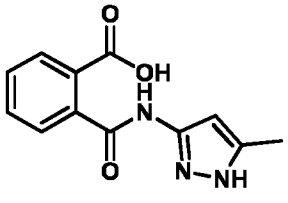
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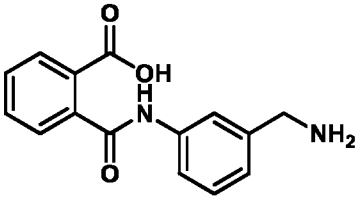
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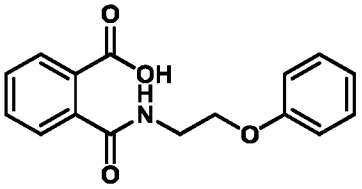
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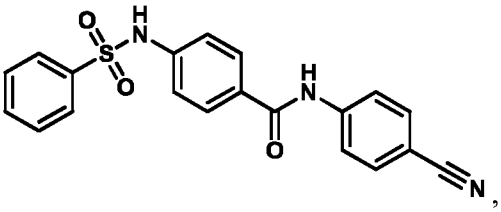
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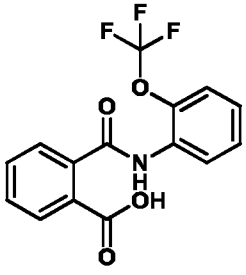
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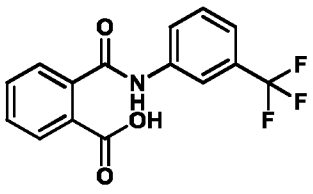
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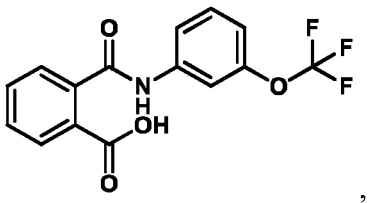
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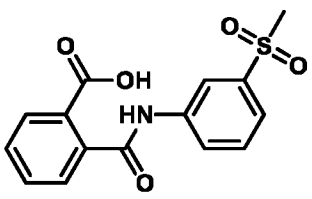
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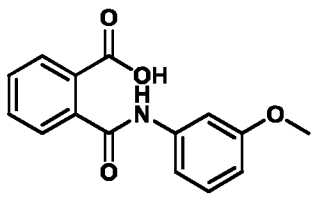
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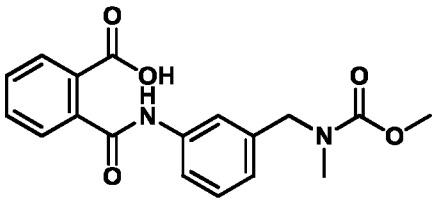
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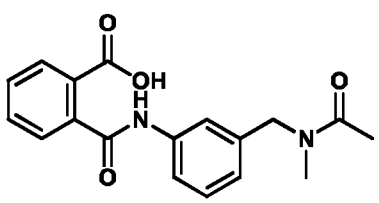
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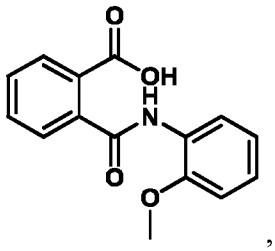
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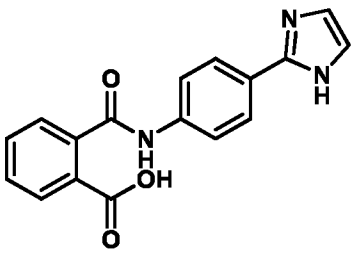
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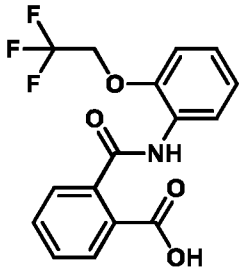
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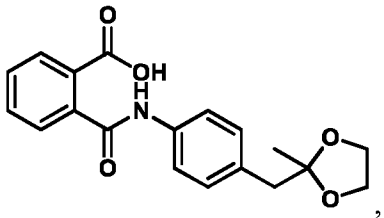
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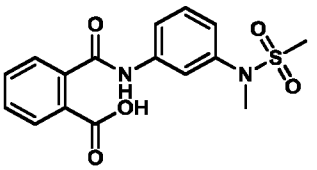
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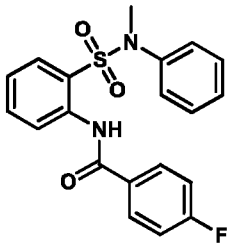
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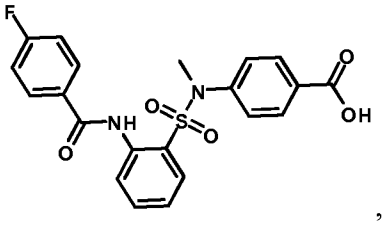
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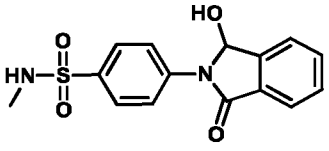
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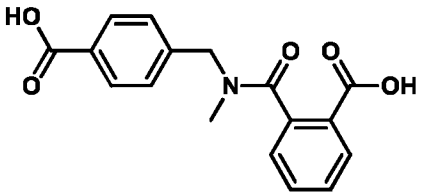
;or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof.

113. A pharmaceutical composition comprising a compound of any one of claims 103-112, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, ester, metabolite, N-oxide, stereoisomer, or isomer thereof, and a pharmaceutically acceptable excipient.

114. The pharmaceutical composition of claim 113 further comprising an additional compound which is therapeutically effective for the treatment of arthritis or joint injury and/or the symptoms associated with arthritis or joint injury in a mammal.

115. The pharmaceutical composition of claim 114 wherein the additional compound is selected from NSAIDS, analgesics, angiopoietin-like 3 protein (ANGPTL3) or chondrogenic variant thereof, oral salmon calcitonin, iNOS inhibitors, vitamin D3, caspase inhibitors, collagen hydrolysate, FGF18, BMP7, avocado soy unsaponifiables (ASU), and hyaluronic acid.

116. The pharmaceutical composition of claim 114, wherein the mammal is human.

117. The pharmaceutical composition of claim 114, wherein the mammal is a companion animal or livestock.

118. The method of any one of claims 1-4, 27-30, 66, 67, or 98, wherein the mammal is human.

119. The method of any one of claims 1-4, 27-30, 66, 67, or 98, wherein the mammal is a domesticated animal or livestock.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/26722

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/505, 39/395 (2014.01)
USPC - 424/134.1; 514/16.7
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A61K 31/505, 39/395 (2014.01)
USPC: 424/134.1; 514/16.7

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); ProQuest; Scifinder; Google/Google Scholar; KEYWORDS: amelioration, arthritis, joint, mesenchymal, stem, cells, chondrocytes, differentiation, inducing, administering, human, livestock, NSAIDS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/129562 A2 (SHULTZ, P et al.) 27 September 2012; formula I; paragraphs [0004]-[0012], [0014]-[0017], [0040], [0042], [0044]-[0045], [0050], [0057], [0059], [0062], [0149]-[0150], [0152]	1-8, 9/1-2, 9/5-6, 10/9/1-2, 10/9/5-6, 11/10/9/1-2, 11/10/9/1-2, 12/11/10/9/1-2, 12/11/10/9/5-6, 13/12/11/10/9/1-2, 13/12/11/10/9/5-6, 14/1, 14/3, 14/5, 14/7, 15/14/1, 15/14/3, 15/14/5, 15/14/7, 16/15/14/1, 16/15/14/3, 16/15/14/5, 16/15/14/7, 17/14/1, 17/14/3, 17/14/5, 17/14/7, 18/17/14/1, 18/17/14/3, 18/17/14/5, 18/17/14/7, 19/1, 19/4-5, 19/8, 20/19/1, 20/19/4-5, 20/19/8, 21/1, 21/4-5, 21/8, 22/21/1, 22/21/4-5, 22/21/8, 27-34, 35/27-28, 35/31-32, 36/35/27-28, 36/35/31-32, 37/35/27-28, 37/35/31-32, 38/36/35/27-28, 38/36/35/31-32, 43/27, 43/29, 43/31, 43/33, 52/27, 52/30-31, 52/34, 53/27, 53/30-31, 53/34,

☒ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 June 2014 (03.06.2014)	18 JUL 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/26722

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y		44/27, 44/29, 44/31, 44/33, 45/44/27, 45/44/29, 45/44/31, 45/44/33, 53/27, 53/30-31, 53/34
Y	US 6,632,961 B1 (KAWAI, M et al.) 14 October 2003; formula I; column 2, lines 5-27; column 10, lines 58-60	44/27, 44/29, 44/31, 44/33, 45/44/27, 45/44/29, 45/44/31, 45/44/33
Y	US 2005/0049286 A1 (WU, C et al.) 03 March 2005; formula I; paragraphs [0022], [0025]-[0026], [0031], [0033] and [0183]	53/27, 53/30-31, 53/34

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/26722

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 23-26, 39-42, 46-51, 56-57, 60-65, 74-88
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 105228626 A
(43)申请公布日 2016.01.06

(21)申请号 201480028421.3

(22)申请日 2014.03.13

(30)优先权数据
61/794,094 2013.03.15 US

(85)PCT国际申请进入国家阶段日
2015.11.16

(86)PCT国际申请的申请数据
PCT/US2014/026722 2014.03.13

(87)PCT国际申请的公布数据
WO2014/151953 EN 2014.09.25

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代理人 郑霞

(51)Int.Cl.
A61K 31/505(2006.01)
A61K 39/395(2006.01)

权利要求书63页 说明书153页

(54)发明名称

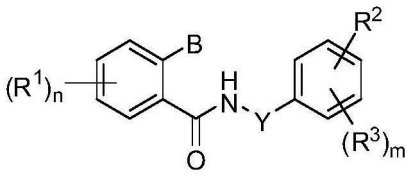
用于诱导软骨形成的化合物和方法

(57)摘要

本文描述了用于通过诱导间充质干细胞成为软骨细胞而改善关节炎或关节损伤的化合物和组合物。

CN 105228626 A

1. 一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 I 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 I)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NR^4R^{11}、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

m 为 1、2、3 或 4；

B 为 CO_2R^4、CH_2CO_2H、$CH_2CO_2R^4$或任选取代的苯基；

Y 为键、$-(CR^5R^6)-$、$-(CR^7R^8)(CR^9R^{10})-$ 或 $-(CR^7R^8)(CR^9R^{10})X-$；

X 为 O 或 CR^5R^6；

R^2为卤代、$C(O)R^4$、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或 $C(=NOR^4)R^4$；

各 R^3独立地选自 H、CN、卤代、$C(O)R^4$、CO_2H、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和 $C(=NOR^4)R^4$；

各 R^4独立地选自 H 和任选取代的烷基；

各 R^5、R^6、R^7、R^8、R^9和 R^{10}独立地选自 H、卤代、任选取代的烷基、OH、CO_2R^4、NR^4R^{11}和任选取代的烷氧基；且

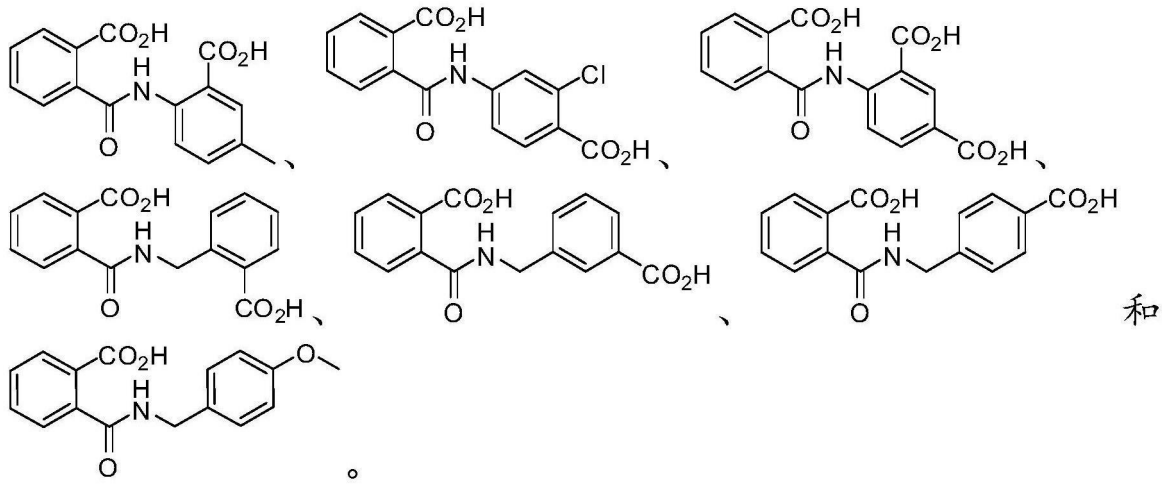
R^{11}为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

条件是

a) 如果 Y 为键且 m 为 0，则 R^2选自 $C(O)NR^4R^{11}$、$(CR^7R^8)OR^4$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和 $C(=NOR^4)R^4$；且

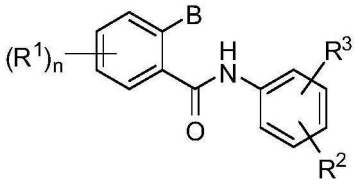
R^2不是 $C(O)NH_2$、$p\text{-}CH_2OR^4$、$p\text{-}CH(OH)CH_2OH$、$p\text{-}CH_2CH_2OH$ 或 $p\text{-}CH_2CH_2CH_2OH$；且

b) 该化合物不选自



。

2. 一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 Ia 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 Ia)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NR^4R^{11}、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 CO_2R^4；

R^2为卤代、$C(O)R^4$、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或 $C(=NOR^4)R^4$；

各 R^3独立地选自 CN、卤代、$C(O)R^4$、CO_2H、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和 $C(=NOR^4)R^4$；

X 为 O 或 CR^5R^6；

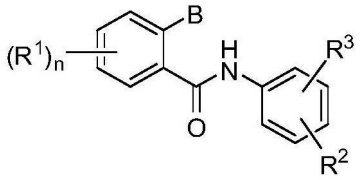
各 R^4独立地选自 H 和任选取代的烷基；

各 R^5、R^6、R^7、R^8、R^9和 R^{10}独立地选自 H、卤代、任选取代的烷基、OH、NR^4R^{11}和任选取代的烷氧基；且

R^{11}为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

条件是该化合物不选自

3.一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 Ib 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 Ib)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NR^4R^{11}、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 CO_2R^4；

R^2为 $C(O)NR^4R^{11}$、$(CR^7R^8)OR^4$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或 $C(=NOR^4)R^4$；

R^3为 H；

X 为 O 或 CR^5R^6；

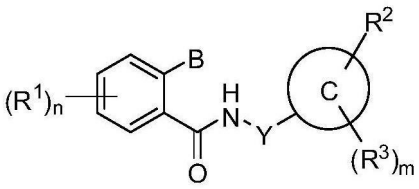
各 R^4独立地选自 H 和任选取代的烷基；

各 R^5、R^6、R^7、R^8、R^9和 R^{10}独立地选自 H、卤代、任选取代的烷基、OH、NR^4R^{11}和任选取代的烷氧基；且

R^{11}为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

条件是如果 n 为 0，则 R^2不是 $C(O)NH_2$、$p\text{-}CH_2OR^4$、$p\text{-}CH(OH)CH_2OH$、$p\text{-}CH_2CH_2OH$ 或 $p\text{-}CH_2CH_2CH_2OH$。

4.一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 Ic 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 Ic)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NR^4R^{11}、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

m 为 1、2、3 或 4；

B 为 CO_2R^4；

Y 为 $-(CR^5R^6)-$；

C 为芳基或杂芳基；

X 为 O 或 CR^5R^6；

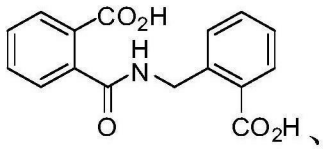
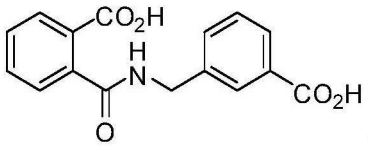
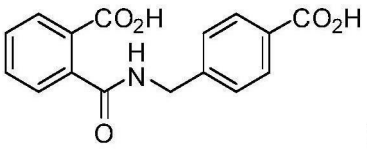
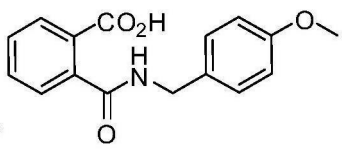
R^2为卤代、$C(O)R^4$、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、SO_2NH_2、SO_3H、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或 $C(=NOR^4)R^4$；

各 R^3独立地选自 H、CN、卤代、$C(O)R^4$、CO_2H、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和 $C(=NOR^4)R^4$；

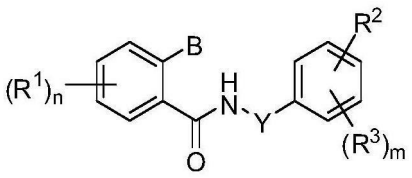
各 R^4独立地选自 H 和任选取代的烷基；

各 R^5、R^6、R^7、R^8、R^9和 R^{10}独立地选自 H、卤代、任选取代的烷基、OH、CO_2R^4、NR^4R^{11}和任选取代的烷氧基；且

R^{11}为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

条件是该化合物不选自  、  、  和  。

5. 一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 I 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 I)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NR^4R^{11}、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

m 为 1、2、3 或 4；

B 为 CO_2R^4、CH_2CO_2H、$CH_2CO_2R^3$或任选取代的苯基；

Y 为键、$-(CR^5R^6)-$、$-(CR^7R^8)(CR^9R^{10})-$ 或 $-(CR^7R^8)(CR^9R^{10})X-$；

X 为 O 或 CR^5R^6；

R^2为卤代、$C(O)R^4$、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或 $C(=NOR^4)R^4$；

各 R^3独立地选自 H、CN、卤代、$C(O)R^4$、CO_2H、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和 $C(=NOR^4)R^4$；

各 R^4独立地选自 H 和任选取代的烷基；

各 R^5、R^6、R^7、R^8、R^9和 R^{10}独立地选自 H、卤代、任选取代的烷基、OH、CO_2R^4、NR^4R^{11}和任选取代的烷氧基；且

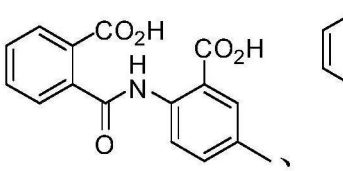
R^{11}为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

条件是

a) 如果 Y 为键且 m 为 0，则 R^2选自 $C(O)NR^4R^{11}$、$(CR^7R^8)OR^4$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和 $C(=NOR^4)R^4$；且

R^2不是 $C(O)NH_2$、$p\text{-}CH_2OR^4$、$p\text{-}CH(OH)CH_2OH$、$p\text{-}CH_2CH_2OH$ 或 $p\text{-}CH_2CH_2CH_2OH$；且

b) 该化合物不选自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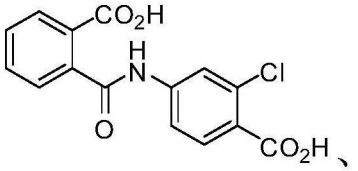
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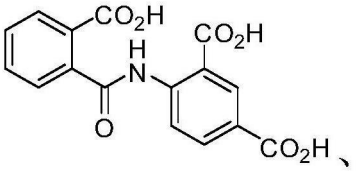
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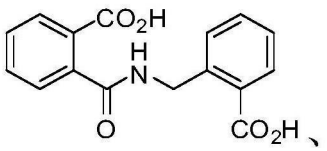
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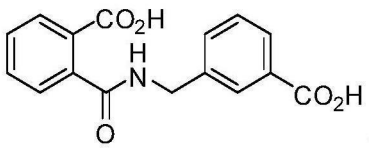
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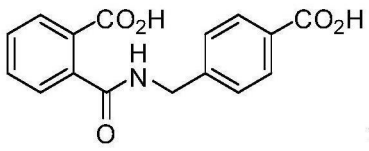
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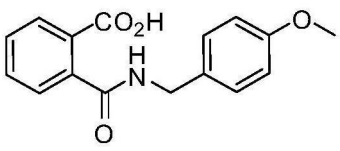
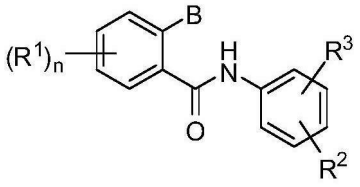

。

6. 一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 Ia 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 Ia)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NR^4R^{11}、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 CO_2R^4；

R^2为卤代、$C(O)R^4$、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或 $C(=NOR^4)R^4$；

各 R^3独立地选自 CN、卤代、$C(O)R^4$、CO_2H、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和 $C(=NOR^4)R^4$；

X 为 O 或 CR^5R^6；

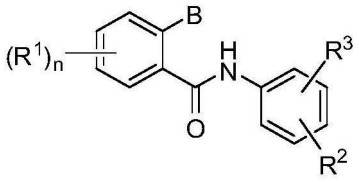
各 R^4独立地选自 H 和任选取代的烷基；

各 R^5、R^6、R^7、R^8、R^9和 R^{10}独立地选自 H、卤代、任选取代的烷基、OH、NR^4R^{11}和任选取代的烷氧基；且

R^{11}为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

条件是该化合物不选自

7. 一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 Ib 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 Ib)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NR^4R^{11}、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 CO_2R^4；

R^2为 $C(O)NR^4R^{11}$、$(CR^7R^8)OR^4$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或 $C(=NOR^4)R^4$；

R^3为 H；

X 为 O 或 CR^5R^6；

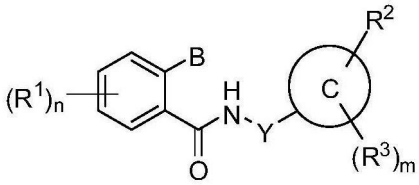
各 R^4独立地选自 H 和任选取代的烷基；

各 R^5、R^6、R^7、R^8、R^9和 R^{10}独立地选自 H、卤代、任选取代的烷基、OH、NR^4R^{11}和任选取代的烷氧基；且

R^{11}为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

条件是如果 n 为 4 且 R^1为 H，则 R^2不是 $C(O)NH_2$、$p\text{-}CH_2OR^4$、$p\text{-}CH(OH)CH_2OH$、$p\text{-}CH_2CH_2OH$ 或 $p\text{-}CH_2CH_2CH_2OH$。

8. 一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 Ic 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 Ic)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NR^4R^{11}、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

m 为 1、2、3 或 4；

B 为 CO_2R^4；

Y 为 $-(CR^5R^6)-$；

C 为芳基或杂芳基；

X 为 O 或 CR^5R^6；

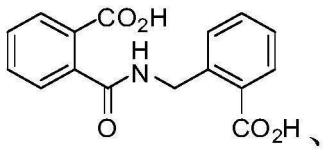
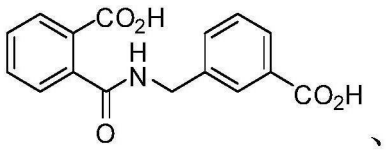
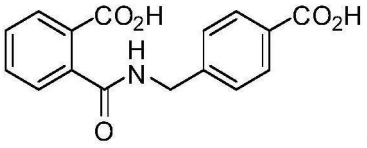
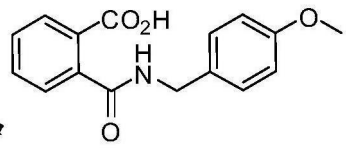
R^2为卤代、C(O)R^4、CO_2R^4、C(O)NR^4R^{11}、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、SO_2NH_2、SO_3H、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或 C(=NOR^4)$R^4$；

各 R^3独立地选自 H、CN、卤代、C(O)R^4、CO_2H、CO_2R^4、C(O)NR^4R^{11}、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和 C(=NOR^4)$R^4$；

各 R^4独立地选自 H 和任选取代的烷基；

各 R^5、R^6、R^7、R^8、R^9和 R^{10}独立地选自 H、卤代、任选取代的烷基、OH、CO_2R^4、NR^4R^{11}和任选取代的烷氧基；且

R^{11}为 H、任选取代的烷基、C(O)R^4、C(O)OR^4、C(O)NR^4R^4或 SO_2R^4；

条件是该化合物不选自  、  、  、  和。

9. 如权利要求 1、2、5 或 6 中任一项所述的方法，其中：

R^2为卤代、C(O)R^4、烷基、任选取代的烷氧基、卤代烷基、$(CR^7R^8)OR^4$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)C(O)OR^4$或 $X(CR^7R^8)C(O)NR^4R^{11}$；且

各 R^3独立地选自 CN、卤代、C(O)R^4、CO_2H、C(O)NR^4R^{11}、烷基或任选取代的烷氧基；

或者 R^3与相邻的 R^3或与 R^2一起形成环。

10. 如权利要求 9 所述的方法，其中：

R^2为 F、Cl、C(O)CH_3、CH_3、CF_3、OCH_3、OEt、OPr、OCF_3、$OCHF_2$、$(CR^7R^8)OR^4$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)C(O)OR^4$或 $X(CR^7R^8)C(O)NR^4R^{11}$；且

各 R^3独立地选自 CN、F、Cl、C(O)CH_3、CO_2H、C(O)NH_2、CH_3、OCF_3或 OCH_3；

或者 R^3与相邻的 R^3或与 R^2一起形成环。

11. 如权利要求 10 所述的方法，其中 R^2为 F、Cl、C(O)CH_3、CH_3、CF_3、OCH_3、OEt、OPr、OCF_3、$OCHF_2$、CH_2OCH_3、CH_2OH、CH_2CH_2OH、$CHOHCH_2OH$、$CH_2CH_2CH_2OH$、$CH_2CHOHCH_2OH$、$OCH_2C(O)OH$ 或 $OCH_2C(O)NH_2$。

12. 如权利要求 11 所述的方法，其中各 R^3独立地选自 CN、F、Cl、C(O)CH_3或 CO_2H。

13. 如权利要求 12 所述的方法，其中 R^2为 F、Cl、C(O)CH_3、CH_3、CF_3、OCH_3、OEt、OPr、OCF_3或 $CH_2CH_2CH_2OH$。

14. 如权利要求 1、3、5 或 7 中任一项所述的方法，其中：

R^2为 $(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或 $C(=NOR^4)R^4$;且

R^3为 H。

15. 如权利要求 14 所述的方法,其中 R^2为 $(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$或 $(CR^7R^8)NR^4SO_2R^4$。

16. 如权利要求 15 所述的方法,其中 R^2为 CH_2CH_2OH、$CH_2CH_2OCH_3$、CH_2CHCH_3OH、$CHCH_3CH_2OH$、$CH_2CH_2CH_2OH$、$CH_2CH_2CH_2NH_2$、$CH_2CH_2CHCH_3OH$、$C(CH_3)_2CH_2CH_2OH$、$CH_2CH_2C(CH_3)_2OH$、OCH_2CH_2OH、$OCH_2CH_2OCH_3$或 $OCH_2CH_2NH_2$。

17. 如权利要求 14 所述的方法,其中 R^2为 $(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$或 $X(CR^7R^8)C(O)NR^4R^{11}$。

18. 如权利要求 17 所述的方法,其中 R^2为 $CH_2C(O)CH_3$、$CH_2C(O)NH_2$、$CH_2CH_2C(O)CH_3$或 $CH_2CH_2C(O)NH_2$。

19. 如权利要求 1、4、5 或 8 中任一项所述的方法,其中 C 为芳基。

20. 如权利要求 19 所述的方法,其中 C 为苯基。

21. 如权利要求 1、4、5 或 8 中任一项所述的方法,其中 C 为杂芳基。

22. 如权利要求 21 所述的方法,其中 C 为吡啶基、嘧啶基、哒嗪基或吡嗪基。

23. 如权利要求 1、4、5、8 或 19-22 中任一项所述的方法,其中 :

R^2为卤代、$C(O)R^4$、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、卤代烷基、SO_2NH_2、SO_3H、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)OR^4$或 $X(CR^7R^8)C(O)NR^4R^{11}$;且

各 R^3独立地选自 H、CN、卤代、CO_2H 或卤代烷基。

24. 如权利要求 23 所述的方法,其中 :

R^2为 Cl、F、$C(O)CH_3$、CO_2H、$C(O)NR^4R^{11}$、CH_3、任选取代的烷氧基、CF_3、SO_2NH_2、SO_3H、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)OR^4$或 $X(CR^7R^8)C(O)NR^4R^{11}$;且

各 R^3独立地选自 H、CN、Cl、F、CO_2H 或 CF_3。

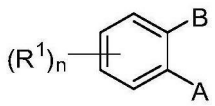
25. 如权利要求 24 所述的方法,其中 :

R^2为 Cl、F、$C(O)CH_3$、CO_2H、CH_3、OCH_3、CF_3;且

各 R^3独立地选自 H、CN 或 CO_2H。

26. 如权利要求 24 所述的方法,其中 R^2为 $CH_2C(O)NH_2$、$CH_2C(O)CH_3$、$CH_2C(O)OH$、$CH_2CH_2C(O)OH$ 或 $CH_2CH_2C(O)NH_2$。

27. 一种改善哺乳动物的关节炎或关节损伤的方法,该方法包括向哺乳动物的关节施用包含治疗有效量的式 II 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物 :



(式 II)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、

SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 $NHC(O)R^2$、$NR^3C(O)R^2$、$NHC(O)NH_2$、$NHC(O)NHR^2$、$NHC(O)NR^2R^4$、$NR^3C(O)NH_2$、$NR^3C(O)NHR^2$、$NR^3C(O)NR^2R^4$、$NHC(O)OR^2$、$NR^3C(O)OR^2$、$NHSO_2R^3$、$NR^3SO_2R^3$、$NHSO_2R^4$、$NR^3SO_2R^4$、$NHSO_2NH_2$、$NHSO_2NHR^2$、$NHSO_2NR^2R^4$、$NR^3SO_2NH_2$、$NR^3SO_2NHR^2$或 $NR^3SO_2NR^2R^4$；

各 R^2和 R^4独立地为任选取代的苯基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳烷基或任选取代的烷基；

R^3为任选取代的烷基或任选取代的芳烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

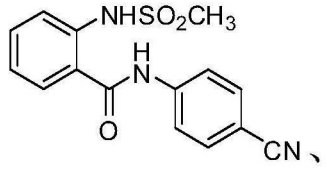
A 为 CO_2H、CO_2R^3、$C(O)NH_2$、$C(O)NHR^2$、$C(O)NR^2R^4$或 $SO_2NR^aR^b$；且

各 R^a和 R^b独立地为任选取代的烷基或者与它们所连接的 N 一起形成环；

条件是

a) 如果 B 为 $NHC(O)R^2$或 $NR^3C(O)R^2$，则 A 不是 CO_2H；且

b) 该化合物不选自



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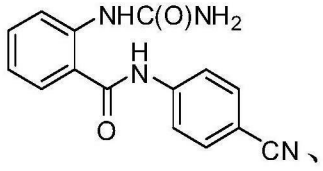

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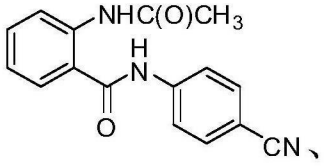

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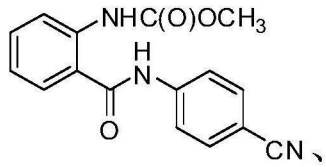

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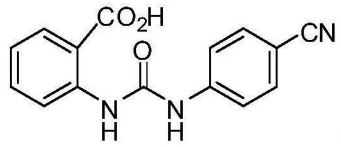

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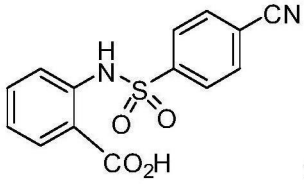
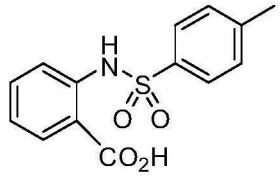


和


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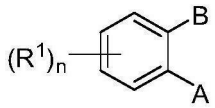
28. 一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 IIa 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 IIa)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 $NHC(O)NH_2$、$NHC(O)NHR^2$、$NHC(O)NR^2R^4$、$NR^3C(O)NH_2$、$NR^3C(O)NHR^2$或 $NR^3C(O)NR^2R^4$；

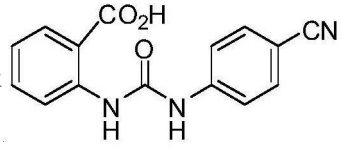
各 R^2和 R^4独立地为任选取代的苯基、任选取代的杂芳基、任选取代的杂环基、任选取代

的芳烷基或任选取代的烷基；

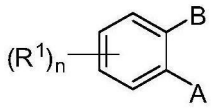
R^3为任选取代的烷基或任选取代的芳烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；且

A 为 CO_2H 或 CO_2R^3；

条件是该化合物不是  。

29. 一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 IIb 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 IIb)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 $NHC(O)R^2$或 $NR^3C(O)R^2$；

R^2为任选取代的苯基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳烷基或任选取代的烷基；

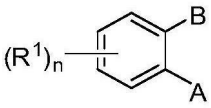
R^3为任选取代的烷基或任选取代的芳烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

A 为 $SO_2NR^aR^b$；且

各 R^a和 R^b独立地为任选取代的烷基或者与它们所连接的 N 一起形成环。

30. 一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 IIc 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 IIc)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 $NHSO_2R^3$、$NR^3SO_2R^3$、$NHSO_2R^4$、$NR^3SO_2R^4$、$NHSO_2NH_2$、$NHSO_2NHR^2$、$NHSO_2NR^2R^4$、$NR^3SO_2NH_2$、$NR^3SO_2NHR^2$或 $NR^3SO_2NR^2R^4$；

各 R^2和 R^4独立地为任选取代的苯基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳烷基或任选取代的烷基；

各 R^3独立地为任选取代的烷基或任选取代的芳烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；且

A 为 $C(O)NHR^2$或 $C(O)NR^2R^4$；

条件是该化合物不是 

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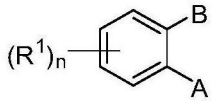
31. 一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 II 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 II)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 $NHC(O)R^2$、$NR^3C(O)R^2$、$NHC(O)NH_2$、$NHC(O)NHR^2$、$NHC(O)NR^2R^4$、$NR^3C(O)NH_2$、$NR^3C(O)NHR^2$、$NR^3C(O)NR^2R^4$、$NHC(O)OR^2$、$NR^3C(O)OR^2$、$NHSO_2R^3$、$NR^3SO_2R^3$、$NHSO_2R^4$、$NR^3SO_2R^4$、$NHSO_2NH_2$、$NHSO_2NHR^2$、$NHSO_2NR^2R^4$、$NR^3SO_2NH_2$、$NR^3SO_2NHR^2$或 $NR^3SO_2NR^2R^4$；

各 R^2和 R^4独立地为任选取代的苯基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳烷基或任选取代的烷基；

R^3为任选取代的烷基或任选取代的芳烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

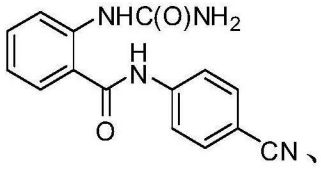
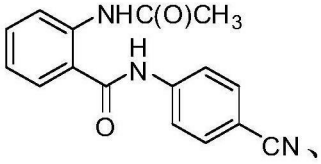
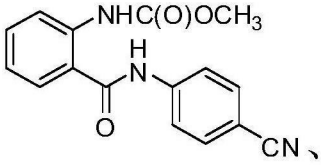
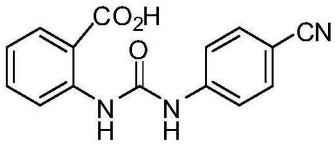
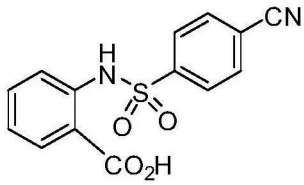
A 为 CO_2H、CO_2R^3、$C(O)NH_2$、$C(O)NHR^2$、$C(O)NR^2R^4$或 $SO_2NR^aR^b$；且

各 R^a和 R^b独立地为任选取代的烷基或者与它们所连接的 N 一起形成环；

条件是

a) 如果 B 为 $NHC(O)R^2$或 $NR^3C(O)R^2$，则 A 不是 CO_2H；且

b) 该化合物不选自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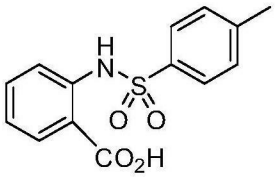
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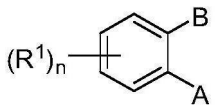
32.一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 IIa 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 IIa)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

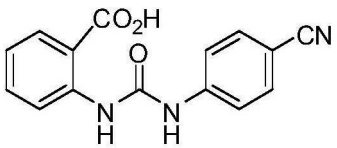
B 为 $NHC(O)NH_2$、$NHC(O)NHR^2$、$NHC(O)NR^2R^4$、$NR^3C(O)NH_2$、$NR^3C(O)NHR^2$或 $NR^3C(O)NR^2R^4$；

各 R^2和 R^4独立地为任选取代的苯基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳烷基或任选取代的烷基；

R^3为任选取代的烷基或任选取代的芳烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；且

A 为 CO_2H 或 CO_2R^3；

条件是该化合物不是 
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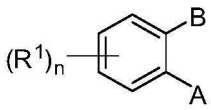
33.一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 IIb 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 IIb)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 $NHC(O)R^2$或 $NR^3C(O)R^2$；

R^2为任选取代的苯基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳烷基或任选取代的烷基；

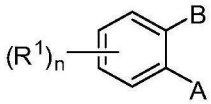
R^3为任选取代的烷基或任选取代的芳烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

A 为 $SO_2NR^aR^b$；且

各 R^a和 R^b独立地为任选取代的烷基或者与它们所连接的 N 一起形成环。

34. 一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 IIc 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 IIc)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

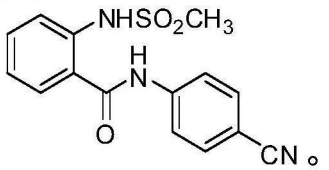
B 为 $NHSO_2R^3$、$NR^3SO_2R^3$、$NHSO_2R^4$、$NR^3SO_2R^4$、$NHSO_2NH_2$、$NHSO_2NHR^2$、$NHSO_2NR^2R^4$、$NR^3SO_2NH_2$、$NR^3SO_2NHR^2$或 $NR^3SO_2NR^2R^4$；

各 R^2和 R^4独立地为任选取代的苯基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳烷基或任选取代的烷基；

各 R^3独立地为任选取代的烷基或任选取代的芳烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；且

A 为 $C(O)NHR^2$或 $C(O)NR^2R^4$；

条件是该化合物不是  。

35. 如权利要求 27、28、31 或 32 中任一项所述的方法，其中 B 为 $NHC(O)NHR^2$、$NHC(O)NR^2R^4$、$NR^3C(O)NHR^2$或 $NR^3C(O)NR^2R^4$。

36. 如权利要求 35 所述的方法，其中 B 为 $NHC(O)NHR^2$ 或 $NR^3C(O)NHR^2$。

37. 如权利要求 35 所述的方法，其中 B 为 $NHC(O)NR^2R^4$ 或 $NR^3C(O)NR^2R^4$。

38. 如权利要求 36 所述的方法，其中 B 为 $NHC(O)NHR^2$。

39. 如权利要求 36-38 中任一项所述的方法，其中 R^2 为任选取代的苯基。

40. 如权利要求 39 所述的方法，其中 R^2 的苯基为双取代的。

41. 如权利要求 39 所述的方法，其中 R^2 的苯基为单取代的。

42. 如权利要求 40 或 41 所述的方法，其中 R^2 的苯基上的取代独立地选自 F、Cl、CO_2H、CN、OCH_3、$C(O)CH_3$、CF_3、CH_3、CH_2OH、CH_2CH_2OH 和 $CH_2CH_2CH_2OH$。

43. 如权利要求 27、29、31 或 33 中任一项所述的方法，其中 B 为 $NHC(O)R^2$。

44. 如权利要求 27、29、31 或 33 中任一项所述的方法，其中 B 为 $NR^3C(O)R^2$。

45. 如权利要求 44 所述的方法，其中 R^3 为任选取代的烷基。

46. 如权利要求 43-45 中任一项所述的方法，其中各 R^a 和 R^b 独立地为任选取代的烷基。

47. 如权利要求 43-45 中任一项所述的方法，其中 R^a 和 R^b 与它们所连接的 N 一起形成环。

48. 如权利要求 43-47 中任一项所述的方法，其中 R^2 为任选取代的苯基。

49. 如权利要求 48 所述的方法，其中 R^2 的苯基为双取代的。

50. 如权利要求 48 所述的方法，其中 R^2 的苯基为单取代的。

51. 如权利要求 49 或 50 所述的方法，其中 R^2 的苯基上的取代独立地选自 F、Cl、CO_2H、CN、OCH_3、$C(O)CH_3$、CF_3、CH_3、CH_2OH、CH_2CH_2OH 和 $CH_2CH_2CH_2OH$。

52. 如权利要求 27、30、31 或 34 中任一项所述的方法，其中 B 为 $NHSO_2R^3$、$NR^3SO_2R^3$、$NHSO_2R^4$ 或 $NR^3SO_2R^4$。

53. 如权利要求 27、30、31 或 34 中任一项所述的方法，其中 B 为 $NHSO_2NH_2$、$NHSO_2NHR^2$、$NHSO_2NR^2R^4$、$NR^3SO_2NH_2$、$NR^3SO_2NHR^2$ 或 $NR^3SO_2NR^2R^4$。

54. 如权利要求 52 所述的方法，其中 B 为 $NHSO_2R^3$ 或 $NR^3SO_2R^3$。

55. 如权利要求 54 所述的方法，其中 B 为 $NHSO_2R^3$。

56. 如权利要求 54 或 55 所述的方法，其中 R^3 为任选取代的烷基。

57. 如权利要求 56 所述的方法，其中 R^3 为 CH_3。

58. 如权利要求 52 所述的方法，其中 B 为 $NHSO_2R^4$ 或 $NR^3SO_2R^4$。

59. 如权利要求 58 所述的方法，其中 R^4 为任选取代的苯基。

60. 如权利要求 52-59 中任一项所述的方法，其中 A 为 $C(O)NHR^2$。

61. 如权利要求 52-59 中任一项所述的方法，其中 A 为 $C(O)NR^2R^4$。

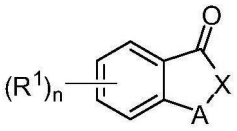
62. 如权利要求 60 或 61 所述的方法，其中 R^2 为任选取代的苯基。

63. 如权利要求 62 所述的方法，其中 R^2 的苯基为双取代的。

64. 如权利要求 62 所述的方法，其中 R^2 的苯基为单取代的。

65. 如权利要求 63 或 64 所述的方法，其中 R^2 的苯基上的取代独立地选自 F、Cl、CO_2H、CN、OCH_3、$C(O)CH_3$、CF_3、CH_3、CH_2OH、CH_2CH_2OH 和 $CH_2CH_2CH_2OH$。

66. 一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 III 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 III)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

X 为 O、NH 或 NR^6；

A 为 C(O)、CH_2或 $CH\text{-}CR^3R^4\text{-}C(O)R^2$；

R^2为任选取代的芳基或任选取代的杂芳基；

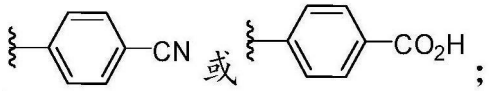
各 R^3和 R^4独立地为 H 或任选取代的烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；且

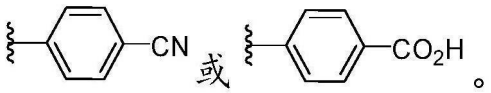
R^6为任选取代的苯基；

条件是

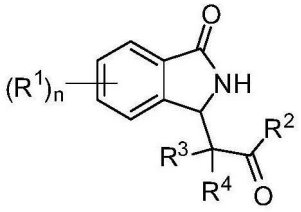
a) 如果 A 为 $CH\text{-}CR^3R^4\text{-}C(O)R^2$，则 X 为 O 或 NH；

b) 如果 n 为 0，A 为 $CHCH_2C(O)R^2$且 X 为 O，则 R^2不是  ；

且

c) 如果 A 为 C(O) 或 CH_2，则 X 为 NR^6且 R^6不是  。

67. 一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 IIIa 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 IIIa)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

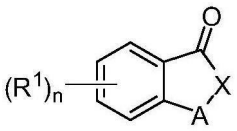
n 为 0、1、2、3 或 4；

R^2为任选取代的芳基或任选取代的杂芳基；

各 R^3和 R^4独立地为 H 或任选取代的烷基；且

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4。

68. 一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 III 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 III)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

X 为 O、NH 或 NR^6；

A 为 C(O)、CH_2或 $CH-CR^3R^4-C(O)R^2$；

R^2为任选取代的芳基或任选取代的杂芳基；

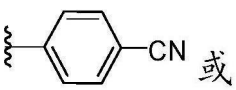
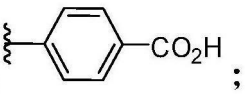
各 R^3和 R^4独立地为 H 或任选取代的烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；且

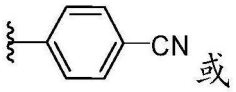
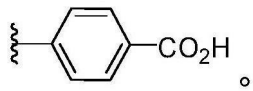
R^6为任选取代的苯基；

条件是

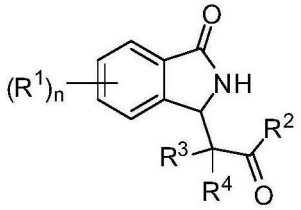
a) 如果 A 为 $CH-CR^3R^4-C(O)R^2$，则 X 为 O 或 NH；

b) 如果 n 为 0，A 为 $CHCH_2C(O)R^2$且 X 为 O，则 R^2不是  或  ；

且

c) 如果 A 为 C(O) 或 CH_2，则 X 为 NR^6且 R^6不是  或  。

69. 一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 IIIa 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 IIIa)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

R^2为任选取代的芳基或任选取代的杂芳基；

各 R^3和 R^4独立地为 H 或任选取代的烷基；且

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4。

70. 如权利要求 66 或 68 所述的方法，其中 X 为 NR^6且 A 为 C(O)。

71. 如权利要求 66 或 68 所述的方法，其中 X 为 NR^6且 A 为 CH_2。

72. 如权利要求 66 或 68 所述的方法，其中 X 为 O 且 A 为 $CH-CR^3R^4-C(O)R^2$。

73. 如权利要求 66 或 68 所述的方法，其中 X 为 NH 且 A 为 $CH-CR^3R^4-C(O)R^2$。

74. 如权利要求 67、69、72 或 73 中任一项所述的方法，其中 R^3和 R^4均为氢。

75. 如权利要求 67、69、72 或 73 中任一项所述的方法，其中 R^3为任选取代的烷基且 R^4为氢。

76. 如权利要求 67、69、72 或 73 中任一项所述的方法，其中 R^3和 R^4独立地为任选取代的烷基。

77. 如权利要求 74-76 中任一项所述的方法，其中 R^2为任选取代的杂芳基。

78. 如权利要求 74-76 中任一项所述的方法，其中 R^2为任选取代的吡啶基、任选取代的嘧啶基、任选取代的哒嗪基或任选取代的吡嗪基。

79. 如权利要求 74-76 中任一项所述的方法，其中 R^2为任选取代的苯基。

80. 如权利要求 79 中任一项所述的方法，其中 R^2的苯基为双取代的。

81. 如权利要求 79 中任一项所述的方法，其中 R^2的苯基为单取代的。

82. 如权利要求 80 或 81 所述的方法，其中苯基上的取代独立地选自 F、Cl、CO_2H、CN、OCH_3、$C(O)CH_3$、CF_3、CH_3、CH_2OH、CH_2CH_2OH 和 $CH_2CH_2CH_2OH$。

83. 如权利要求 1-65 中任一项所述的方法，其中 B 为 CO_2R^4且 R^4为任选取代的烷基。

84. 如权利要求 1-65 中任一项所述的方法，其中 B 为 CO_2R^4且 R^4为氢。

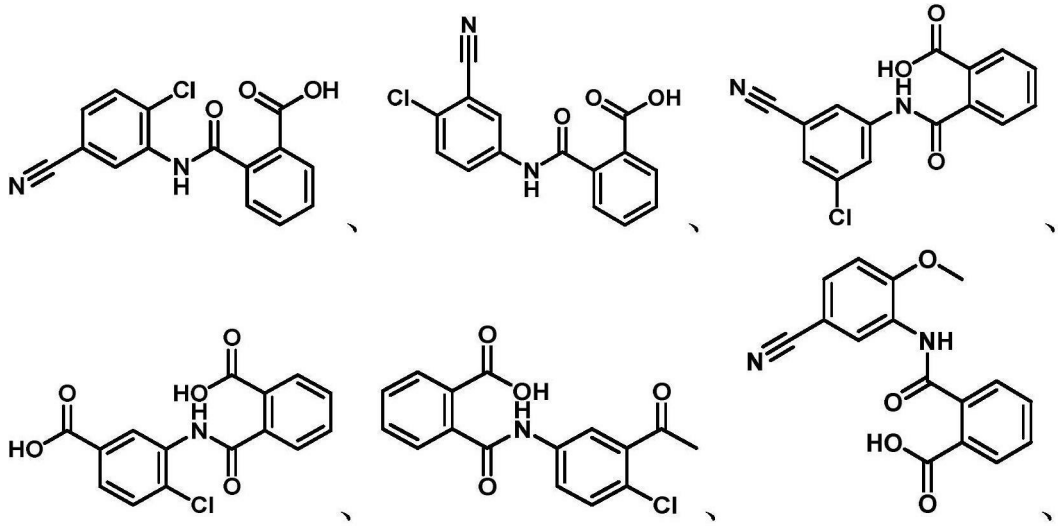
85. 如权利要求 1-84 中任一项所述的方法，其中 n 为 0、1 或 2。

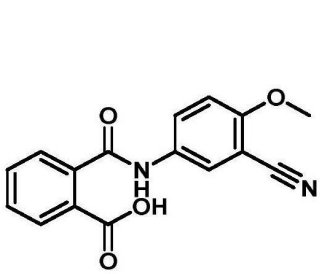
86. 如权利要求 84 所述的方法，其中 n 为 0。

87. 如权利要求 84 所述的方法，其中 n 为 1。

88. 如权利要求 85 所述的方法，其中 R^1独立地选自 Cl、F、CH_2OH、CH_2NH_2、OCH_3、OCF_3、$OCHF_2$、CN、NO_2、CO_2H 和 CO_2CH_3。

89. 如权利要求 1 或 5 所述的方法，其中所述化合物选自

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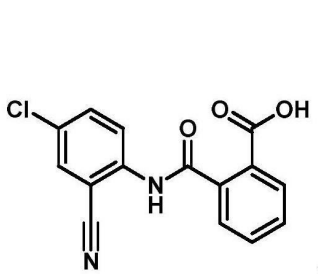
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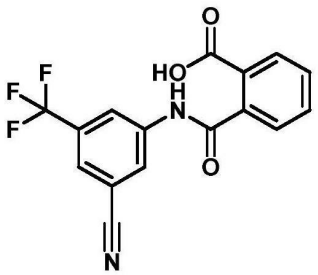
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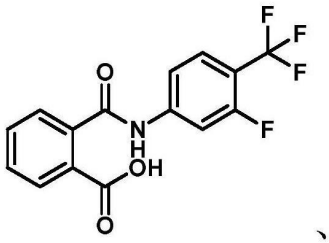
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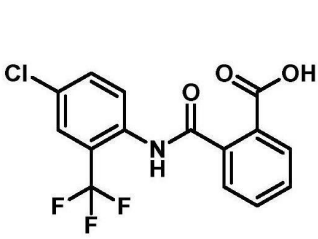
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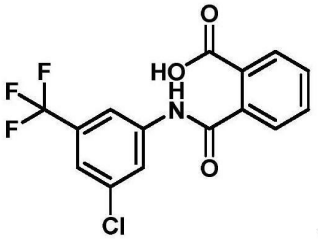
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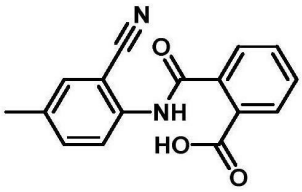
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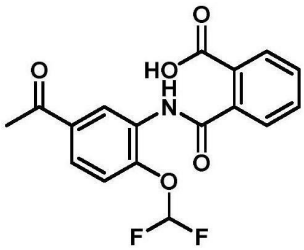
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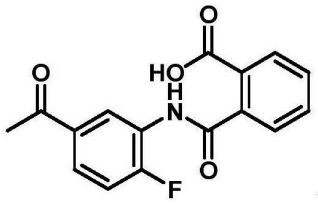
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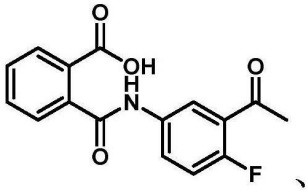
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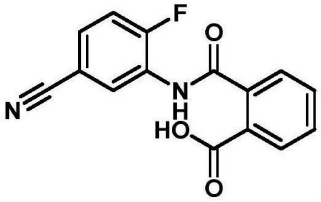
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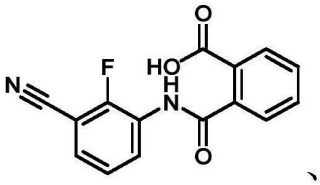
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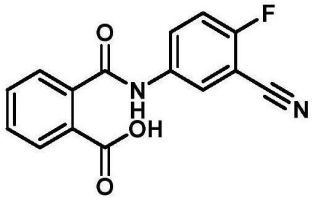
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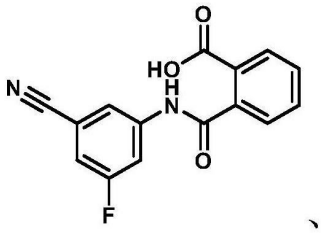
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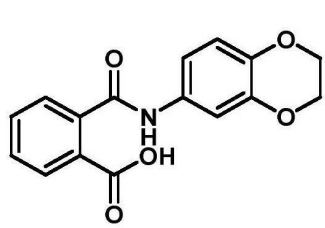
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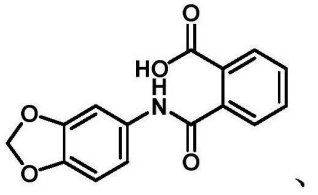
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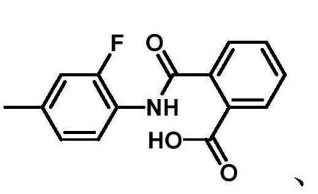
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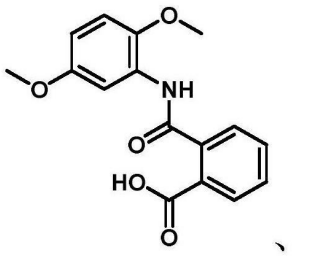
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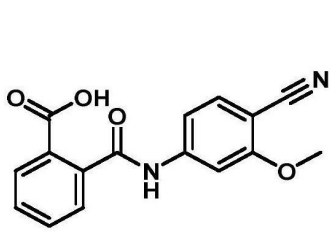
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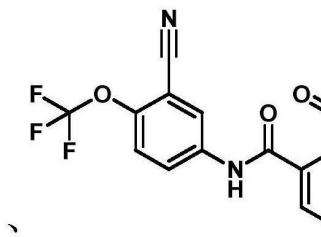
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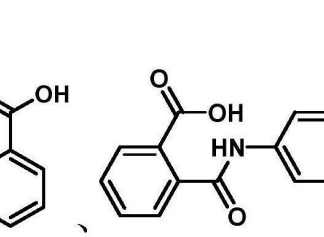
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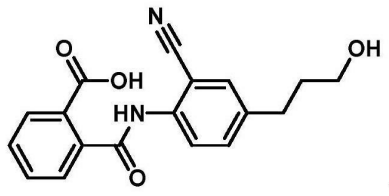
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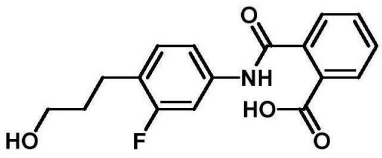
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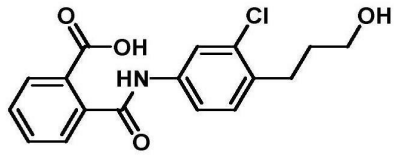
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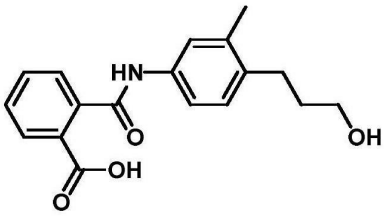
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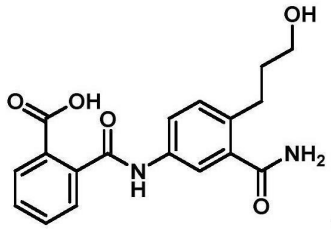
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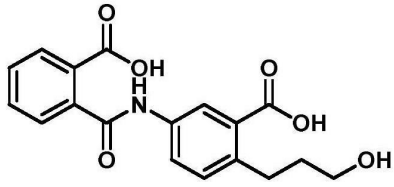
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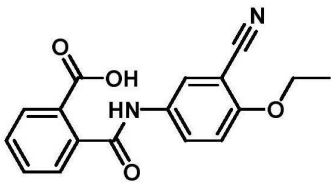
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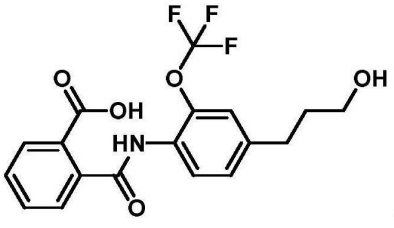
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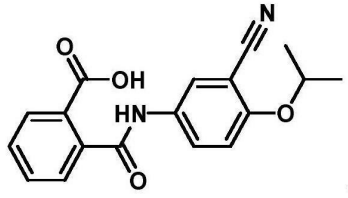
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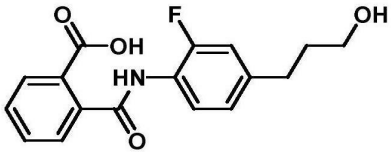
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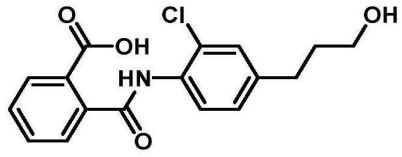
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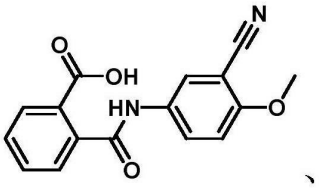
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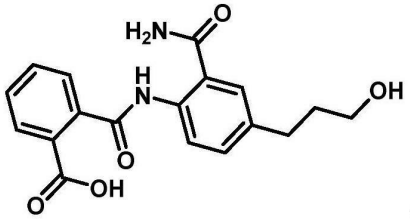
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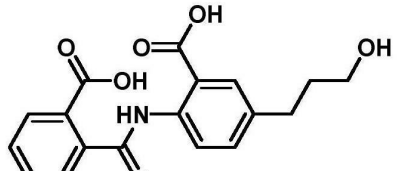
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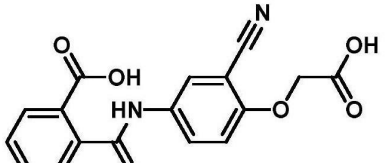
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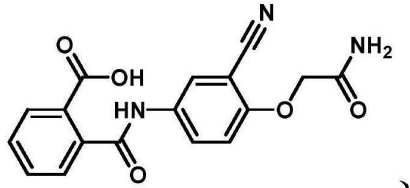
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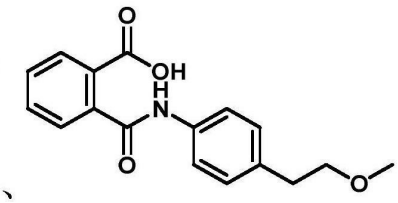
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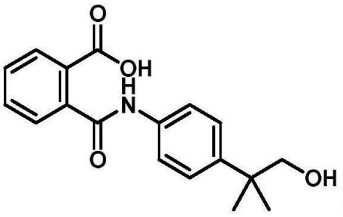
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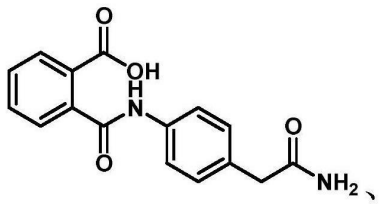
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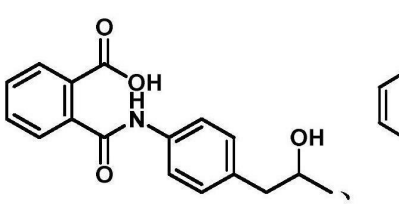
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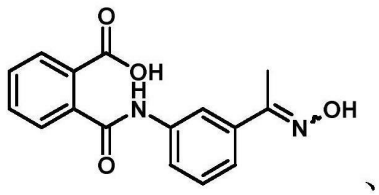
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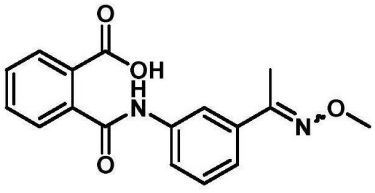
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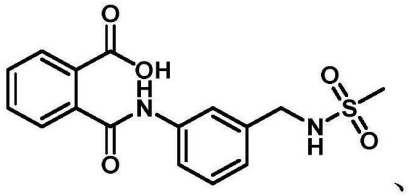
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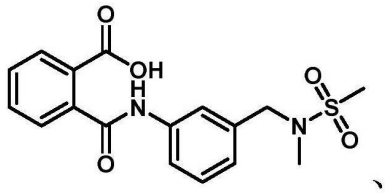
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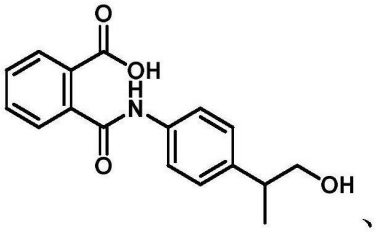
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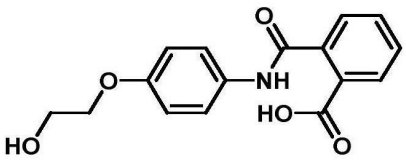
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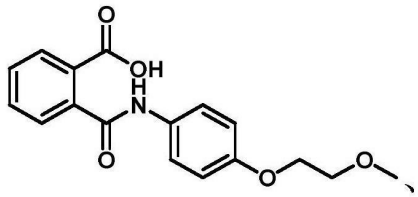
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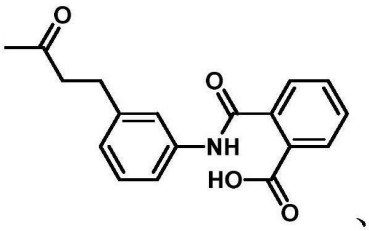
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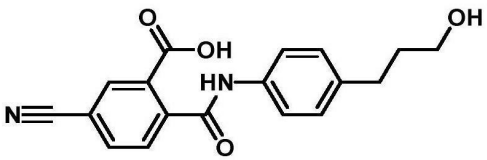
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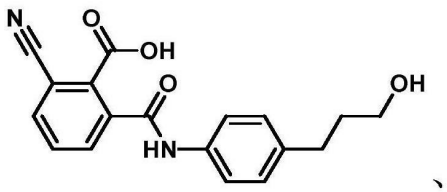
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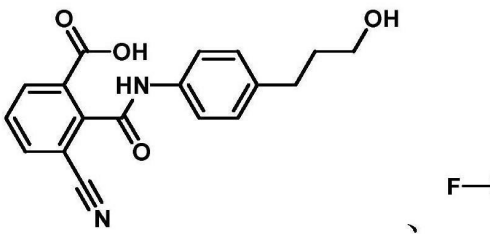
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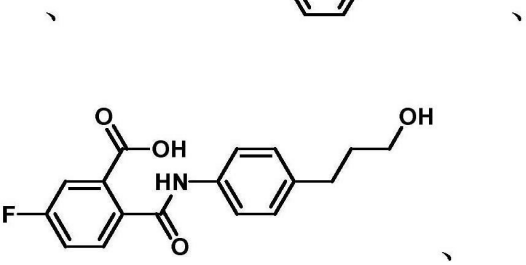
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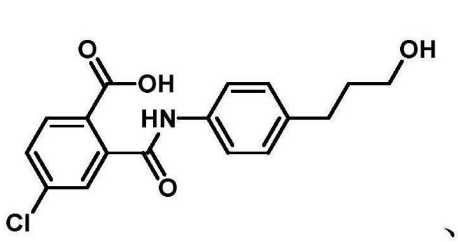
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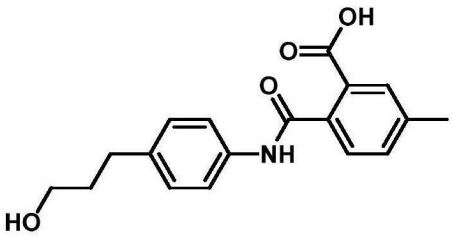
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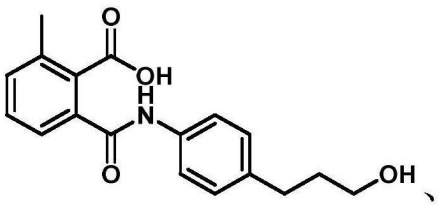
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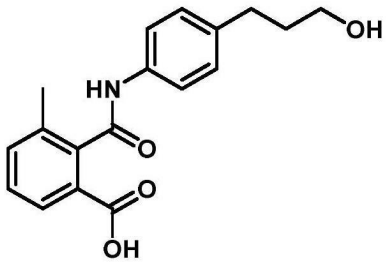
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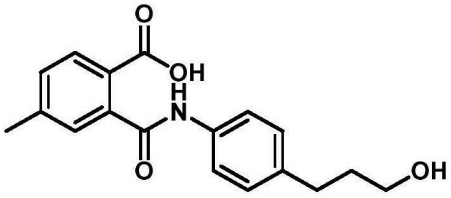
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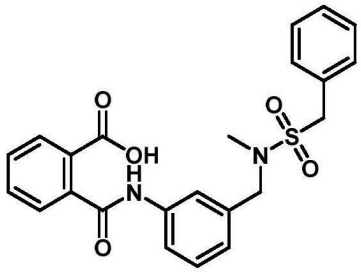
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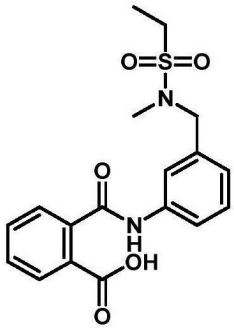
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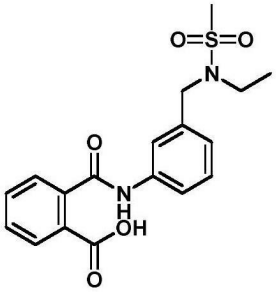
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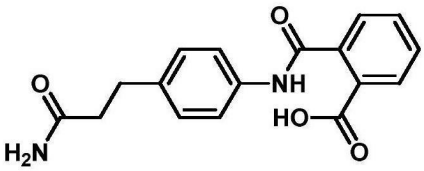
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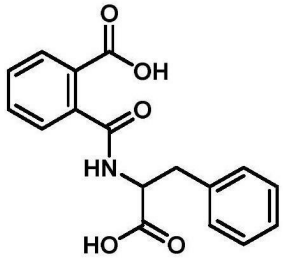
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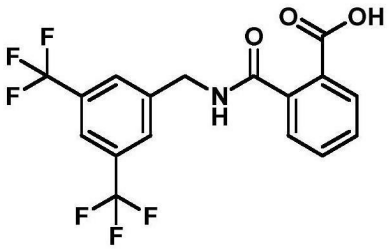
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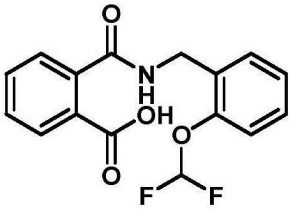
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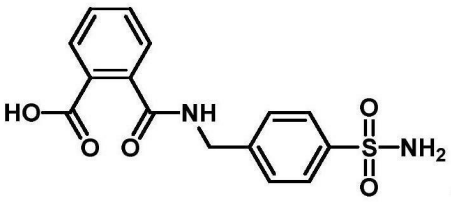
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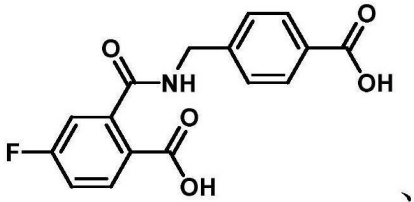
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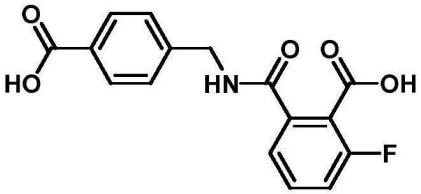
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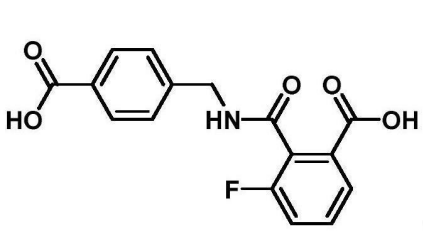
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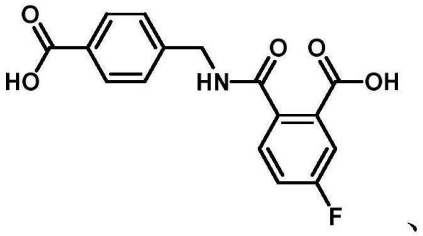
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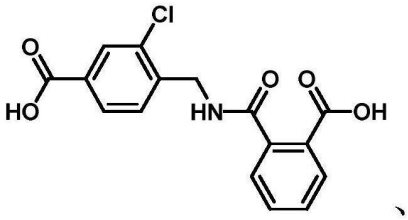
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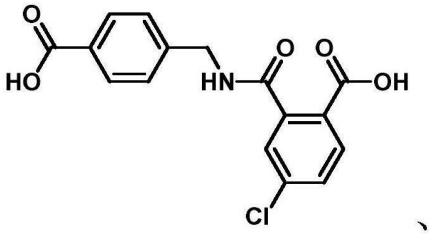
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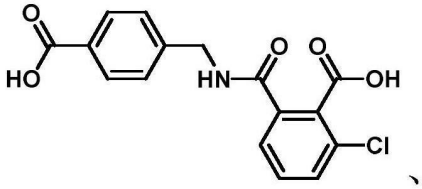
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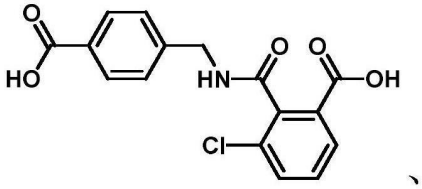
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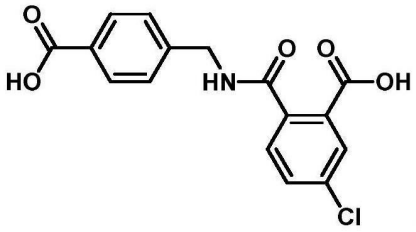
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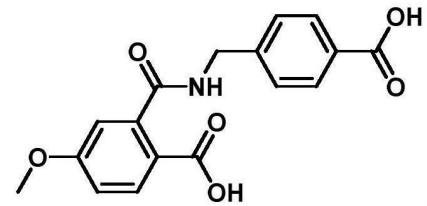
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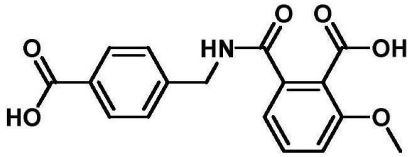
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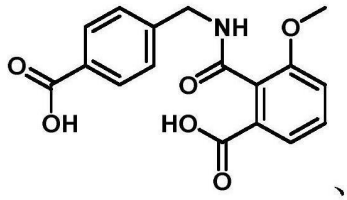
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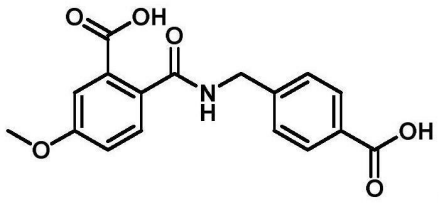
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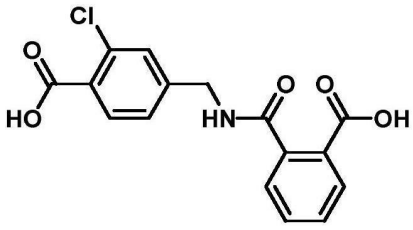
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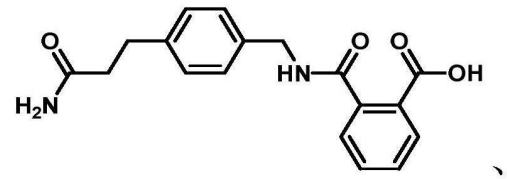
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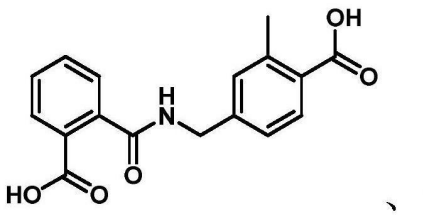
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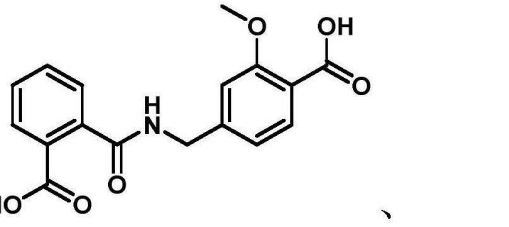
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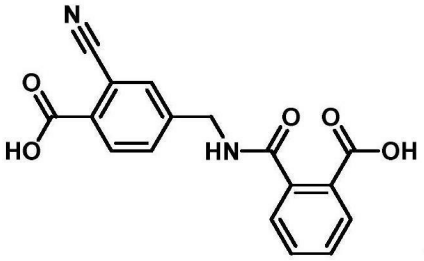
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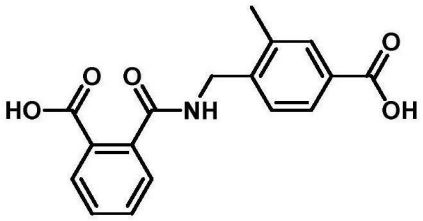
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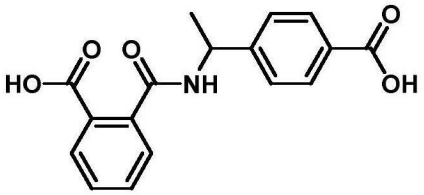
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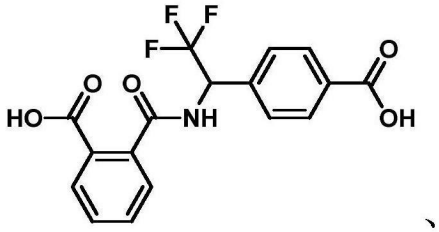
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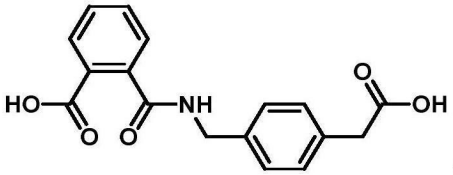
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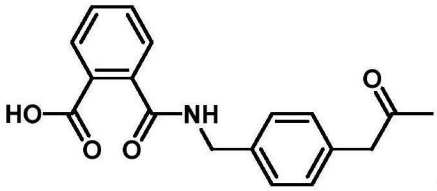
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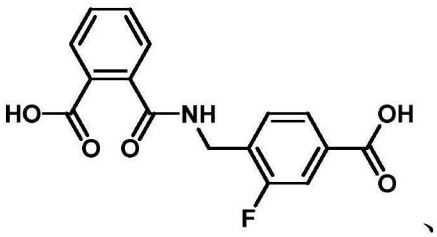
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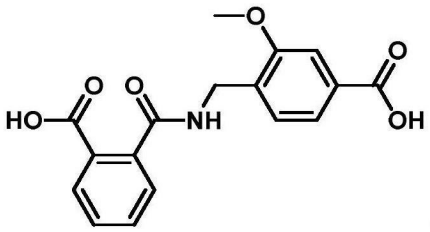
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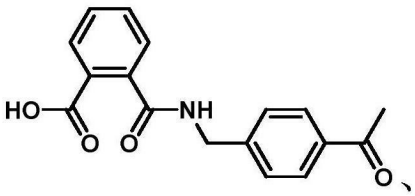
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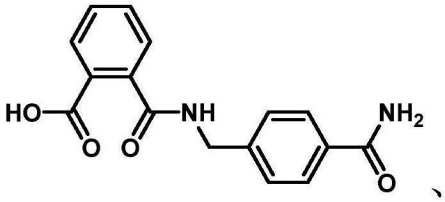
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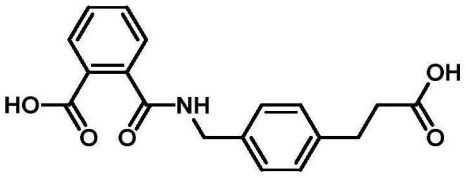
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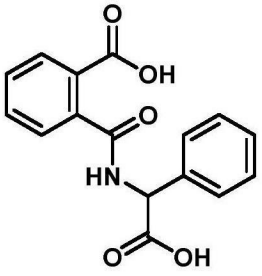
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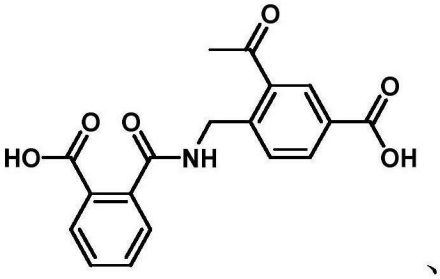
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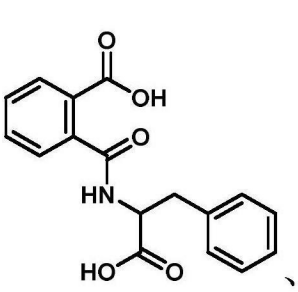
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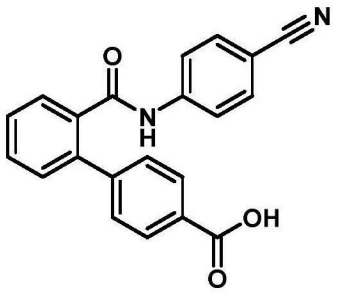
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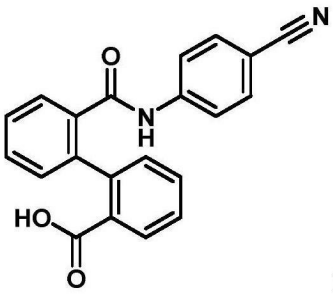
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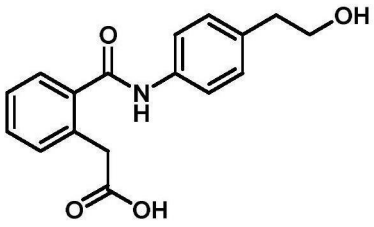
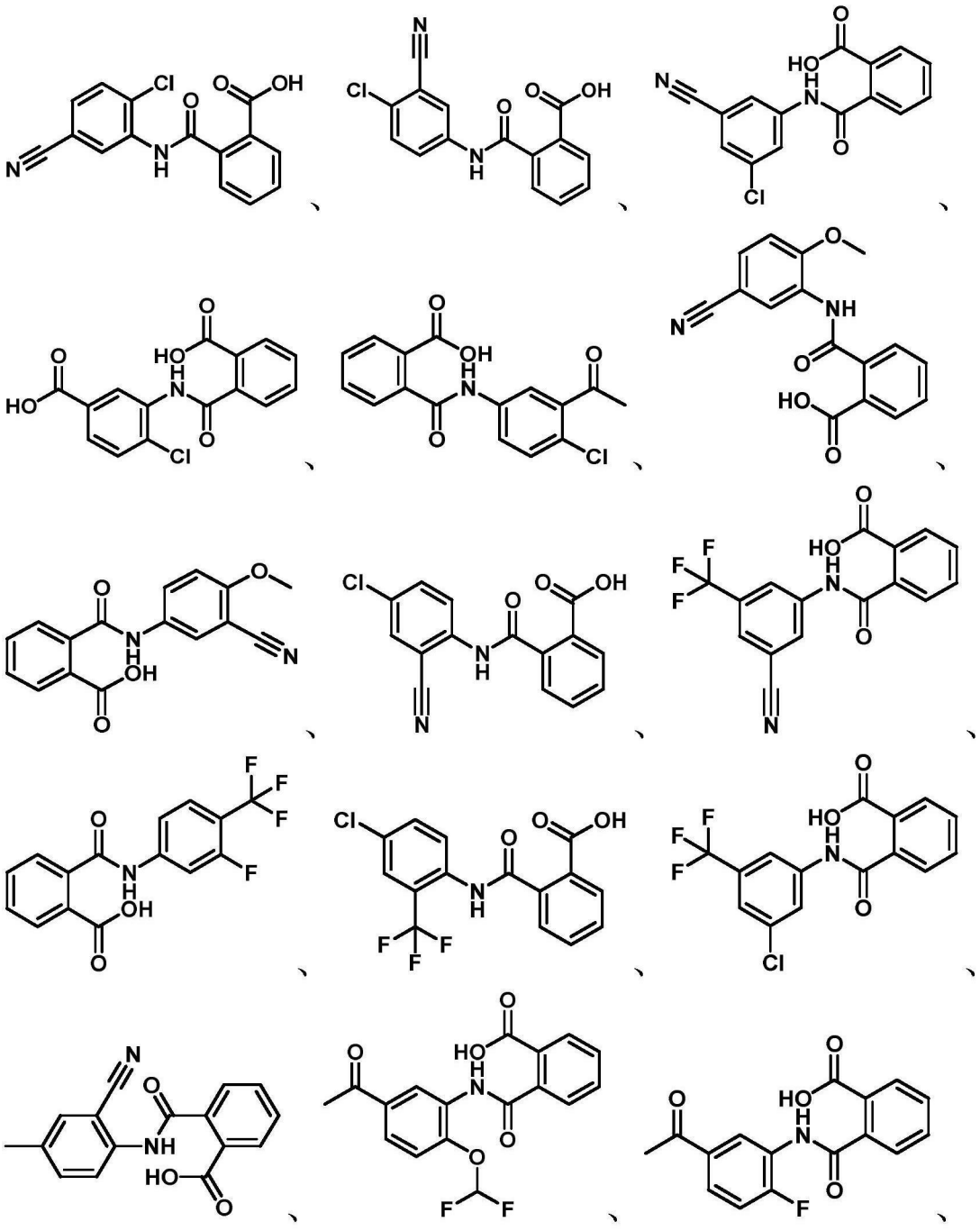
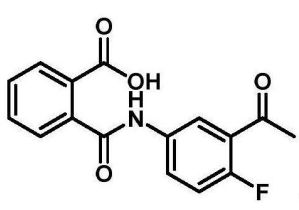


或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体；

90. 如权利要求 2 或 6 所述的方法，其中所述化合物选自

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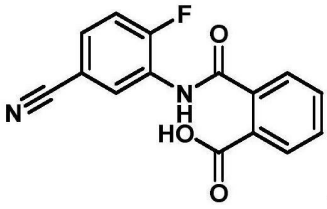
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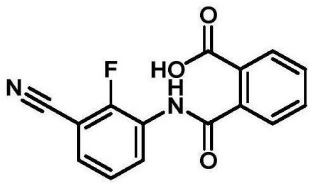
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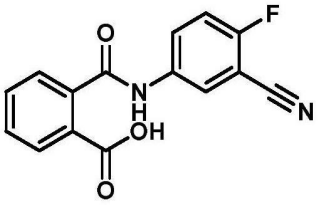
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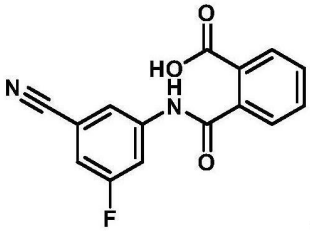
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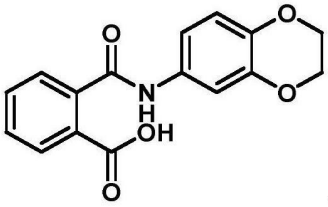
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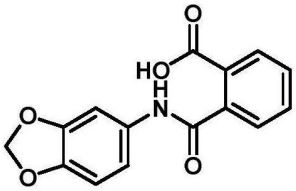
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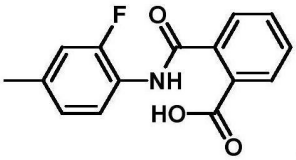
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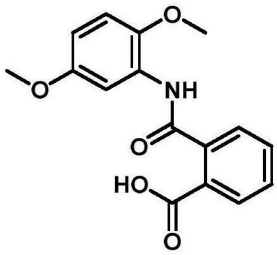
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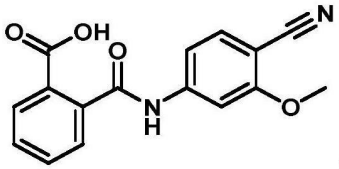
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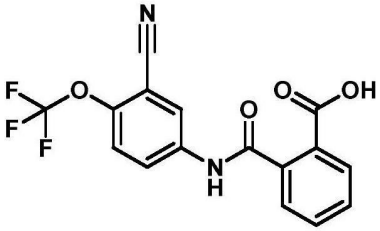
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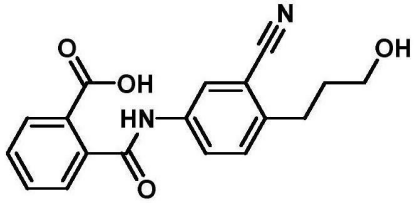
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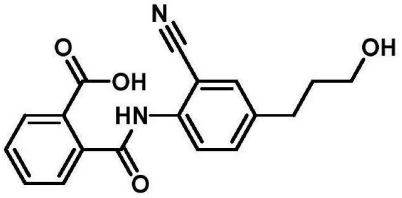
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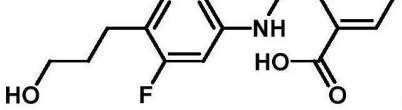
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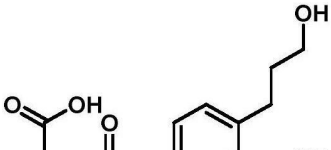
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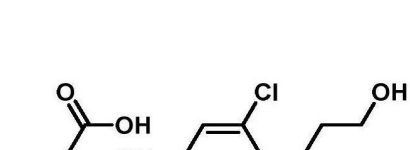
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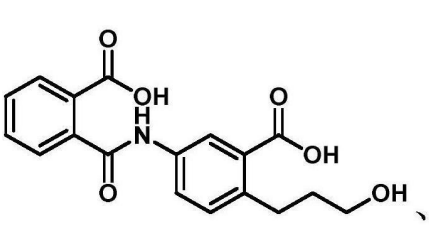
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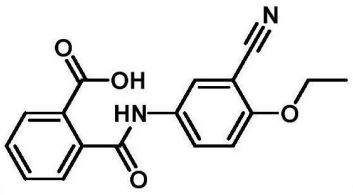
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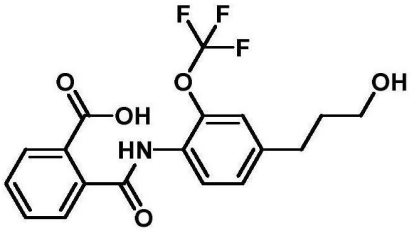
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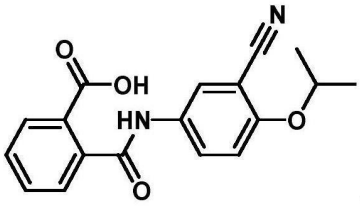
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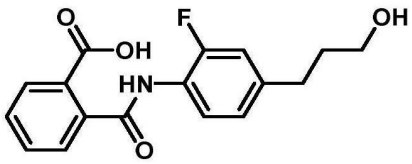
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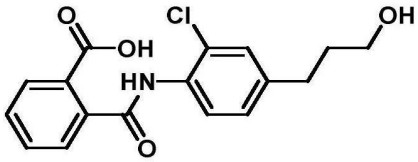
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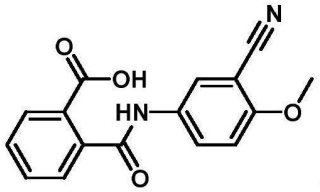
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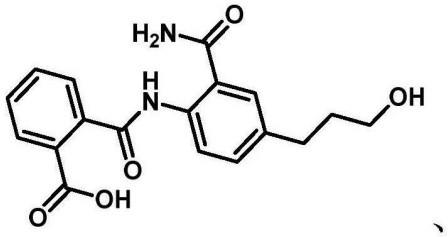
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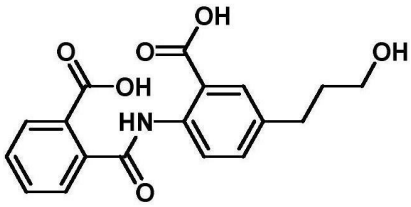
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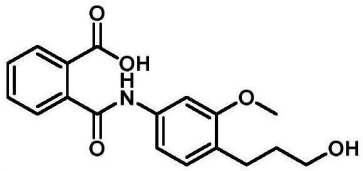
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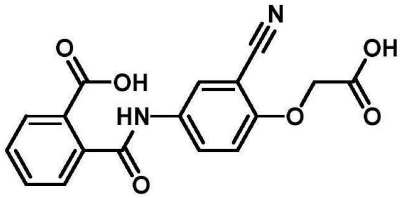
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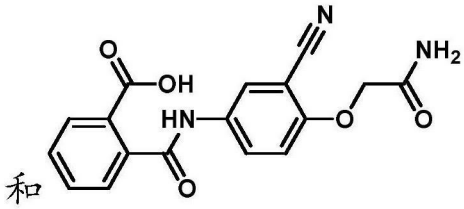
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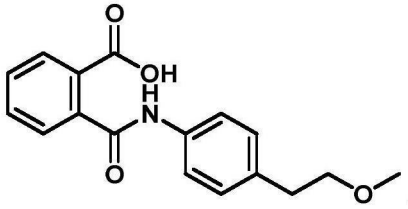
或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

91. 如权利要求 3 或 7 所述的方法，其中所述化合物选自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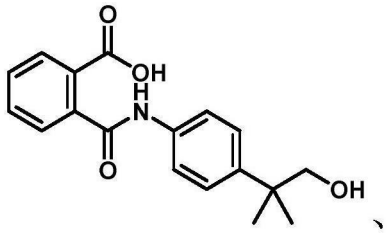
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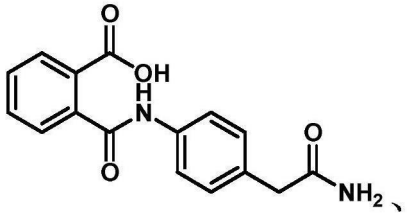
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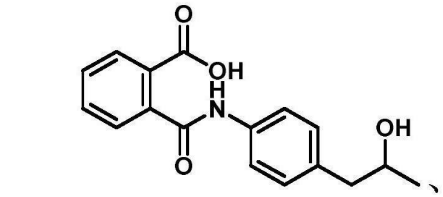
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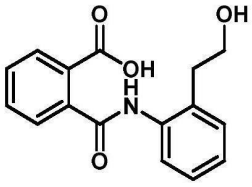
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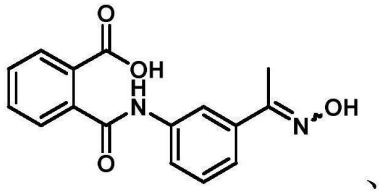
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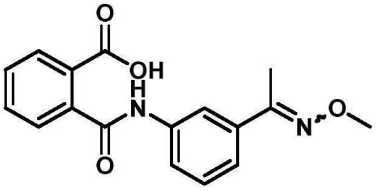
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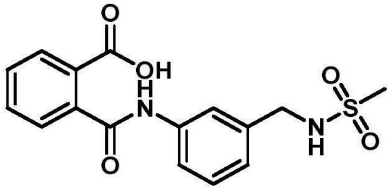
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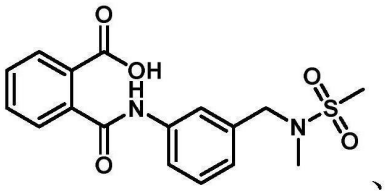
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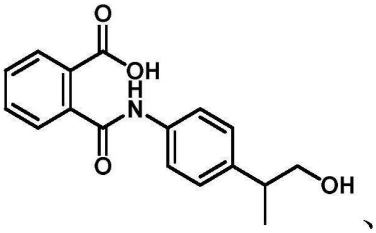
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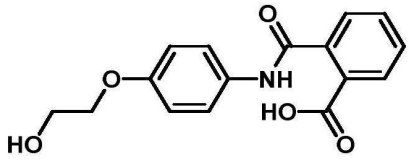
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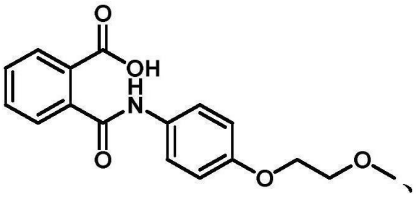
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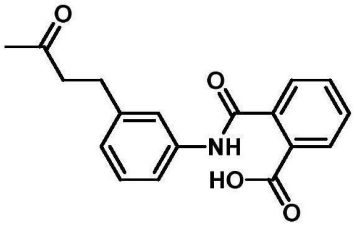
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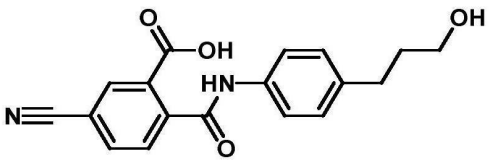
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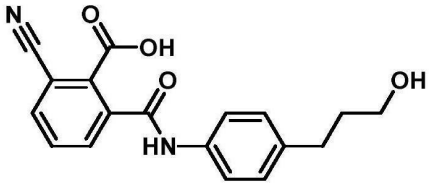
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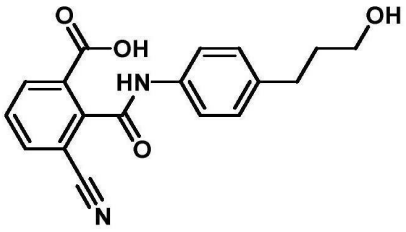
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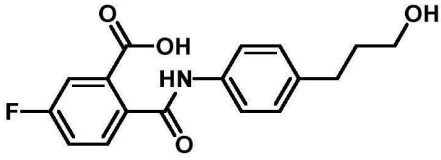
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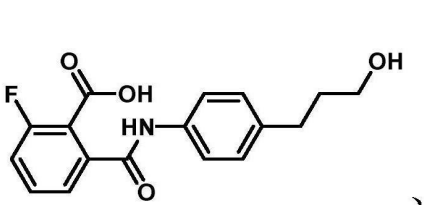
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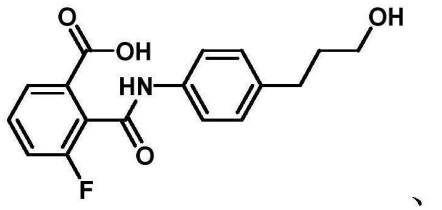
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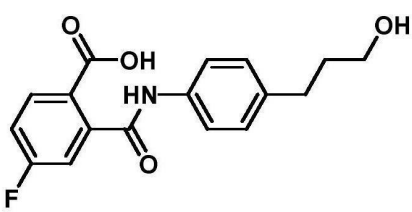
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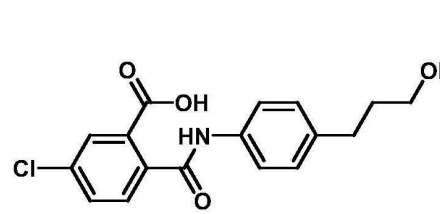
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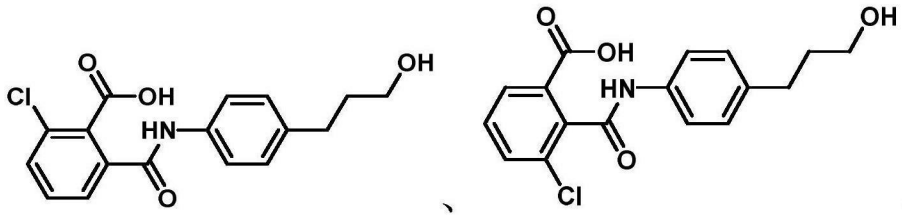
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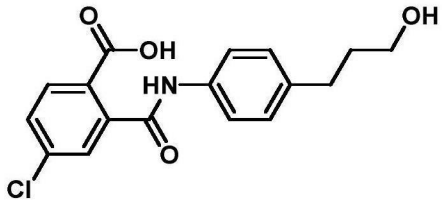
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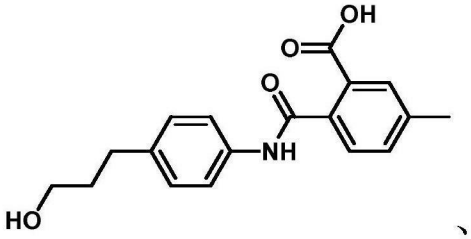
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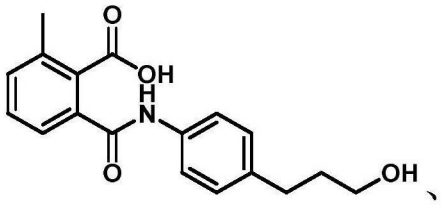
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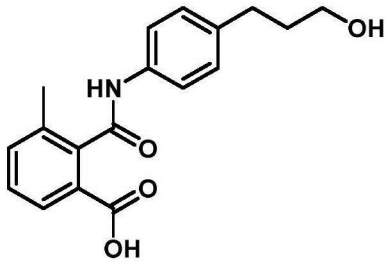
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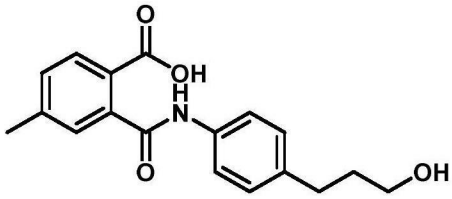
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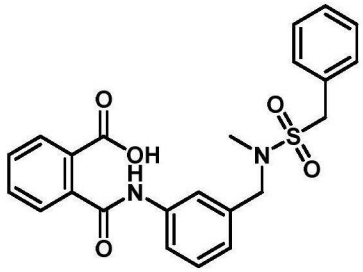
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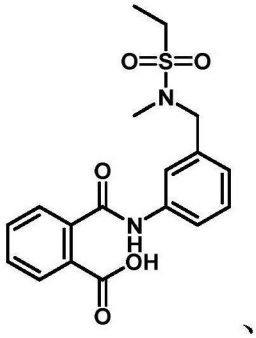
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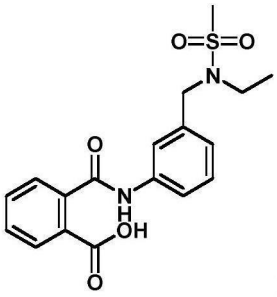
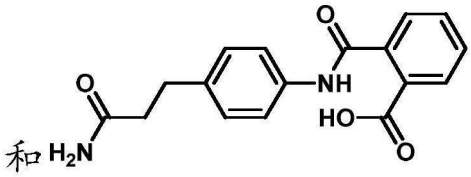
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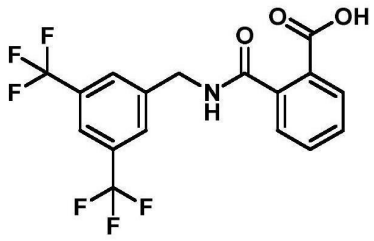
或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

92. 如权利要求 4 或 8 所述的方法，其中所述化合物选自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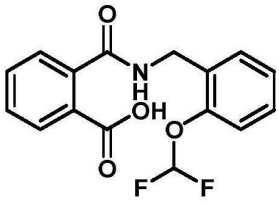
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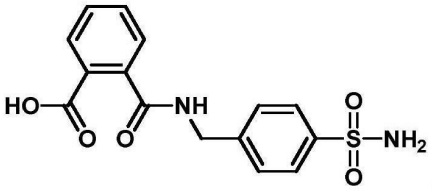
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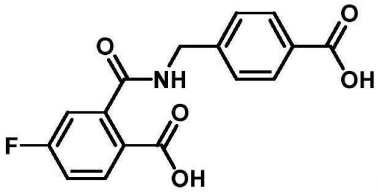
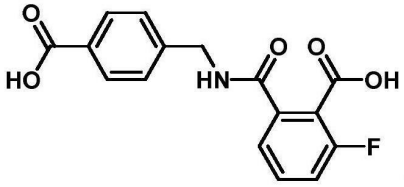
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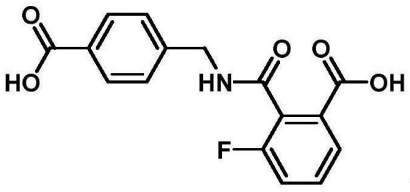
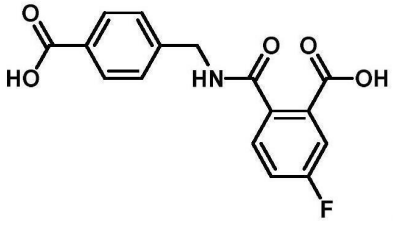
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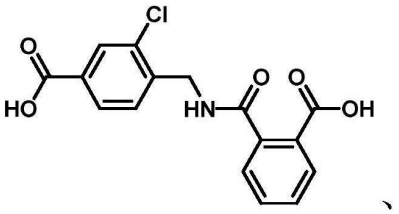
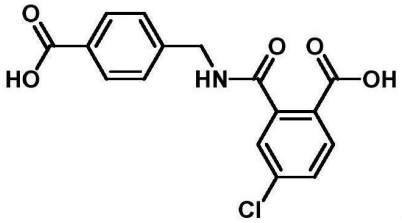
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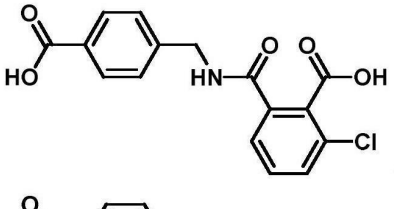
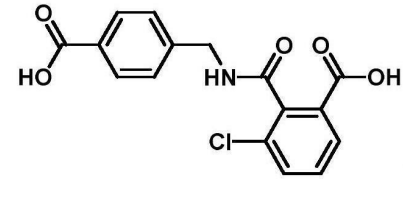
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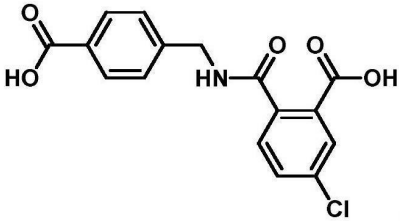
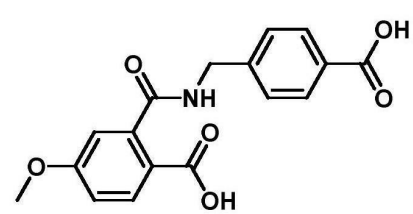
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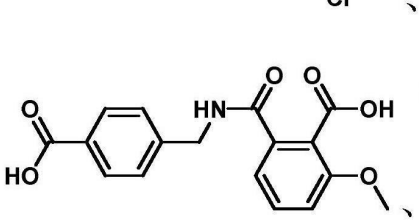

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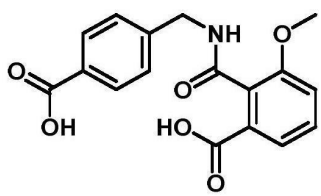
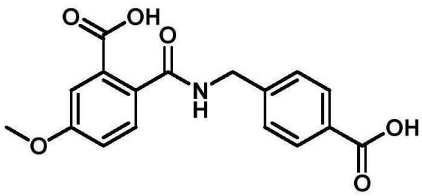
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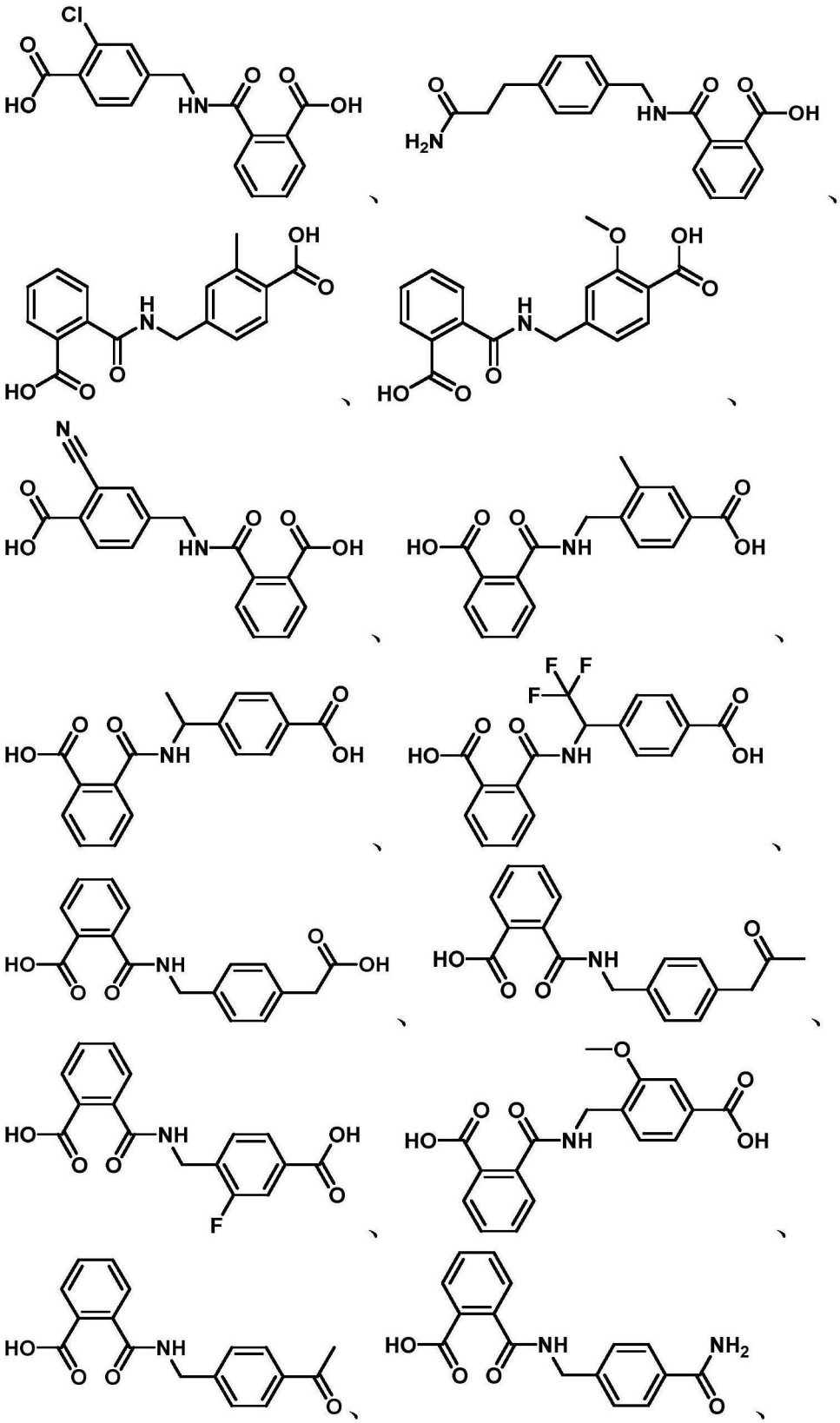
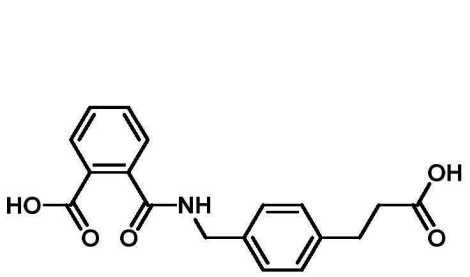
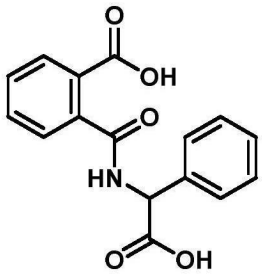
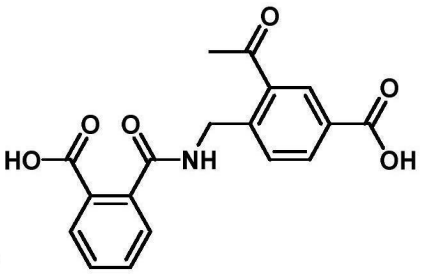



、 
和 
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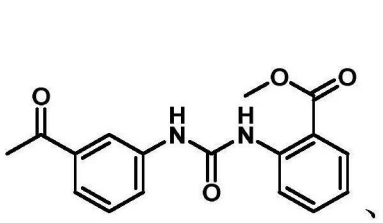
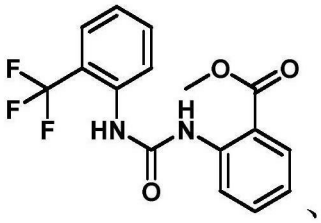
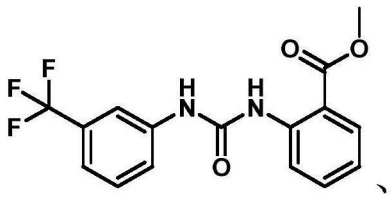
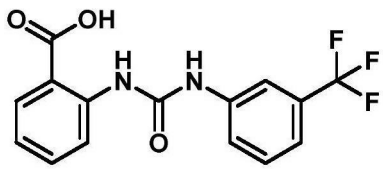
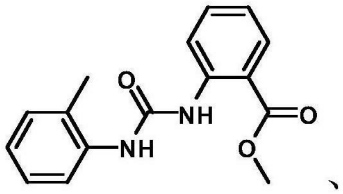
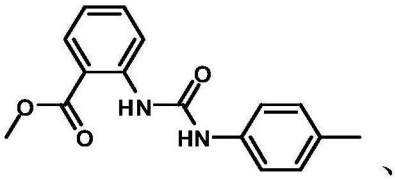
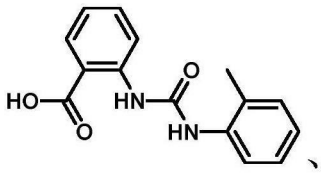
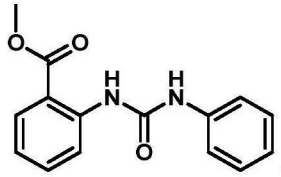
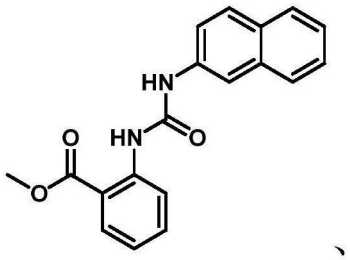
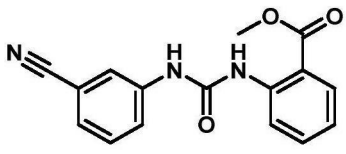
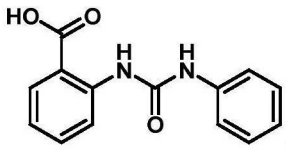
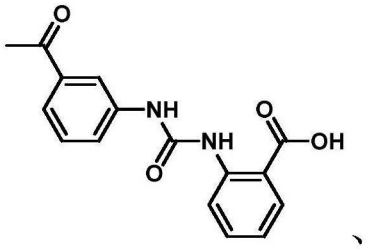
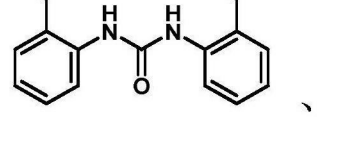
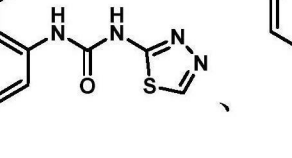
或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

93. 如权利要求 27 或 31 所述的方法，其中所述化合物选自


、 
、 
、 
、 
、 
、 
、 
、 
、 
、 
、 
、 
、 
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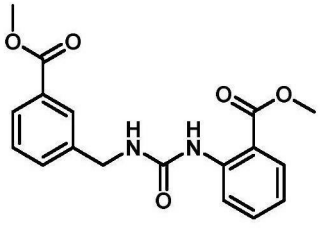
、 
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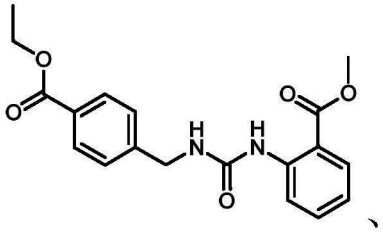
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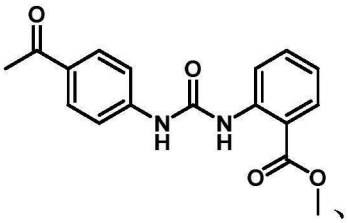
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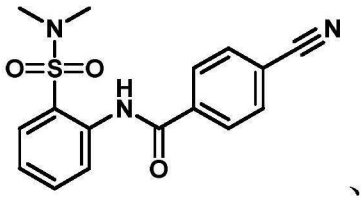
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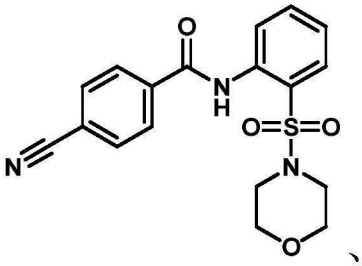
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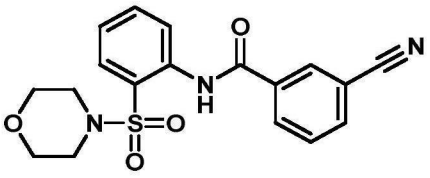
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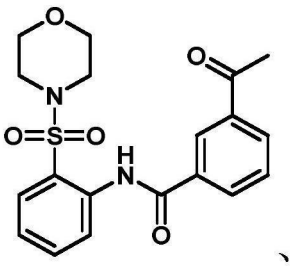
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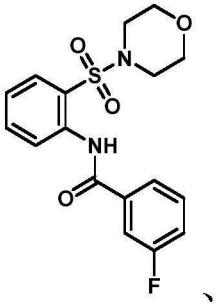
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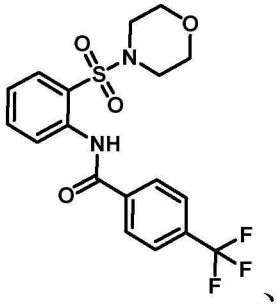
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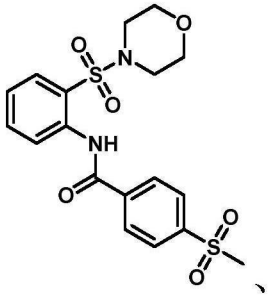
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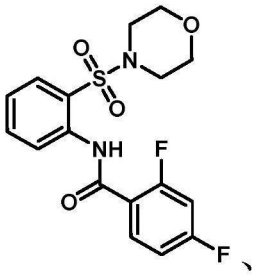
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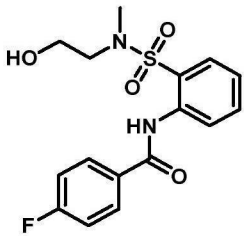
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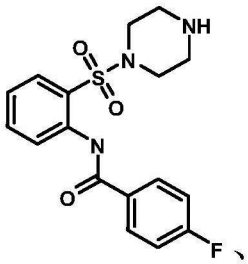
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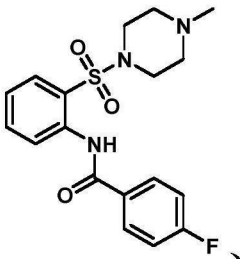
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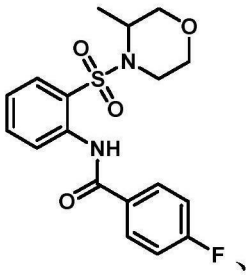
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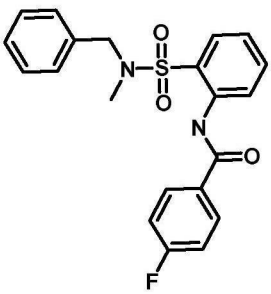
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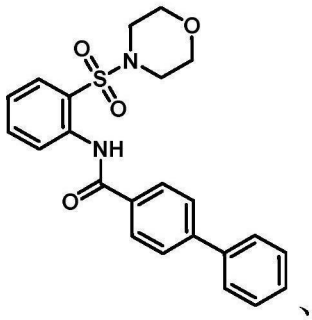
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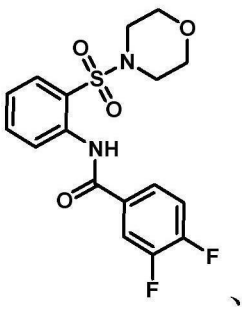
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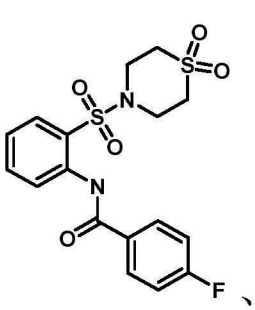
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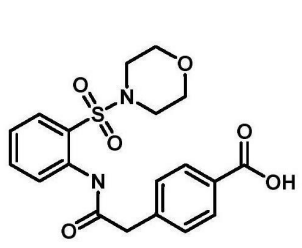

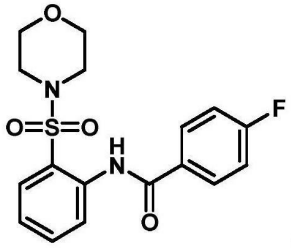

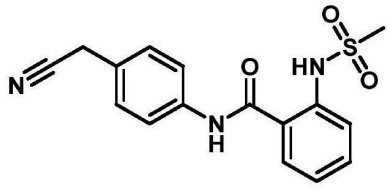

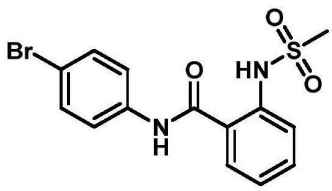

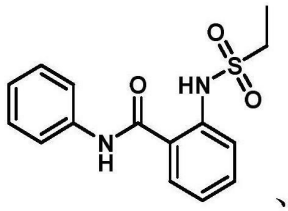

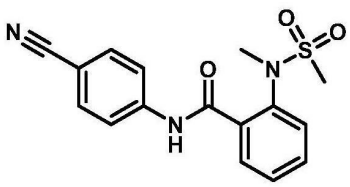

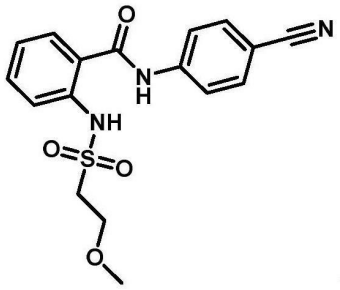

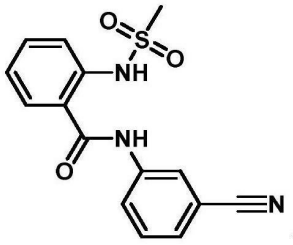

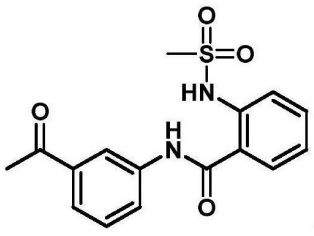

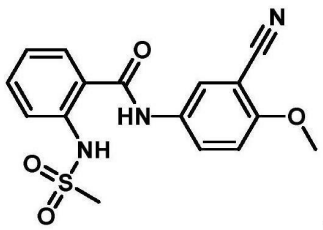

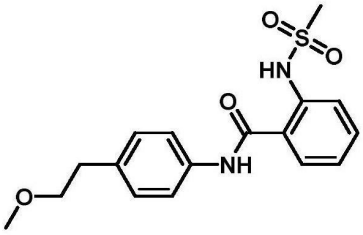

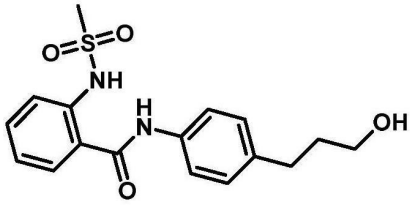

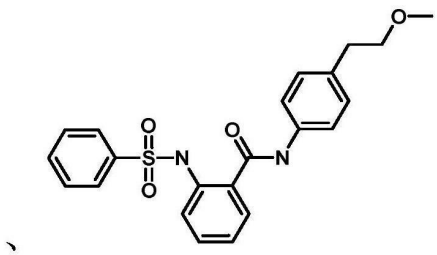

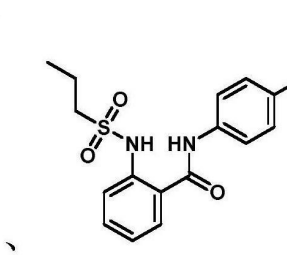

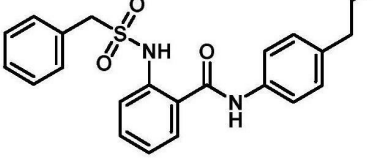

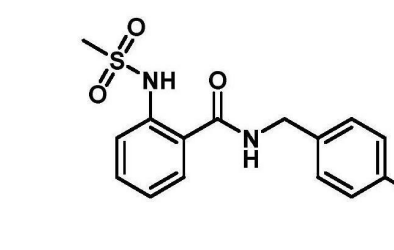

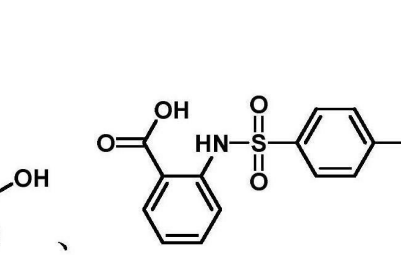

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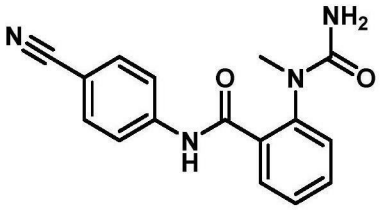
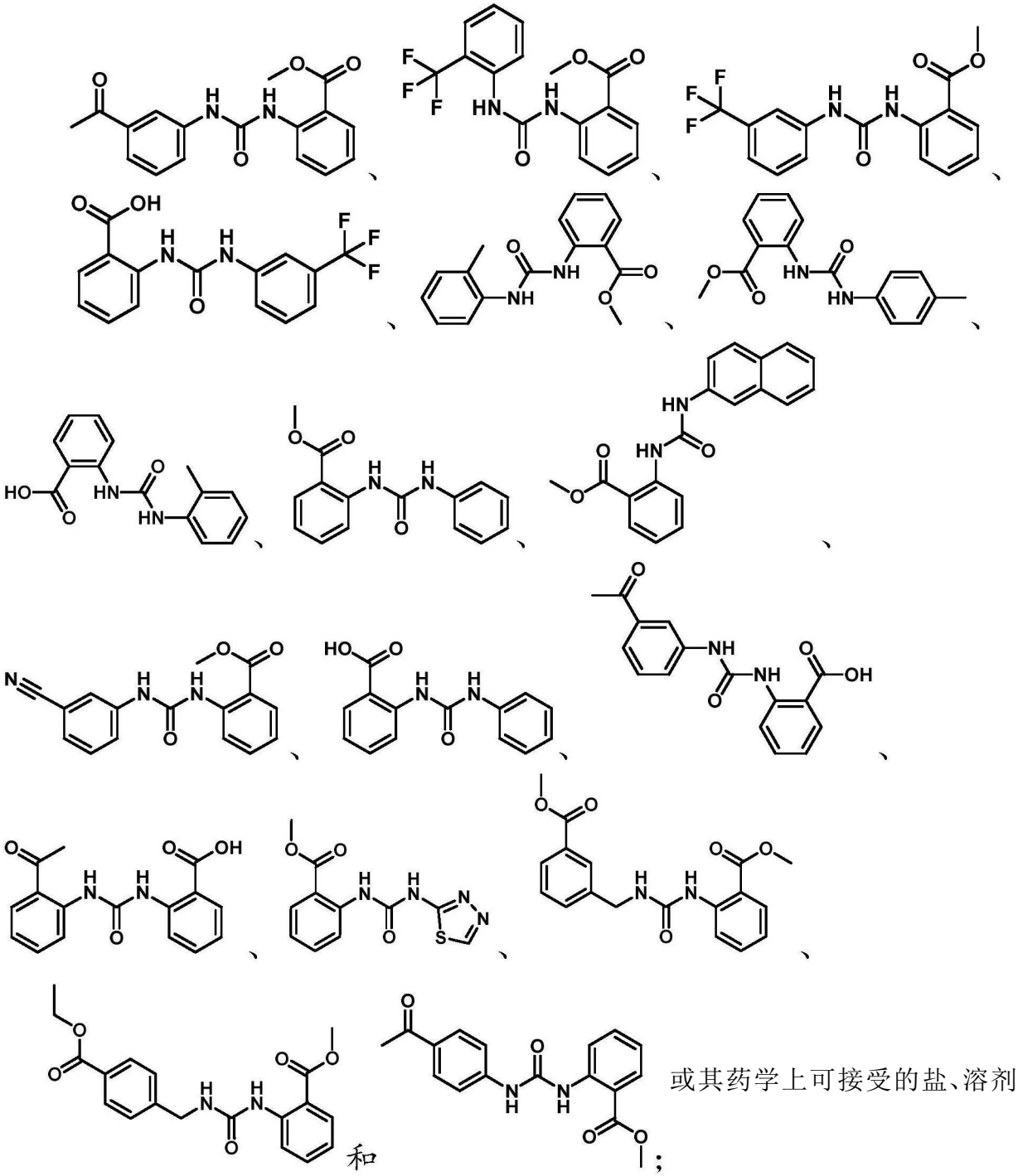


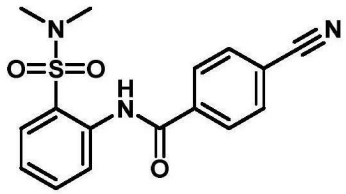
或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

94. 如权利要求 28 或 32 所述的方法，其中所述化合物选自



或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

95. 如权利要求 29 或 33 所述的方法，其中所述化合物选自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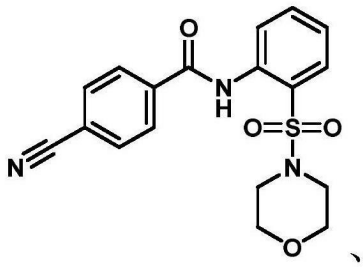
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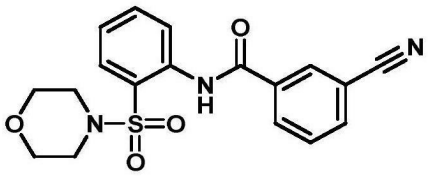
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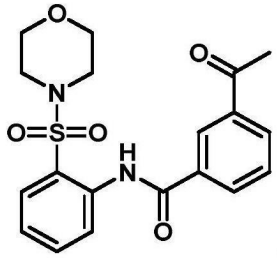
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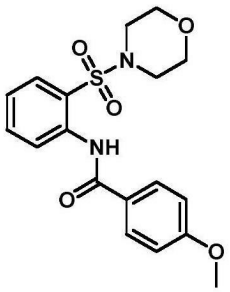
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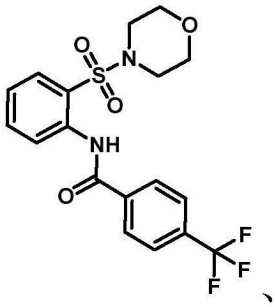
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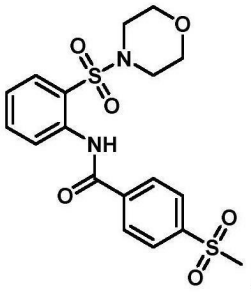
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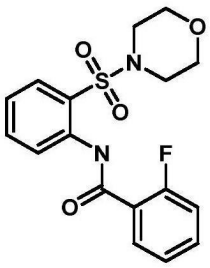
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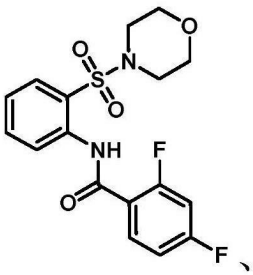
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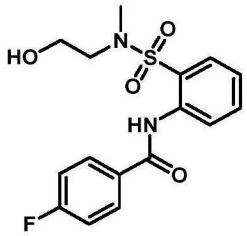
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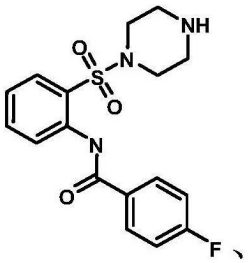
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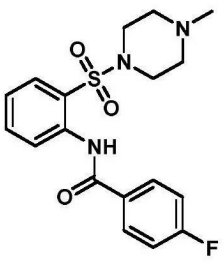
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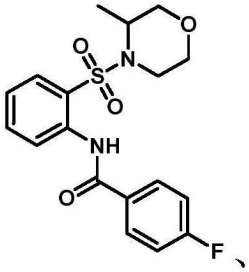
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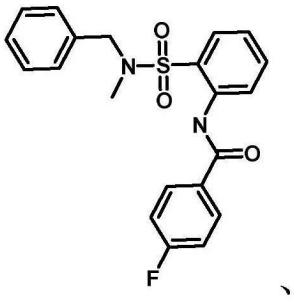
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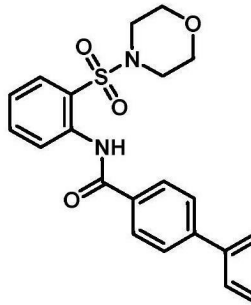
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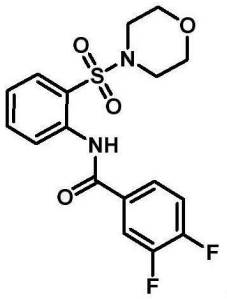
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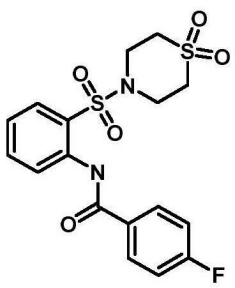
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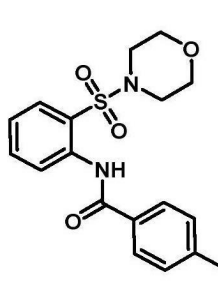
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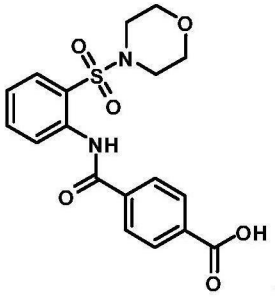
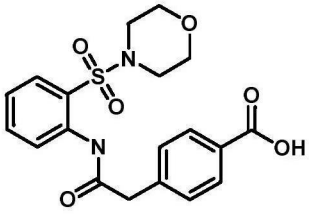
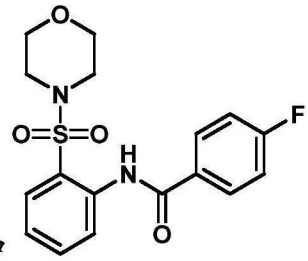

、 
和 
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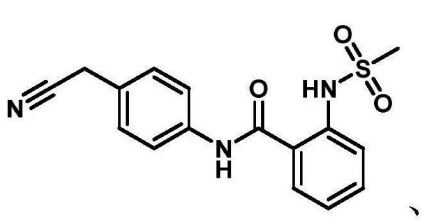
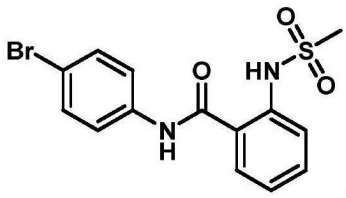
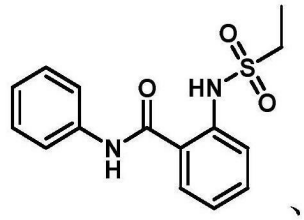
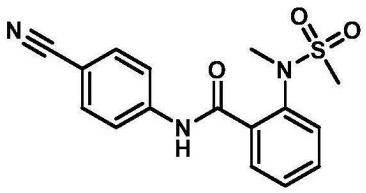
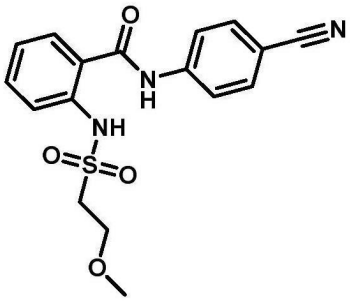
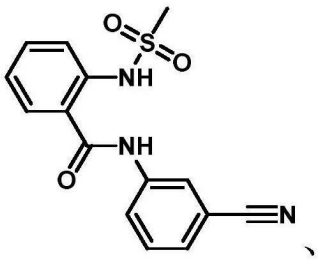
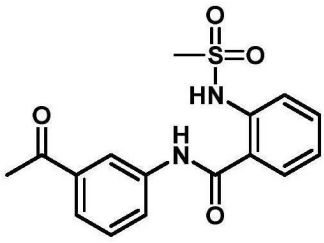
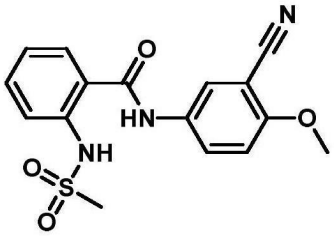
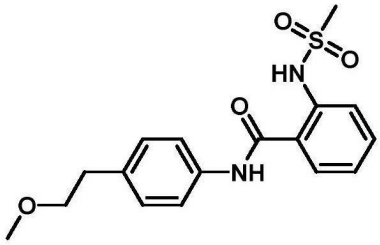
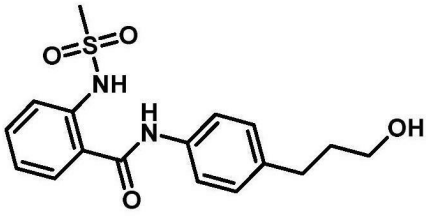
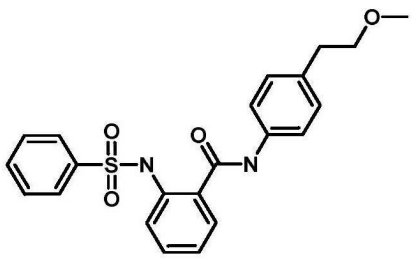
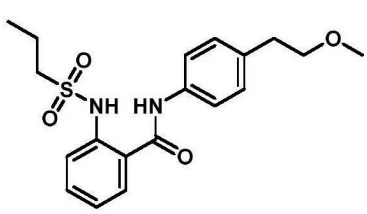
96. 如权利要求 30 或 34 所述的方法，其中所述化合物选自


、 
、 
、 
、 
、 
、 
、 
、 
、 
、 
、 
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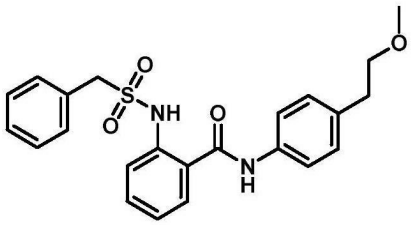
、 
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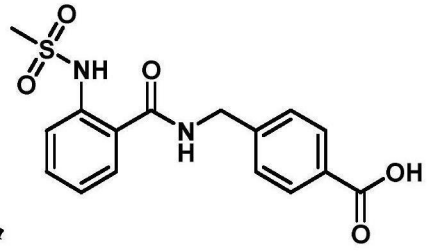
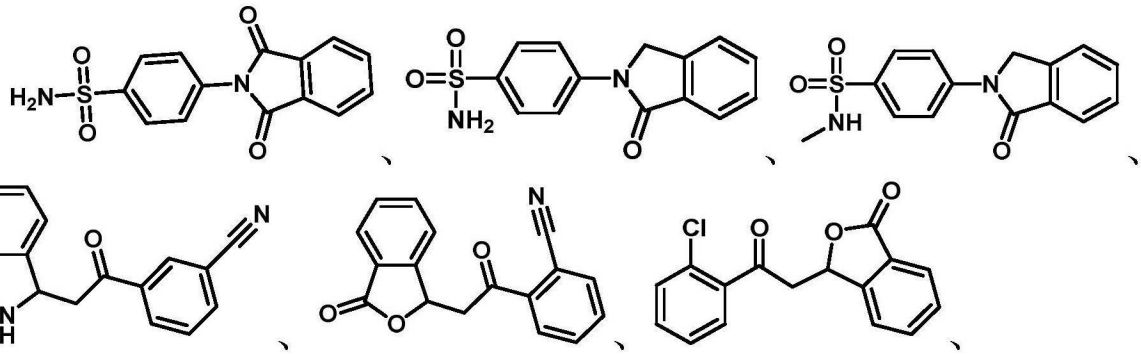
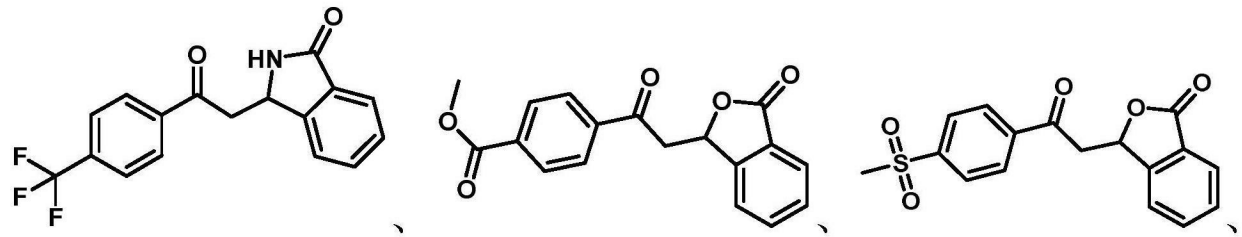
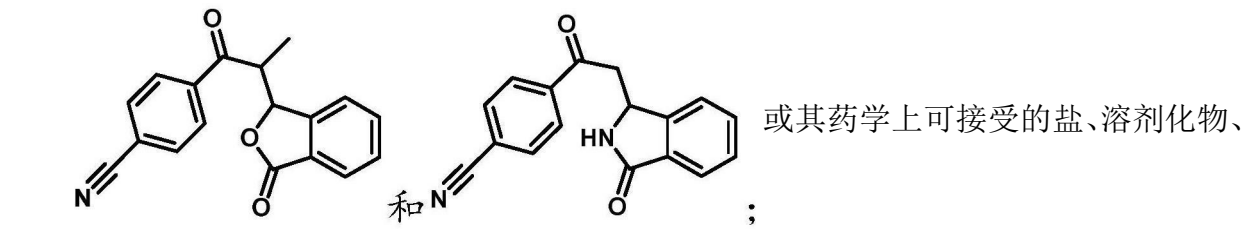
和  ；或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

97. 如权利要求 66 或 68 所述的方法，其中所述化合物选自

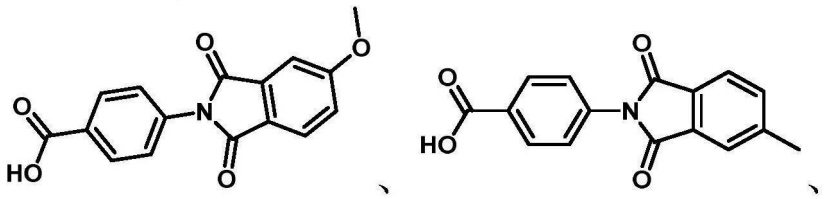


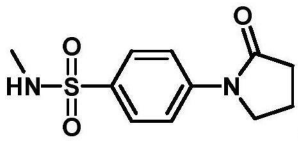
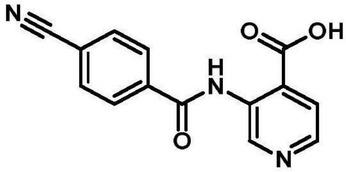
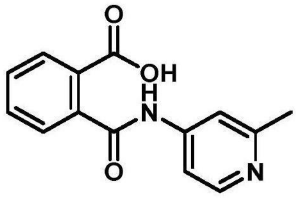


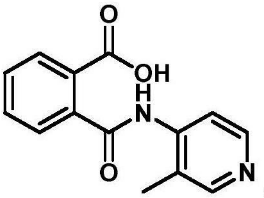
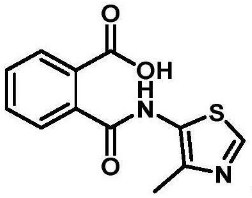
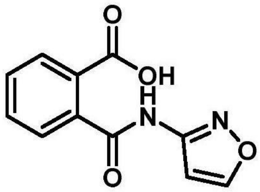
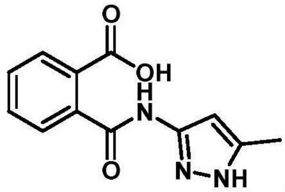


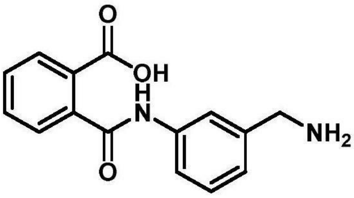
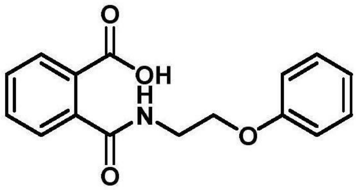
和 ；或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

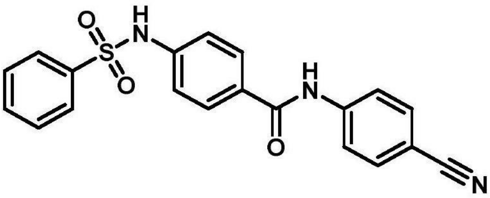
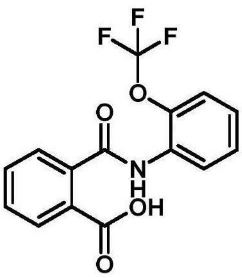
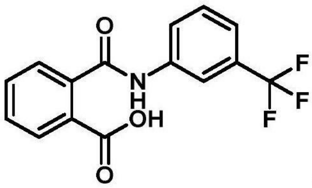
98. 一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的化合物的组合物，该化合物选自

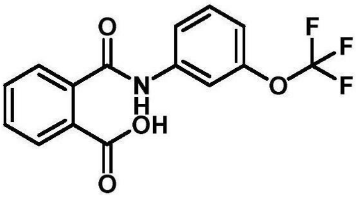
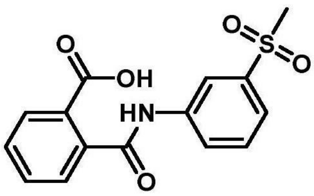
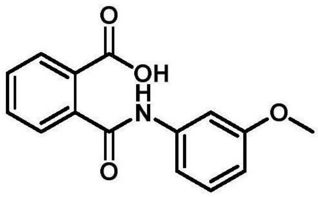


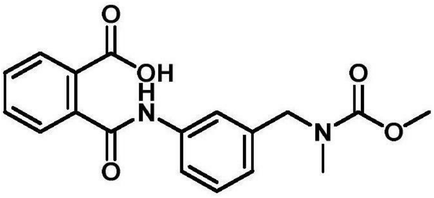
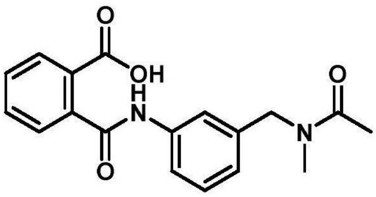
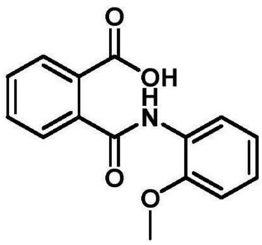
 、  、  、

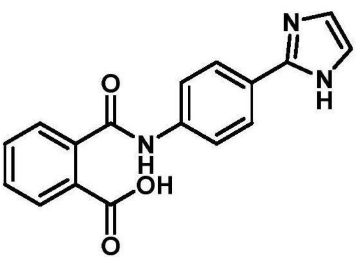
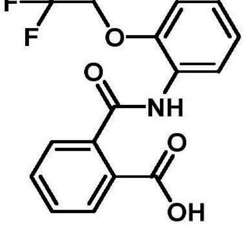
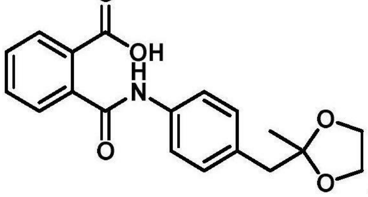
 、  、  、  、

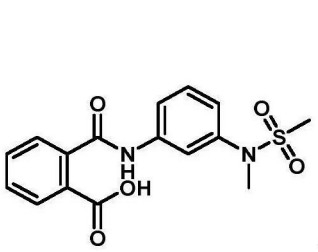
 、  、

 、  、  、

 、  、  、

 、  、  、

 、  、  、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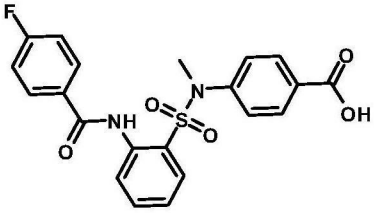
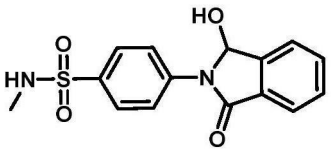
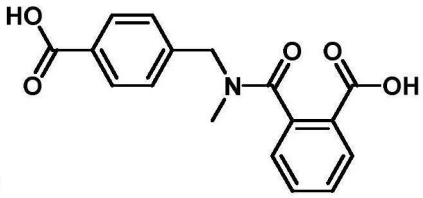
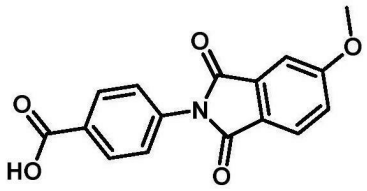
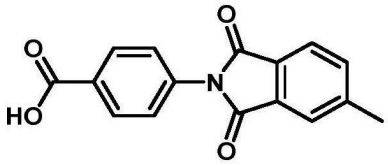
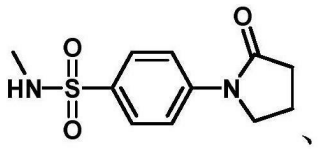
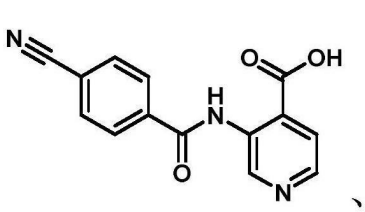
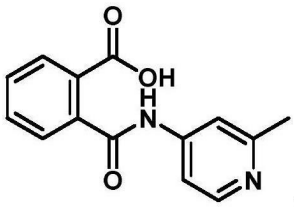
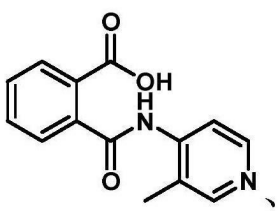
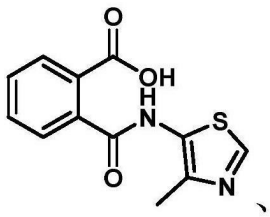
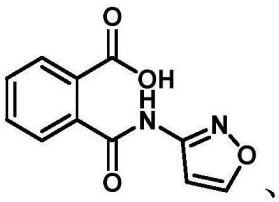
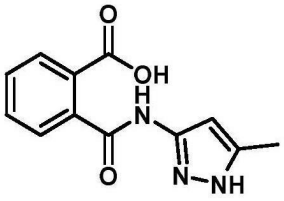
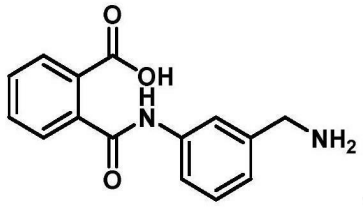
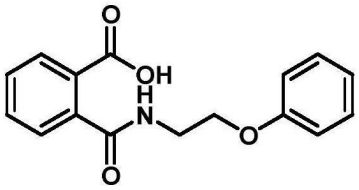
、 
、 
和 
或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体；

99. 一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的选自以下的化合物


、 
、 
、 
、 
、 
、 
、 
、 
、 
、 
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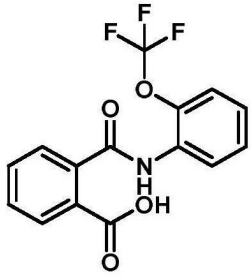
、 
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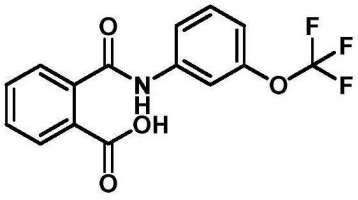
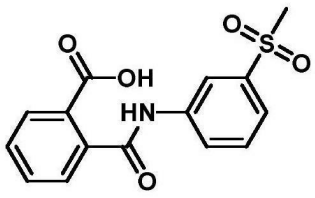
、 
、 
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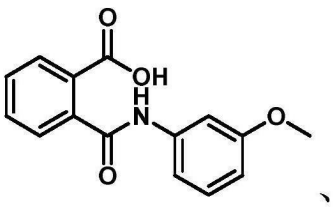
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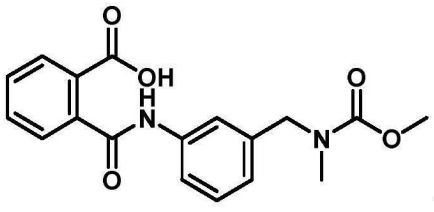
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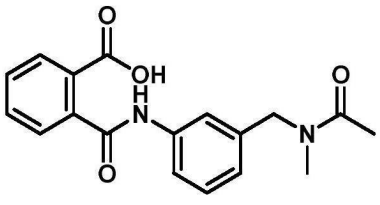
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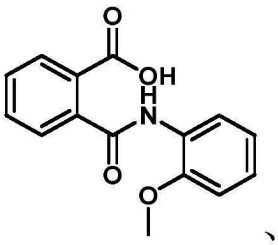
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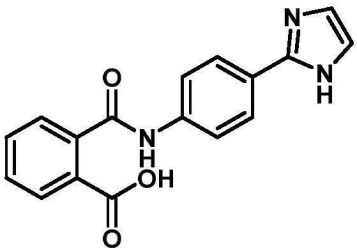
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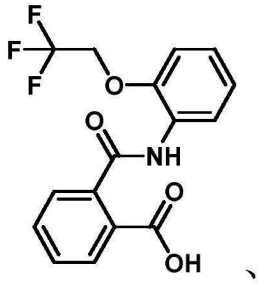
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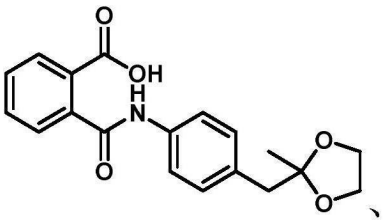
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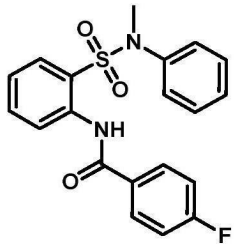
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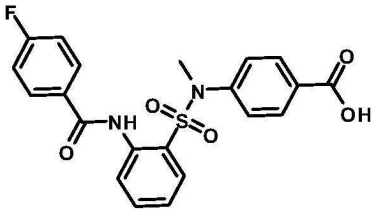
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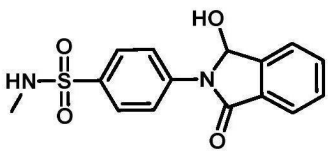
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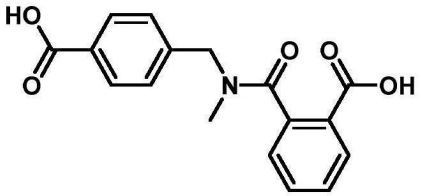
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或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

100. 如权利要求 5-8、31-34、68、69 或 99 中任一项所述的方法，其中该方法在体外进行。

101. 如权利要求 5-8、31-34、68、69 或 99 中任一项所述的方法，其中该方法在哺乳动物体内进行并且所述干细胞存在于该哺乳动物中。

102. 如权利要求 101 所述的方法，其中所述哺乳动物是人、狗、猫或马。

103. 式 I 的化合物，其选自


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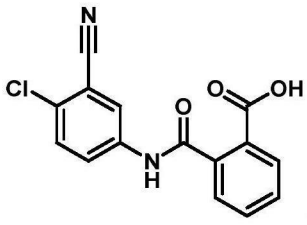
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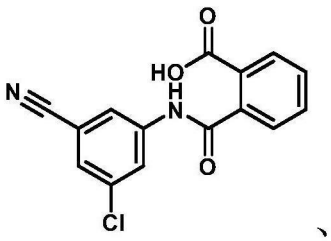
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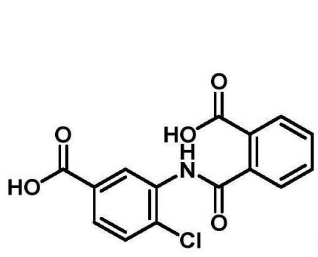
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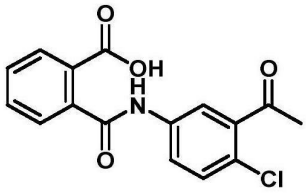
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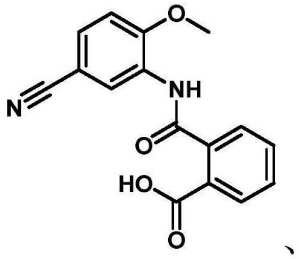
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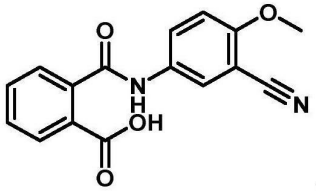
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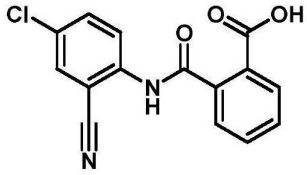
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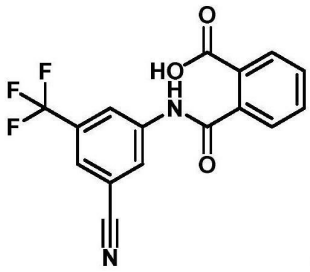
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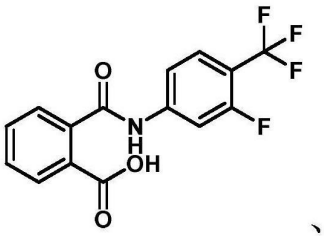
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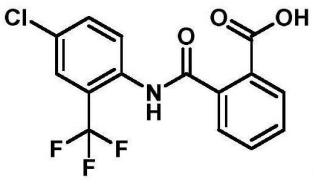
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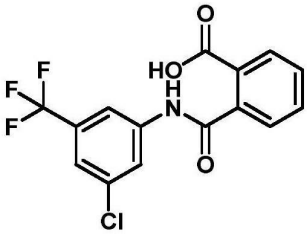
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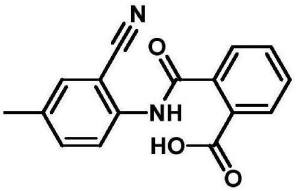
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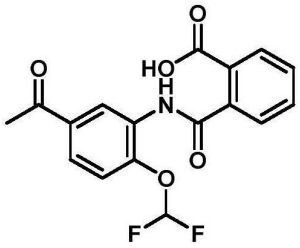
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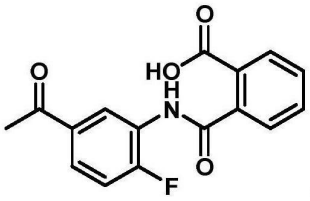
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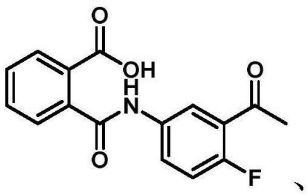
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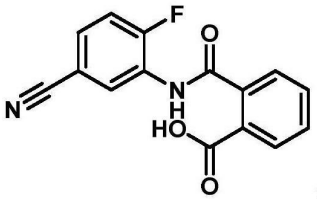
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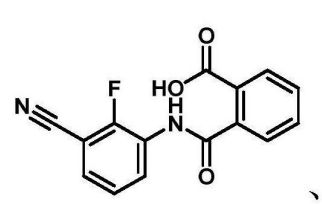
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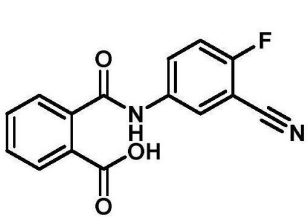
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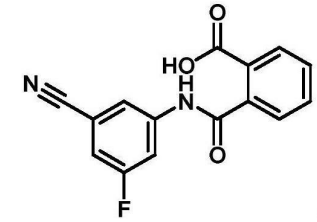
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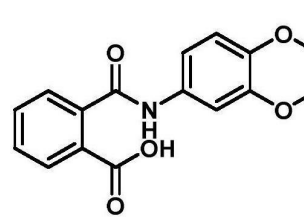
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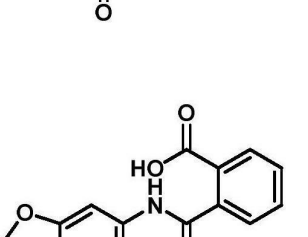
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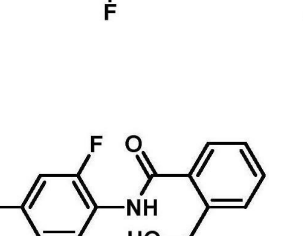
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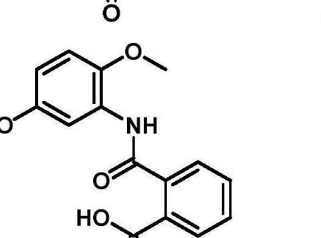
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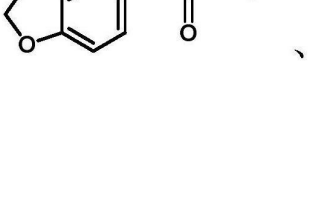
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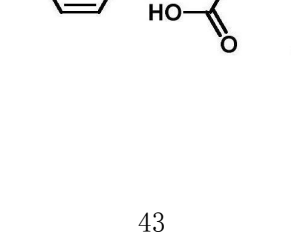
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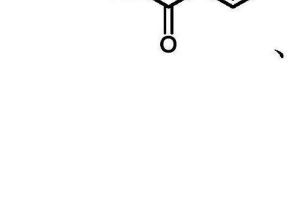
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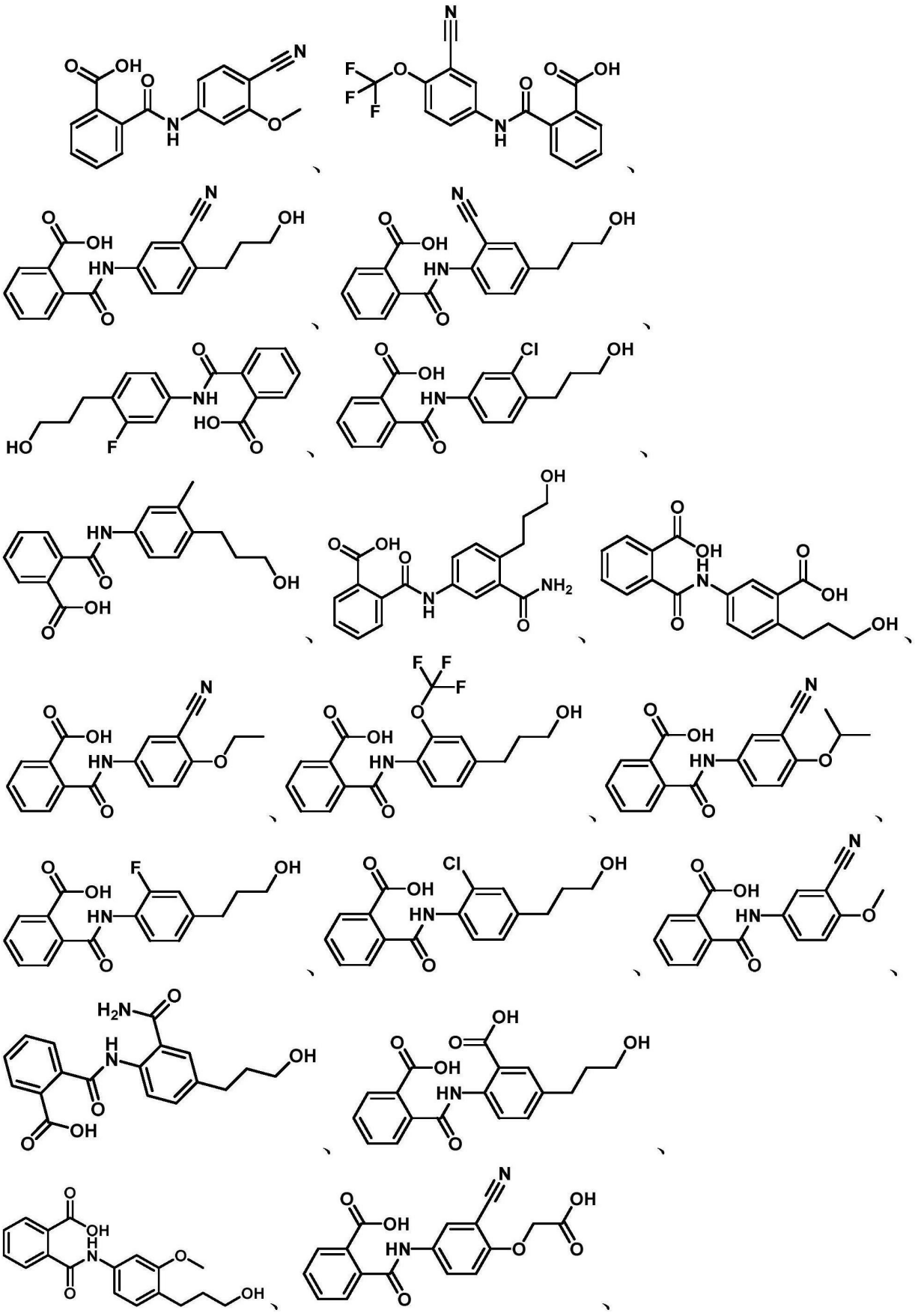

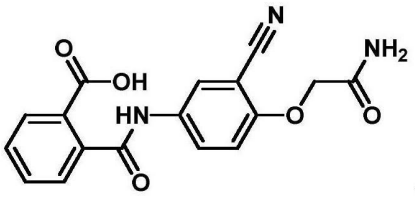
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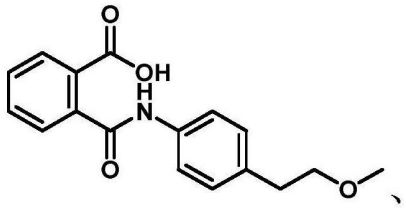
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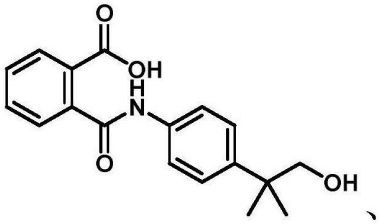
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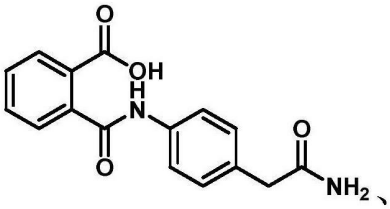
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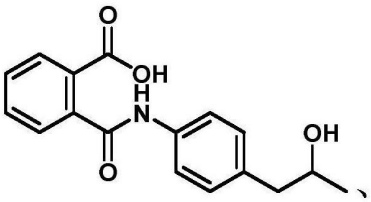
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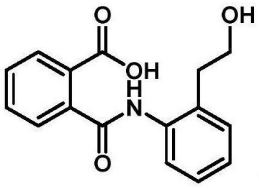
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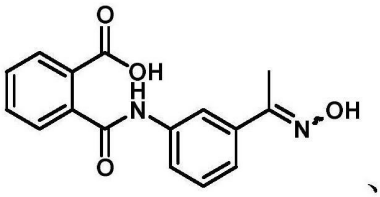
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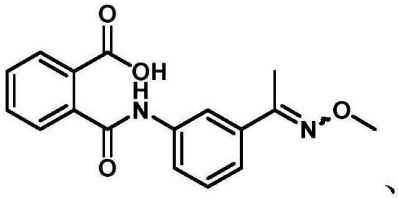
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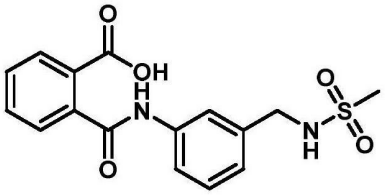
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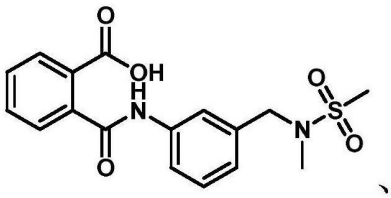
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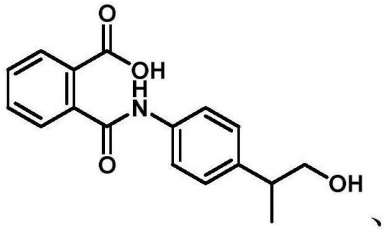
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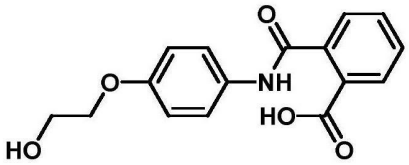
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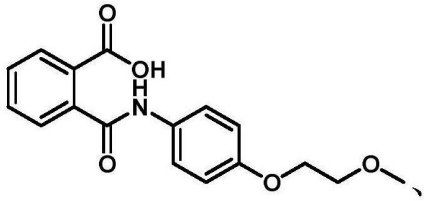
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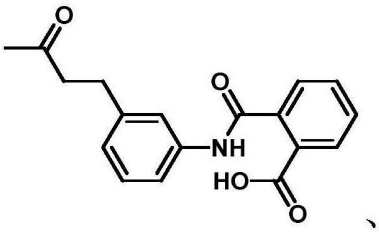
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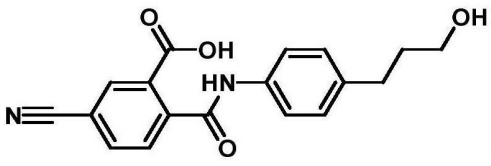
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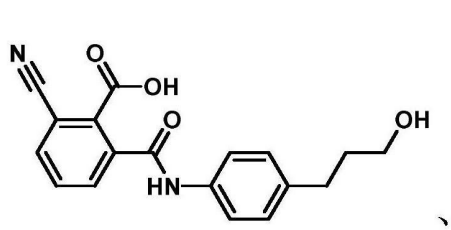
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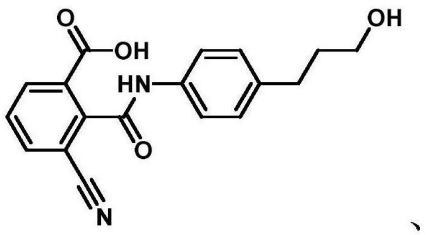
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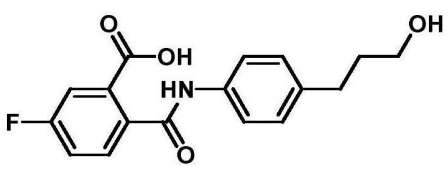
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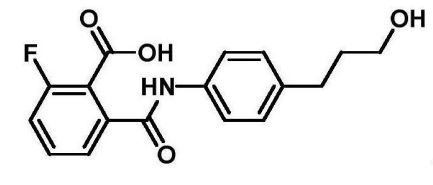
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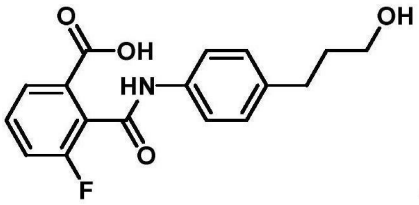
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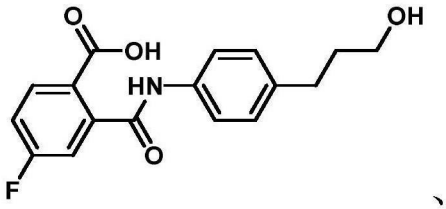
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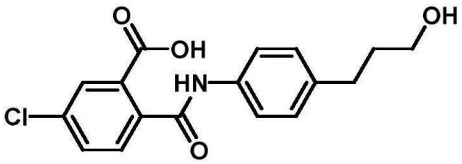
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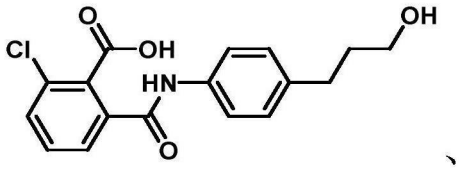
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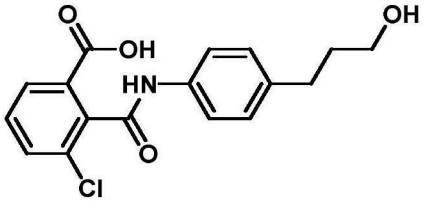
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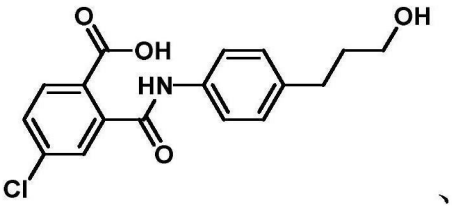
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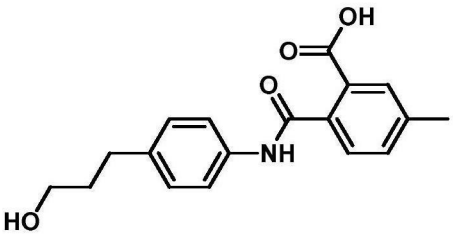
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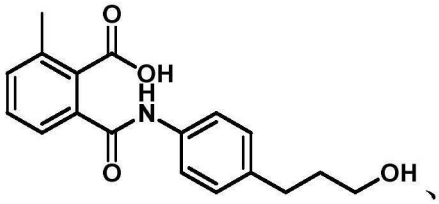
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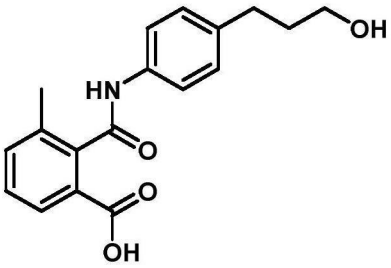
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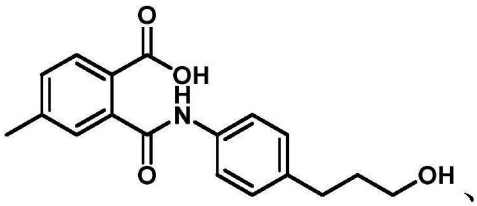
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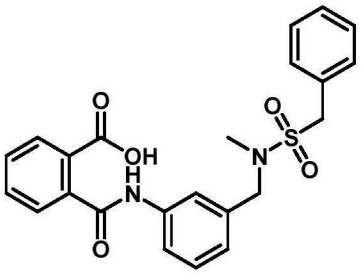
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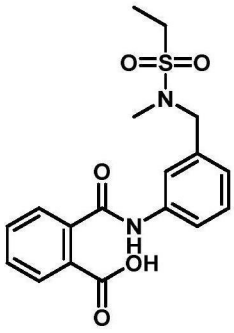
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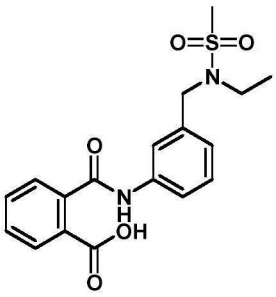
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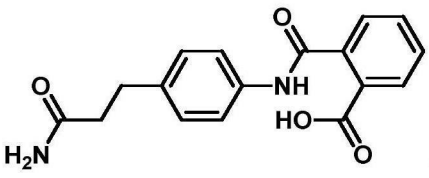
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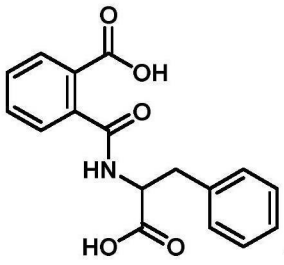
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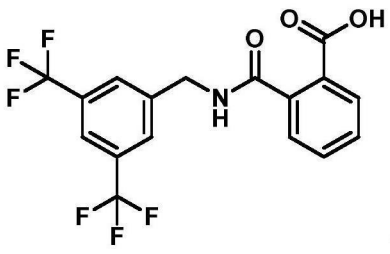
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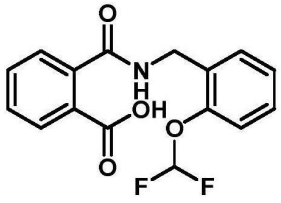
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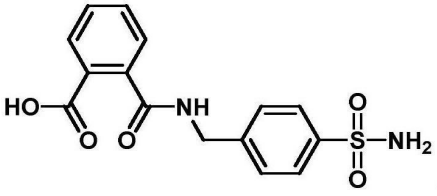
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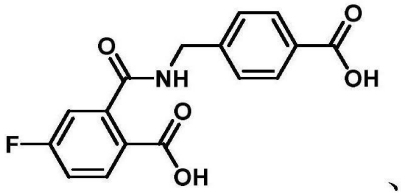
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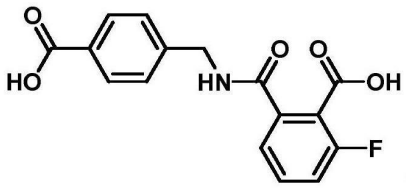
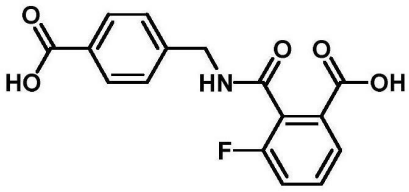
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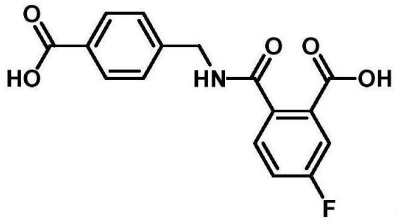
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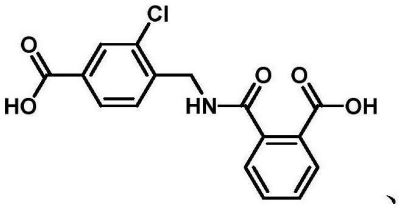
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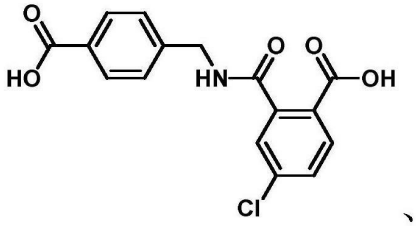
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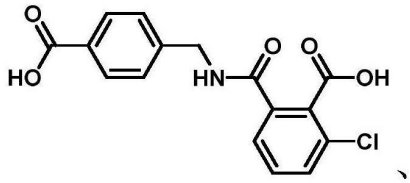
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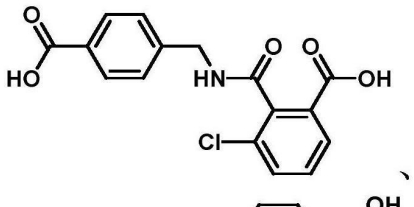
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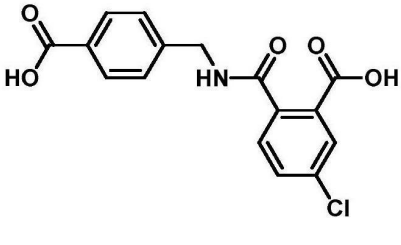
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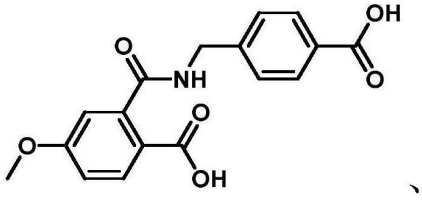
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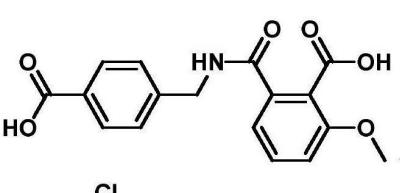
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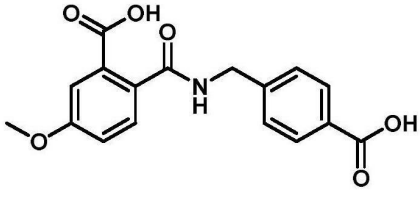
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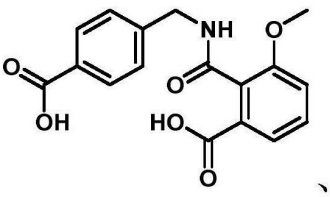
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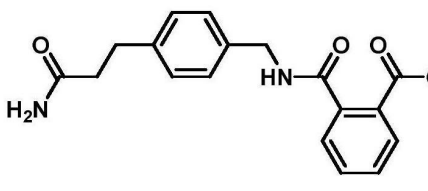
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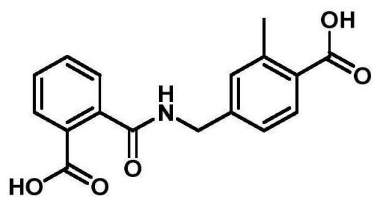
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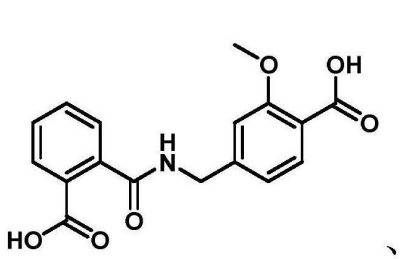
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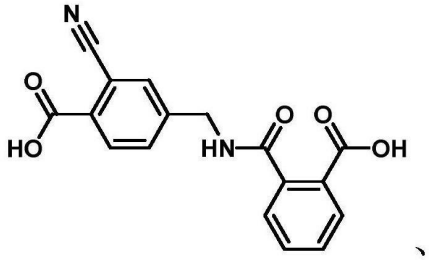
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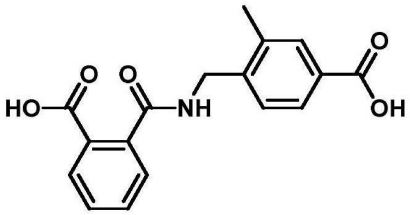
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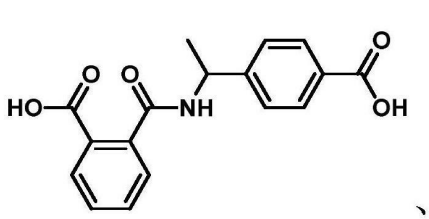
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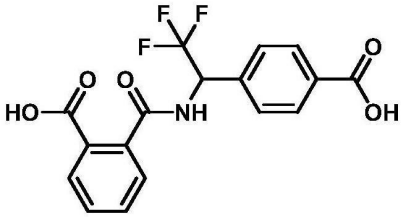
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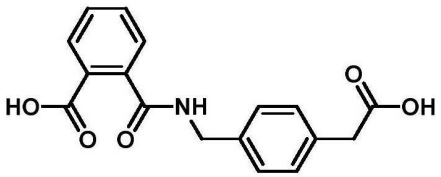
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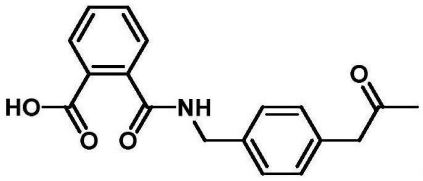
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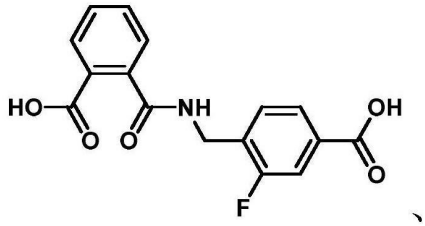
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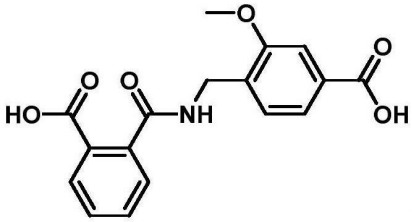
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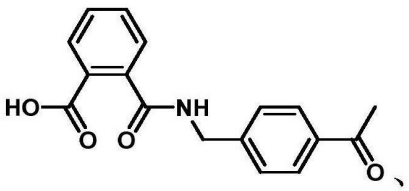
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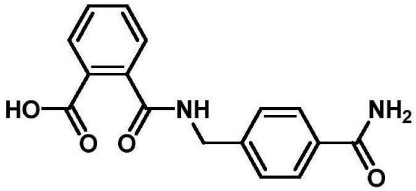
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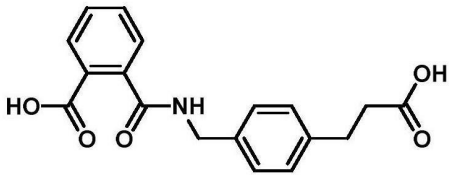
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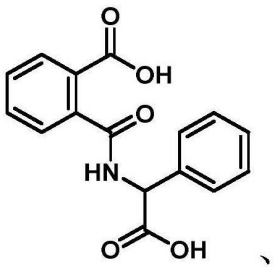
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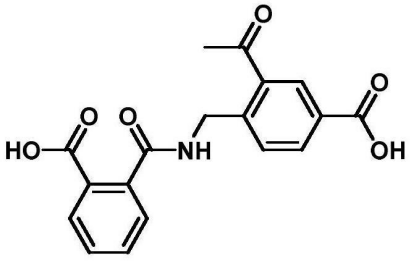
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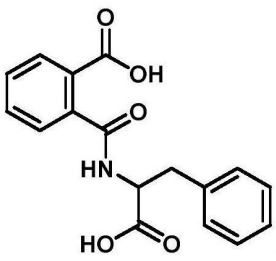
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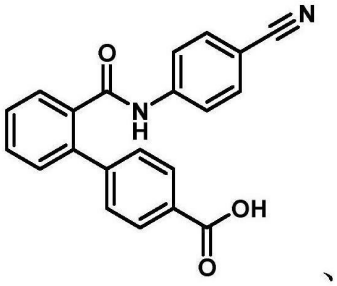
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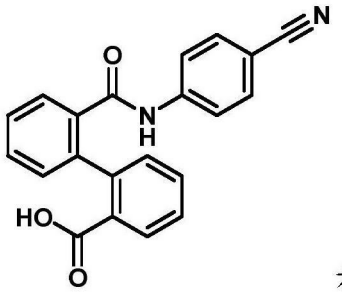

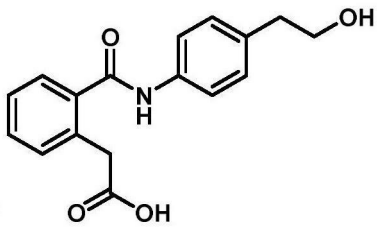

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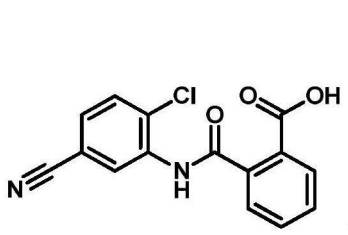
或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

104. 式 Ia 的化合物，其选自



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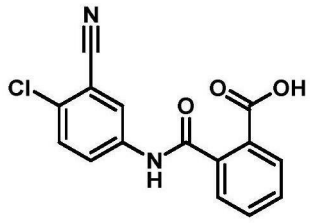

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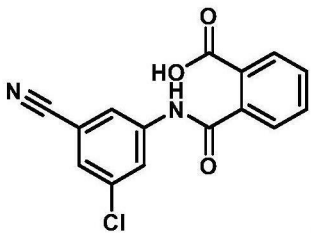

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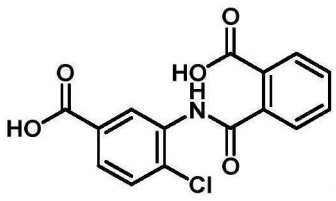

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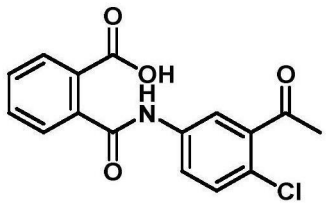

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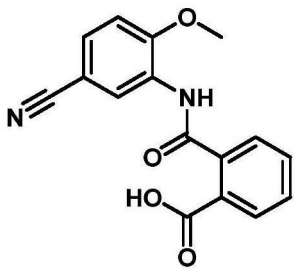

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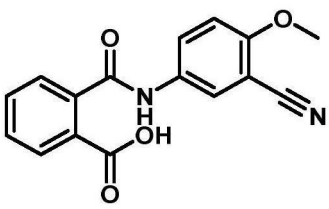

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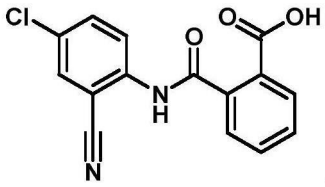

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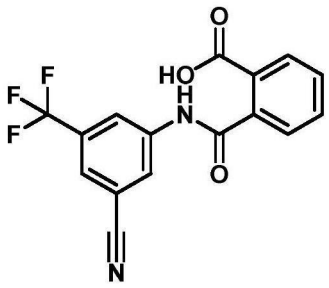

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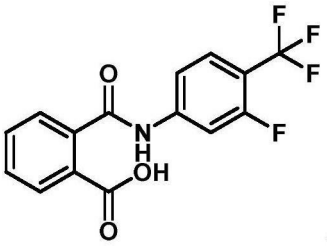

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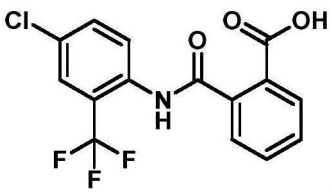

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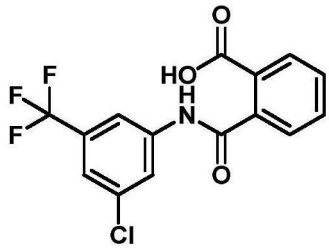

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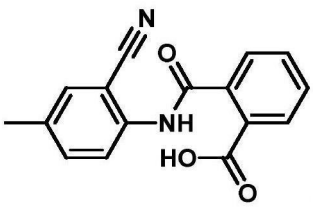

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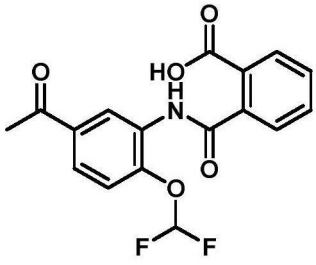

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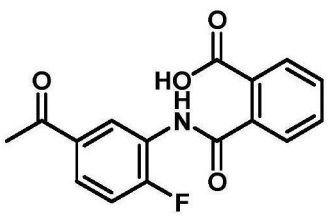

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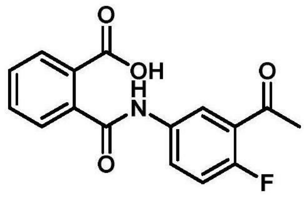
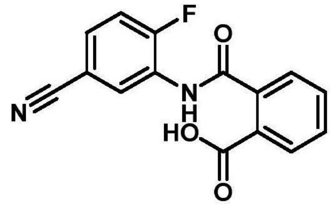
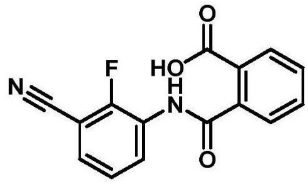
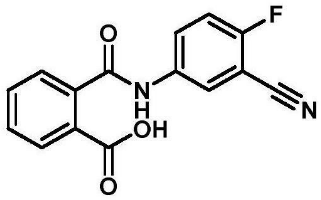
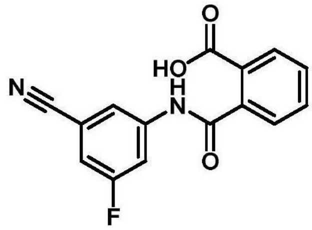
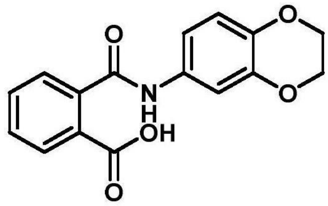
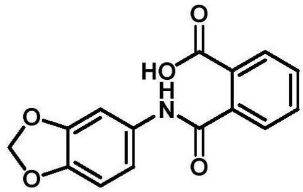
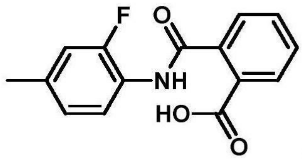
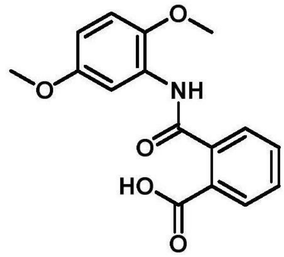
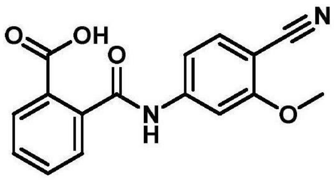
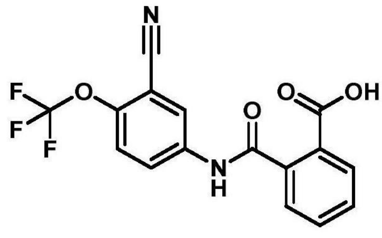
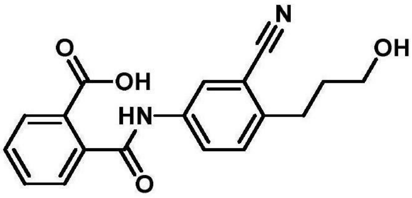
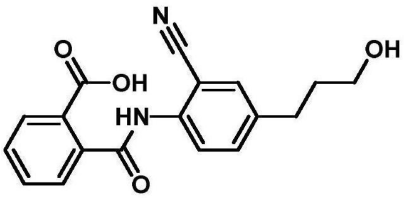
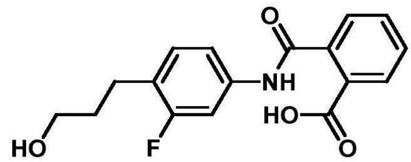
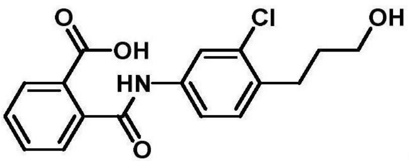
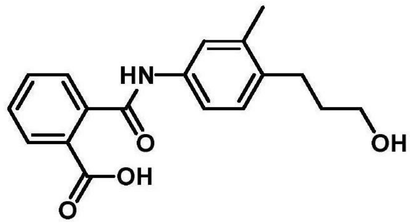
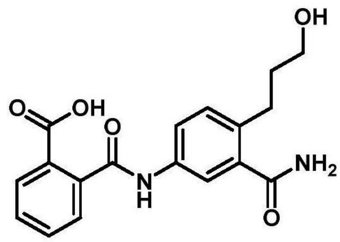
 、  、  、

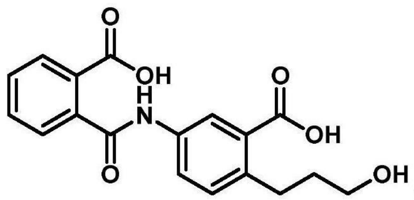
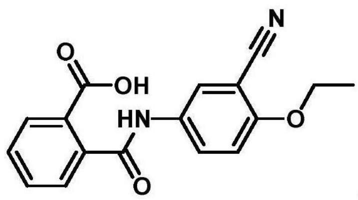
 、  、  、

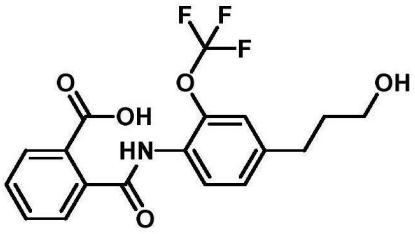
 、  、  、

 、  、  、

 、  、

 、  、  、

 、  、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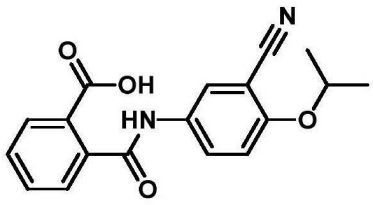
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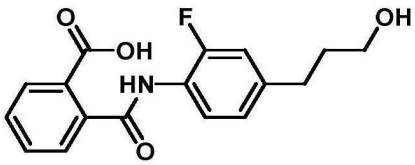
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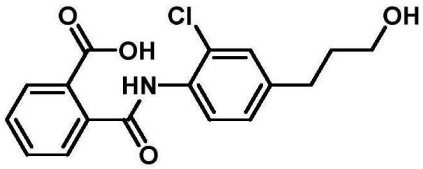
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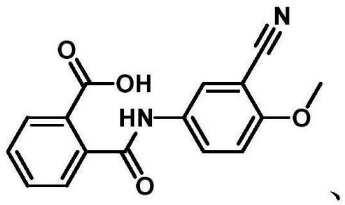
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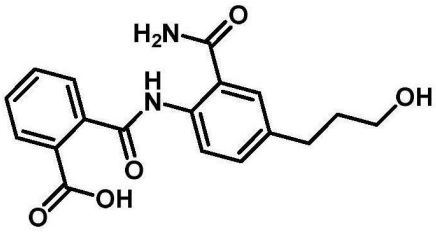
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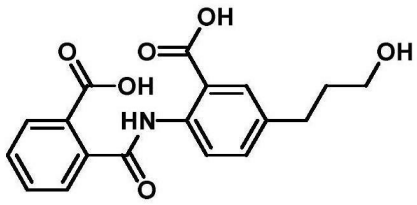
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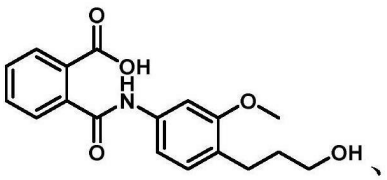
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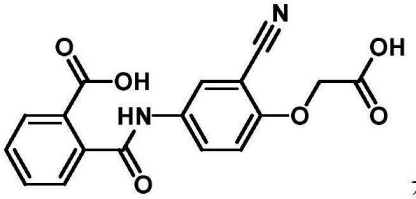
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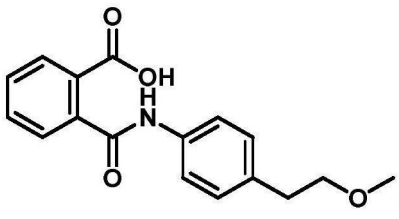
105. 式 Ib 的化合物，其选自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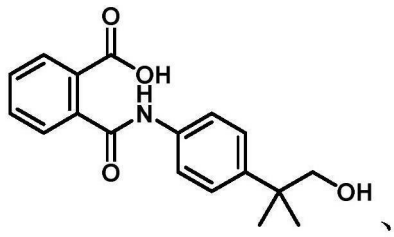
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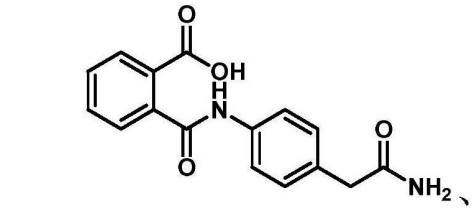
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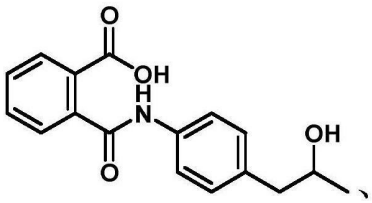
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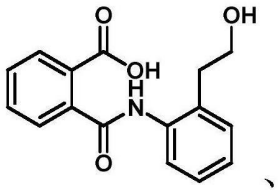
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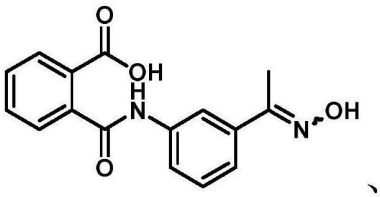
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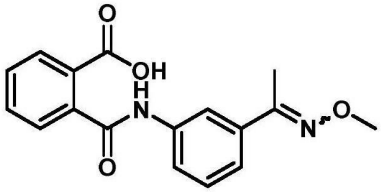
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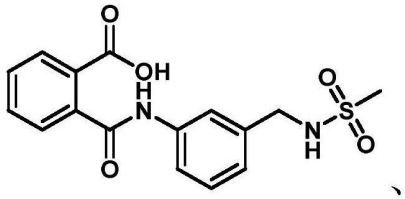
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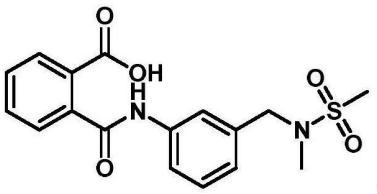
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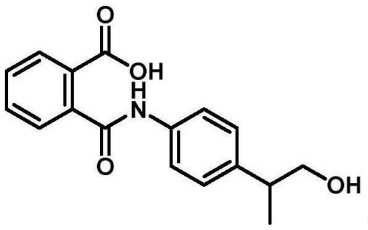
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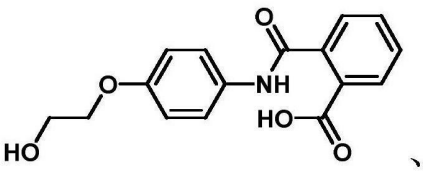
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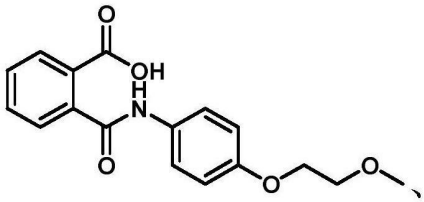
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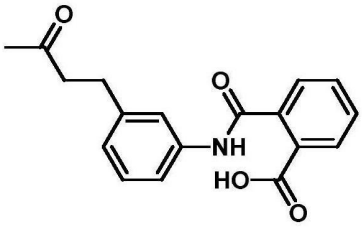
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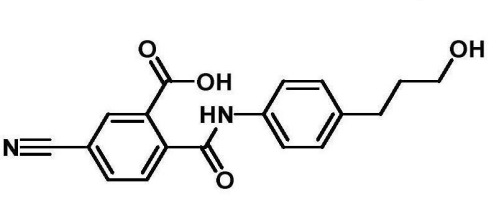
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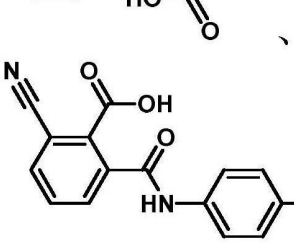
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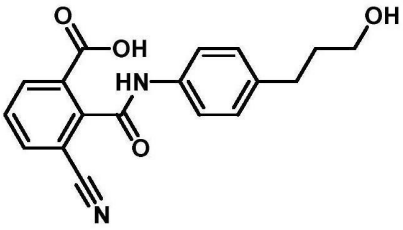
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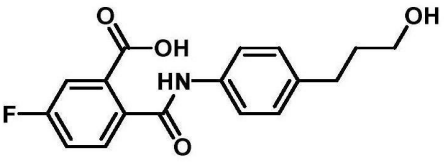
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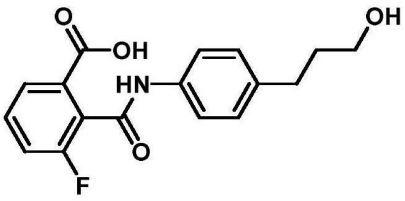
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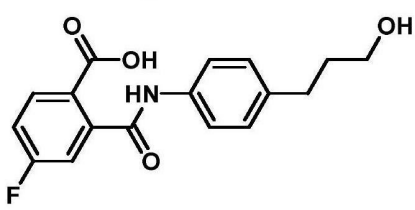
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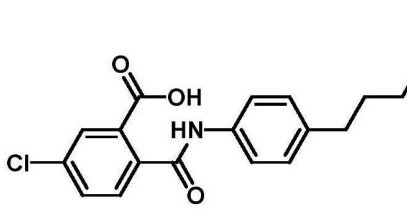
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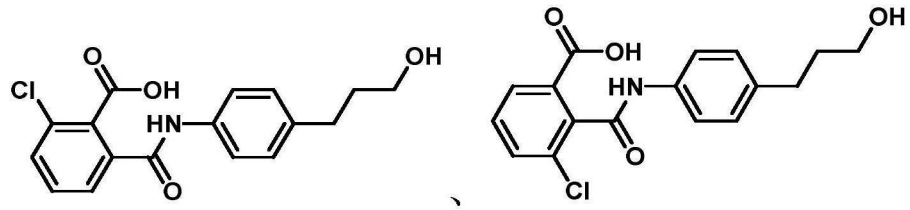
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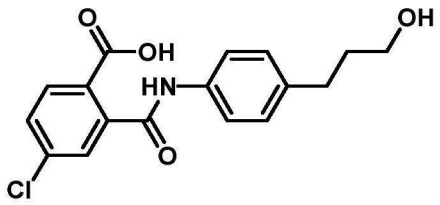
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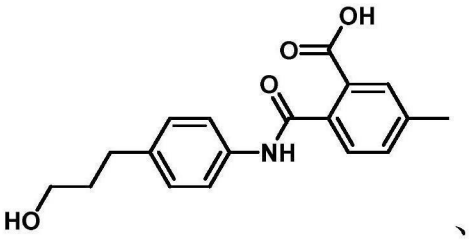
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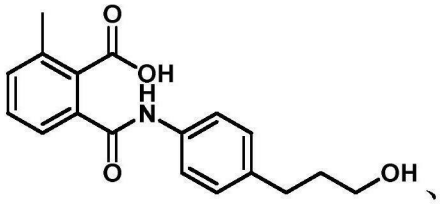
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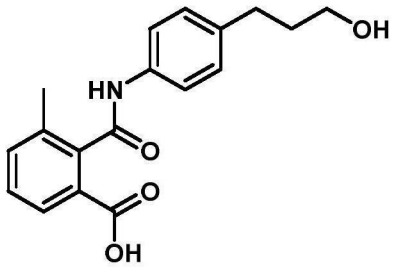
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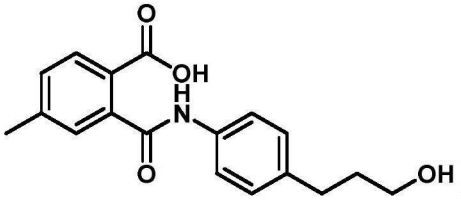
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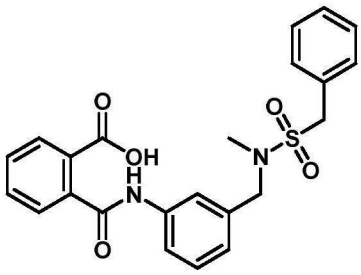
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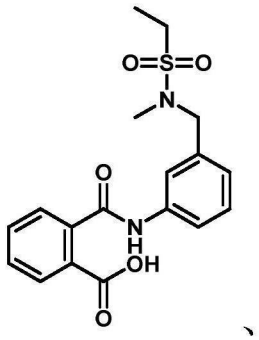
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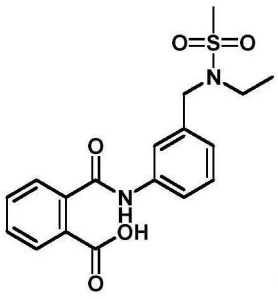
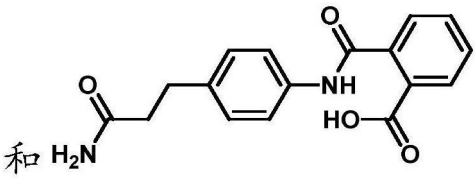
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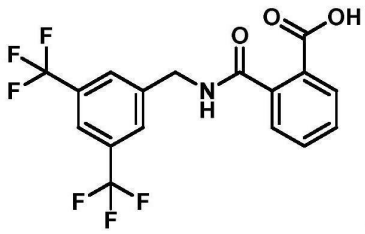
或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

106. 式 Ic 的化合物，其选自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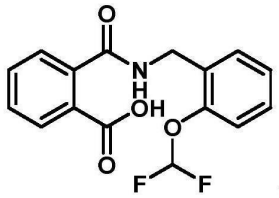
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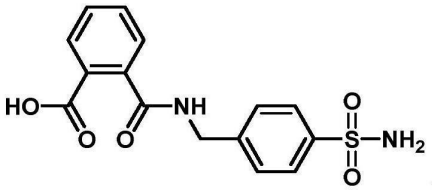
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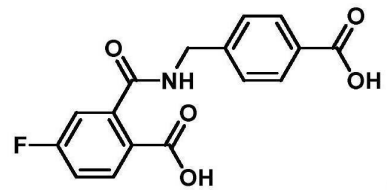
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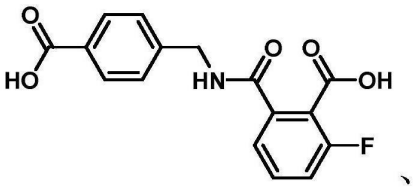
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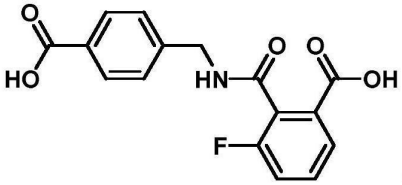
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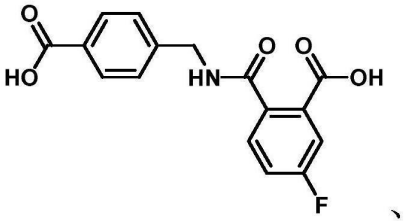
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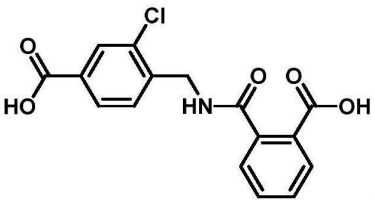
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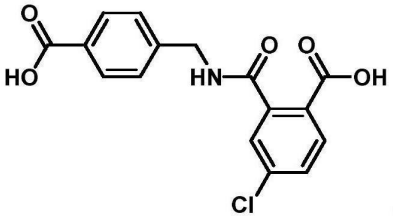
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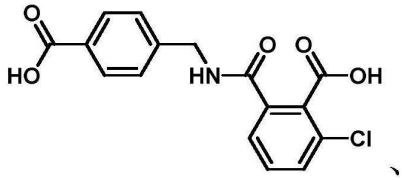
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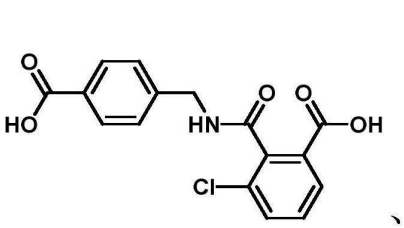
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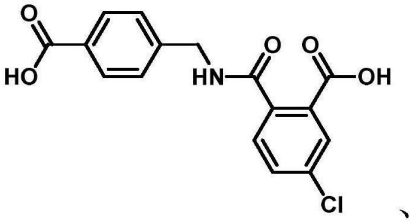
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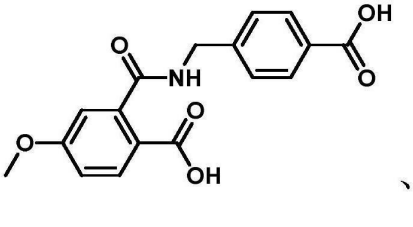
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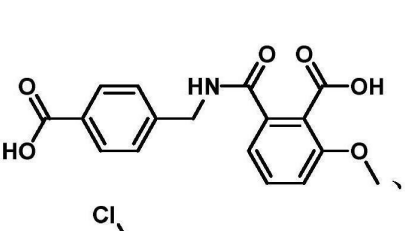
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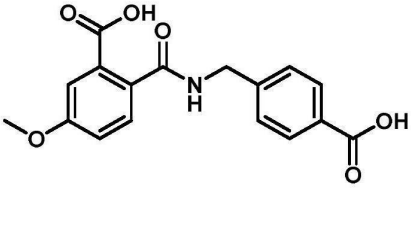
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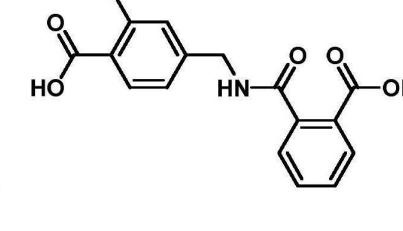
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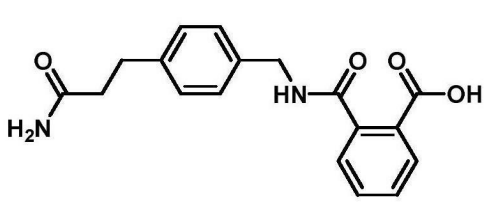
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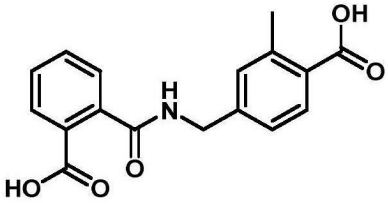
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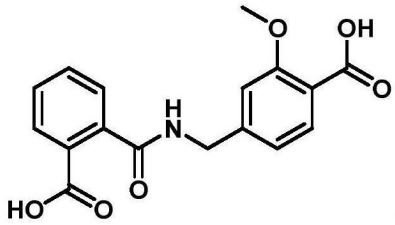
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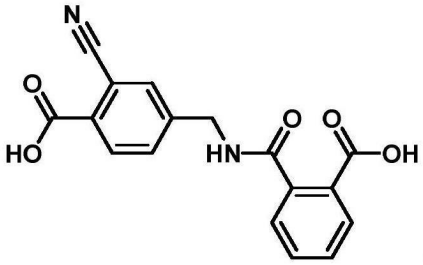
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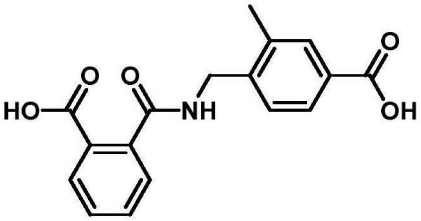
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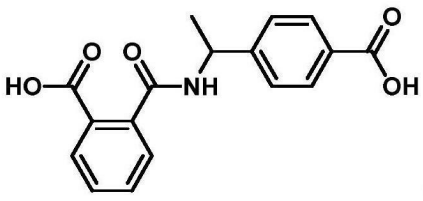
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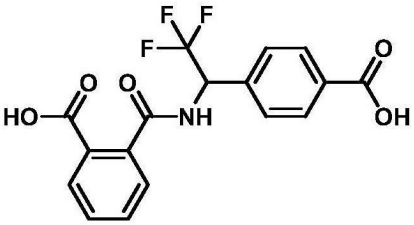
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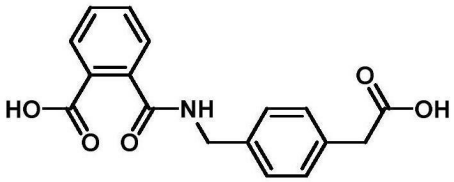
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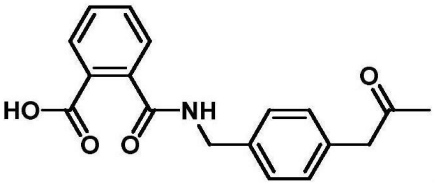
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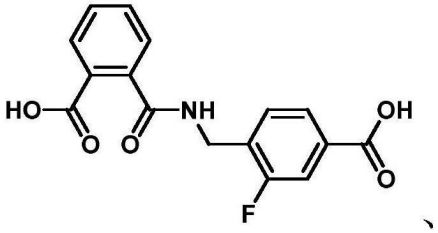
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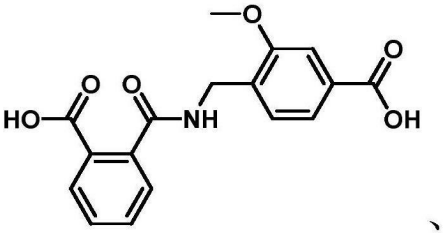
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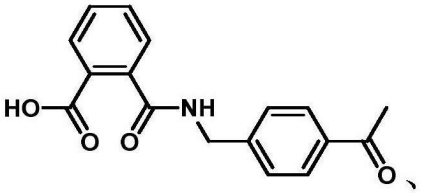
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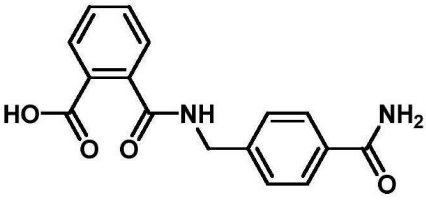
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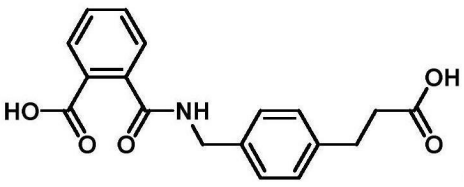
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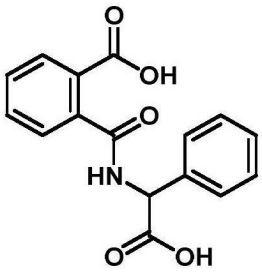
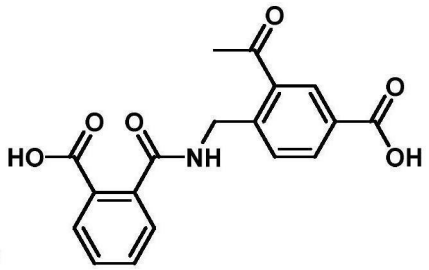
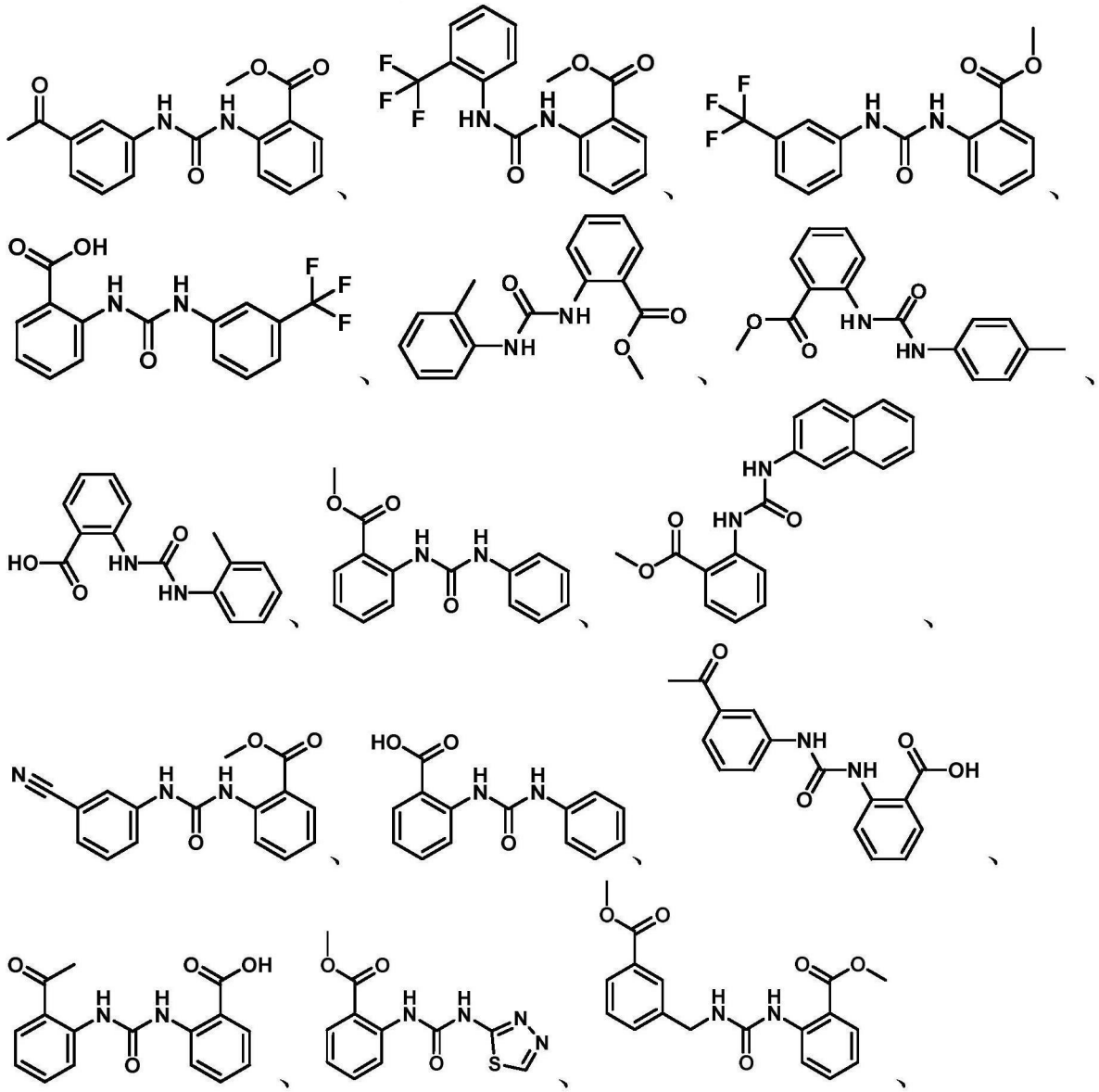


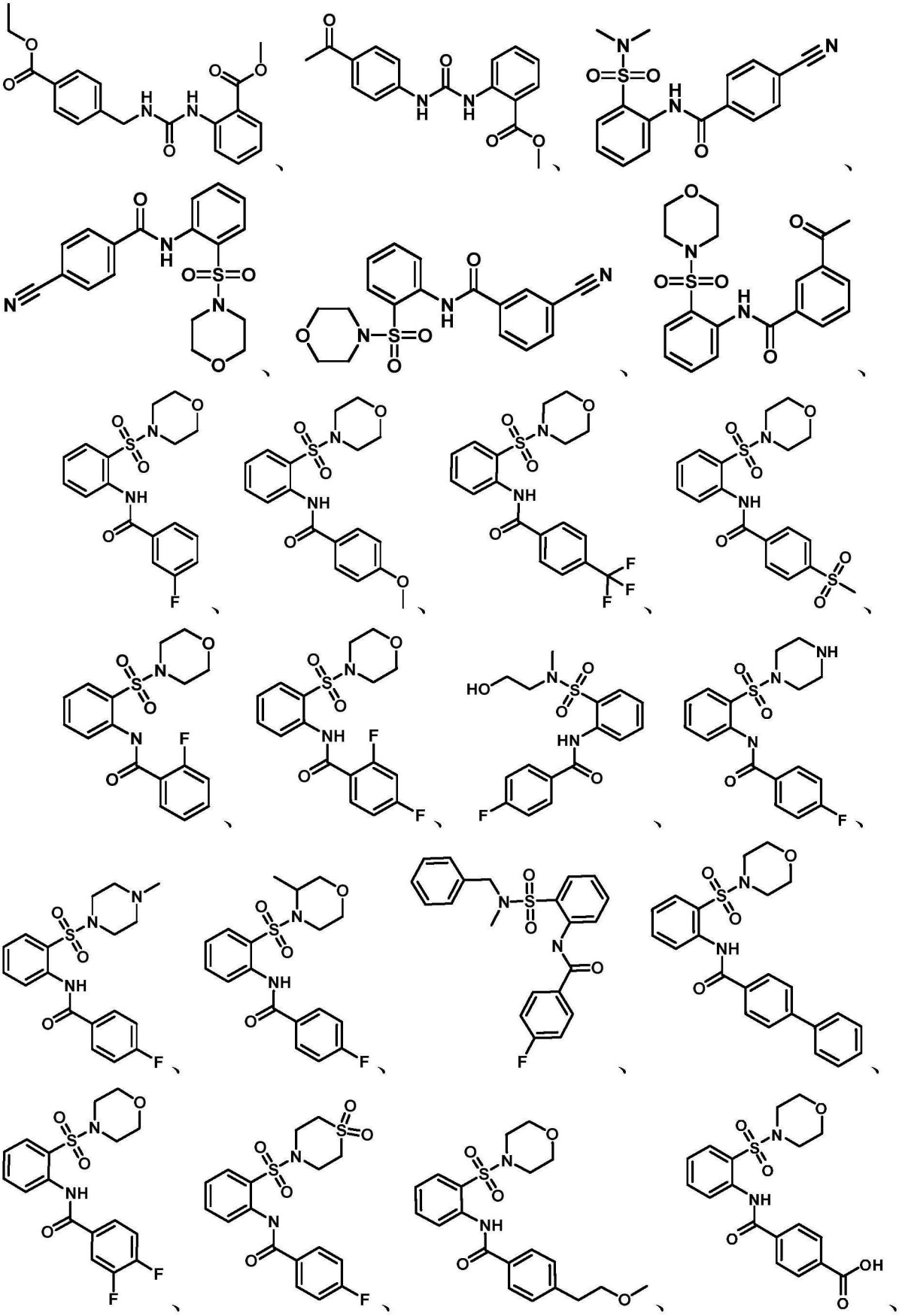


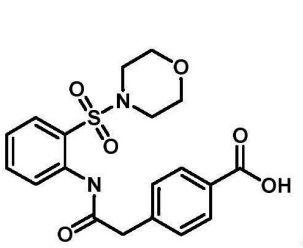
或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

和 ；

107. 式 II 的化合物，其选自



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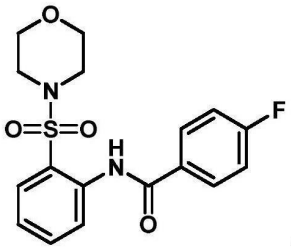
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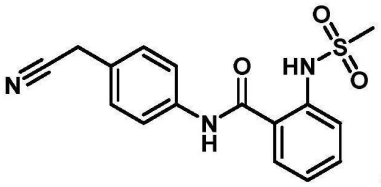
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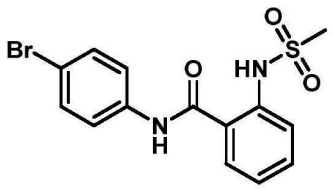
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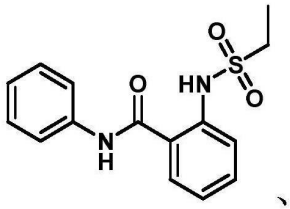
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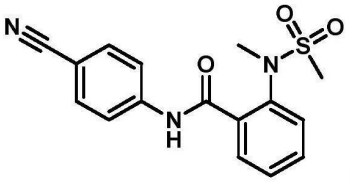
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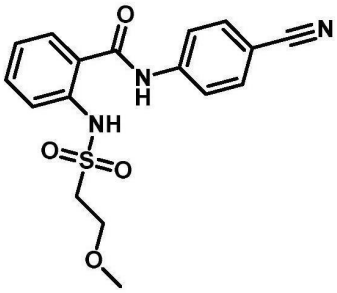
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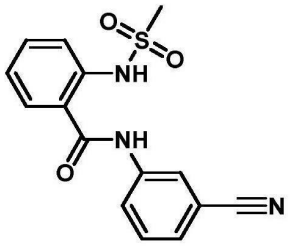
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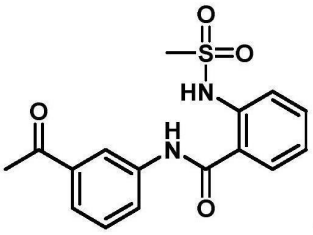
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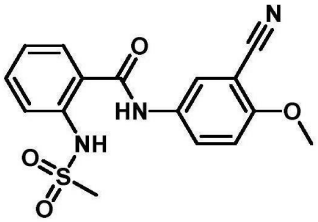
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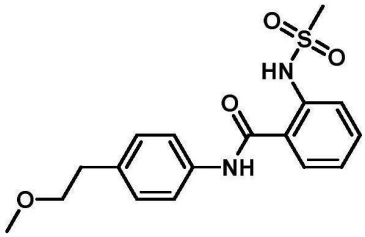
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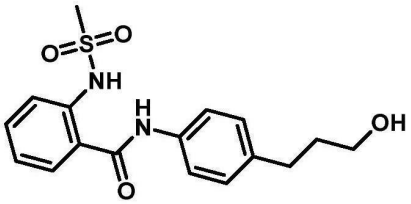
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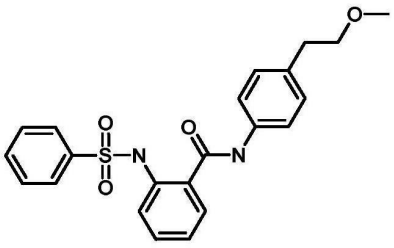
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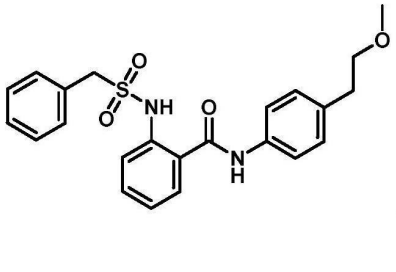
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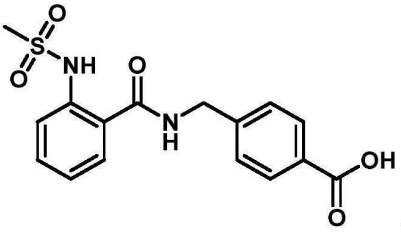
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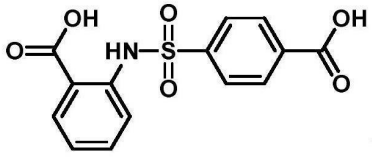
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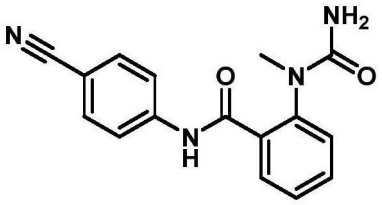
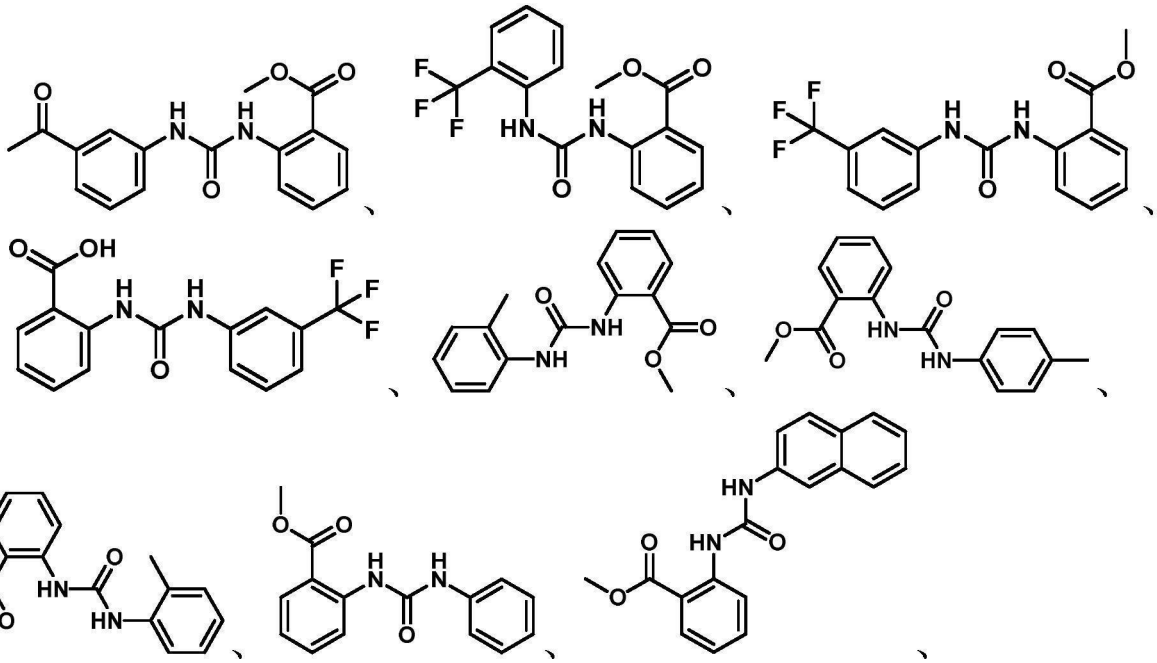


或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

108. 式 IIa 的化合物，其选自



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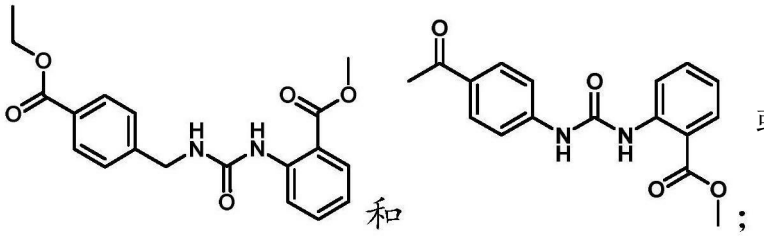
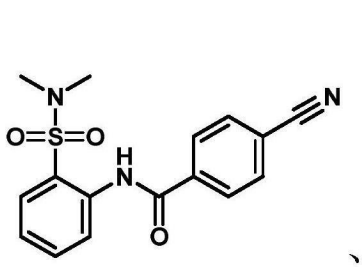


或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

109. 式 IIb 的化合物，其选自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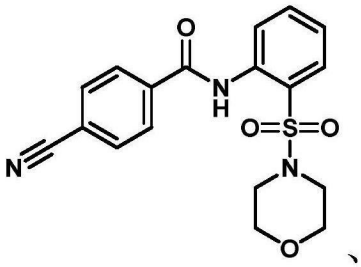
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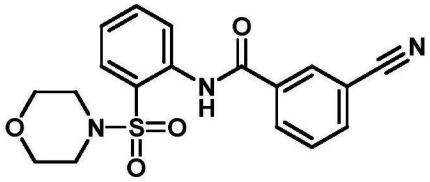
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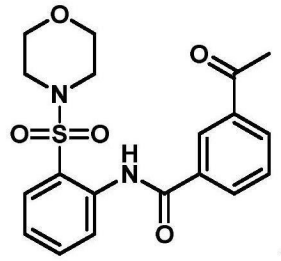
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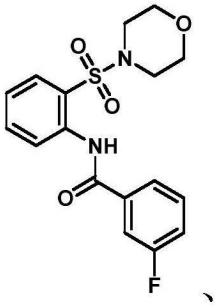
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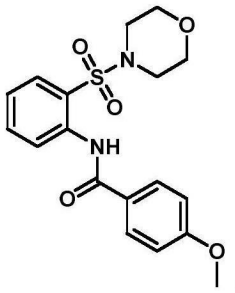
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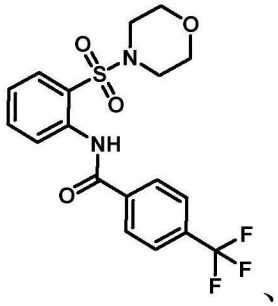
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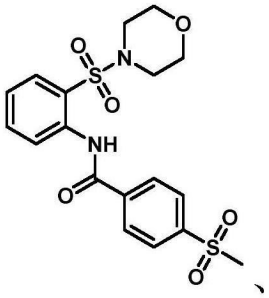
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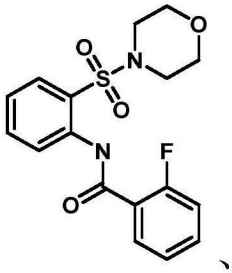
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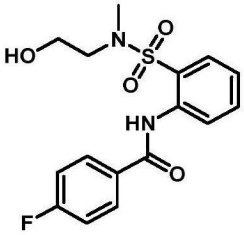
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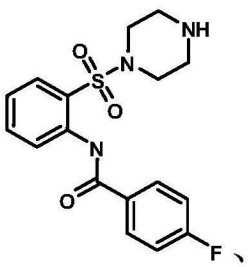
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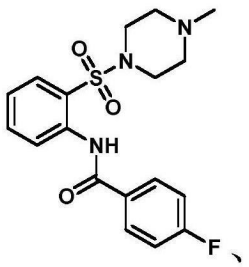
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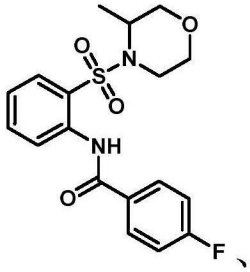
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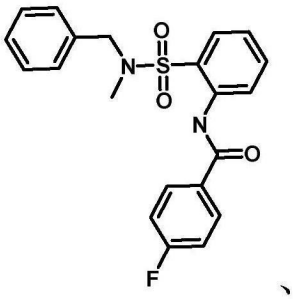
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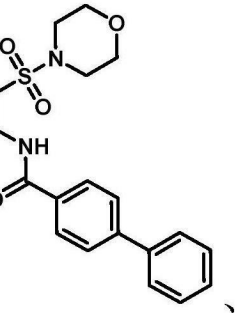
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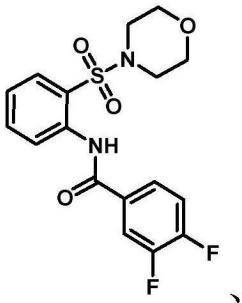
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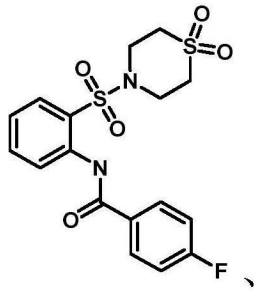
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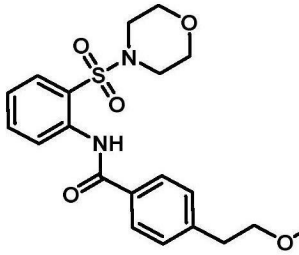
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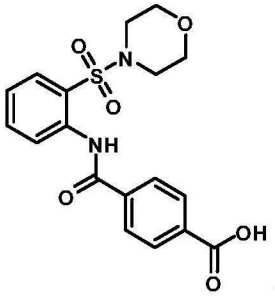
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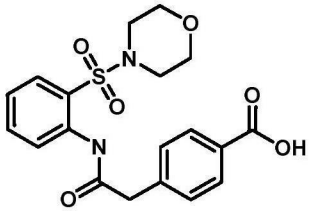
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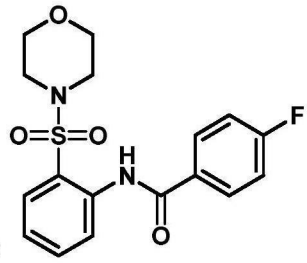
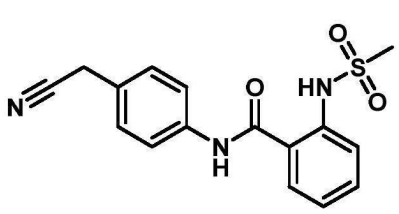

；或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

110. 式 IIc 的化合物，其选自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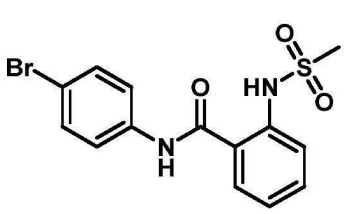
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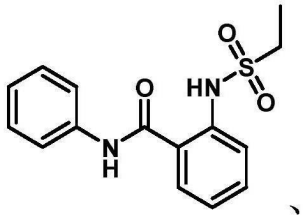
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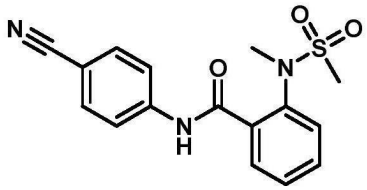
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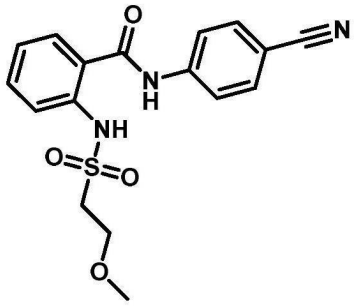
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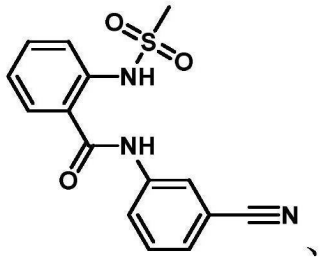
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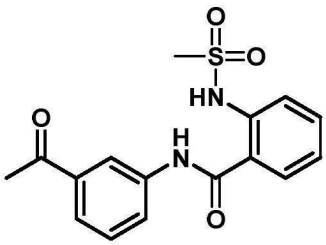
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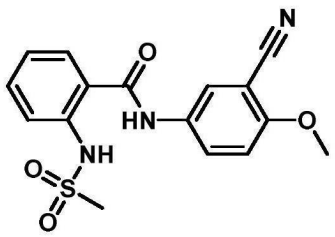
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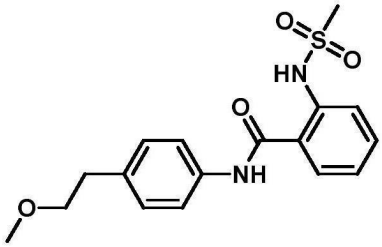
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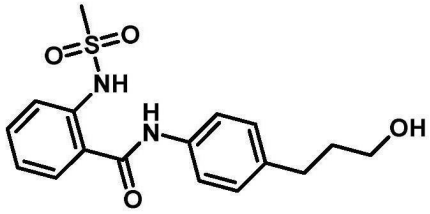
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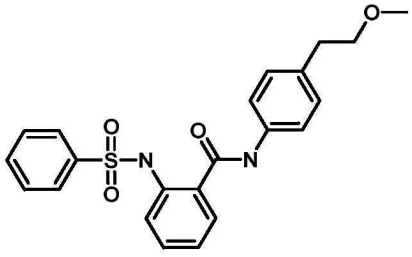
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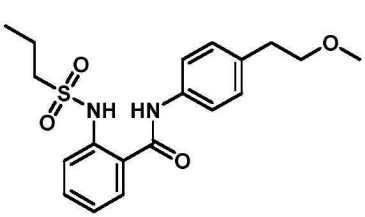
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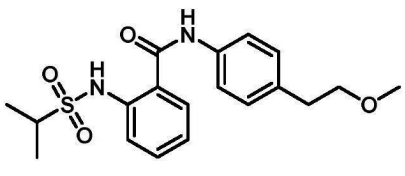
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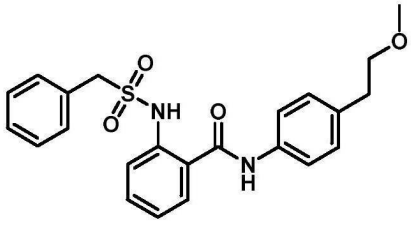
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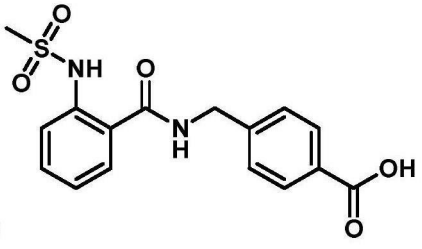
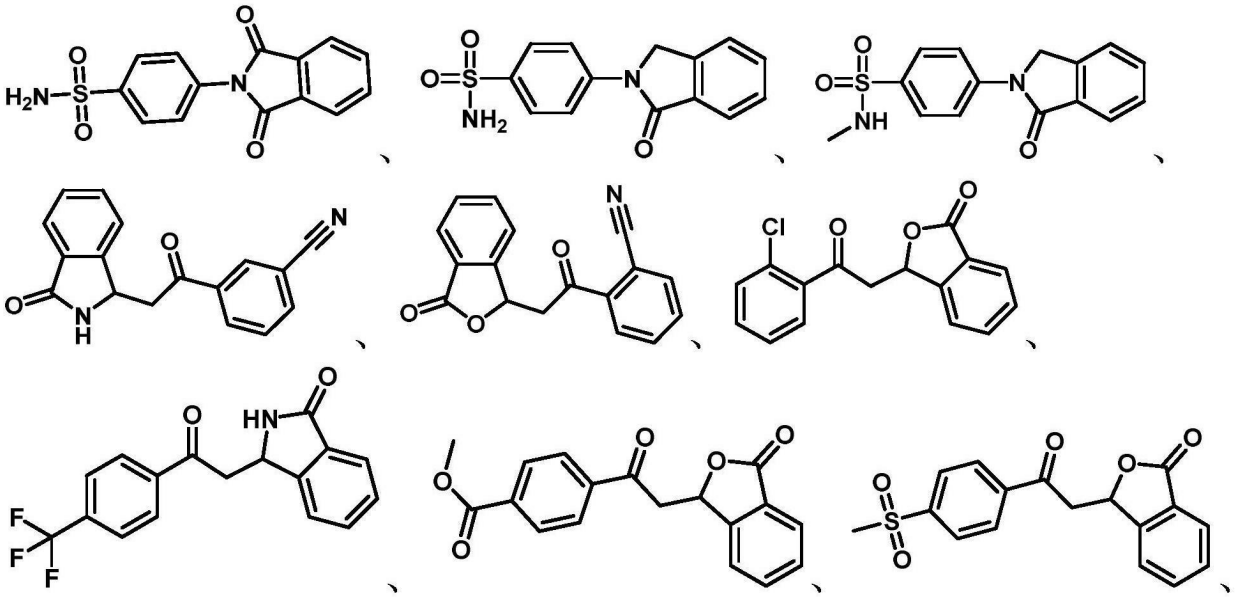
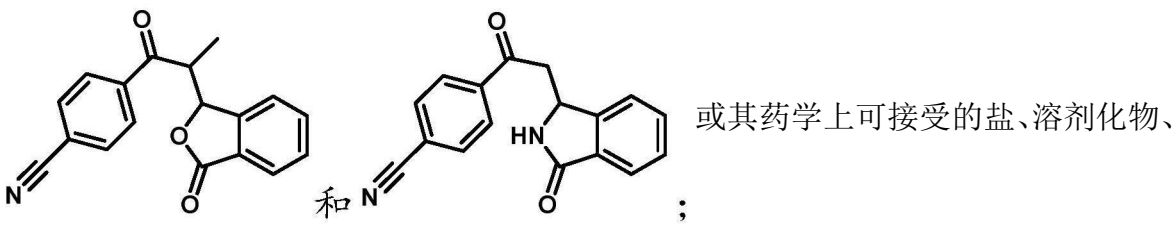


和 ；或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

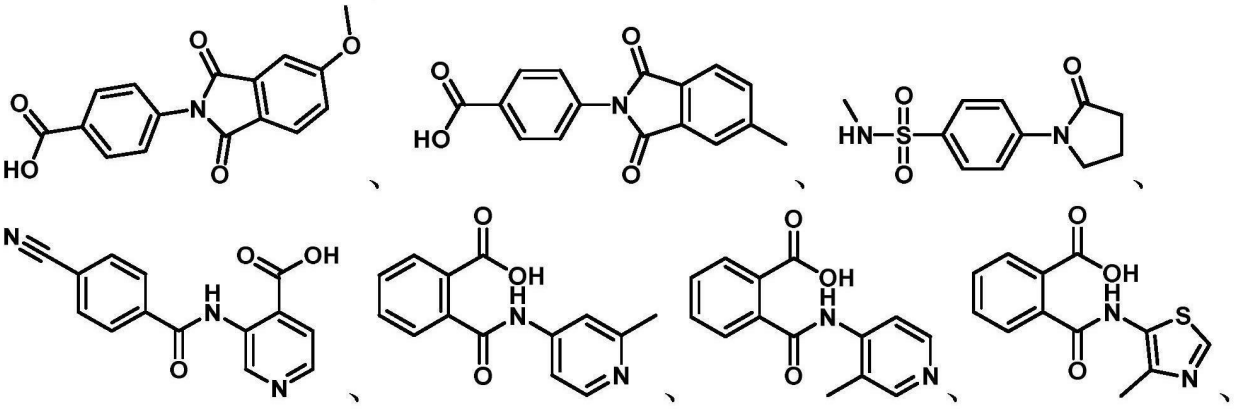
111. 式 III 的化合物，其选自

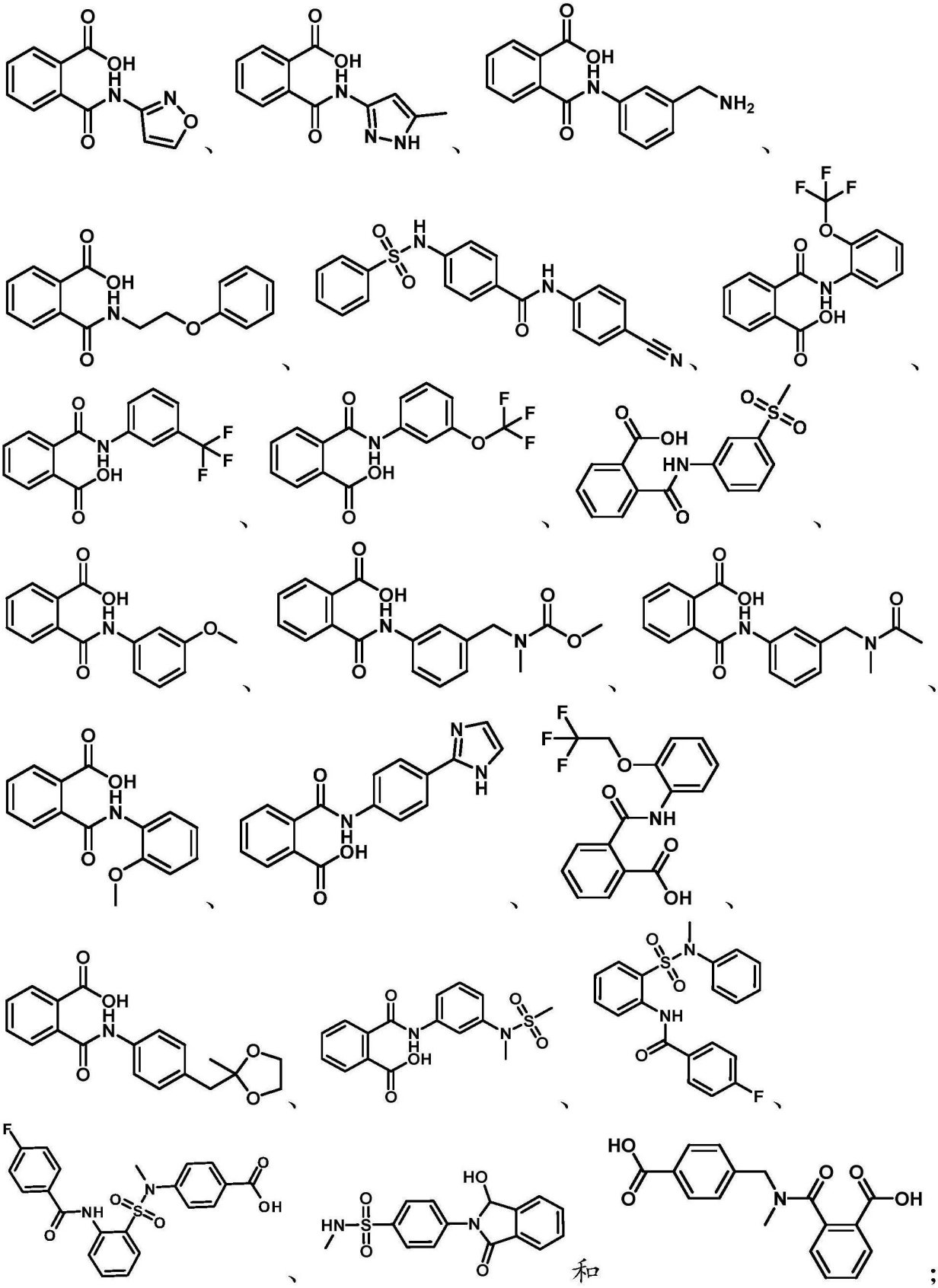




和 ；或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

112. 一种化合物，其选自





或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

113. 一种药物组合物，其包含如权利要求 103-112 中任一项所述的化合物或其药学上

可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体以及药学上可接受的赋形剂。

114. 如权利要求 113 所述的药物组合物，其进一步包含额外的化合物，该额外的化合物对于治疗哺乳动物的关节炎或关节损伤和 / 或与关节炎或关节损伤相关的症状是治疗上有效的。

115. 如权利要求 114 所述的药物组合物，其中所述额外的化合物选自 NSAIDS、镇痛药、血管生成素样 3 蛋白 (ANGPTL3) 或其软骨形成变体、口服鲑降钙素、iNOS 抑制剂、维生素 D3、胱天蛋白酶抑制剂、胶原水解物、FGF18、BMP7、鳄梨大豆不皂化物 (ASU) 和透明质酸。

116. 如权利要求 114 所述的药物组合物，其中所述哺乳动物是人。

117. 如权利要求 114 所述的药物组合物，其中所述哺乳动物是陪伴动物或家畜。

118. 如权利要求 1-4、27-30、66、67 或 98 中任一项所述的方法，其中所述哺乳动物是人。

119. 如权利要求 1-4、27-30、66、67 或 98 中任一项所述的方法，其中所述哺乳动物是驯养动物或家畜。

用于诱导软骨形成的化合物和方法

相关申请的交叉引用

[0001] 本申请要求 2014 年 3 月 15 日提交的美国申请号 61/794,094 的权益，该申请通过引用整体并入本文。

技术领域

[0002] 本发明涉及化合物、组合物、制品及其用于诱导软骨形成以及用于治疗关节炎或关节损伤的用途。

背景技术

[0003] 骨关节炎 (OA) 是最常见的肌骨病症。大约 4 千万美国人目前患该病，并且由于人口老化和预期寿命延长，这一数字预计将在下一个二十年内增加至 6 千万，使其成为失能的第四大原因。OA 的特征在于关节的缓慢退化性分解，该关节包括关节软骨（含有为关节产生润滑和缓冲的细胞和基质）和处于关节软骨下方的软骨下骨。目前的 OA 疗法包括通过口服 NSAID 或选择性环加氧酶 2(COX-2) 抑制剂、关节内 (IA) 注射诸如皮质类固醇和透明质酸等药剂以及手术方法缓解疼痛。

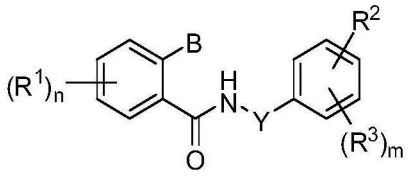
[0004] 间充质干细胞 (MSC) 存在于成年关节软骨中，并且在分离后可以在体外程序化，以分化为软骨细胞和其他间充质细胞谱系。部分地，它通过生长因子 (TGF、BMP)、血清条件和细胞 - 细胞接触来调节。

发明内容

[0005] 本文提供了一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用具有治疗有效量的本文公开的化合物的组合物。

[0006] 本文提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的本文公开的化合物，从而诱导干细胞分化为软骨细胞。

[0007] 在一方面，本文提供了一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 I 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 I)

其中：

各 R^1 独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NR^4R^{11}、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

m 为 1、2、3 或 4；

B 为 CO_2R^4、CH_2CO_2H、$CH_2CO_2R^4$或任选取代的苯基；

Y 为键、$-(CR^5R^6)-$、$-(CR^7R^8)(CR^9R^{10})-$ 或 $-(CR^7R^8)(CR^9R^{10})X-$；

X 为 O 或 CR^5R^6；

R^2为卤代、$C(O)R^4$、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或 $C(=NOR^4)R^4$；

各 R^3独立地选自 H、CN、卤代、$C(O)R^4$、CO_2H、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和 $C(=NOR^4)R^4$；

各 R^4独立地选自 H 和任选取代的烷基；

各 R^5、R^6、R^7、R^8、R^9和 R^{10}独立地选自 H、卤代、任选取代的烷基、OH、CO_2R^4、NR^4R^{11}和任选取代的烷氧基；且

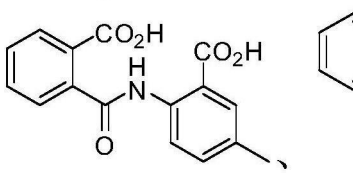
R^{11}为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

条件是

a) 如果 Y 为键且 m 为 0，则 R^2选自 $C(O)NR^4R^{11}$、$(CR^7R^8)OR^4$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和 $C(=NOR^4)R^4$；且

R^2不是 $C(O)NH_2$、$p\text{-}CH_2OR^4$、$p\text{-}CH(OH)CH_2OH$、$p\text{-}CH_2CH_2OH$ 或 $p\text{-}CH_2CH_2CH_2OH$；且

b) 该化合物不选自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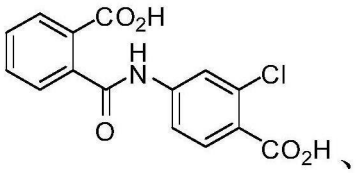
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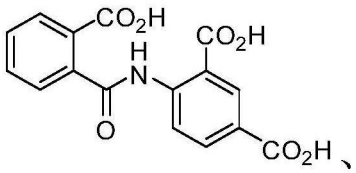
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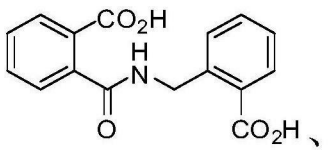
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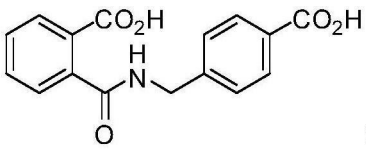
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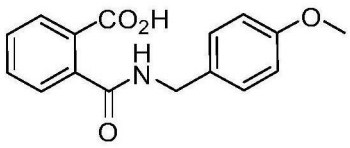
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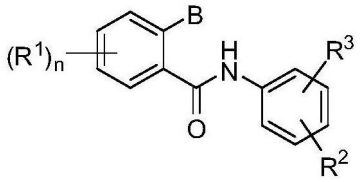
[0008] 在另一方面，本文提供了一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 Ia 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 Ia)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NR^4R^{11}、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 CO_2R^4；

R^2为卤代、$C(O)R^4$、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或 $C(=NOR^4)R^4$；

各 R^3独立地选自 CN、卤代、$C(O)R^4$、CO_2H、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和 $C(=NOR^4)R^4$；

X 为 O 或 CR^5R^6；

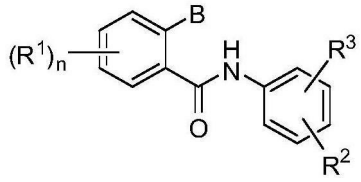
各 R^4独立地选自 H 和任选取代的烷基；

各 R^5、R^6、R^7、R^8、R^9和 R^{10}独立地选自 H、卤代、任选取代的烷基、OH、NR^4R^{11}和任选取代的烷氧基；且

R^{11}为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

条件是该化合物不选自

[0009] 在另一方面，本文提供了一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 Ib 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 Ib)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NR^4R^{11}、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 CO_2R^4；

R^2为 $C(O)NR^4R^{11}$、$(CR^7R^8)OR^4$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或 $C(=NOR^4)R^4$；

R^3为 H；

X 为 O 或 CR^5R^6；

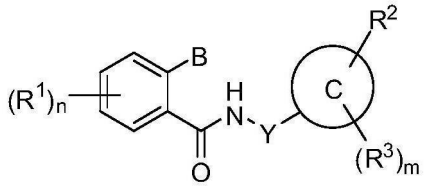
各 R^4独立地选自 H 和任选取代的烷基；

各 R^5、R^6、R^7、R^8、R^9和 R^{10}独立地选自 H、卤代、任选取代的烷基、OH、NR^4R^{11}和任选取代的烷氧基；且

R^{11}为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

条件是如果 n 为 0，则 R^2不是 $C(O)NH_2$、$p\text{-}CH_2OR^4$、$p\text{-}CH(OH)CH_2OH$、$p\text{-}CH_2CH_2OH$ 或 $p\text{-}CH_2CH_2CH_2OH$。

[0010] 在另一方面，本文提供了一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 Ic 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 Ic)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NR^4R^{11}、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

m 为 1、2、3 或 4；

B 为 CO_2R^4；

Y 为 $-(CR^5R^6)-$；

C 为芳基或杂芳基；

X 为 O 或 CR^5R^6；

R^2为卤代、$C(O)R^4$、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、SO_2NH_2、SO_3H、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)$

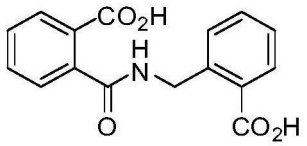
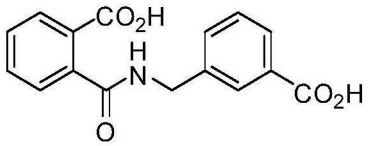
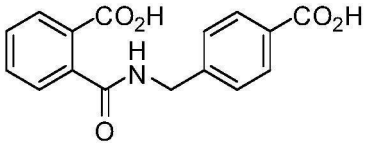
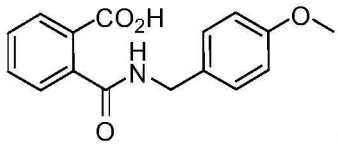
NR^4R^{11}、$(CR^7R^8)NR^4SO_2R^4$或 $C(=NOR^4)R^4$；

各 R^3独立地选自 H、CN、卤代、$C(O)R^4$、CO_2H、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和 $C(=NOR^4)R^4$；

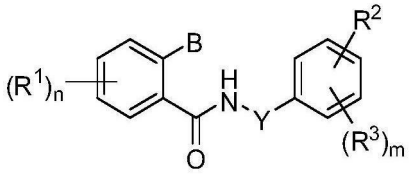
各 R^4独立地选自 H 和任选取代的烷基；

各 R^5、R^6、R^7、R^8、R^9和 R^{10}独立地选自 H、卤代、任选取代的烷基、OH、CO_2R^4、NR^4R^{11}和任选取代的烷氧基；且

R^{11}为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

条件是该化合物不选自  、  、  和  。

[0011] 在另一方面，本文提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 I 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 I)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NR^4R^{11}、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

m 为 1、2、3 或 4；

B 为 CO_2R^4、CH_2CO_2H、$CH_2CO_2R^3$或任选取代的苯基；

Y 为键、$-(CR^5R^6)-$、$-(CR^7R^8)(CR^9R^{10})-$ 或 $-(CR^7R^8)(CR^9R^{10})X-$；

X 为 O 或 CR^5R^6；

R^2为卤代、$C(O)R^4$、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或 $C(=NOR^4)R^4$；

各 R^3独立地选自 H、CN、卤代、$C(O)R^4$、CO_2H、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和 $C(=NOR^4)R^4$；

各 R^4独立地选自 H 和任选取代的烷基；

各 R^5、R^6、R^7、R^8、R^9和 R^{10}独立地选自 H、卤代、任选取代的烷基、OH、CO_2R^4、NR^4R^{11}和任选取代的烷氧基；且

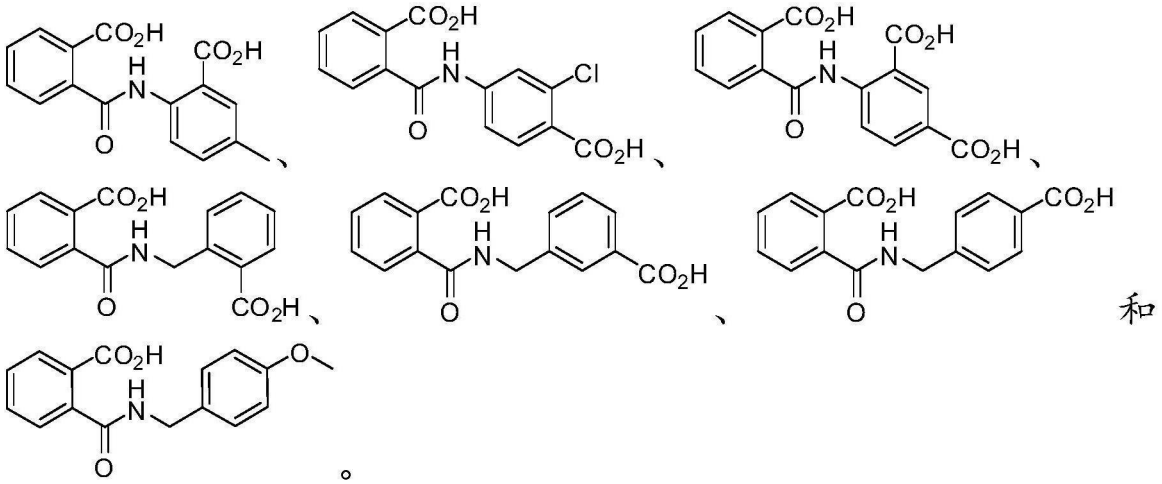
R^{11}为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

条件是

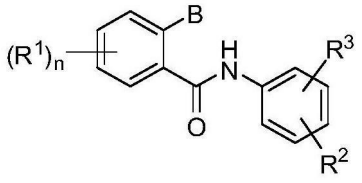
a) 如果 Y 为键且 m 为 0，则 R^2选自 $C(O)NR^4R^{11}$、$(CR^7R^8)OR^4$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和 $C(=NOR^4)R^4$；且

R^2不是 $C(O)NH_2$、$p\text{-}CH_2OR^4$、$p\text{-}CH(OH)CH_2OH$、$p\text{-}CH_2CH_2OH$ 或 $p\text{-}CH_2CH_2CH_2OH$；且

b) 该化合物不选自



[0012] 在另一方面，本文提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 Ia 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 Ia)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NR^4R^{11}、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 CO_2R^4；

R^2为卤代、C(O)R^4、CO_2R^4、C(O)NR^4R^{11}、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或 C(=NOR^4)$R^4$；

各 R^3独立地选自 CN、卤代、C(O)R^4、CO_2H、CO_2R^4、C(O)NR^4R^{11}、烷基、任选取代的烷氧基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和 C(=NOR^4)$R^4$；

X 为 O 或 CR^5R^6；

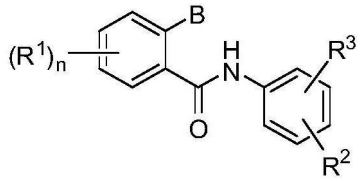
各 R^4独立地选自 H 和任选取代的烷基；

各 R^5、R^6、R^7、R^8、R^9和 R^{10}独立地选自 H、卤代、任选取代的烷基、OH、NR^4R^{11}和任选取代的烷氧基；且

R^{11}为 H、任选取代的烷基、C(O)R^4、C(O)OR^4、C(O)NR^4R^4或 SO_2R^4；

条件是该化合物不选自

[0013] 在另一方面，本文提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 Ib 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N-氧化物、立体异构体或异构体：



(式 Ib)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、S(O)R^4、SO_2R^4、NR^4R^{11}、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 CO_2R^4；

R^2为 C(O)NR^4R^{11}、$(CR^7R^8)OR^4$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或 C(=NOR^4)$R^4$；

R^3为 H；

X 为 O 或 CR^5R^6；

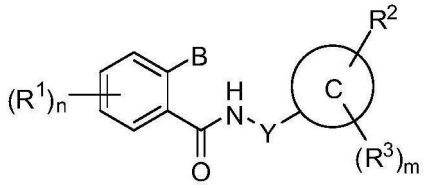
各 R^4独立地选自 H 和任选取代的烷基；

各 R^5、R^6、R^7、R^8、R^9和 R^{10}独立地选自 H、卤代、任选取代的烷基、OH、NR^4R^{11}和任选取代的烷氧基；且

R^{11}为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

条件是如果 n 为 4 且 R^1为 H，则 R^2不是 $C(O)NH_2$、$p\text{-}CH_2OR^4$、$p\text{-}CH(OH)CH_2OH$、$p\text{-}CH_2CH_2OH$或 $p\text{-}CH_2CH_2CH_2OH$。

[0014] 在另一方面，本文提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 Ic 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 Ic)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NR^4R^{11}、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

m 为 1、2、3 或 4；

B 为 CO_2R^4；

Y 为 $-(CR^5R^6)-$；

C 为芳基或杂芳基；

X 为 O 或 CR^5R^6；

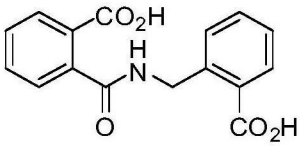
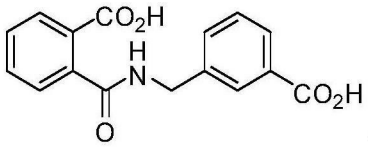
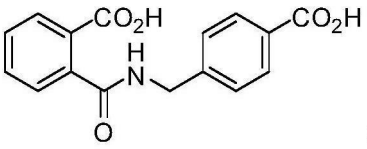
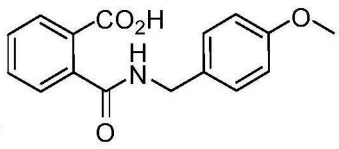
R^2为卤代、$C(O)R^4$、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、SO_2NH_2、SO_3H、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或 $C(=NOR^4)R^4$；

各 R^3独立地选自 H、CN、卤代、$C(O)R^4$、CO_2H、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和 $C(=NOR^4)R^4$

各 R^4独立地选自 H 和任选取代的烷基；

各 R^5、R^6、R^7、R^8、R^9和 R^{10}独立地选自 H、卤代、任选取代的烷基、OH、CO_2R^4、NR^4R^{11}和任选取代的烷氧基；且

R^{11}为H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或SO_2R^4；

条件是该化合物不选自  、  、  和  。

[0015] 在式I或Ia化合物的上文或下文描述的一些实施方案中：

R^2为卤代、$C(O)R^4$、烷基、任选取代的烷氧基、卤代烷基、$(CR^7R^8)OR^4$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)C(O)OR^4$或$X(CR^7R^8)C(O)NR^4R^{11}$；且

各R^3独立地选自CN、卤代、$C(O)R^4$、CO_2H、$C(O)NR^4R^{11}$、烷基或任选取代的烷氧基；

或者R^3与相邻的R^3或与R^2一起形成环。

[0016] 在式I或Ia化合物的上文或下文描述的某些实施方案中：

R^2为F、Cl、$C(O)CH_3$、CH_3、CF_3、OCH_3、OEt、OPr、OCF_3、$OCHF_2$、$(CR^7R^8)OR^4$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)C(O)OR^4$或$X(CR^7R^8)C(O)NR^4R^{11}$；且

各R^3独立地选自CN、F、Cl、$C(O)CH_3$、CO_2H、$C(O)NH_2$、CH_3、OCF_3或OCH_3；

或者R^3与相邻的R^3或与R^2一起形成环。

在某些实施方案中，R^3独立地选自CN、F、Cl、$C(O)CH_3$或CO_2H。在某些实施方案中，R^2为F、Cl、$C(O)CH_3$、CH_3、CF_3、OCH_3、OEt、OPr、OCF_3或$CH_2CH_2CH_2OH$。

[0017] 在式Ib化合物的上文或下文描述的一些实施方案中：

R^2为$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或$C(=NOR^4)R^4$；且

R^3为H。

在某些实施方案中，R^2为$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$或$(CR^7R^8)NR^4SO_2R^4$。在某些实施方案中，$R^2$为$CH_2CH_2OH$、$CH_2CH_2OCH_3$、$CH_2CHCH_3OH$、$CHCH_3CH_2OH$、$CH_2CH_2CH_2OH$、$CH_2CH_2CH_2NH_2$、$CH_2CH_2CHCH_3OH$、$C(CH_3)_2CH_2CH_2OH$、$CH_2CH_2C(CH_3)_2OH$、$OCH_2CH_2OH$、$OCH_2CH_2OCH_3$或$OCH_2CH_2NH_2$。在某些实施方案中，$R^2$为$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$或$X(CR^7R^8)C(O)NR^4R^{11}$。在某些实施方案中，$R^2$为$CH_2C(O)CH_3$、$CH_2C(O)NH_2$、$CH_2CH_2C(O)CH_3$或$CH_2CH_2C(O)NH_2$。

[0018] 在式Ic化合物的上文或下文描述的一些实施方案中，C为芳基。在某些实施方案中，C为苯基。

[0019] 在式Ic化合物的上文或下文描述的一些实施方案中，C为杂芳基。在某些实施方案中，C为吡啶基、嘧啶基、哒嗪基或吡嗪基。

[0020] 在式Ic化合物的上文或下文描述的一些实施方案中：

R^2为卤代、$C(O)R^4$、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、卤代烷基、SO_2NH_2、SO_3H、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)OR^4$或$X(CR^7R^8)C(O)NR^4R^{11}$；且

各R^3独立地选自H、CN、卤代、CO_2H或卤代烷基。

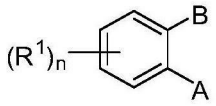
[0021] 在式 Ic 化合物的上文或下文描述的某些实施方案中：

R^2为 Cl、F、C(O)CH_3、CO_2H、C(O)NR^4R^{11}、CH_3、任选取代的烷氧基、CF_3、SO_2NH_2、SO_3H、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)OR^4$或 $X(CR^7R^8)C(O)NR^4R^{11}$；且

各 R^3独立地选自 H、CN、Cl、F、CO_2H 或 CF_3。

在某些实施方案中，R^2为 Cl、F、C(O)CH_3、CO_2H、CH_3、OCH_3、CF_3；且各 R^3独立地选自 H、CN 或 CO_2H。在某些实施方案中，R^2为 $CH_2C(O)NH_2$、$CH_2C(O)CH_3$、$CH_2C(O)OH$、$CH_2CH_2C(O)OH$ 或 $CH_2CH_2C(O)NH_2$。

[0022] 在一方面，本文提供了一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 II 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 II)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 $NHC(O)R^2$、$NR^3C(O)R^2$、$NHC(O)NH_2$、$NHC(O)NHR^2$、$NHC(O)NR^2R^4$、$NR^3C(O)NH_2$、$NR^3C(O)NHR^2$、$NR^3C(O)NR^2R^4$、$NHC(O)OR^2$、$NR^3C(O)OR^2$、$NHSO_2R^3$、$NR^3SO_2R^3$、$NHSO_2R^4$、$NR^3SO_2R^4$、$NHSO_2NH_2$、$NHSO_2NHR^2$、$NHSO_2NR^2R^4$、$NR^3SO_2NH_2$、$NR^3SO_2NHR^2$或 $NR^3SO_2NR^2R^4$；

各 R^2和 R^4独立地为任选取代的苯基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳烷基或任选取代的烷基；

R^3为任选取代的烷基或任选取代的芳烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

A 为 CO_2H、CO_2R^3、$C(O)NH_2$、$C(O)NHR^2$、$C(O)NR^2R^4$或 $SO_2NR^aR^b$；且

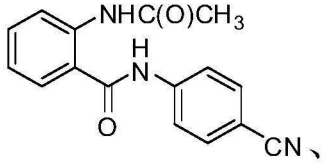
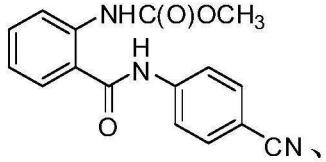
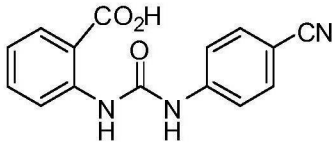
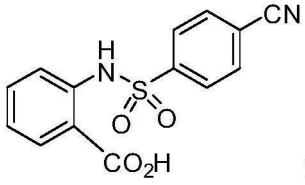
各 R^a和 R^b独立地为任选取代的烷基或者与它们所连接的 N 一起形成环；

条件是

a) 如果 B 为 $NHC(O)R^2$或 $NR^3C(O)R^2$，则 A 不是 CO_2H；且

b) 该化合物不选自

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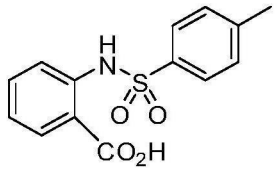
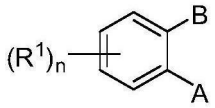

。

[0023] 在另一方面，本文提供了一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 IIa 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 IIa)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

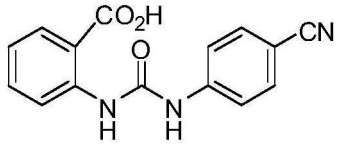
B 为 $NHC(O)NH_2$、$NHC(O)NHR^2$、$NHC(O)NR^2R^4$、$NR^3C(O)NH_2$、$NR^3C(O)NHR^2$或 $NR^3C(O)NR^2R^4$；

各 R^2和 R^4独立地为任选取代的苯基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳烷基或任选取代的烷基；

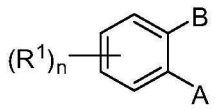
R^3为任选取代的烷基或任选取代的芳烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；且

A 为 CO_2H 或 CO_2R^3；

条件是该化合物不是 
。

[0024] 在另一方面，本文提供了一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 IIb 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 IIb)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 $NHC(O)R^2$或 $NR^3C(O)R^2$；

R^2为任选取代的苯基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳烷基或任选取代的烷基；

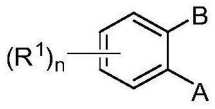
R^3为任选取代的烷基或任选取代的芳烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

A 为 $SO_2NR^aR^b$；且

各 R^a和 R^b独立地为任选取代的烷基或者与它们所连接的 N 一起形成环。

[0025] 在另一方面，本文提供了一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 IIc 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 IIc)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

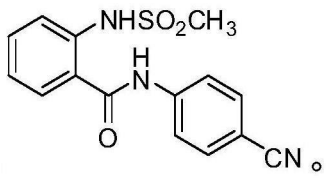
B 为 $NHSO_2R^3$、$NR^3SO_2R^3$、$NHSO_2R^4$、$NR^3SO_2R^4$、$NHSO_2NH_2$、$NHSO_2NHR^2$、$NHSO_2NR^2R^4$、$NR^3SO_2NH_2$、$NR^3SO_2NHR^2$或 $NR^3SO_2NR^2R^4$；

各 R^2和 R^4独立地为任选取代的苯基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳烷基或任选取代的烷基；

各 R^3独立地为任选取代的烷基或任选取代的芳烷基；

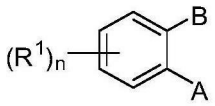
R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；且

A 为 $C(O)NHR^2$或 $C(O)NR^2R^4$；

条件是该化合物不是  。

[0026] 在另一方面，本文提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 II 化合物或其药学上可接受的盐、溶剂化物、多晶型

物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 II)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 $NHC(O)R^2$、$NR^3C(O)R^2$、$NHC(O)NH_2$、$NHC(O)NHR^2$、$NHC(O)NR^2R^4$、$NR^3C(O)NH_2$、$NR^3C(O)NHR^2$、$NR^3C(O)NR^2R^4$、$NHC(O)OR^2$、$NR^3C(O)OR^2$、$NHSO_2R^3$、$NR^3SO_2R^3$、$NHSO_2R^4$、$NR^3SO_2R^4$、$NHSO_2NH_2$、$NHSO_2NHR^2$、$NHSO_2NR^2R^4$、$NR^3SO_2NH_2$、$NR^3SO_2NHR^2$或 $NR^3SO_2NR^2R^4$；

各 R^2和 R^4独立地为任选取代的苯基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳烷基或任选取代的烷基；

R^3为任选取代的烷基或任选取代的芳烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

A 为 CO_2H、CO_2R^3、$C(O)NH_2$、$C(O)NHR^2$、$C(O)NR^2R^4$或 $SO_2NR^aR^b$；且

各 R^a和 R^b独立地为任选取代的烷基或者与它们所连接的 N 一起形成环；

条件是

a) 如果 B 为 $NHC(O)R^2$或 $NR^3C(O)R^2$，则 A 不是 CO_2H；且

b) 该化合物不选自

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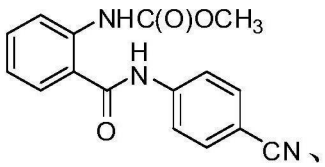

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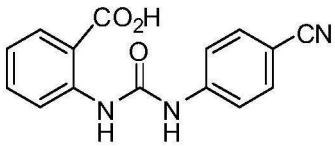
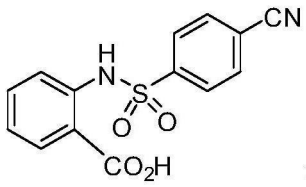
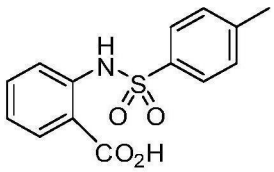


、


和


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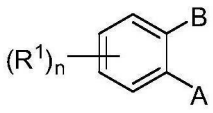
[0027] 在另一方面，本文提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 IIa 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 IIa)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

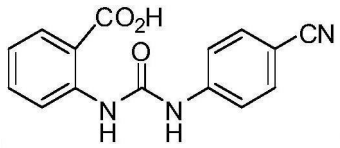
B 为 $NHC(O)NH_2$、$NHC(O)NHR^2$、$NHC(O)NR^2R^4$、$NR^3C(O)NH_2$、$NR^3C(O)NHR^2$或 $NR^3C(O)NR^2R^4$；

各 R^2和 R^4独立地为任选取代的苯基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳烷基或任选取代的烷基；

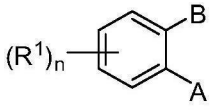
R^3为任选取代的烷基或任选取代的芳烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；且

A 为 CO_2H 或 CO_2R^3；

条件是该化合物不是  。

[0028] 在另一方面，本文提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 IIb 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 IIb)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 $NHC(O)R^2$或 $NR^3C(O)R^2$；

R^2为任选取代的苯基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳烷基或任选取代的烷基；

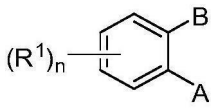
R^3为任选取代的烷基或任选取代的芳烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

A 为 $SO_2NR^aR^b$；且

各 R^a和 R^b独立地为任选取代的烷基或者与它们所连接的 N 一起形成环。

[0029] 在另一方面，本文提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 IIc 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 IIc)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 $NHSO_2R^3$、$NR^3SO_2R^3$、$NHSO_2R^4$、$NR^3SO_2R^4$、$NHSO_2NH_2$、$NHSO_2NHR^2$、$NHSO_2NR^2R^4$、$NR^3SO_2NH_2$、$NR^3SO_2NHR^2$或 $NR^3SO_2NR^2R^4$；

各 R^2和 R^4独立地为任选取代的苯基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳烷基或任选取代的烷基；

各 R^3独立地为任选取代的烷基或任选取代的芳烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；且

A 为 $C(O)NHR^2$或 $C(O)NR^2R^4$；

条件是该化合物不是  。

[0030] 在式 IIa 化合物的上文或下文描述的一些实施方案中，B 为 $NHC(O)NHR^2$、$NHC(O)NR^2R^4$、$NR^3C(O)NHR^2$或 $NR^3C(O)NR^2R^4$。在某些实施方案中，B 为 $NHC(O)NHR^2$或 $NR^3C(O)NHR^2$。在某些实施方案中，B 为 $NHC(O)NR^2R^4$或 $NR^3C(O)NR^2R^4$。在某些实施方案中，B 为 $NHC(O)NHR^2$。

[0031] 在式 IIa 化合物的上文或下文描述的一些实施方案中，R^2为任选取代的苯基。在某些实施方案中，R^2的苯基为双取代的。在某些实施方案中，R^2的苯基为单取代的。在某些实施方案中，R^2的苯基独立地选自 F、Cl、CO_2H、CN、OCH_3、$C(O)CH_3$、CF_3、CH_3、CH_2OH、CH_2CH_2OH和 $CH_2CH_2CH_2OH$。

[0032] 在式 IIb 化合物的上文或下文描述的一些实施方案中，B 为 $NHC(O)R^2$。

[0033] 在式 IIb 化合物的上文或下文描述的一些实施方案中，B 为 $NR^3C(O)R^2$。在某些实施方案中，R^3为任选取代的烷基。

[0034] 在式 IIb 化合物的上文或下文描述的一些实施方案中，各 R^a和 R^b独立地为任选取代的烷基。在式 IIb 化合物的上文或下文描述的一些实施方案中，R^a和 R^b与它们所连接的 N 一起形成环。

[0035] 在式 IIb 化合物的上文或下文描述的一些实施方案中，R^2为任选取代的苯基。在某些实施方案中，R^2的苯基为双取代的。在某些实施方案中，R^2的苯基为单取代的。在某些实施方案中，R^2的苯基上的取代独立地选自 F、Cl、CO_2H、CN、OCH_3、$C(O)CH_3$、CF_3、CH_3、CH_2OH、CH_2CH_2OH 和 $CH_2CH_2CH_2OH$。

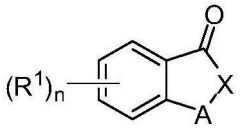
[0036] 在式 IIc 化合物的上文或下文描述的一些实施方案中，B 为 $NHSO_2R^3$、$NR^3SO_2R^3$、$NHSO_2R^4$或 $NR^3SO_2R^4$。在某些实施方案中，B 为 $NHSO_2R^3$或 $NR^3SO_2R^3$。在某些实施方案中，B 为 $NHSO_2R^3$。在某些实施方案中，R^3为任选取代的烷基。在某些实施方案中，R^3为 CH_3。在某些

实施方案中，B 为 $NHSO_2R^4$ 或 $NR^3SO_2R^4$。在某些实施方案中，R^4 为任选取代的苯基。

[0037] 在式 IIc 化合物的上文或下文描述的一些实施方案中，B 为 $NHSO_2NH_2$、$NHSO_2NHR^2$、$NHSO_2NR^2R^4$、$NR^3SO_2NH_2$、$NR^3SO_2NHR^2$ 或 $NR^3SO_2NR^2R^4$。

[0038] 在式 IIc 化合物的上文或下文描述的一些实施方案中，A 为 $C(O)NHR^2$。在式 IIc 化合物的上文或下文描述的一些实施方案中，A 为 $C(O)NR^2R^4$。在某些实施方案中，R^2 为任选取代的苯基。在某些实施方案中，R^2 的苯基为双取代的。在某些实施方案中，R^2 的苯基为单取代的。在某些实施方案中，R^2 的苯基上的取代独立地选自 F、Cl、CO_2H、CN、OCH_3、$C(O)CH_3$、CF_3、CH_3、CH_2OH、CH_2CH_2OH 和 $CH_2CH_2CH_2OH$。

[0039] 在另一方面，本文提供了一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 III 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 III)

其中

各 R^1 独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

X 为 O、NH 或 NR^6；

A 为 C(O)、CH_2 或 $CH-CR^3R^4-C(O)R^2$；

R^2 为任选取代的芳基或任选取代的杂芳基；

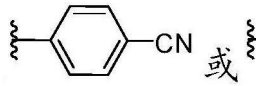
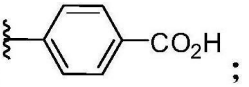
各 R^3 和 R^4 独立地为 H 或任选取代的烷基；

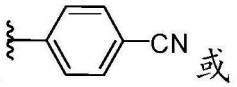
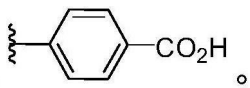
R^5 为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$ 或 SO_2R^4；且

R^6 为任选取代的苯基；

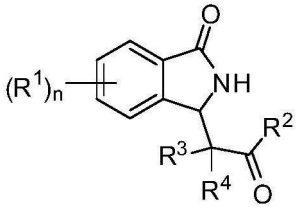
条件是

a) 如果 A 为 $CH-CR^3R^4-C(O)R^2$，则 X 为 O 或 NH；

b) 如果 n 为 0，A 为 $CHCH_2C(O)R^2$ 且 X 为 O，则 R^2 不是  或  ；且

c) 如果 A 为 C(O) 或 CH_2，则 X 为 NR^6 且 R^6 不是  或  。

[0040] 在另一方面，本文提供了一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 IIIa 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 IIIa)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

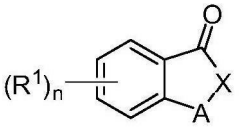
n 为 0、1、2、3 或 4；

R^2为任选取代的芳基或任选取代的杂芳基；

各 R^3和 R^4独立地为 H 或任选取代的烷基；且

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4。

[0041] 在另一方面，本文提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 III 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 III)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

X 为 O、NH 或 NR^6；

A 为 C(O)、CH_2或 $CH-CR^3R^4-C(O)R^2$；

R^2为任选取代的芳基或任选取代的杂芳基；

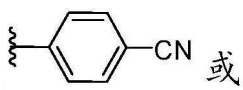
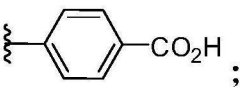
各 R^3和 R^4独立地为 H 或任选取代的烷基；

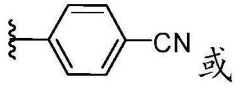
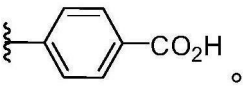
R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；且

R^6为任选取代的苯基；

条件是

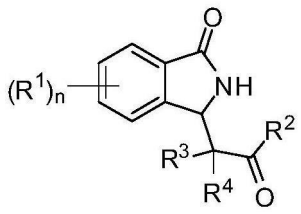
a) 如果 A 为 $CH-CR^3R^4-C(O)R^2$，则 X 为 O 或 NH；

b) 如果 n 为 0，A 为 $CHCH_2C(O)R^2$且 X 为 O，则 R^2不是  或  ；且

c) 如果 A 为 C(O) 或 CH_2，则 X 为 NR^6且 R^6不是  或  。

[0042] 在另一方面，本文提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法

包括使间充质干细胞接触足量的式 IIIa 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 IIIa)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

R^2为任选取代的芳基或任选取代的杂芳基；

各 R^3和 R^4独立地为 H 或任选取代的烷基；且

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4。

[0043] 在式 III 化合物的上文或下文描述的一些实施方案中，X 为 NR^6且 A 为 C(O)。在式 III 化合物的上文或下文描述的一些实施方案中，X 为 NR^6且 A 为 CH_2。在式 III 化合物的上文或下文描述的一些实施方案中，X 为 O 且 A 为 $CH\text{-}CR^3R^4\text{-}C(O)R^2$。在式 III 化合物的上文或下文描述的一些实施方案中，X 为 NH 且 A 为 $CH\text{-}CR^3R^4\text{-}C(O)R^2$。

[0044] 在式 III 或 IIIa 化合物的上文或下文描述的一些实施方案中，R^3和 R^4均为氢。在式 III 或 IIIa 化合物的上文或下文描述的一些实施方案中，R^3为任选取代的烷基且 R^4为氢。在式 III 或 IIIa 化合物的上文或下文描述的一些实施方案中，R^3和 R^4独立地为任选取代的烷基。

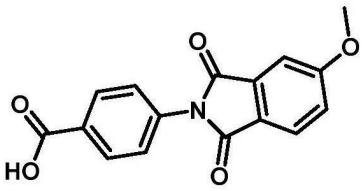
[0045] 在式 III 或 IIIa 化合物的上文或下文描述的一些实施方案中，R^2为任选取代的杂芳基。在某些实施方案中，R^2为任选取代的吡啶基、任选取代的嘧啶基、任选取代的哒嗪基或任选取代的吡嗪基。

[0046] 在式 III 或 IIIa 化合物的上文或下文描述的一些实施方案中，R^2为苯基。在某些实施方案中，R^2的苯基为双取代的。在某些实施方案中，R^2的苯基为单取代的。在某些实施方案中，苯基上的取代独立地选自 F、Cl、CO_2H、CN、OCH_3、$C(O)CH_3$、CF_3、CH_3、CH_2OH、CH_2CH_2OH和 $CH_2CH_2CH_2OH$。

[0047] 在本文公开的化合物的上文或下文描述的一些实施方案中，B 为 CO_2R^4且 R^4为任选取代的烷基。在本文公开的化合物的上文或下文描述的一些实施方案中，B 为 CO_2R^4且 R^4为氢。

[0048] 在本文公开的化合物的上文或下文描述的一些实施方案中，n 为 0、1 或 2。在某些实施方案中，n 为 0。在某些实施方案中，n 为 1。在某些实施方案中，R^1独立地选自 Cl、F、CH_2OH、CH_2NH_2、OCH_3、OCF_3、$OCHF_2$、CN、NO_2、CO_2H 和 CO_2CH_3。

[0049] 在一方面，本文提供了一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物，该化合物选自：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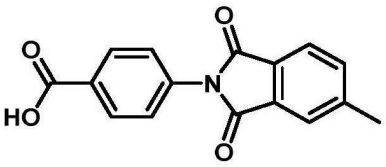
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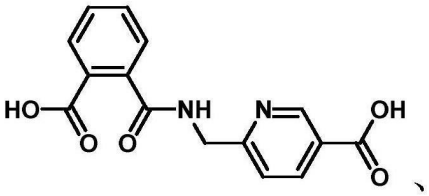
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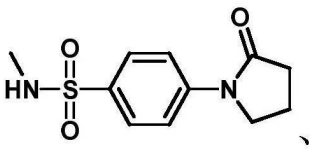
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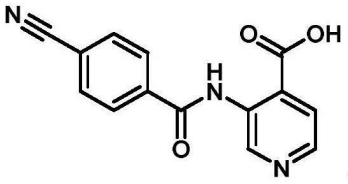
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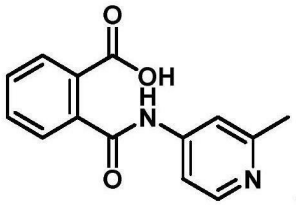
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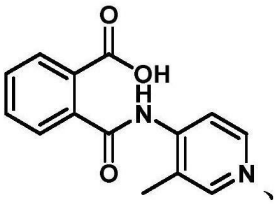
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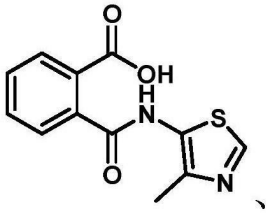
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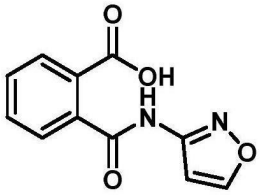
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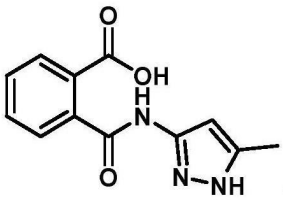
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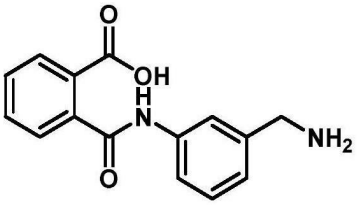
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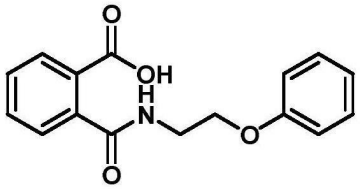
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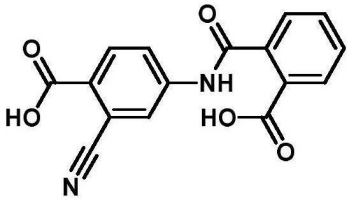
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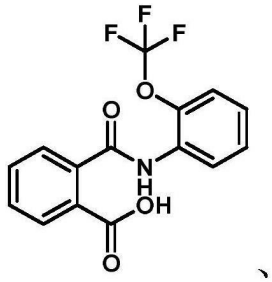
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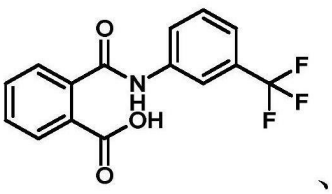
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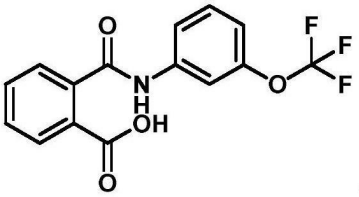
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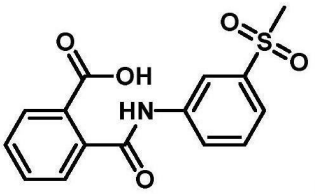
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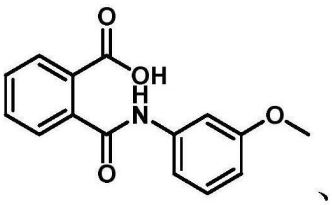
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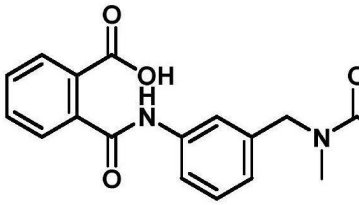
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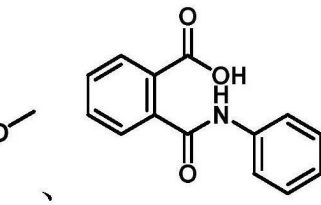
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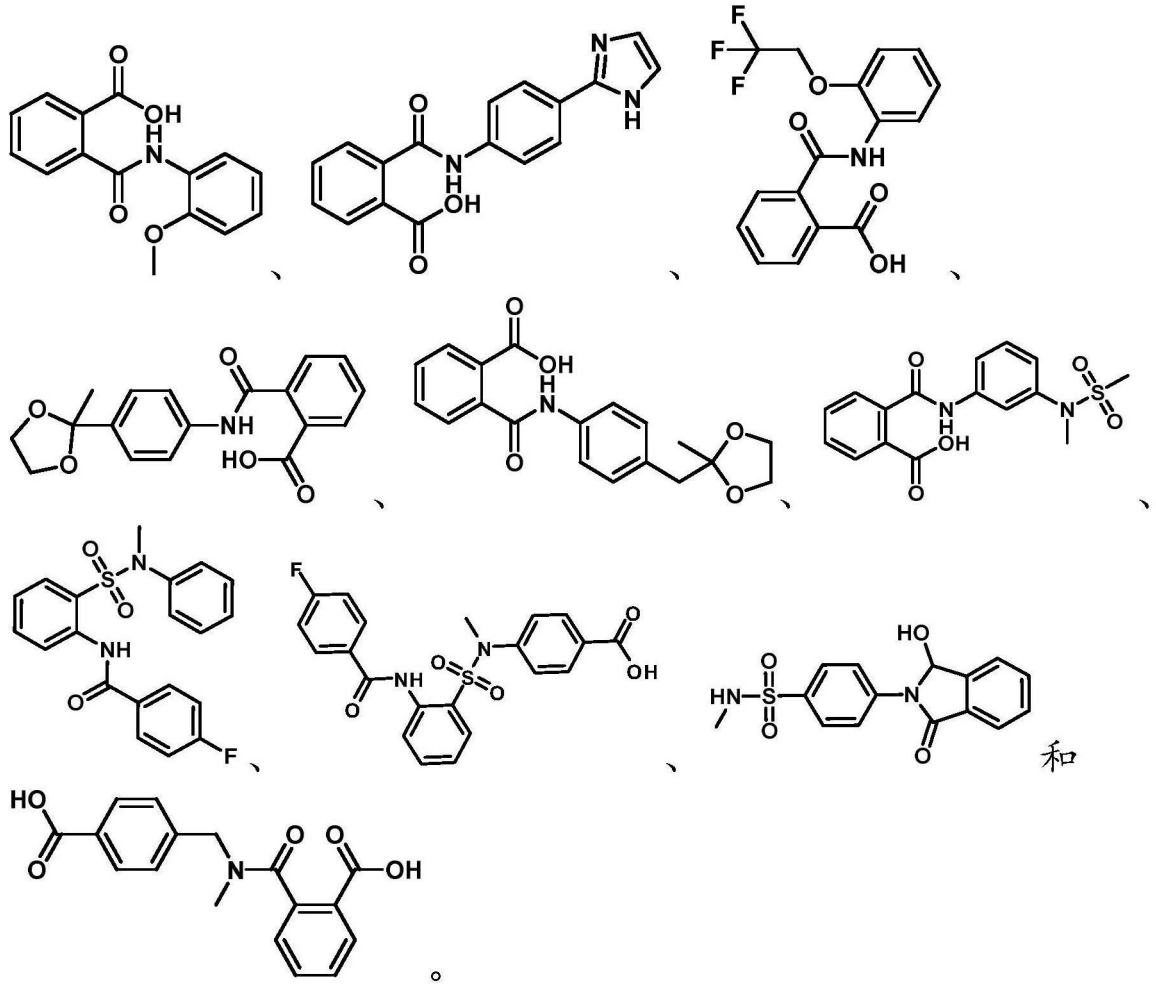
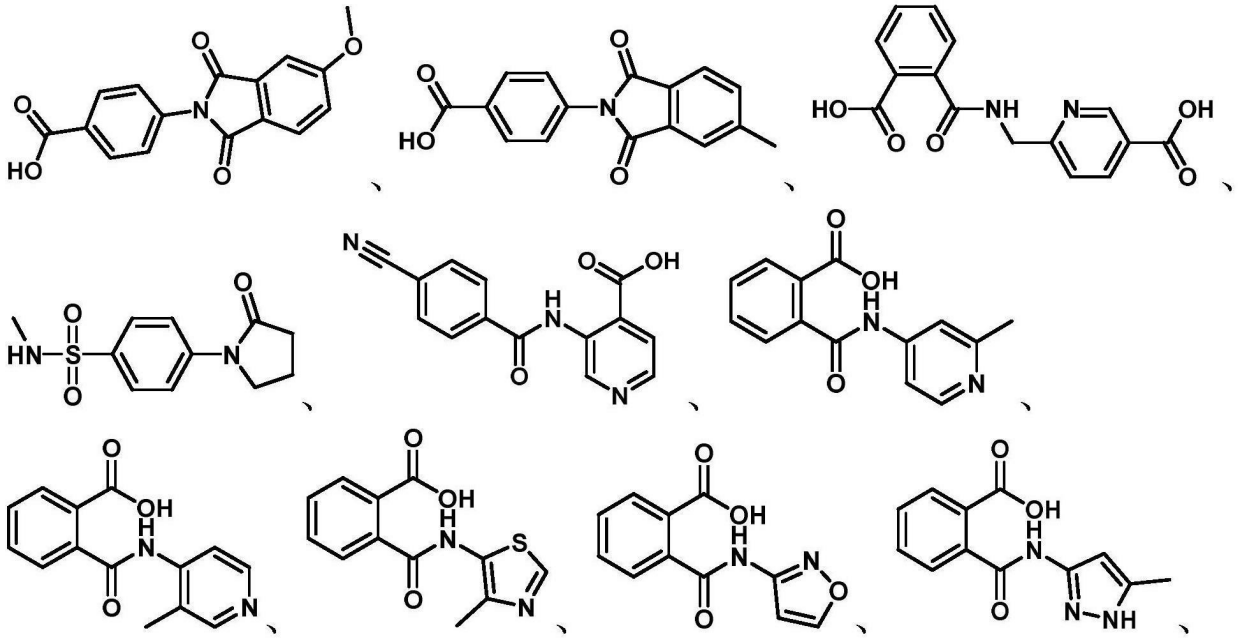
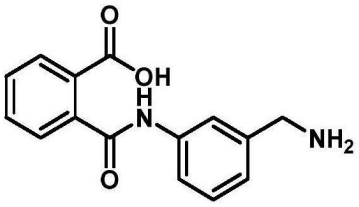


和

[0050] 在另一方面，本文提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体，该化合物选自：

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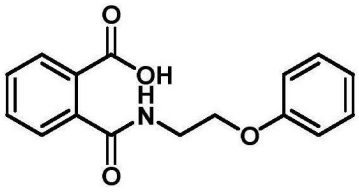
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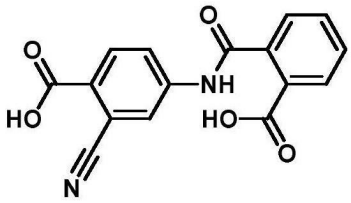
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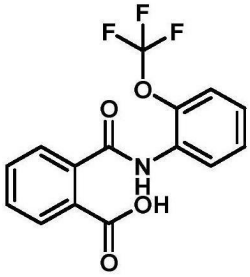
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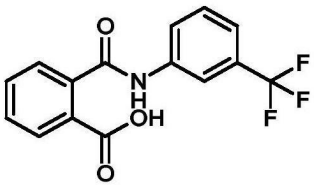
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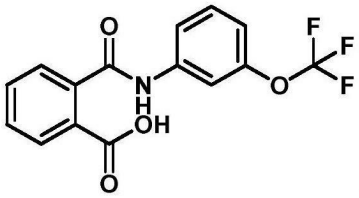
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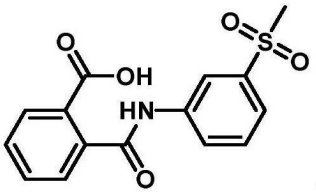
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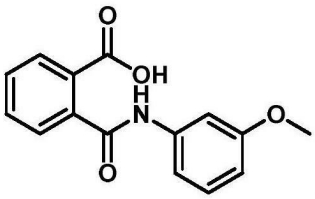
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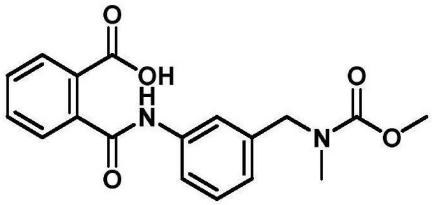
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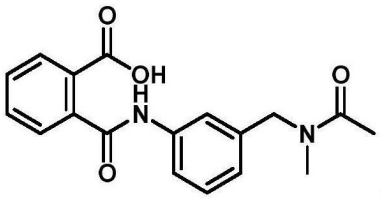
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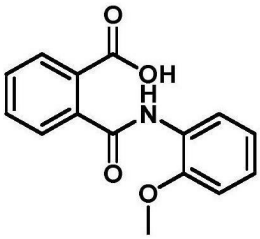
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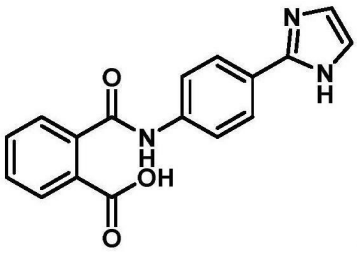
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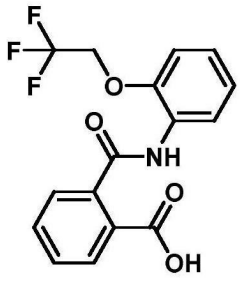
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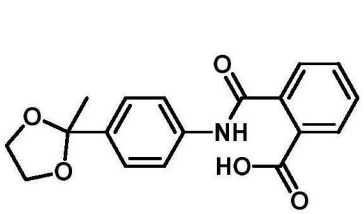
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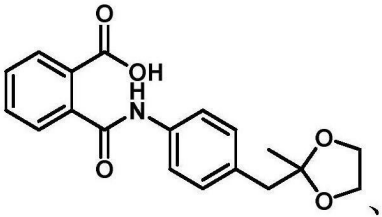
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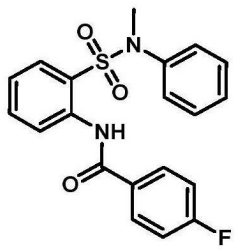
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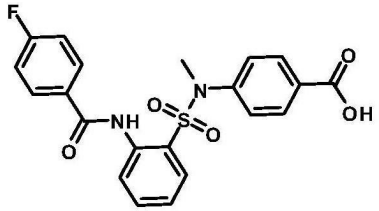
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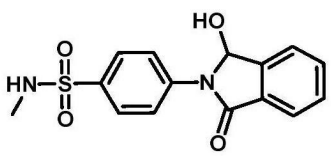
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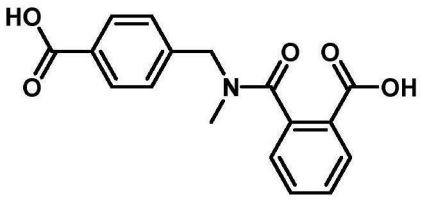

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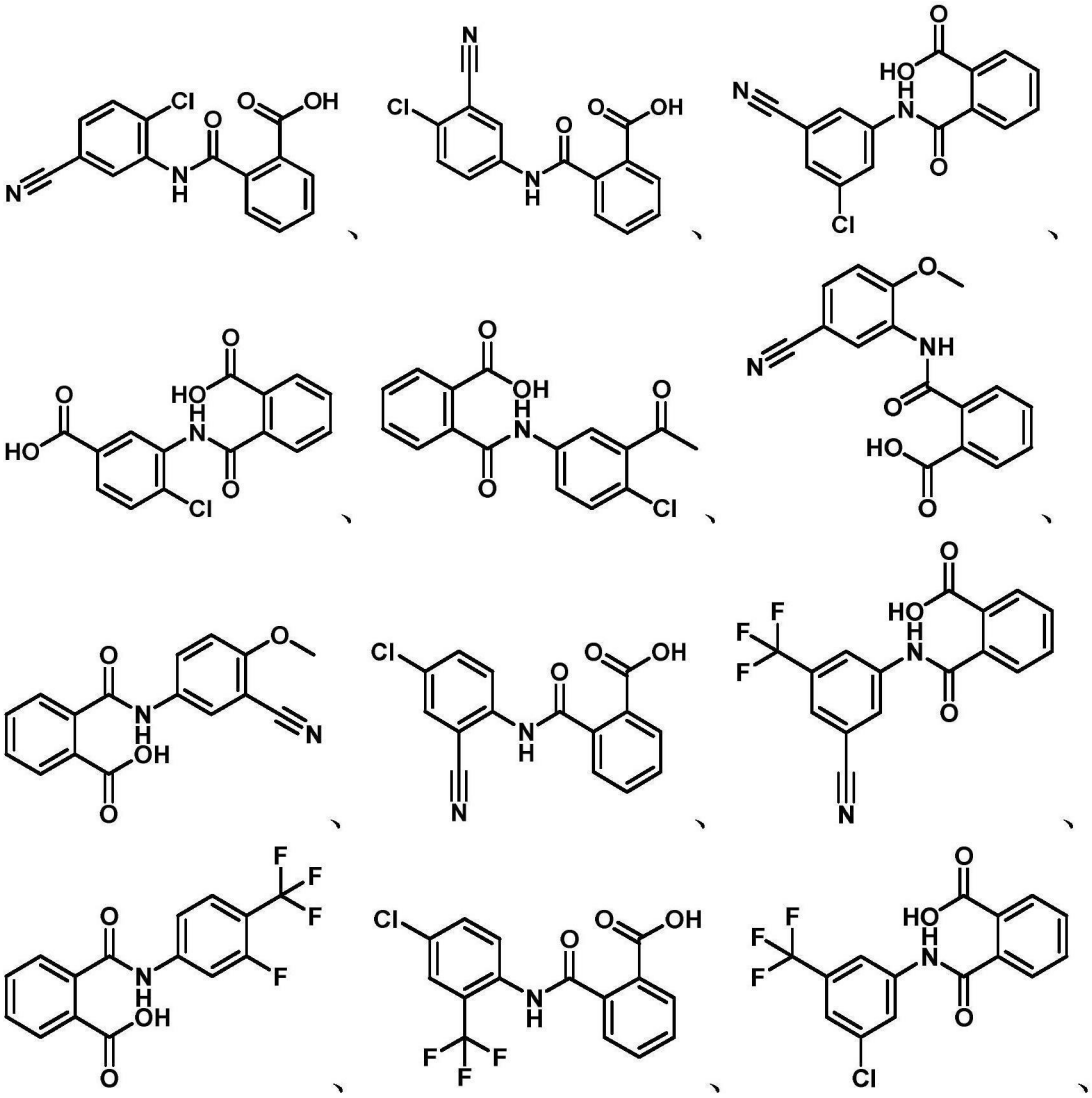
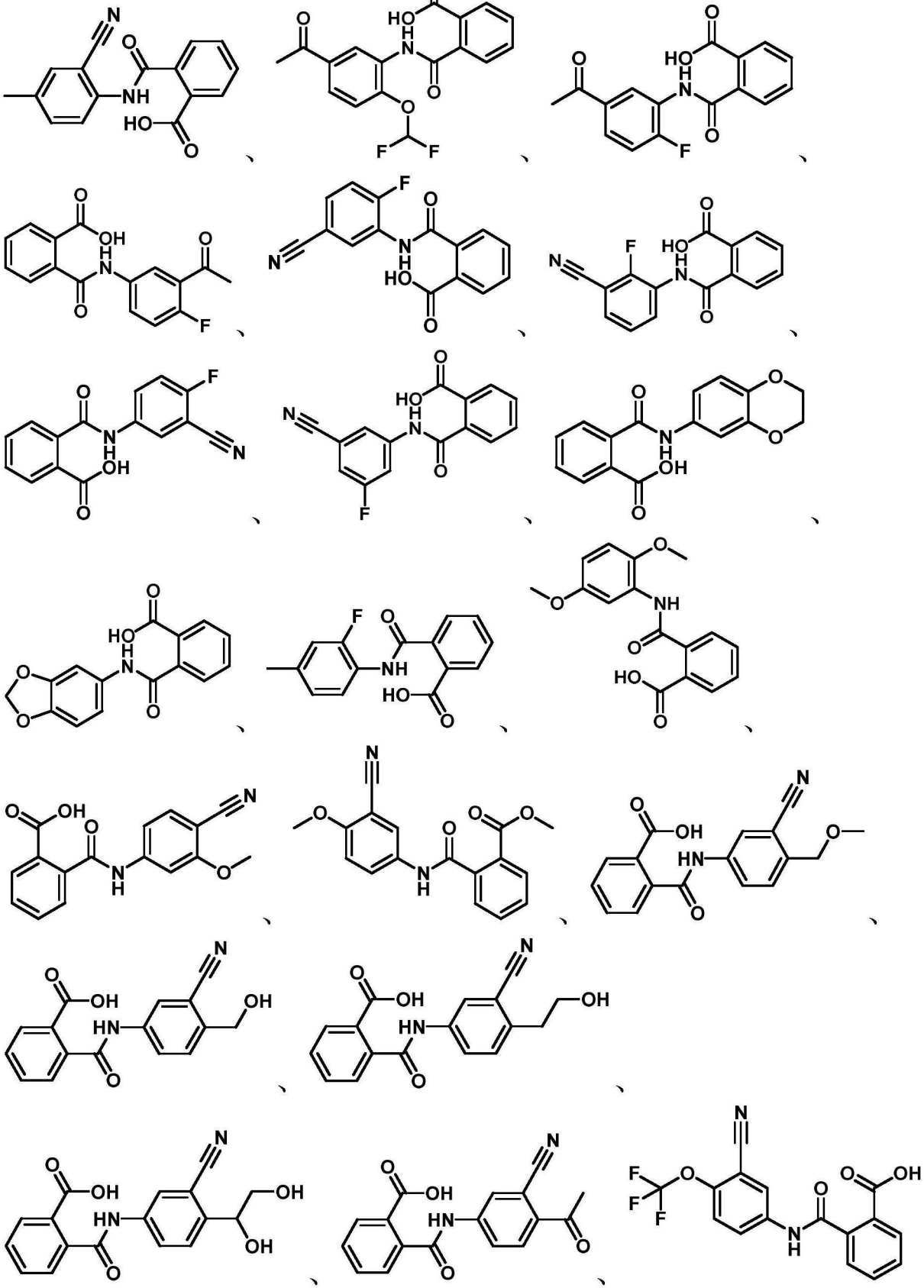
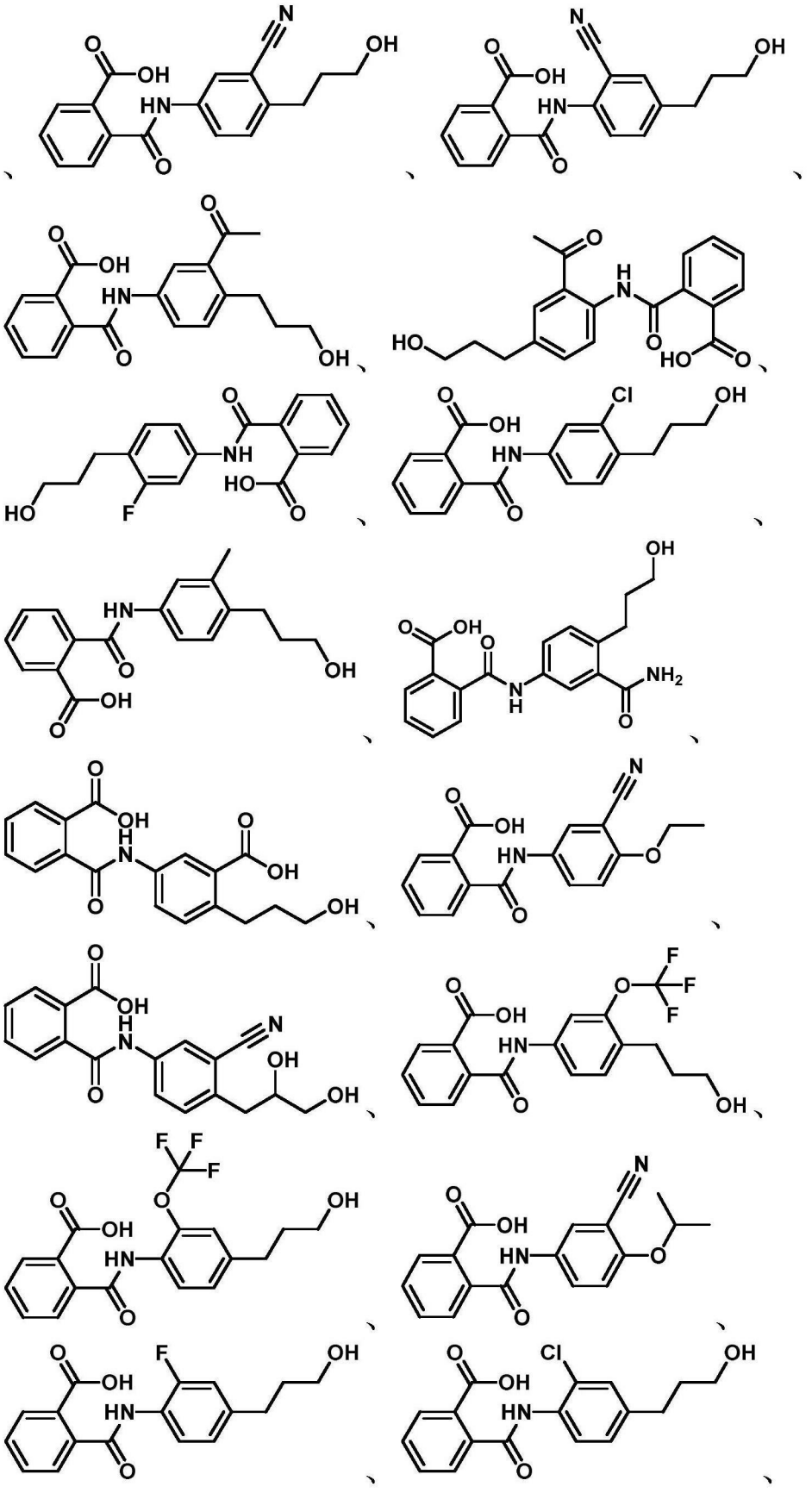
[0051] 在以上描述的一些实施方案中，所述方法在体外进行。

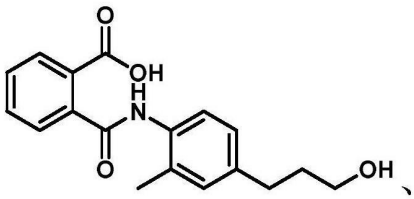
[0052] 在以上描述的一些实施方案中，所述方法在哺乳动物体内进行，并且所述干细胞存在于哺乳动物中。在一些实施方案中，该哺乳动物是驯养动物或家畜。在某些实施方案中，该哺乳动物是人、狗、猫或马。

[0053] 在一方面，本文提供了式 I 的化合物，或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体，该化合物选自 ：





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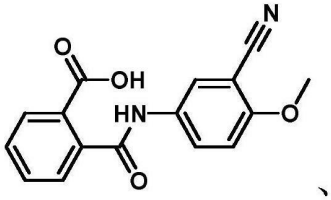
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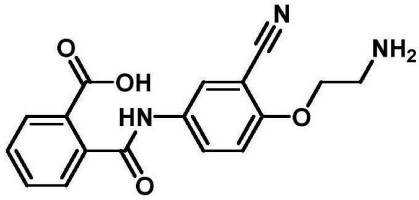
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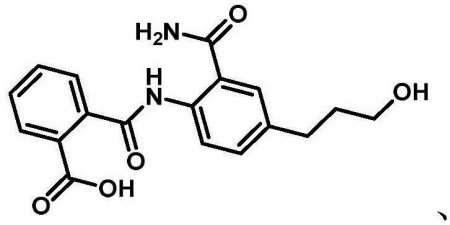
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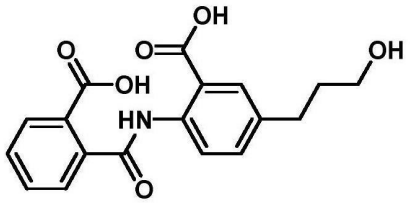
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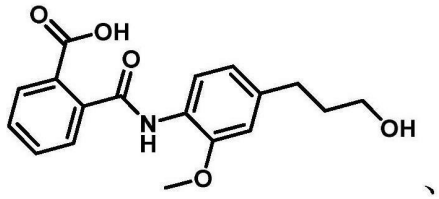
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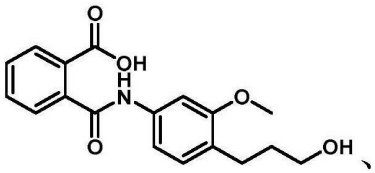
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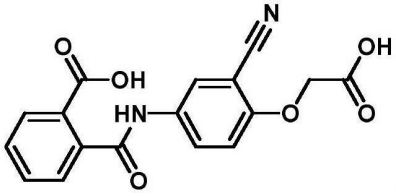
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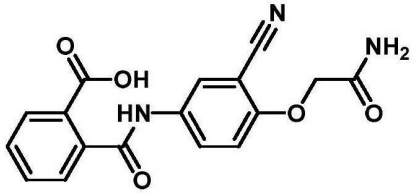
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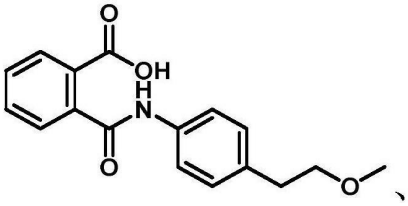
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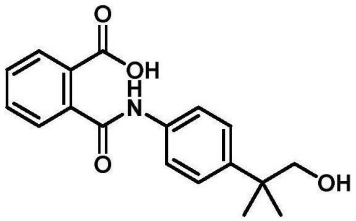
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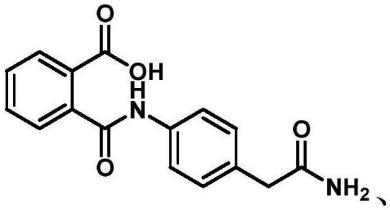
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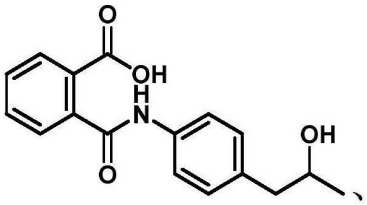
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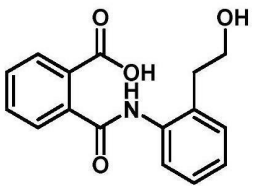
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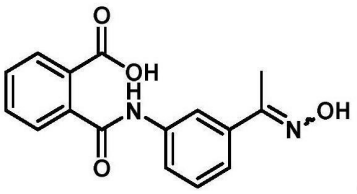
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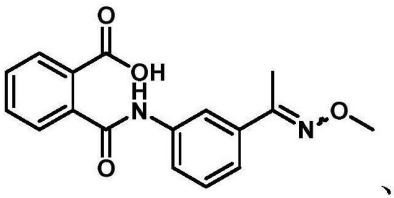
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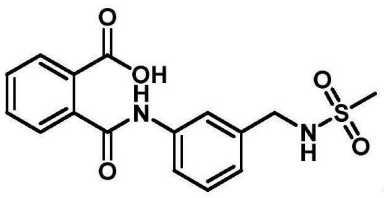
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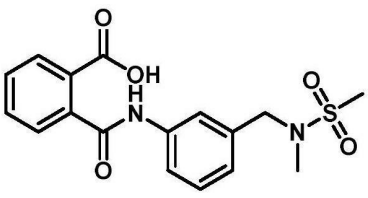
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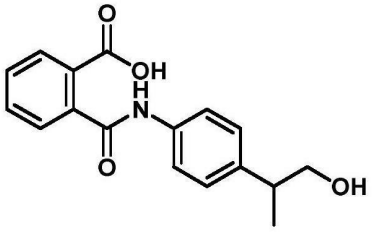
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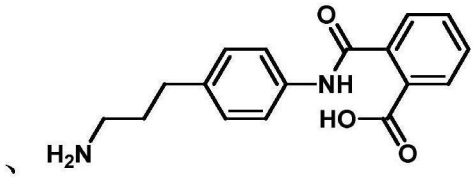
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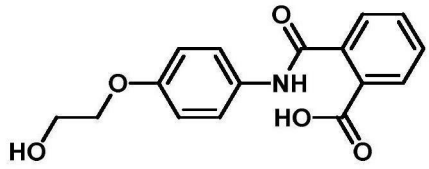
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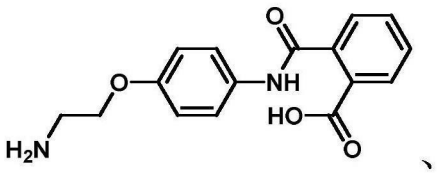
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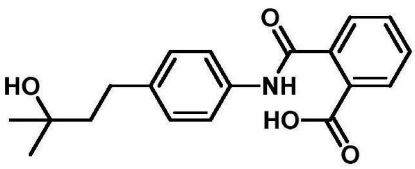
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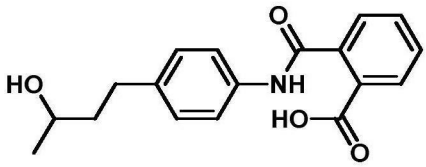
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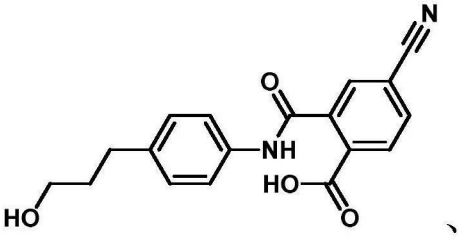
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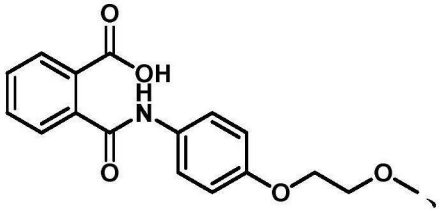
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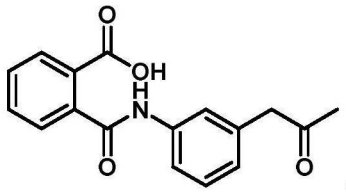
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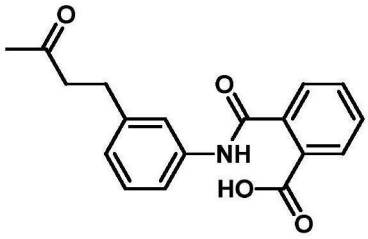
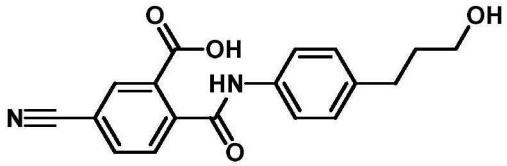
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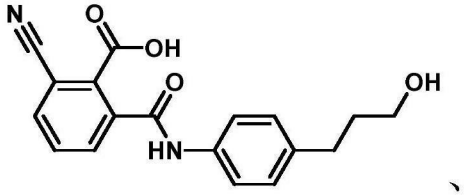
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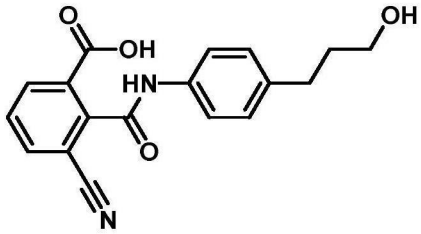
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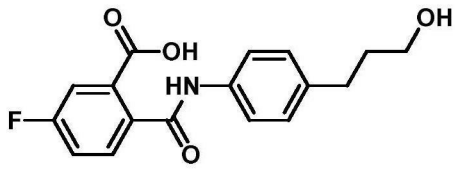
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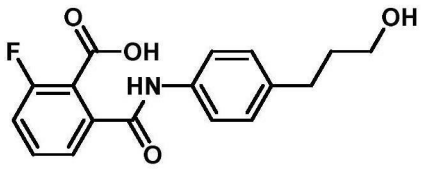
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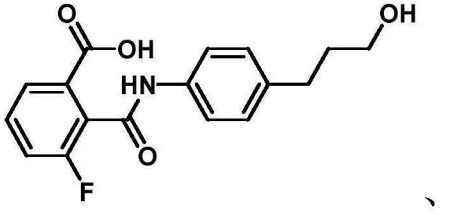
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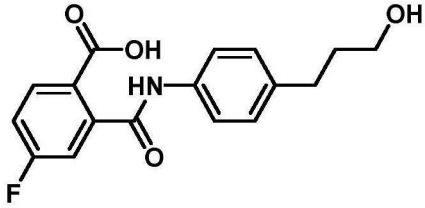
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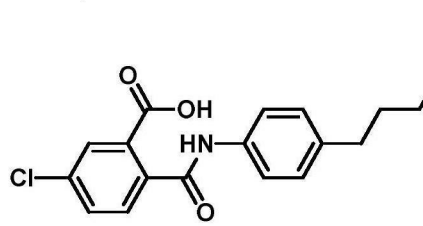
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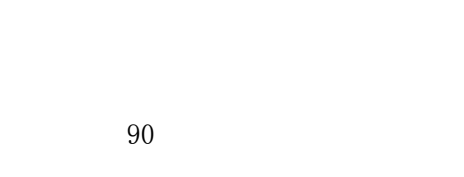
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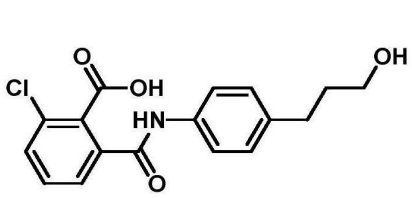
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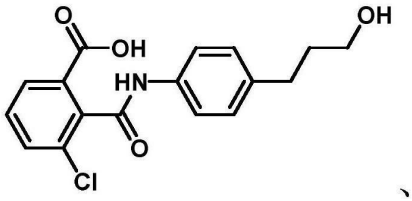
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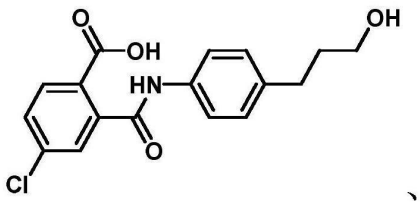
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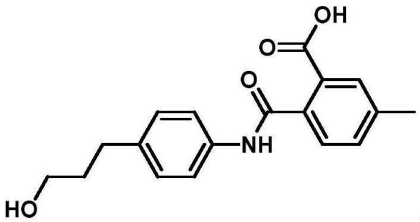
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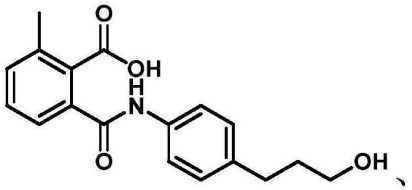
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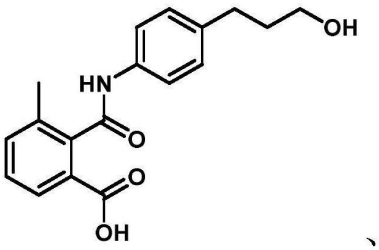
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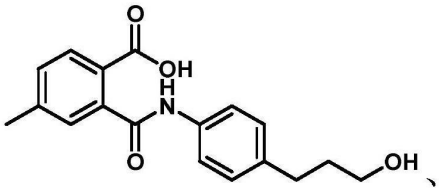
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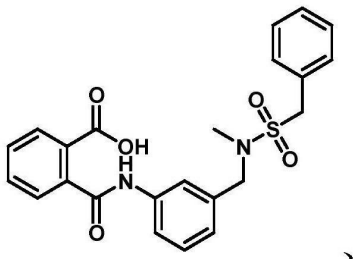
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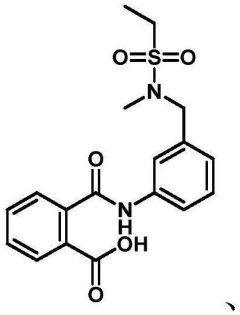
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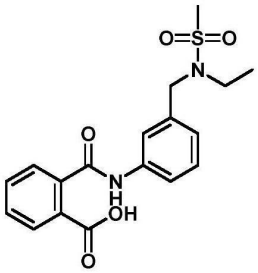
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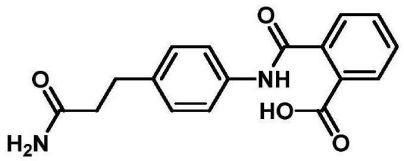
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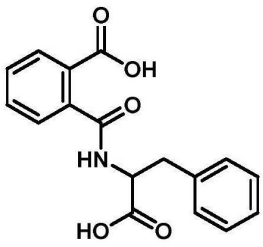
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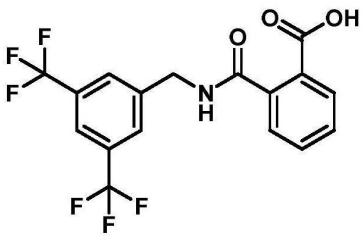
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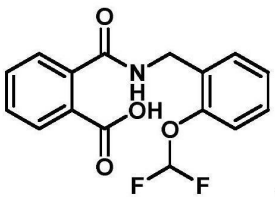
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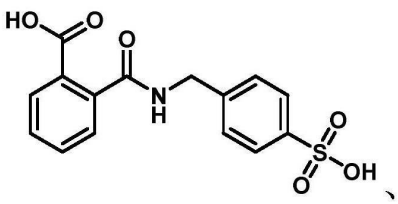
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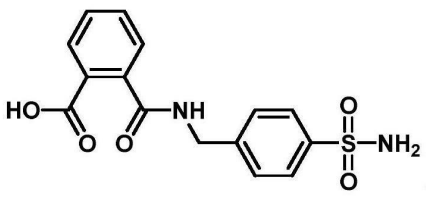
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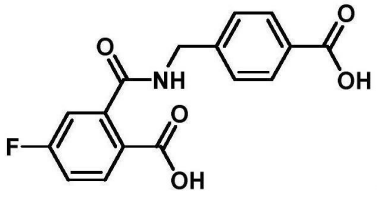
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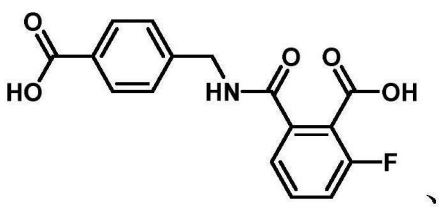
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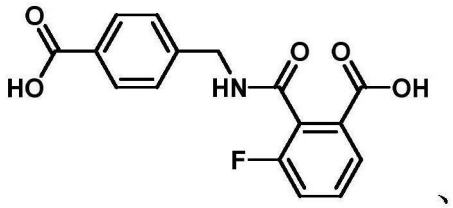
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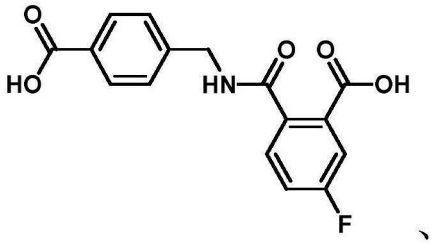
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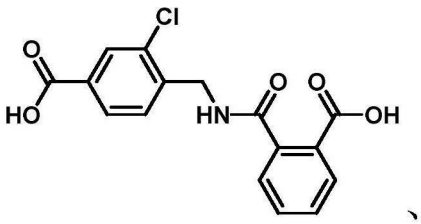
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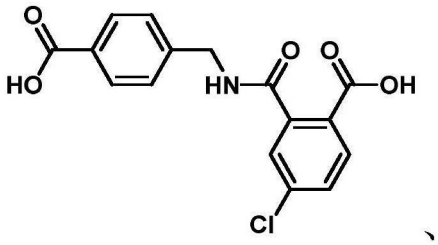
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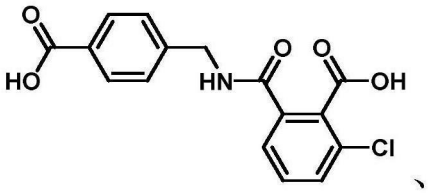
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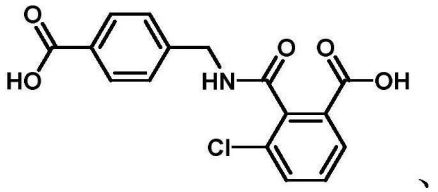
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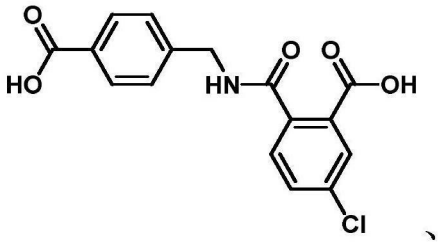
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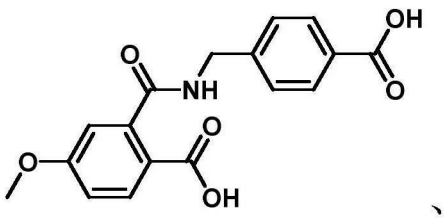
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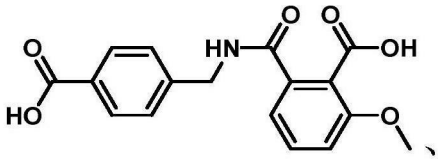
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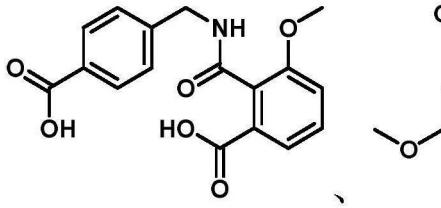
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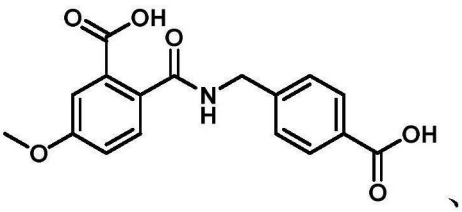
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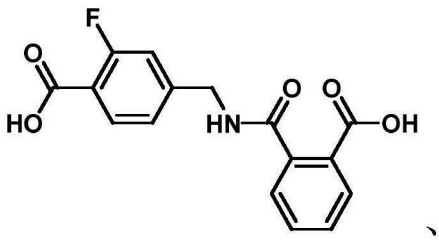
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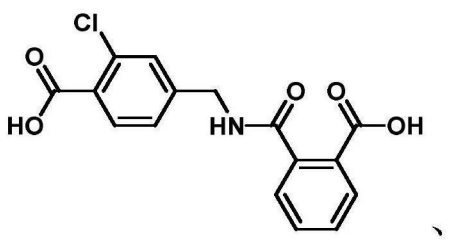
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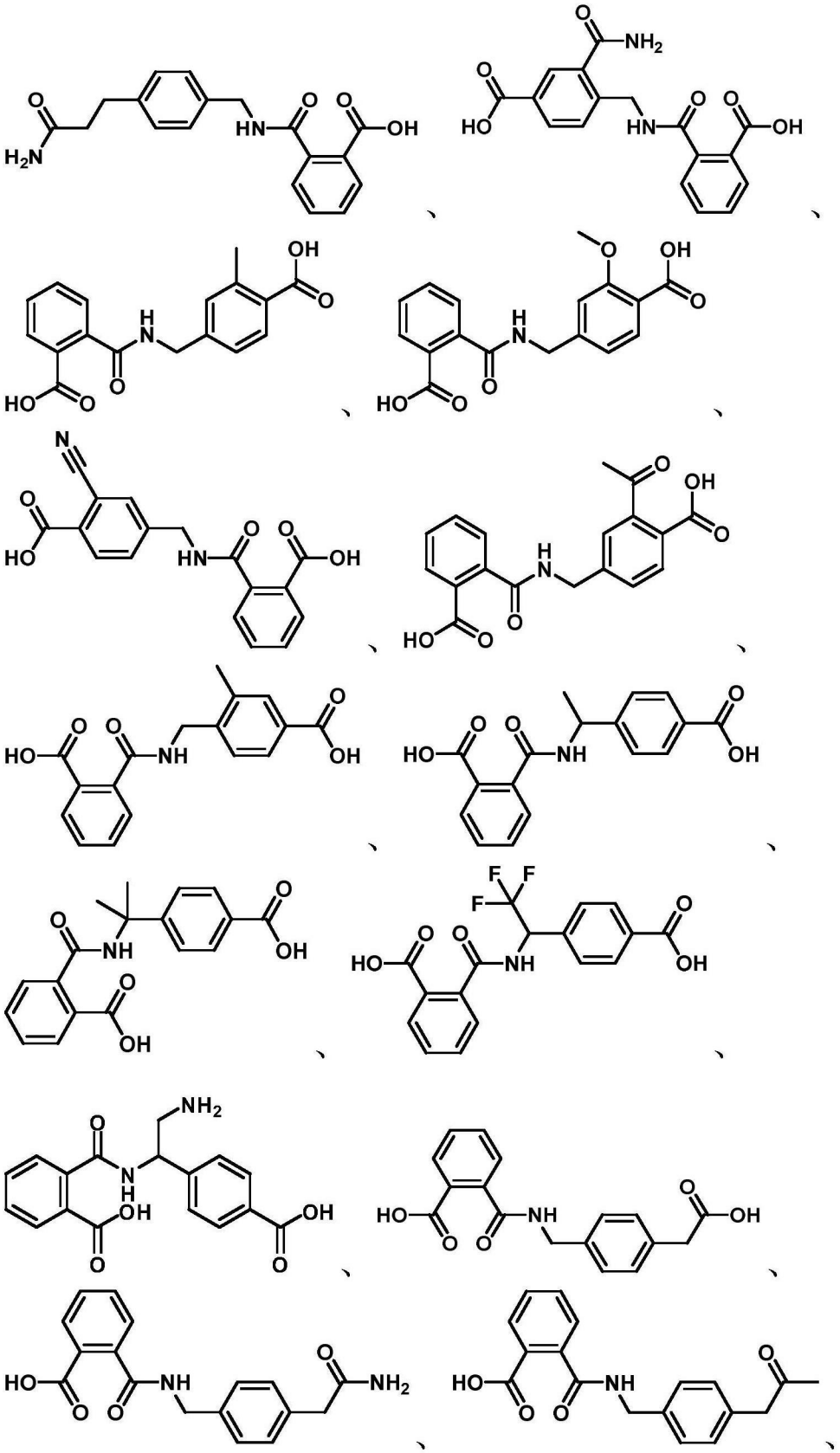

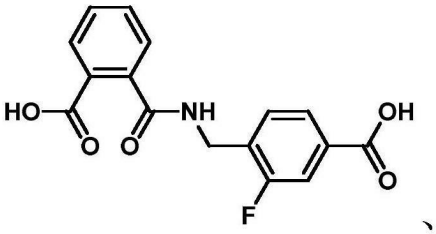
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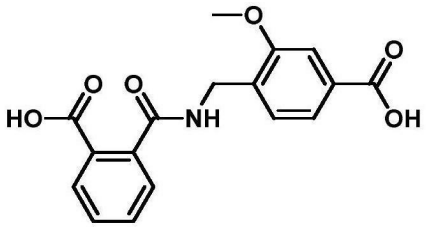
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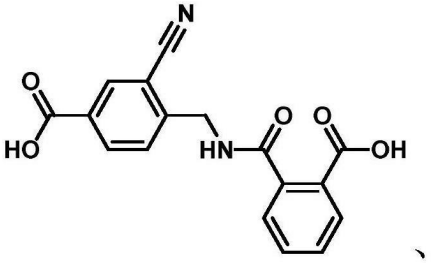
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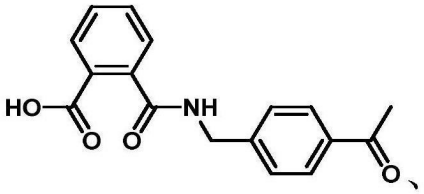
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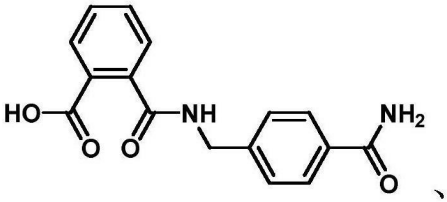
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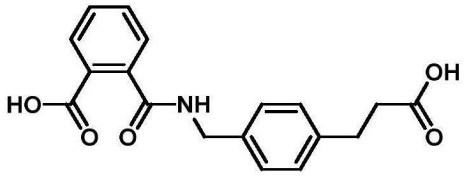
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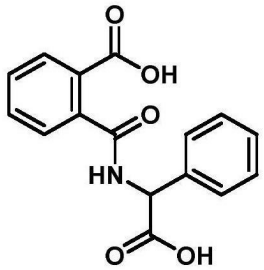
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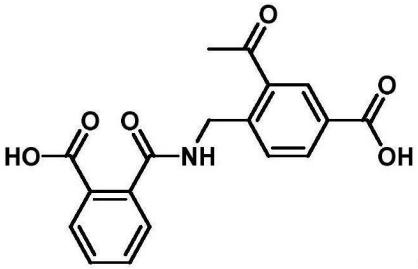
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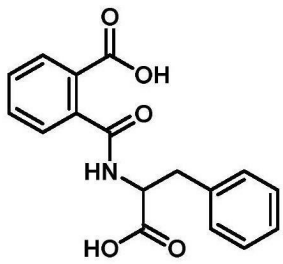
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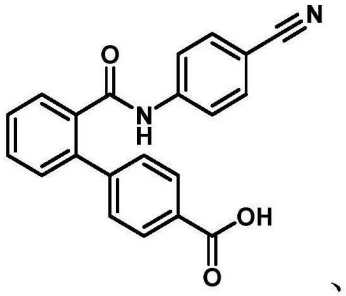
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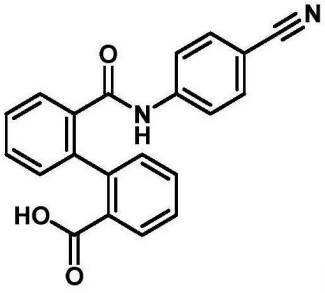
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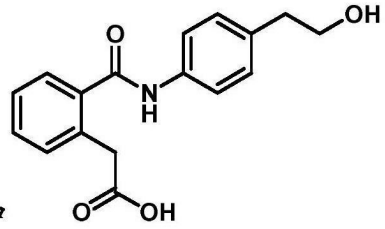
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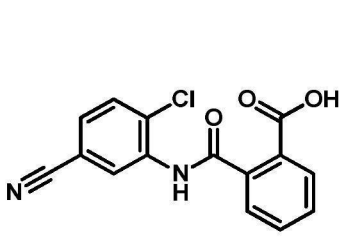
[0054] 在另一方面，本文提供了式 Ia 的化合物，或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体，该化合物选自：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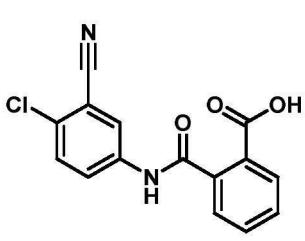
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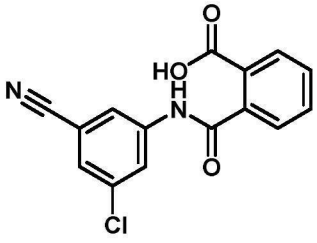
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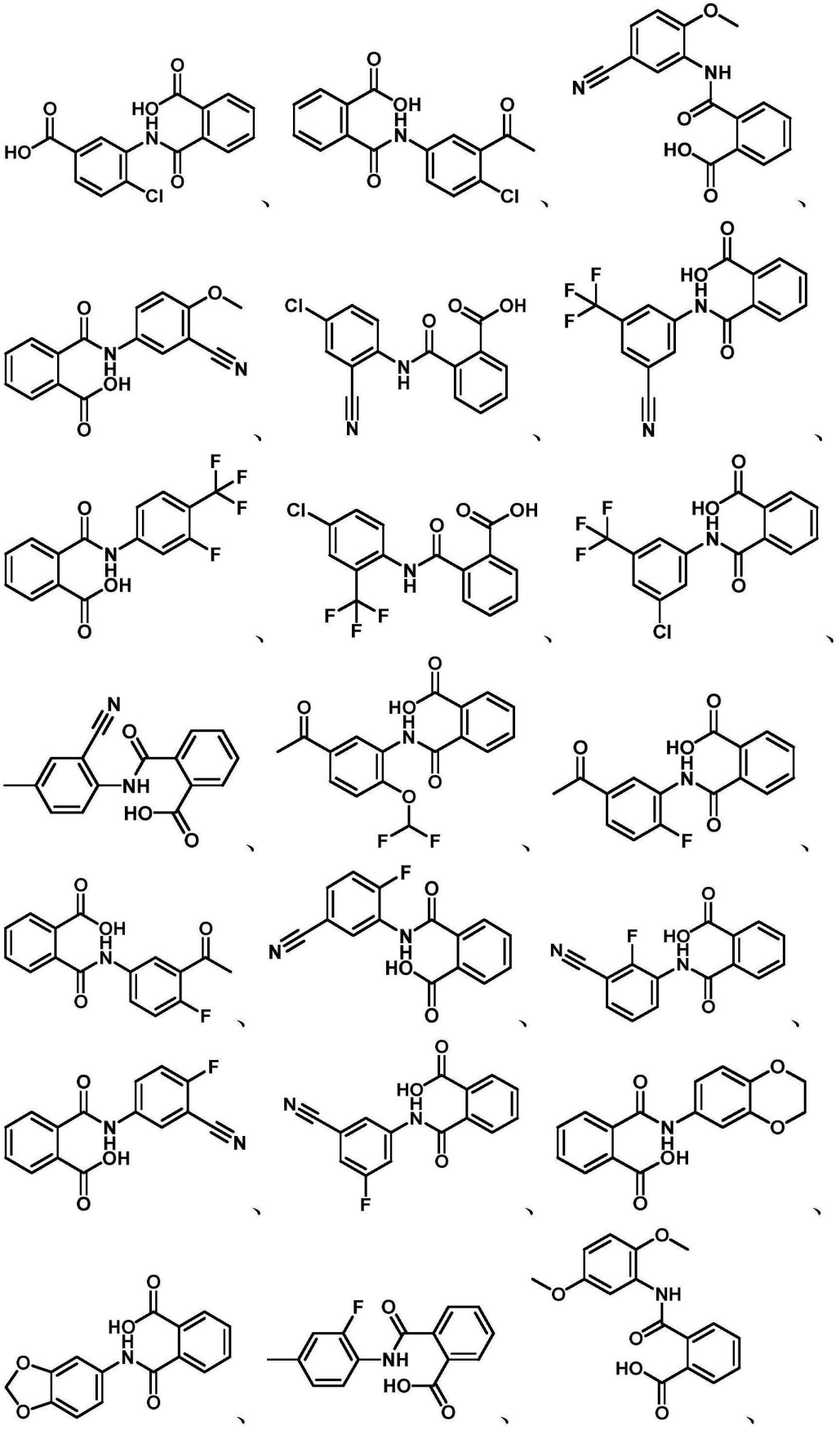
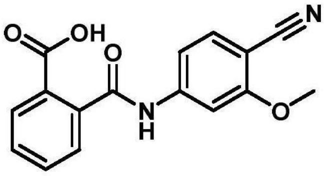
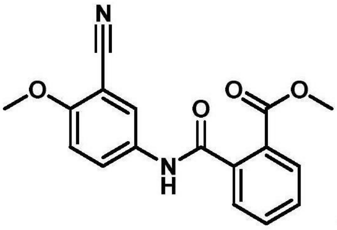
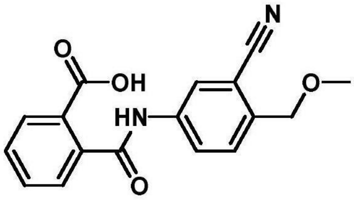
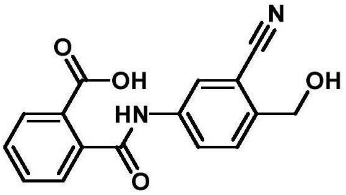
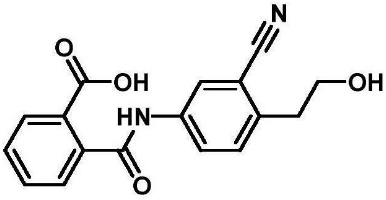
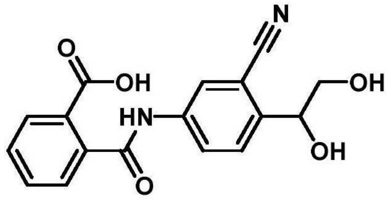
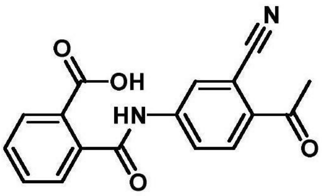
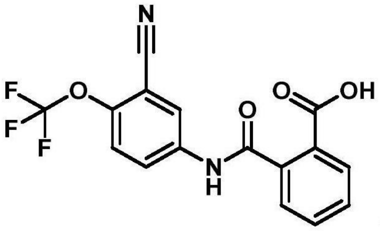
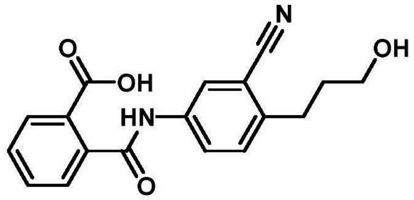
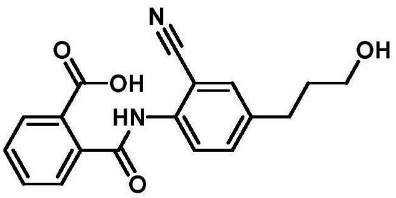
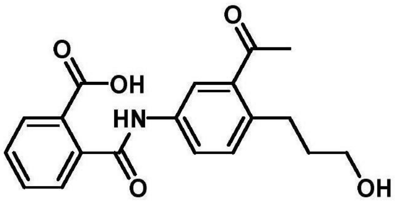
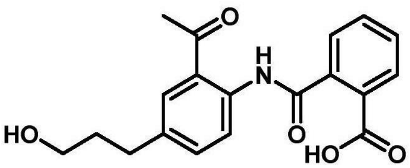
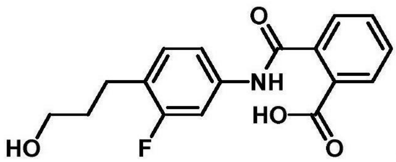


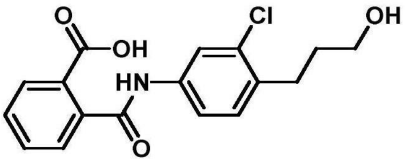
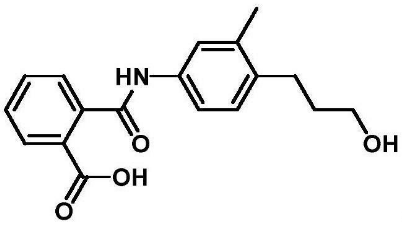
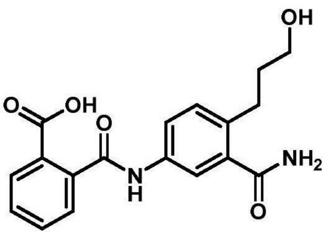
 、  、  、

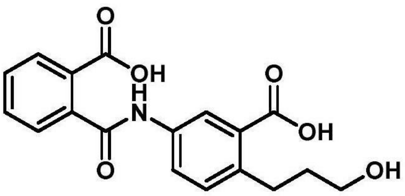
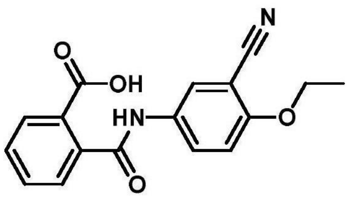
 、  、  、

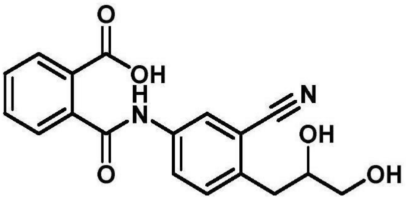
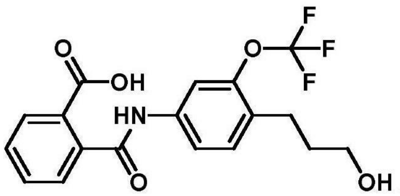
 、  、  、

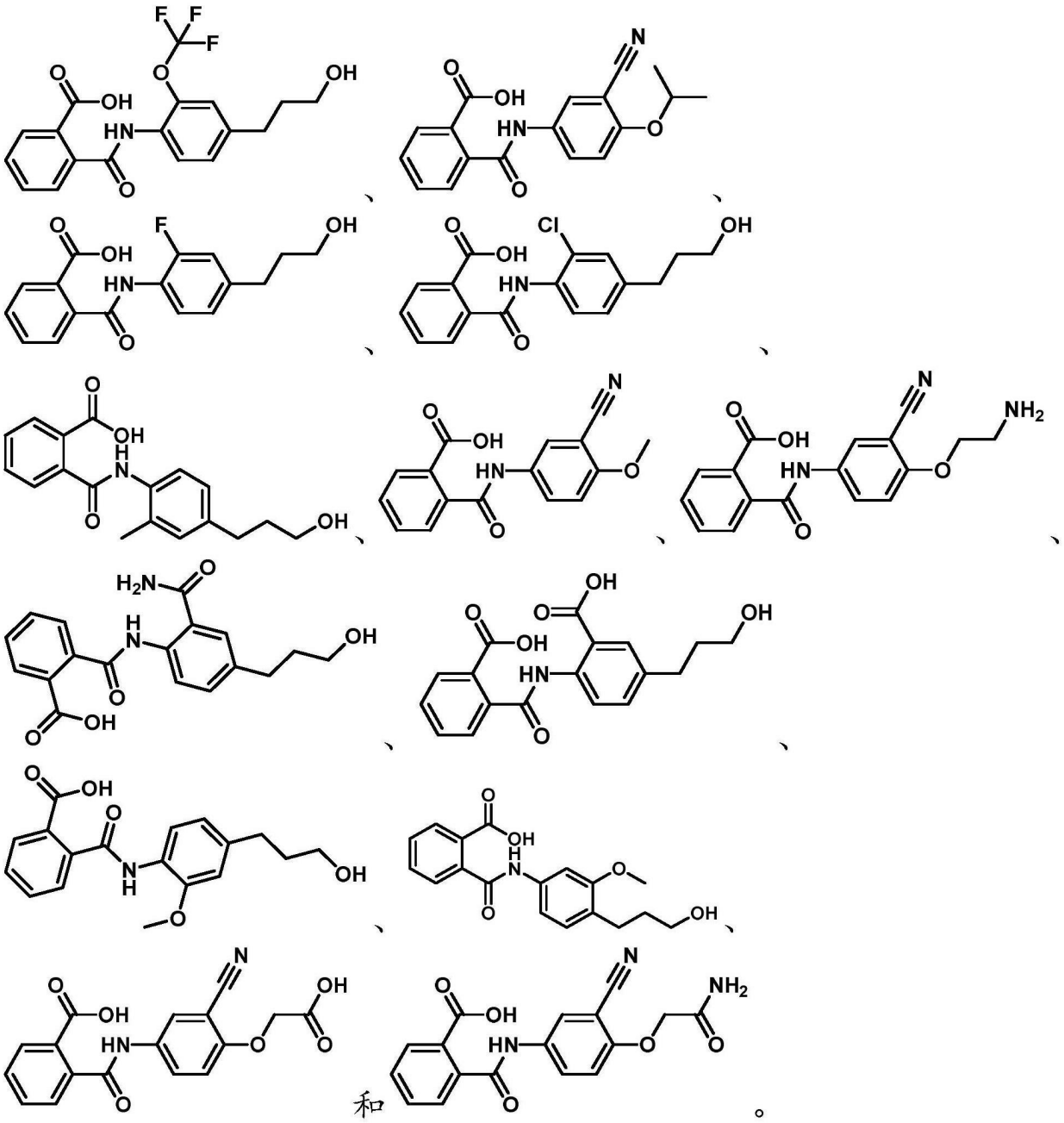
 、  、

 、  、

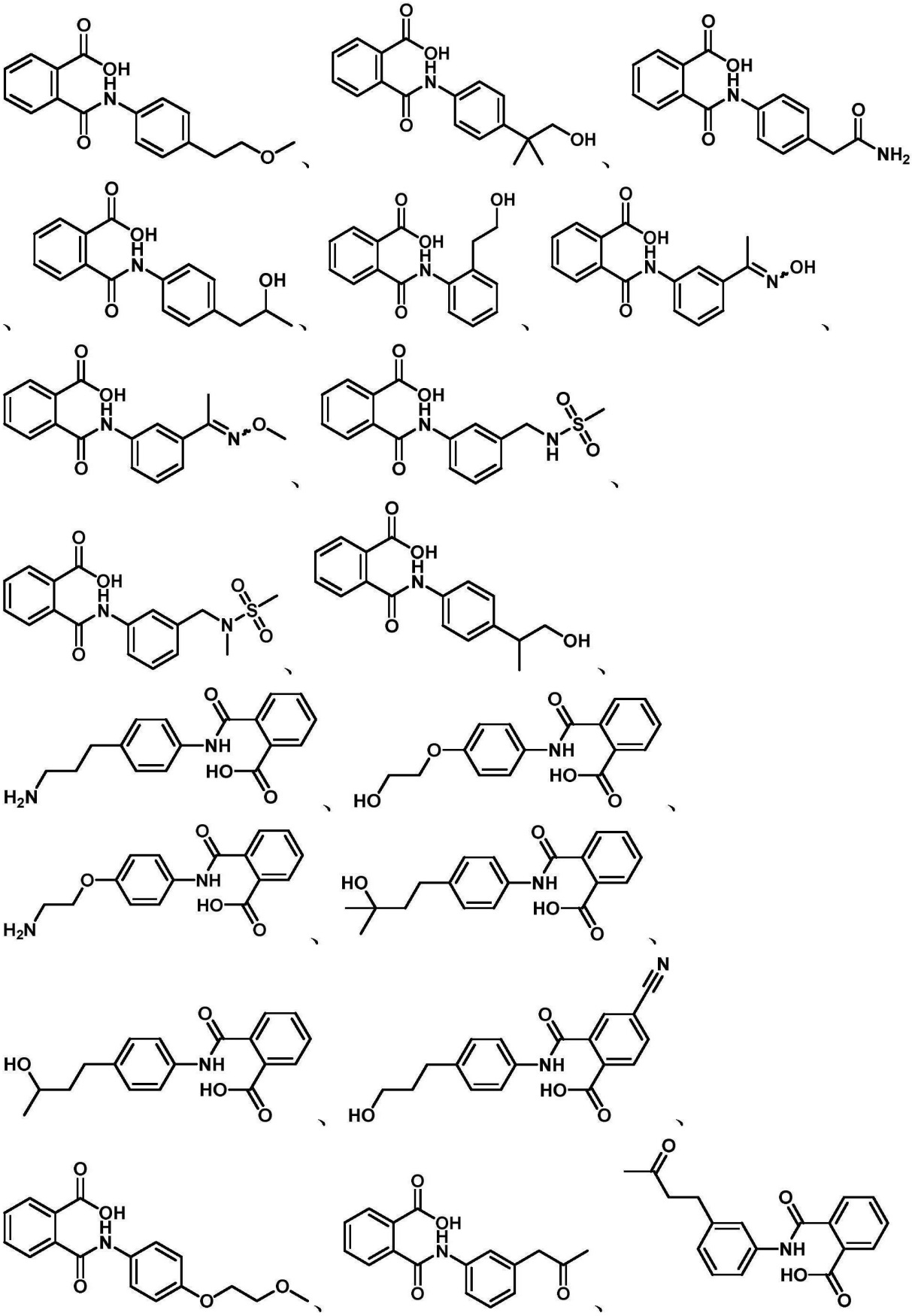
 、  、  、

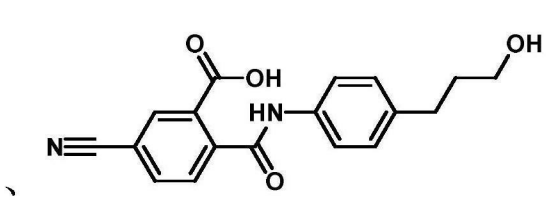
 、  、

 、  、



[0055] 在另一方面，本文提供了式 Ib 的化合物，或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体，该化合物选自：

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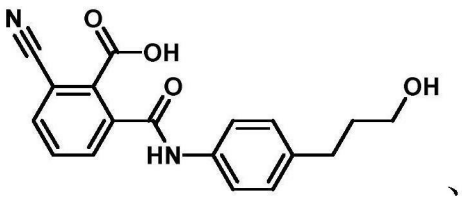
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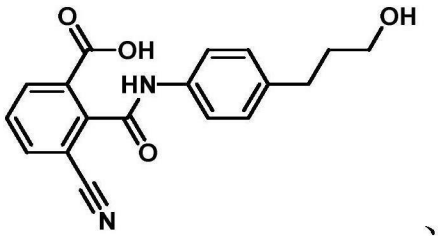
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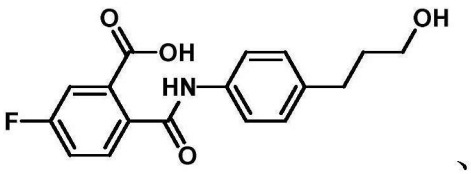
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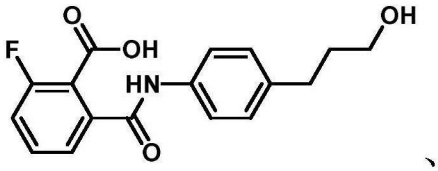
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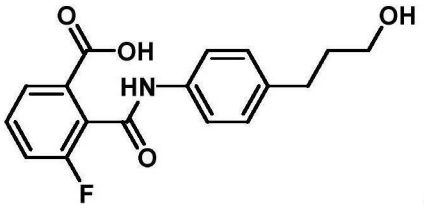
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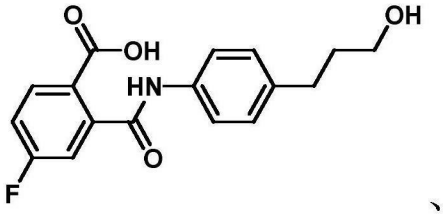
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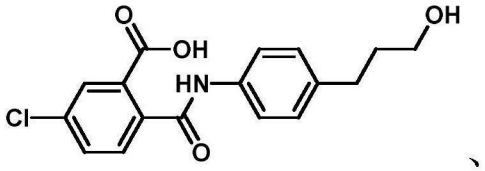
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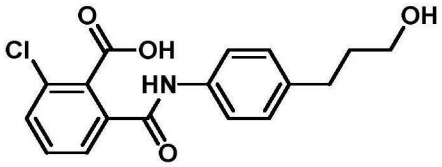
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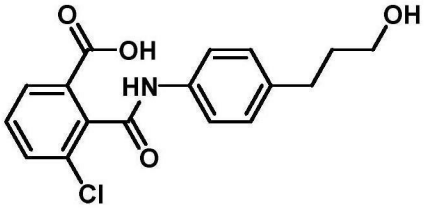
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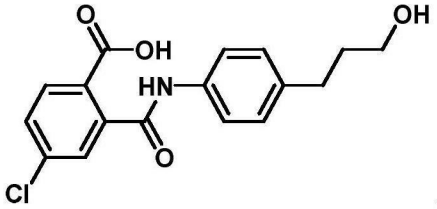
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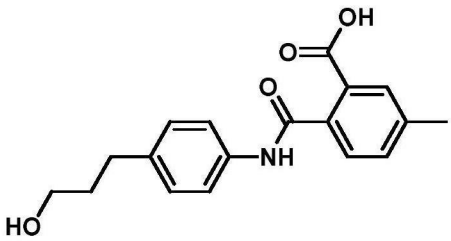
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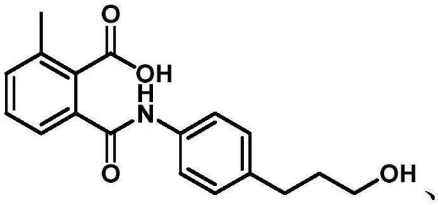
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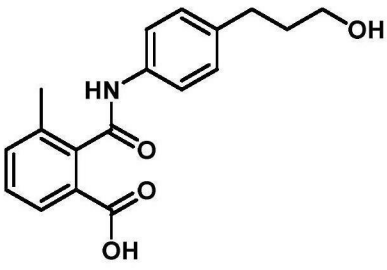
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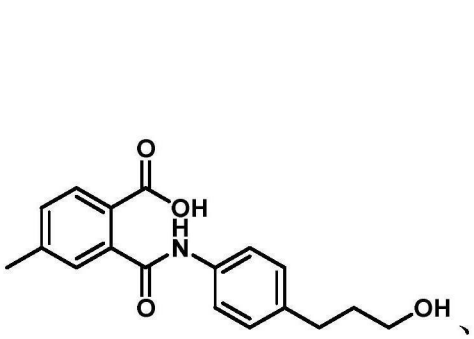
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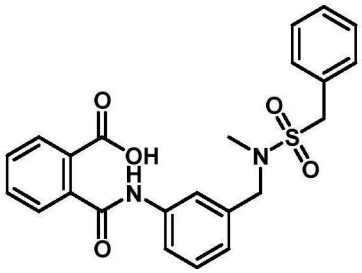
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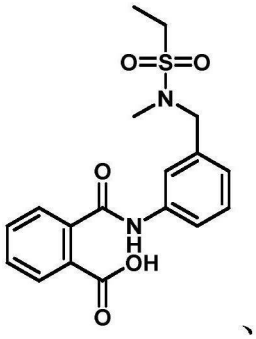
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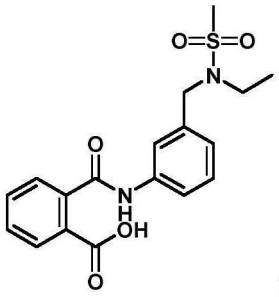
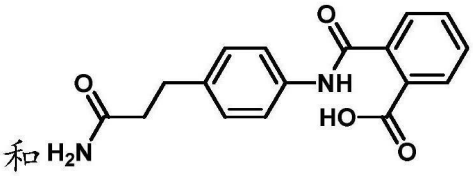
和
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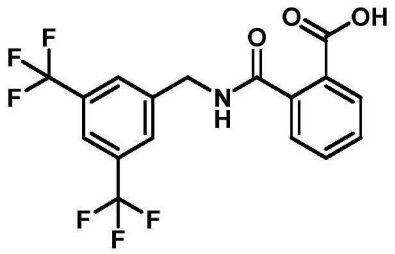
[0056] 在另一方面，本文提供了式 Ic 的化合物，或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体，该化合物选自：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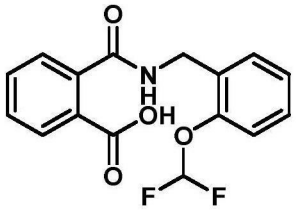
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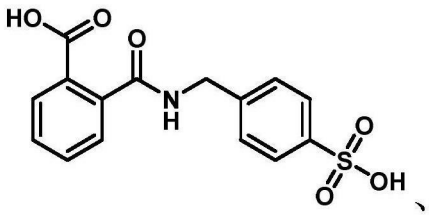
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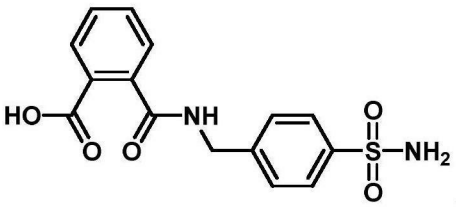
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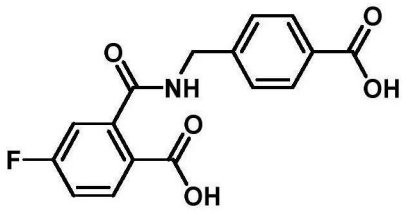
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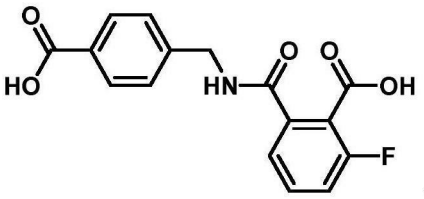
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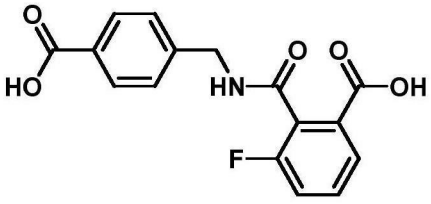
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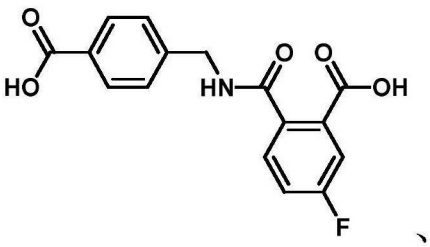
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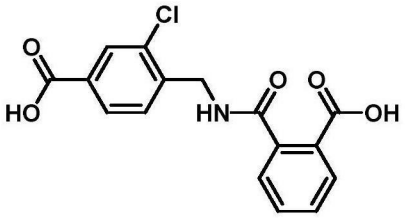
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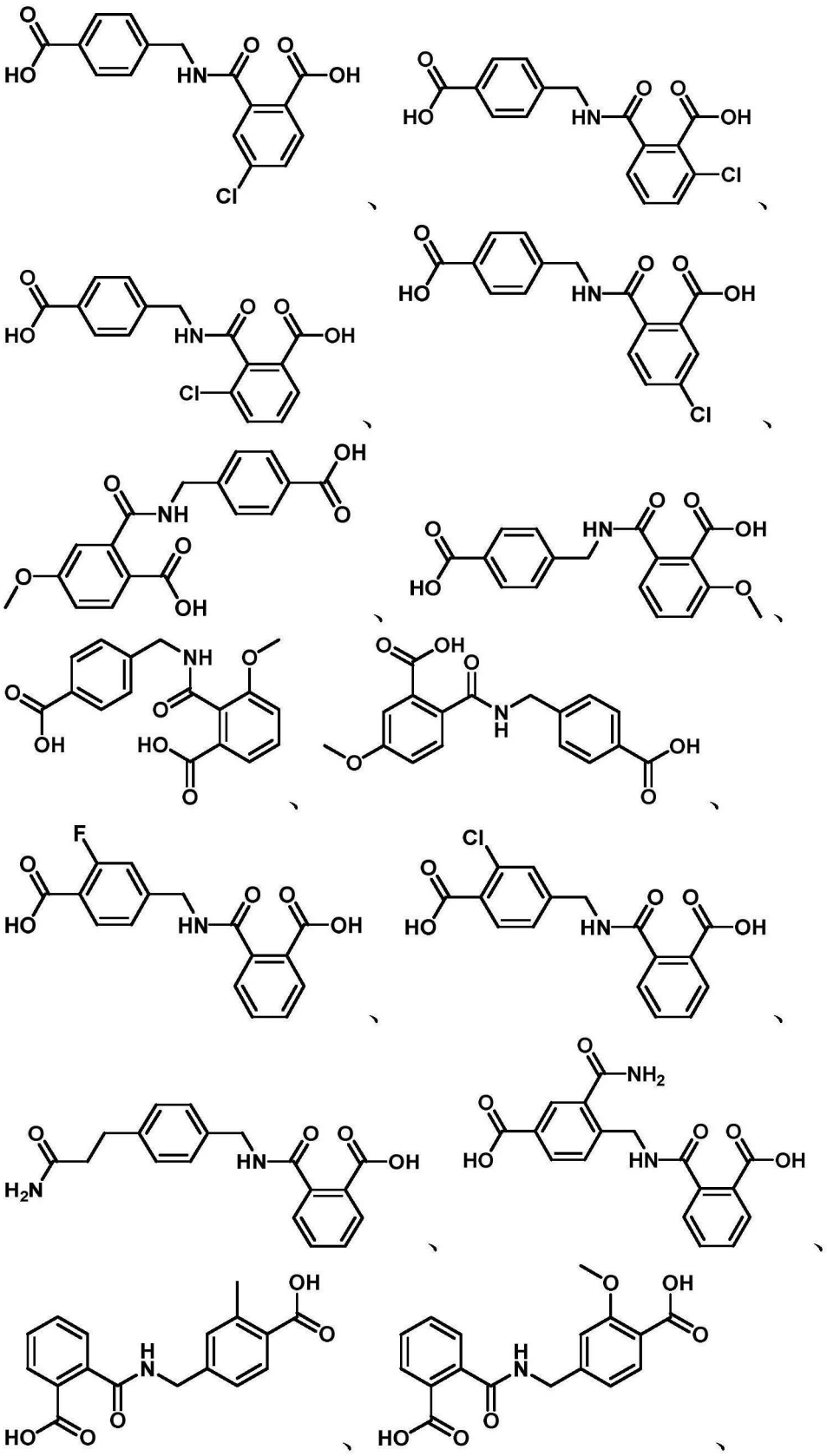

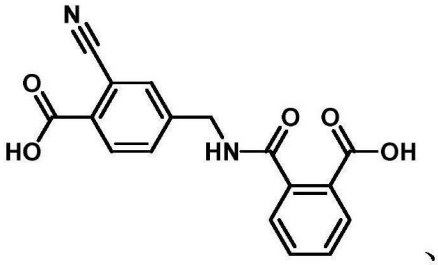
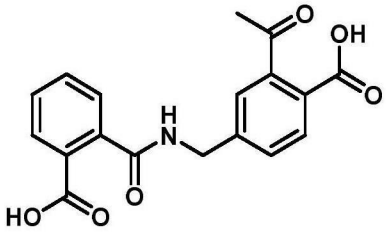
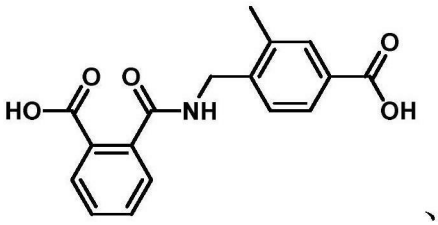
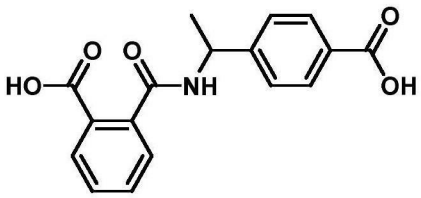
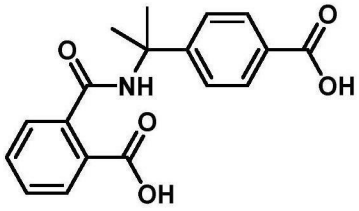
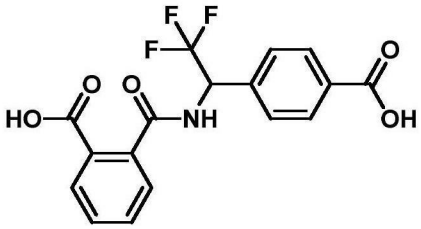
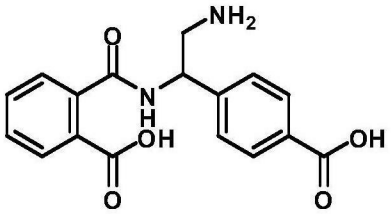
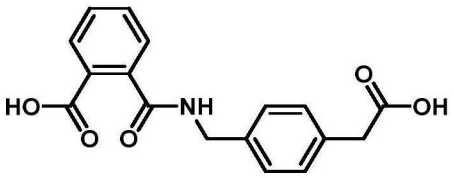
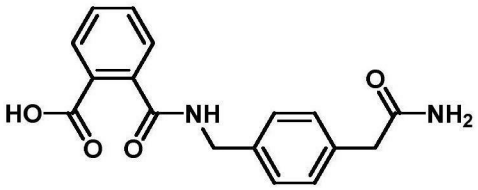
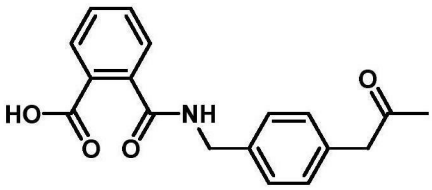
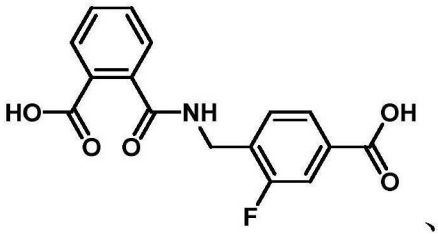
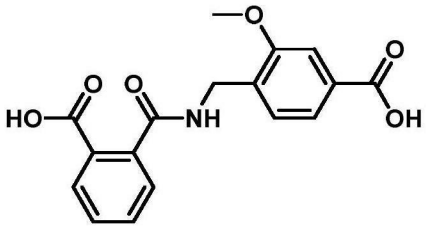
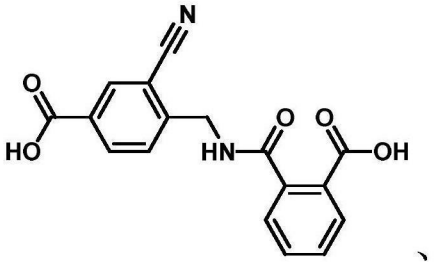
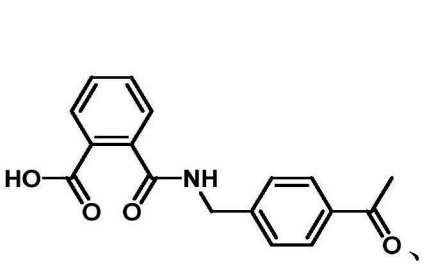

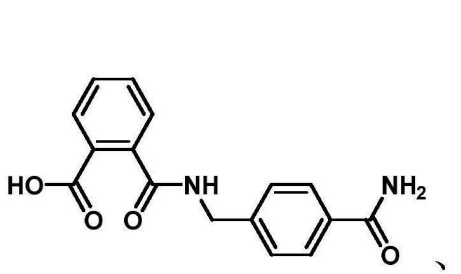
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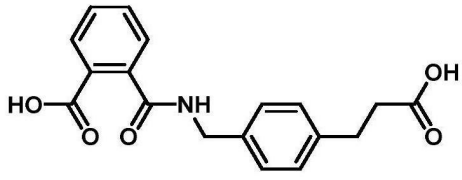
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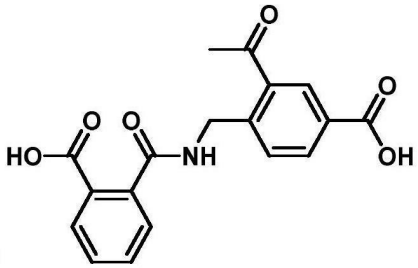
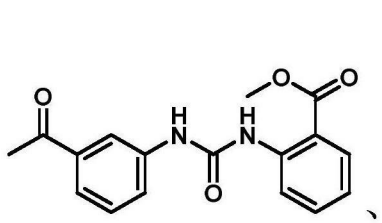

和 。

[0057] 在另一方面，本文提供了式 II 的化合物，或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体，该化合物选自：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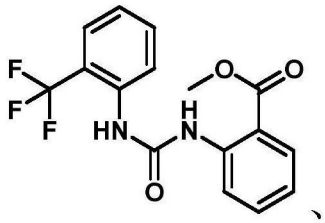
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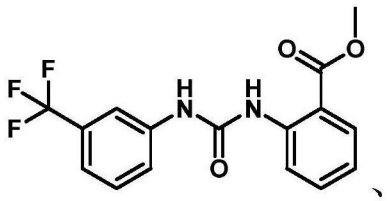
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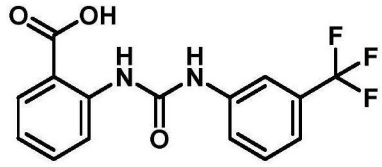
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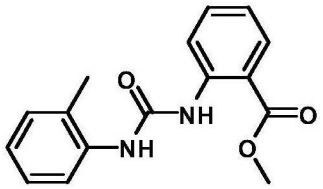
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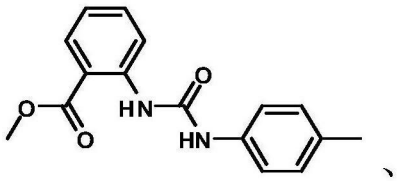
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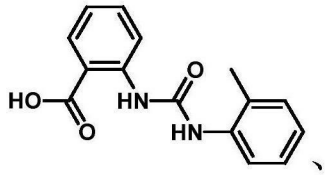
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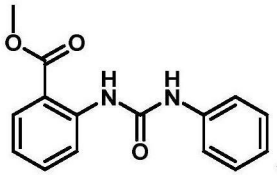
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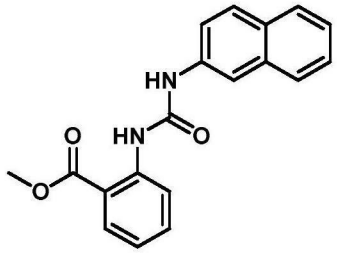
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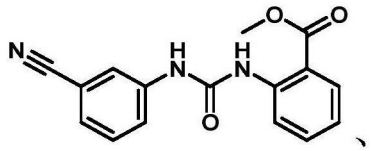
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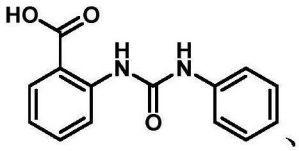
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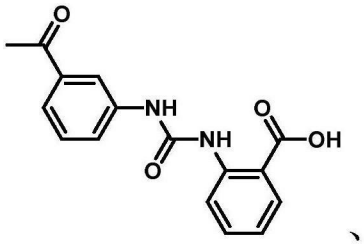
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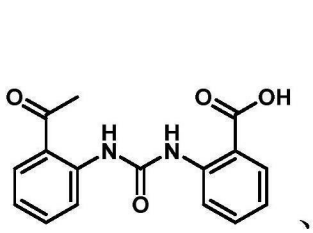
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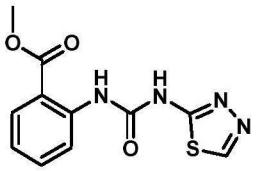
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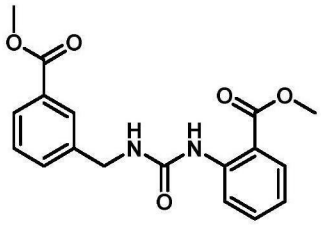
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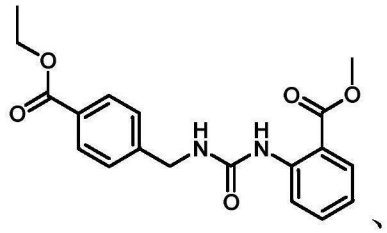
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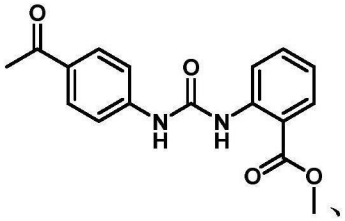
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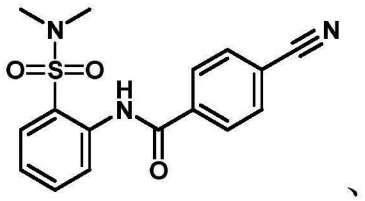
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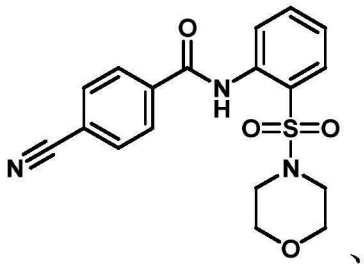
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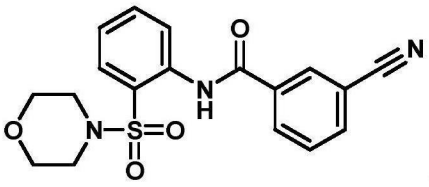
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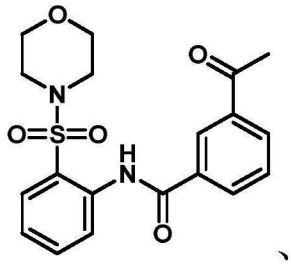
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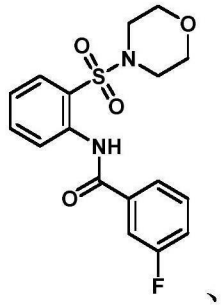
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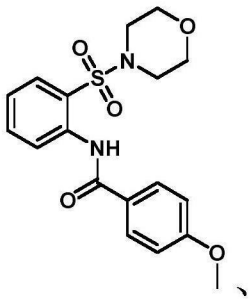
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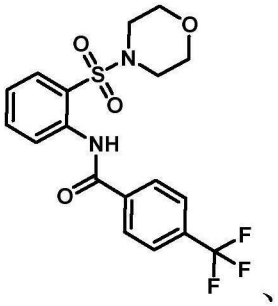
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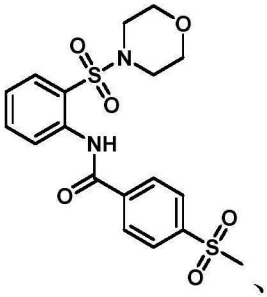
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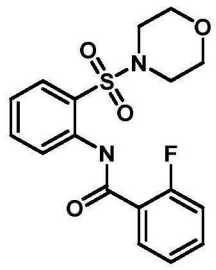
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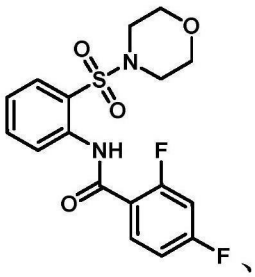
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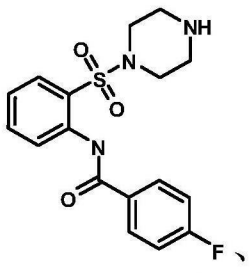
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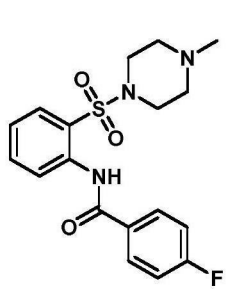
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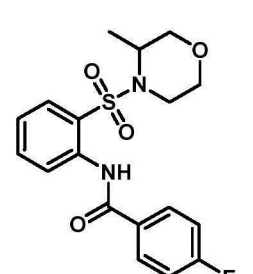
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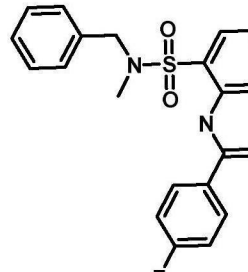
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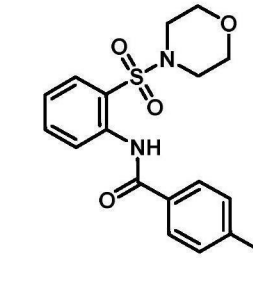
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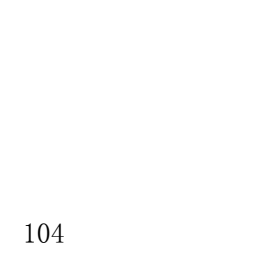
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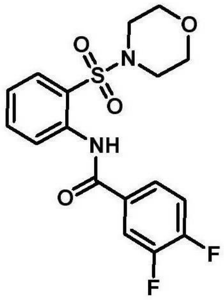
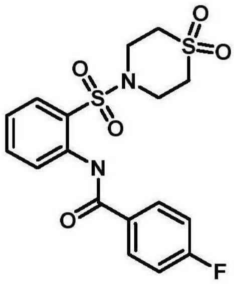
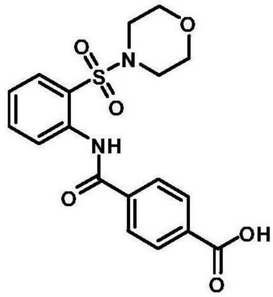
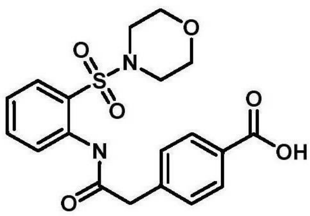
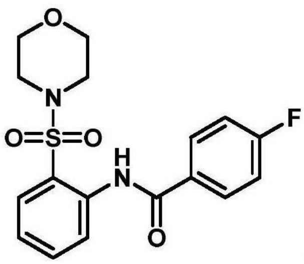
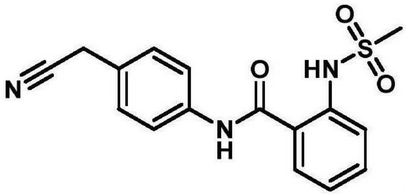
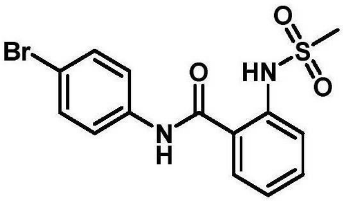
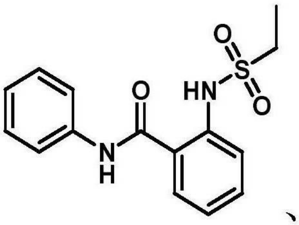
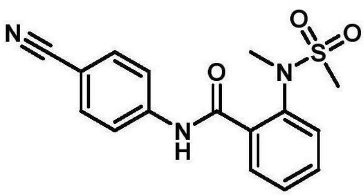
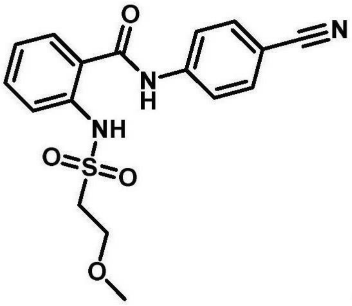
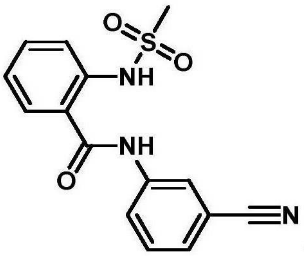
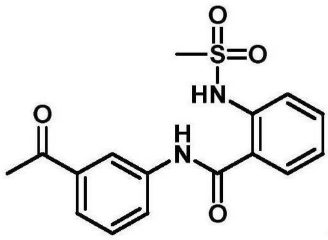
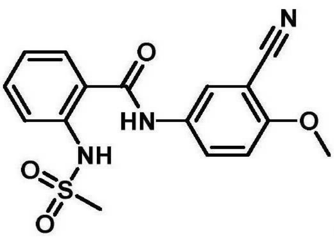
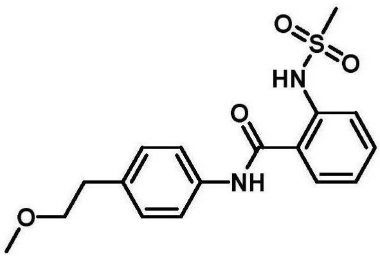
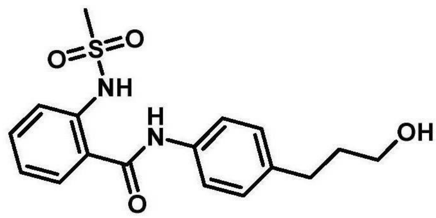
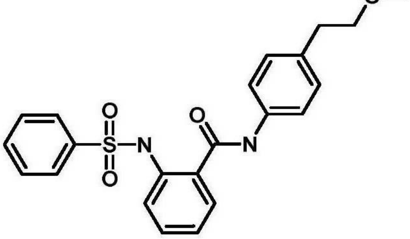
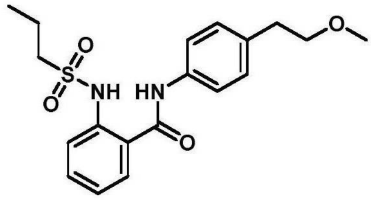
 、  、  、  、

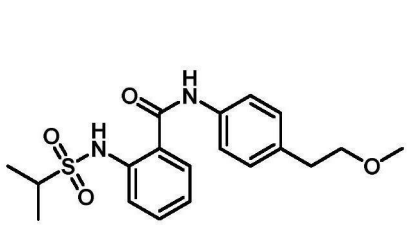
 、  、  、

 、  、  、

 、  、  、

 、  、 

、  、  、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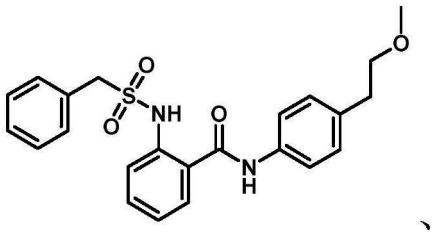
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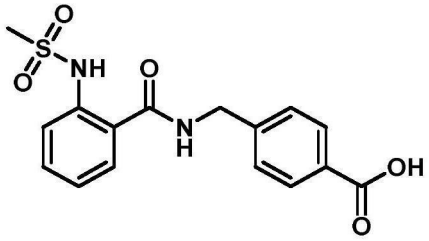
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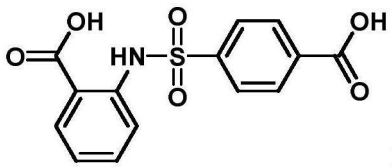
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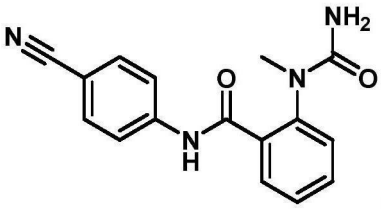
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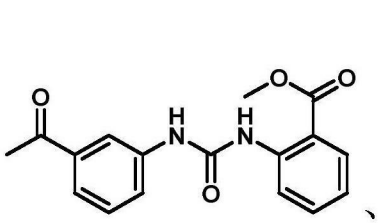
[0058] 在另一方面，本文提供了式 IIa 的化合物，或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体，该化合物选自：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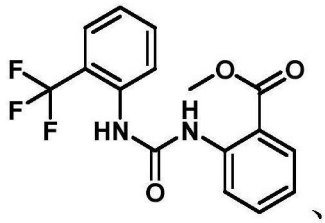
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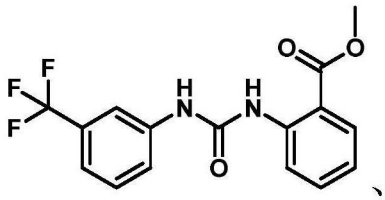
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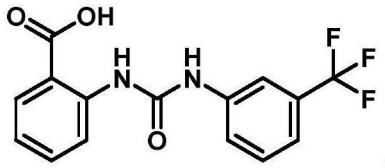
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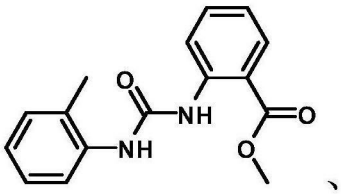
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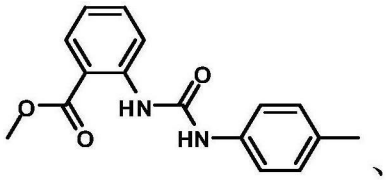
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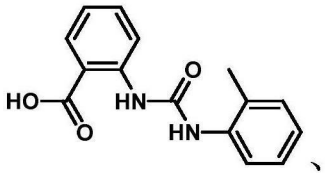
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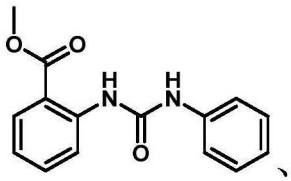
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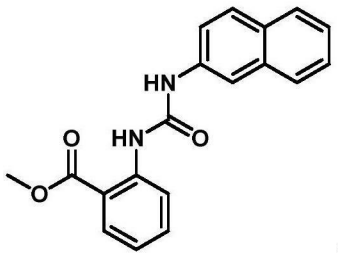
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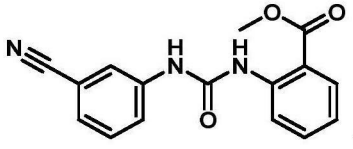
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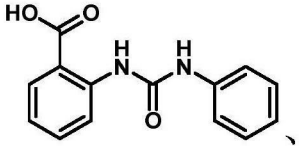
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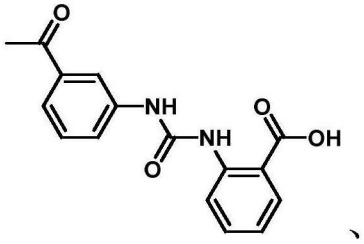
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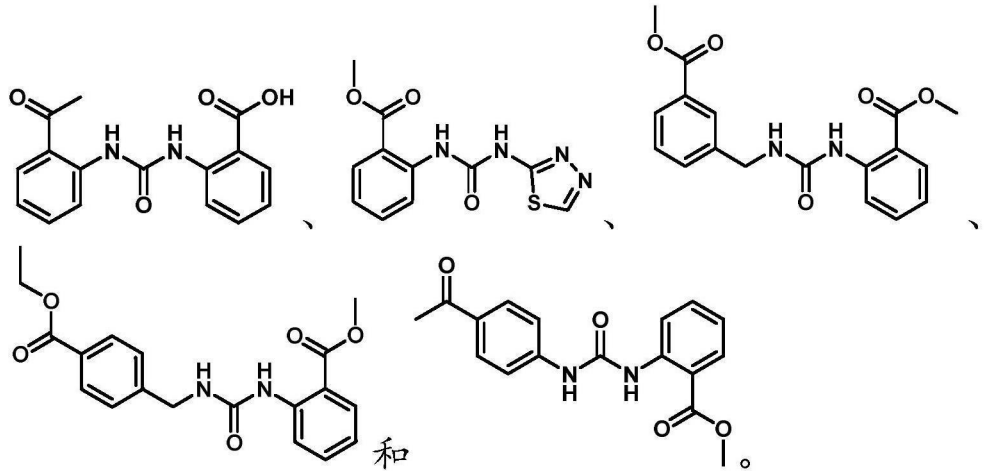
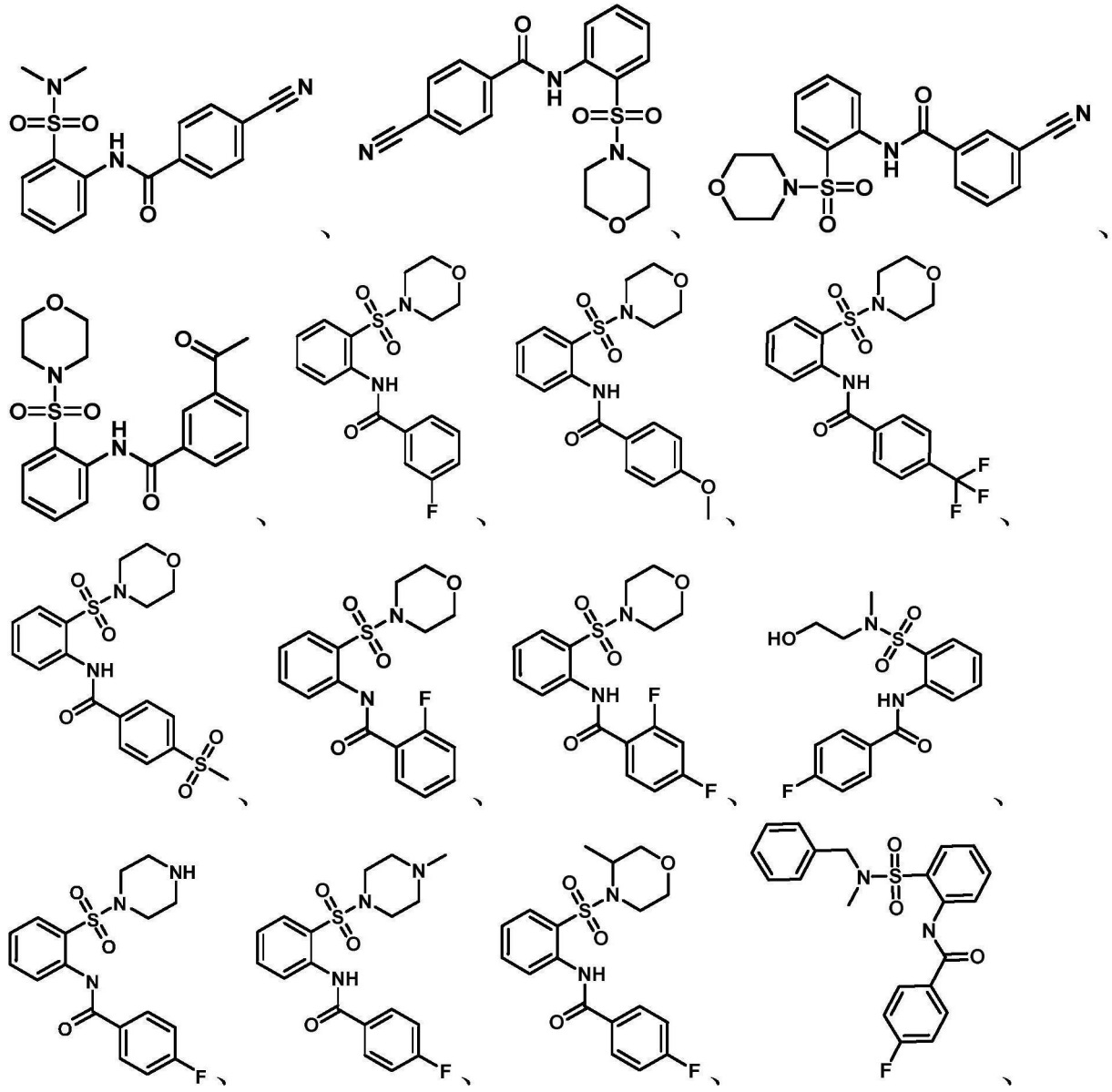
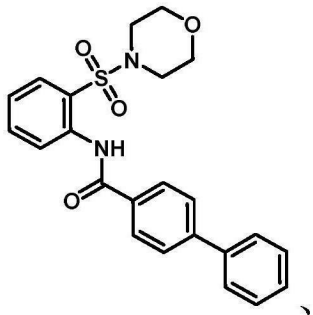


[0059] 在另一方面，本文提供了式 IIb 的化合物，或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体，该化合物选自：

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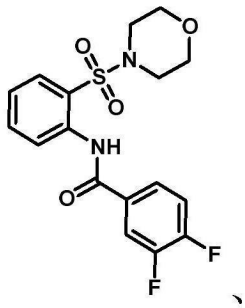
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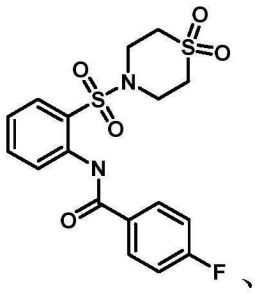
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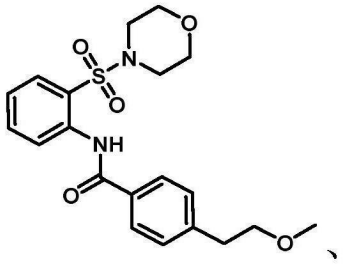
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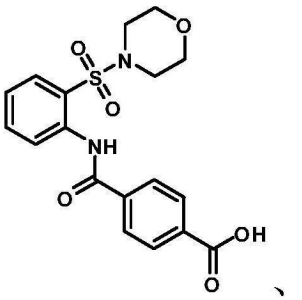
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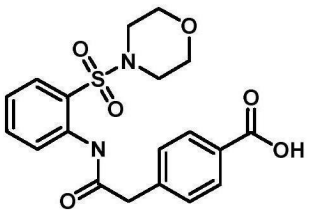
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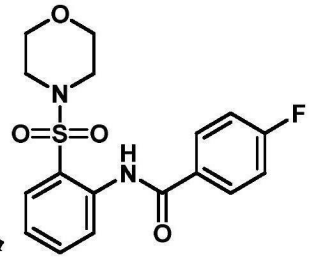
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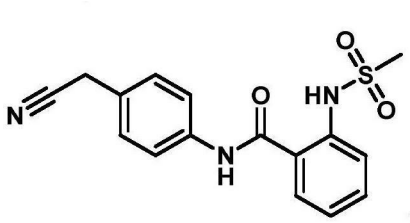
[0060] 在另一方面，本文提供了式 IIc 的化合物，或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体，该化合物选自：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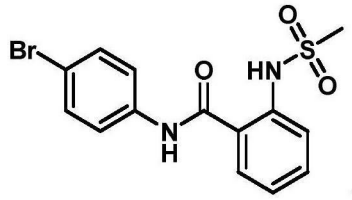
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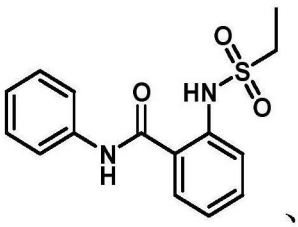
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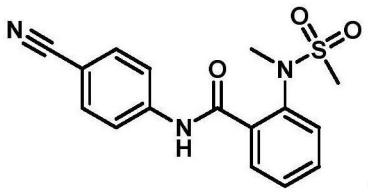
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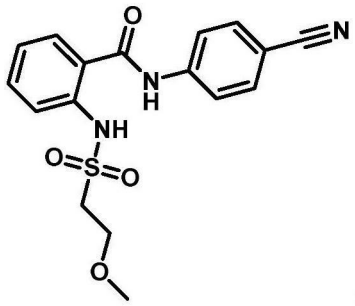
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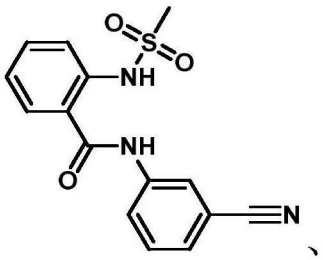
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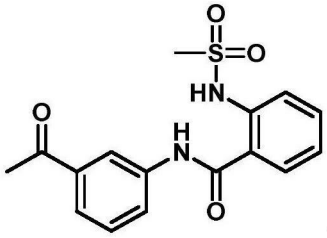
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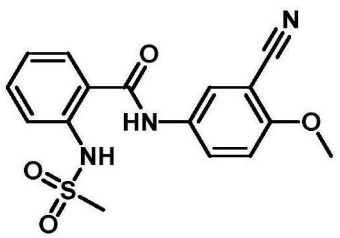
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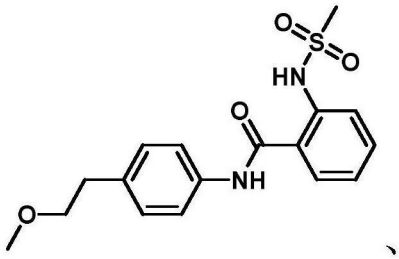
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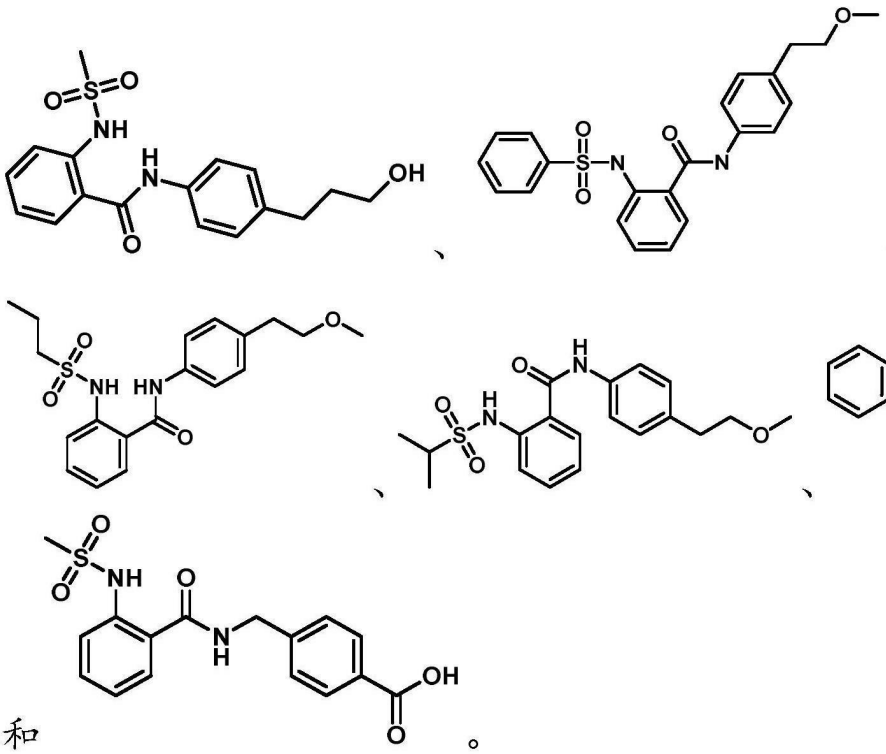
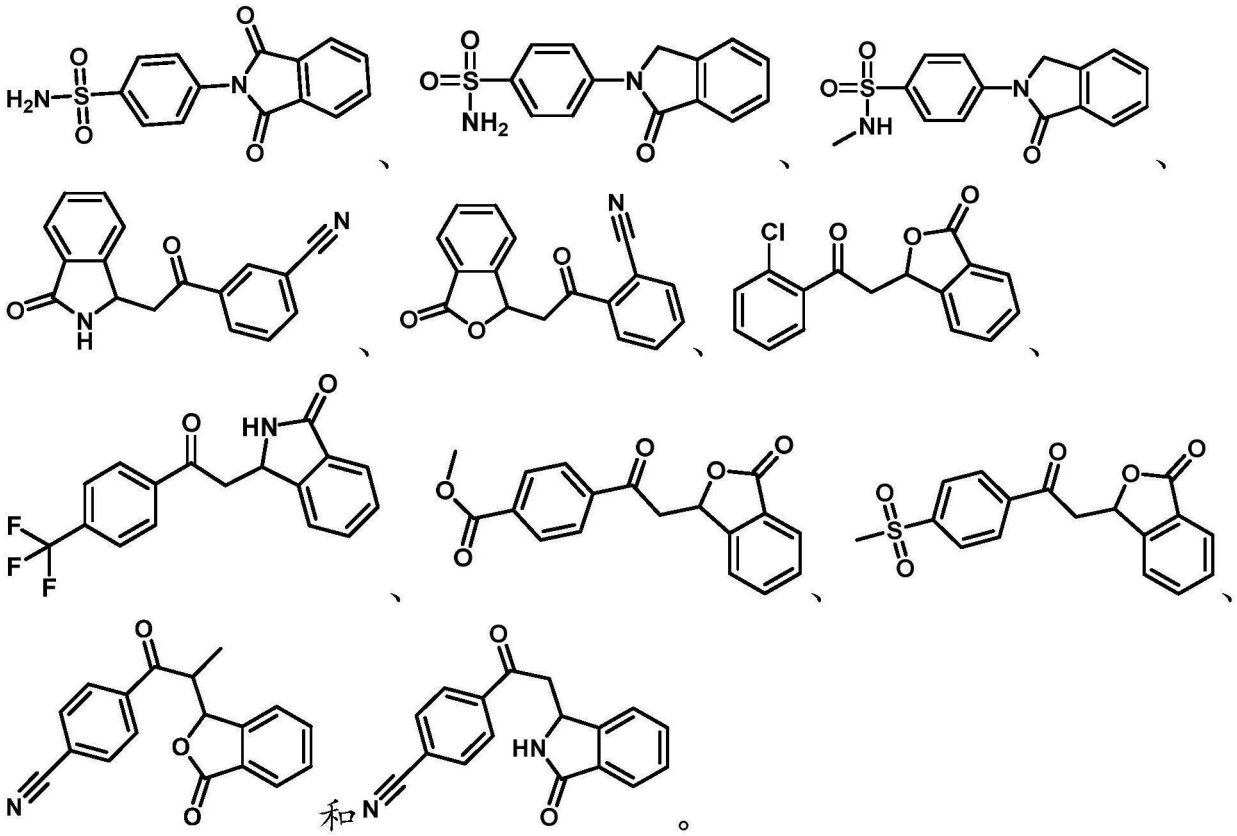


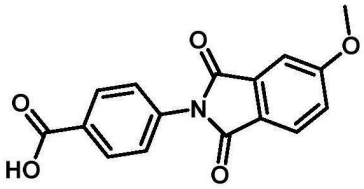
和 。

[0061] 在另一方面，本文提供了式 III 的化合物，或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体，该化合物选自：



和 。

[0062] 在另一方面，本文提供了化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体，该化合物选自：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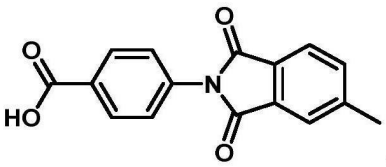
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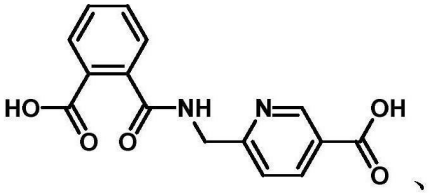
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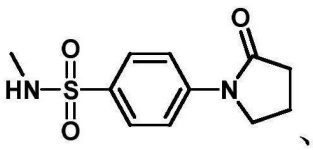
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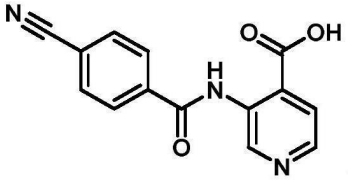
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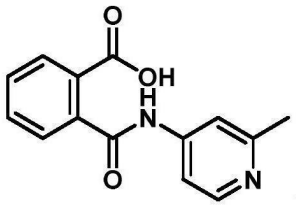
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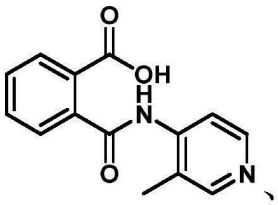
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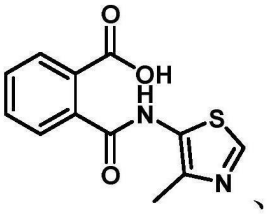
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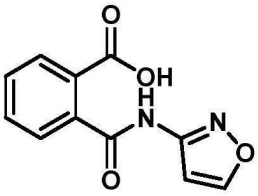
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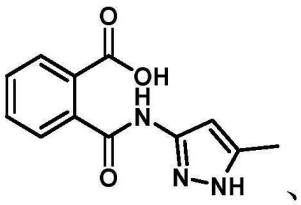
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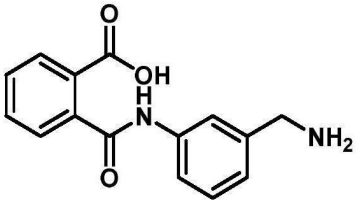
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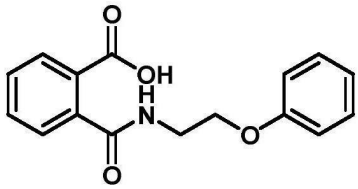
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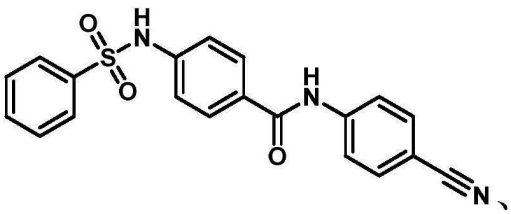
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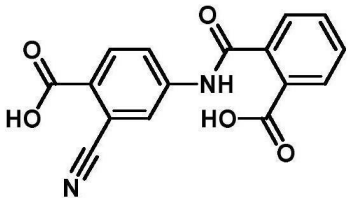
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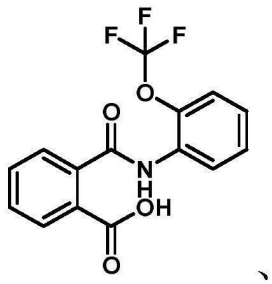
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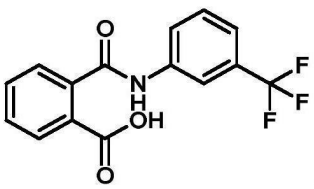
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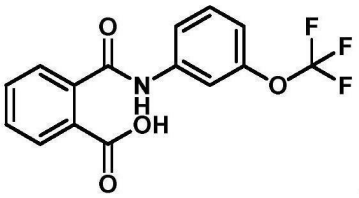
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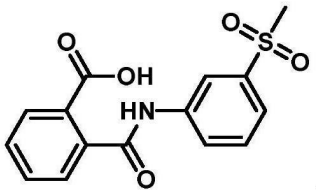
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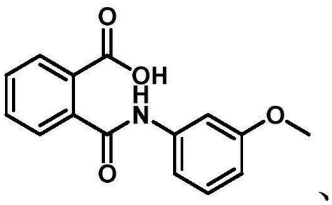
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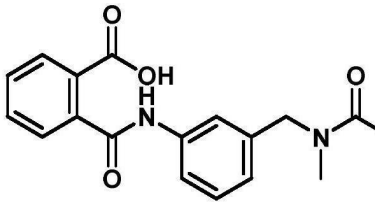
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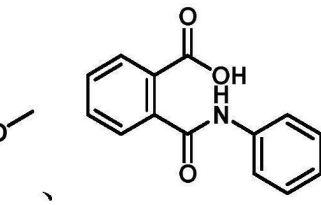
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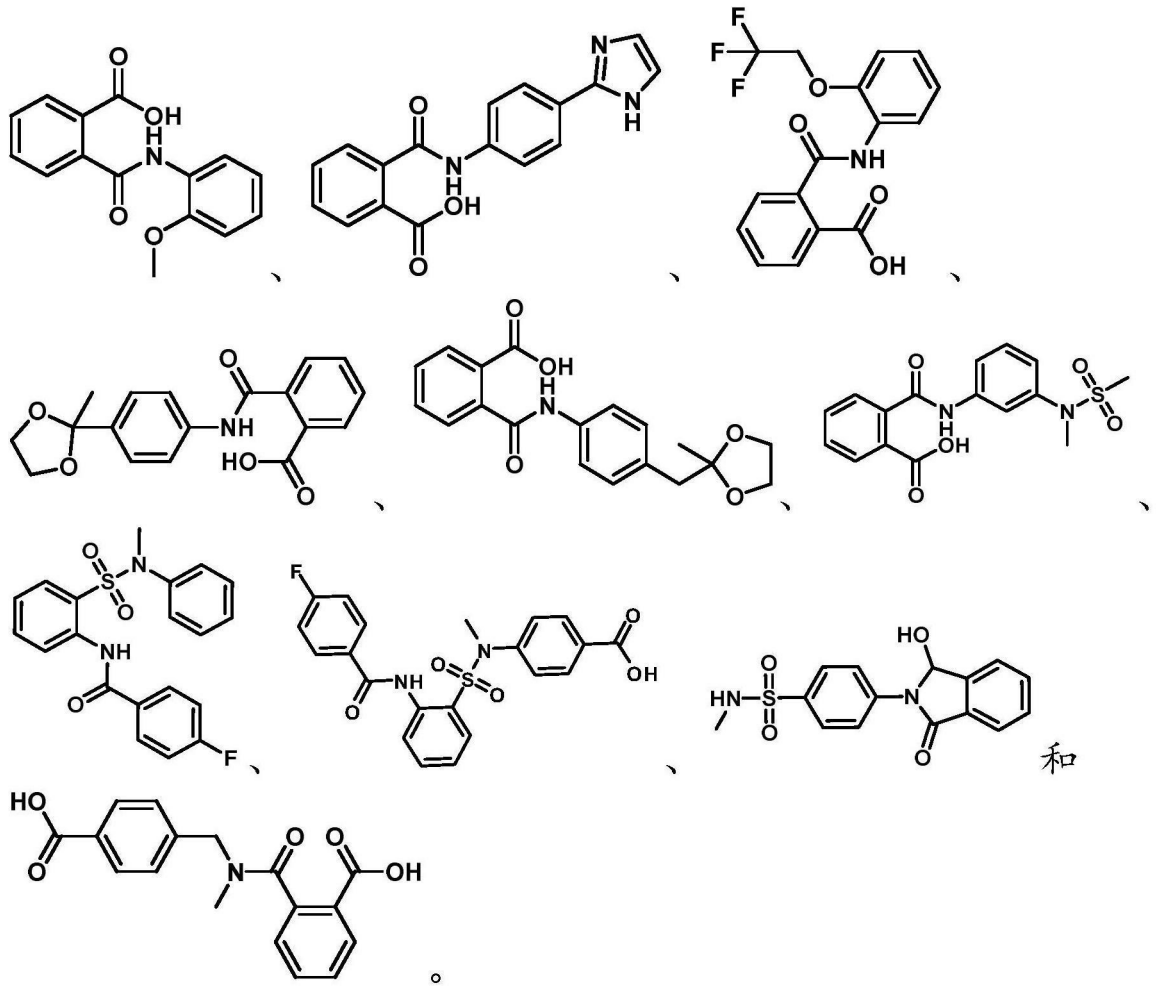


[0063] 在一方面，本文提供了一种药物组合物，其包含本文公开的化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体以及药学上可接受的赋形剂。在某些实施方案中，该药物组合物进一步包含额外的化合物，该额外的化合物对于治疗哺乳动物的关节炎或关节损伤和 / 或与关节炎或关节损伤相关的症状是治疗上有效的。在某些实施方案中，该额外的化合物选自 NSAIDS、镇痛药、血管生成素样 3 蛋白 (ANGPTL3) 或其软骨形成变体、口服鲑降钙素、SD-6010(iNOS 抑制剂)、维生素 D3(胆骨化醇)、凋亡 / 胱天蛋白酶抑制剂 (恩利卡生)、胶原水解物、FGF18、BMP7、鳄梨大豆不皂化物 (avocado soy unsaponifiables)(ASU) 和透明质酸。在一些实施方案中，该哺乳动物是人。在其他实施方案中，该哺乳动物是陪伴动物或家畜。在进一步的实施方案中，该陪伴动物或家畜是狗、猫或马。

援引并入

[0064] 本说明书中所提到的所有出版物、专利和专利申请均通过引用并入本文，其程度如同特别且单独地指出每个单独的出版物、专利或专利申请通过引用而并入。

具体实施方式

[0065] 骨关节炎 (OA) 的特征在于关节软骨的进行性分解，并最终导致滑膜关节的功能障 碍 [Reginster, J.Y. 和 N.G.Khaltaev, Introduction and WHO perspective on the global burden of musculoskeletal conditions. Rheumatology(Oxford), 2002. 41Supp

1:p.1-2]。OA 由数种发病机理介导,包括胞外基质的酶降解、缺陷的新基质形成、细胞死亡以及软骨细胞的异常活化和肥大性分化 [Goldring,M.B. 和 S.R.Goldring,Articular cartilage and subchondral bone in the pathogenesis of osteoarthritis.Ann N Y Acad Sci,2010.1192(1):p.230-7]。目前对于 OA 仅有的治疗选择是疼痛处置和手术干预 [Hunter,D.J.,Pharmacologic therapy for osteoarthritis-the era of disease modification.Nat Rev Rheumatol,2011.7(1):p.13-22]。

[0066] 存在于骨髓和大多数成体组织中的间充质干细胞 (MSC) 能够自我更新并分化为多种细胞谱系,包括软骨细胞、成骨细胞和脂肪细胞 [Pittenger,M.F. 等 人 ,Multilineage potential of adult human mesenchymal stem cells. Science,1999.284(5411):p.143-7]。最近的研究发现,成体关节软骨含有能够多谱系分化的 MSC(细胞的大约 3 %)。在 OA 软骨中,这些细胞的数目大致加倍。这些存在的干细胞仍然保留分化成软骨细胞的能力,因此保留修复受损的软骨的能力 [Grogan,S.P. 等 人 ,Mesenchymal progenitor cell markers in human articular cartilage:normal distribution and changes in osteoarthritis.Arthritis Res Ther,2009.11(3):p.R85 ;Koelling,S. 等人,Migratory chondrogenic progenitor cells from repair tissue during the later stages of human osteoarthritis.Cell Stem Cell,2009.4(4):p.324-35]。

[0067] 本发明部分地基于以下发现 :本发明的化合物刺激间充质干细胞中的软骨细胞分化。因此,本发明提供了诱导间充质干细胞分化为软骨细胞的方法。进一步地,本发明提供了通过向关节、脊椎、椎间盘内或全身性地施用本发明的化合物或组合物,施用本发明的化合物和组合物以预防或改善关节炎或关节损伤。

定义

[0068] 在以下描述中,对某些具体的细节进行了阐述,以便透彻地理解各实施方案。然而,本领域技术人员将理解,本发明可以在没有这些细节的情况下实施。在其他情形下,没有详细示出或描述公知的结构,以避免对实施方案的不必要的模糊描述。除非上下文另有要求,在整个说明书及其后的权利要求书中,词语“包含”及其变体,诸如“包括”和“含有”应当解释为开放式、包括性含义,即作为“包括但不限于”。此外,本文提供的标题仅为了方便,并不解释所请求保护的发明的范围或含义。

[0069] 在整个说明书中提到“一个实施方案”或“实施方案”意指与该实施方案结合描述的特定的特征、结构或特性包含在至少一个实施方案中。因此,在整个说明书的各个位置出现的短语“在一个实施方案中”或“在实施方案中”并不必要均指相同的实施方案。此外,特定的特征、结构或特性可在一个或多个实施方案中以任何合适的方式进行组合。另外,如在本说明书和所附的权利要求书中所使用的,除非内容另有明确说明,单数形式的“一”、“一个”及“该 (所述)”包括复数对象。还应指出的是,除非内容另有明确说明,术语“或 (或者)”通常以其包括“和 / 或”的含义使用。

[0070] 除非另有说明,如本文所使用的下列术语具有以下含义 :

[0071] “氨基”指 $-NH_2$基团。

[0072] “氰基”或“腈”指 -CN 基团。

[0073] “羟基 (Hydroxy 或 hydroxyl)”指 -OH 基团。

[0074] “硝基”指 $-NO_2$基团。

[0075] “氧代”指＝ O 取代基。

[0076] “肟”指＝ N-OH 取代基。

[0077] “硫代”指＝ S 取代基。

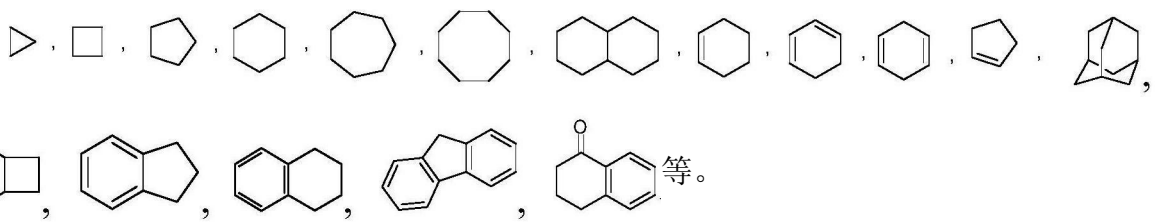
[0078] “烷基”指完全饱和或包含不饱和键的直链或支链的烃链基团，其具有 1 至 30 个碳原子，并且通过单键与分子的其余部分连接。涵盖包含 1 至 30 个中的任何数目的碳原子的烷基。包含最高达 30 个碳原子的烷基被称为 C_1-C_{30}烷基，同样地，例如，包含最高达 12 个碳原子的烷基为 C_1-C_{12}烷基。包含其他数目的碳原子的烷基（和本文所定义的其他部分）以相似的方式表示。烷基包括但不限于，C_1-C_{30}烷基、C_1-C_{20}烷基、C_1-C_{15}烷基、C_1-C_{10}烷基、C_1-C_8烷基、C_1-C_6烷基、C_1-C_4烷基、C_1-C_3烷基、C_1-C_2烷基、C_2-C_8烷基、C_3-C_8烷基和 C_4-C_8烷基。代表性的烷基包括但不限于，甲基、乙基、正丙基、1- 甲基乙基（异丙基）、正丁基、异丁基、仲丁基、正戊基、1,1- 二甲基乙基（叔丁基）、3- 甲基己基、2- 甲基己基、乙烯基、烯丙基、丙炔基等等。包含不饱和键的烷基包括烯基和炔基。除非在说明书中另外具体说明，烷基可任选地如下所述被取代。

[0079] “亚烷基”或“亚烷基链”指如以上针对烷基所述的直链或支链的二价烃链。除非在说明书中另外具体说明，亚烷基可任选地如下所述被取代。

[0080] “烷氧基”指式 $-OR_a$的基团，其中 R_a为如上定义的烷基。除非在说明书中另外具体说明，烷氧基可任选地如下所述被取代。

[0081] “芳基”指由包含氢、6 至 30 个碳原子和至少一个芳香环的烃环体系衍生的基团。该芳基可为单环、双环、三环或四环环系，可包括稠合或桥接的环系。芳基包括但不限于由醋蒽烯、苊、醋菲烯、蒽、蒽、苯、䓛、荧蒽、芴、不对称引达省 (as-indacene)、对称引达省 (s-indacene)、茚满、茚、萘、非那烯、菲、七曜烯、苉和苯并菲的烃环体系衍生的芳基。除非在说明书中另外具体说明，术语“芳基”或前缀“芳”（如在“芳烷基”中）意在包括任选取代的芳基。

[0082] “环烷基”或“碳环”指稳定的、非芳族的单环或多环碳环状环，其可包括稠合或桥接的环系，其为饱和或不饱和的。代表性的环烷基或碳环包括但不限于，具有 3 至 15 个碳原子、3 至 10 个碳原子、3 至 8 个碳原子、3 至 6 个碳原子、3 至 5 个碳原子或 3 至 4 个碳原子的环烷基。单环环烷基或碳环包括，例如，环丙基、环丁基、环戊基、环己基、环庚基和环辛基。多环基团环烷基或碳环包括，例如，金刚烷基、降冰片基、十氢化萘基、双环 [3.3.0] 辛烷、双环 [4.3.0] 壬烷、顺式十氢化萘、反式十氢化萘、双环 [2.1.1] 己烷、双环 [2.2.1] 庚烷、双环 [2.2.2] 辛烷、双环 [3.2.2] 壬烷和双环 [3.3.2] 癸烷和 7,7- 二甲基 - 双环 [2.2.1] 庚烷基。除非在说明书中另外具体说明，环烷基或碳环可任选地被取代。环烷基的说明性实例包括但不限于下列部分：



[0083] “稠合的”指与存在的环结构稠合的本文所述的任何环结构。当稠环为杂环基环或

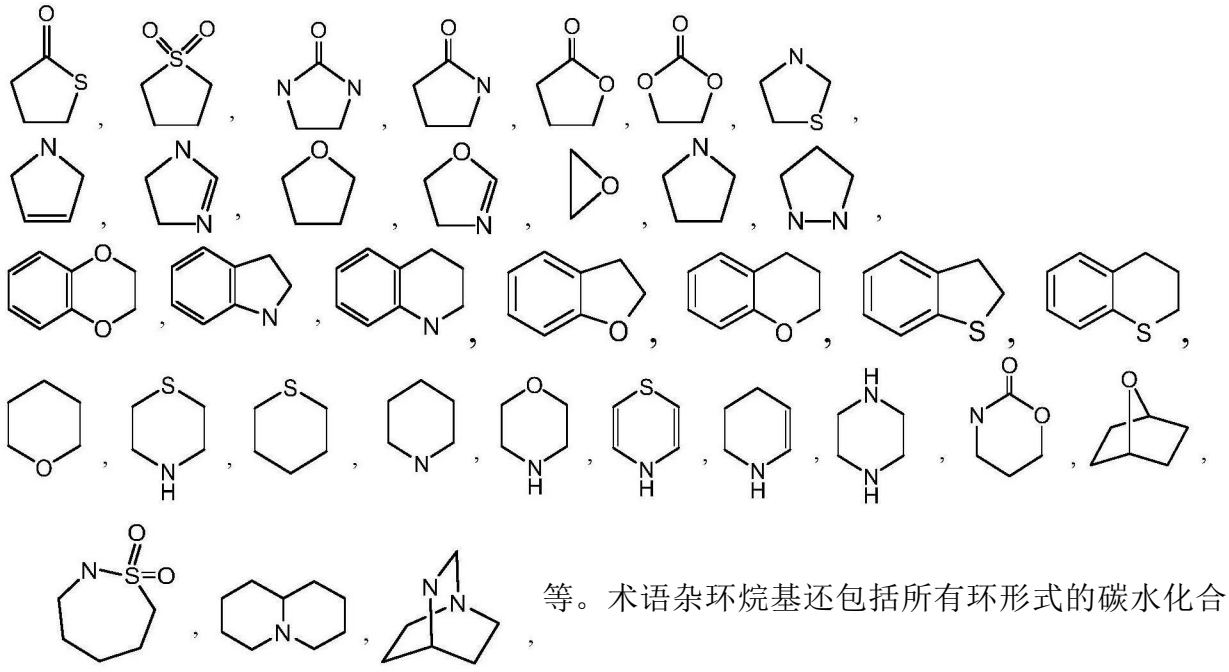
杂芳基环时，在成为稠合的杂环基环或稠合的杂芳基环的一部分的该存在的环结构上的任何碳原子可被氮原子所替代。

[0084] “卤（卤代）”或“卤素”指溴、氯、氟或碘。

[0085] “卤代烷基”指被如上所定义的一个或多个卤素基团取代的如上所定义的烷基，例如，三氟甲基、二氟甲基、氟甲基、三氯甲基、2,2,2-三氟乙基、1,2-二氟乙基、3-溴-2-氟丙基、1,2-二溴乙基等。除非在说明书中另外具体说明，卤代烷基可任选地被取代。

[0086] 类似地，“卤代烷氧基”指式 $-OR_a$ 的基团，其中 R_a 为如上所定义的卤代烷基。除非在说明书中另外具体说明，卤代烷氧基可任选地如下所述被取代。

[0087] “杂环烷基”或“杂环基”或“杂环状环”或“杂环”指包含 2 至 23 个碳原子和 1 至 8 个选自氮、氧、磷和硫的杂原子的稳定的 3 至 24 元非芳香族环基团。除非在说明书中另外具体说明，所述杂环基可为单环、双环、三环或四环环系，可包括稠合或桥接的环系；并且杂环基中的氮、碳或硫原子可任选地被氧化；氮原子可任选地被季铵化；且杂环基可以是部分或完全饱和的。这样的杂环基的实例包括但不限于，氮杂环丁基、二氧戊环基、噻吩基 [1,3] 二噻烷基、十氢异喹啉基、咪唑啉基、咪唑烷基、异噻唑烷基、异噁唑烷基、吗啉基、八氢吲哚基、八氢异吲哚基、2-氧代哌嗪基、2-氧代哌啶基、2-氧代吡咯烷基、噁唑烷基、哌啶基、哌嗪基、4-哌啶酮基 (4-piperidonyl)、吡咯烷基、吡唑烷基、奎宁环基、噻唑烷基、四氢呋喃基、三噻烷基 (trithianyl)、四氢吡喃基、硫代吗啉基 (thiomorpholinyl)、硫杂吗啉基 (thiamorpholinyl)、1-氧代-硫代吗啉基、1,1-二氧代-硫代吗啉基、12-冠醚-4、15-冠醚-5、18-冠醚-6、21-冠醚-7、氮杂-18-冠醚-6、二氮杂-18-冠醚-6、氮杂-21-冠醚-7 和二氮杂-21-冠醚-7。除非在说明书中另外具体说明，杂环基可任选地被取代。杂环烷基的说明性实例也称为非芳香族杂环，包括：



等。术语杂环烷基还包括所有环形式的碳水化合物，包括但不限于单糖、二糖和寡糖。除非另有说明，杂环烷基在环中具有 2 至 10 个碳。应理解，当提到杂环烷基中的碳原子的数目时，在该杂环烷基中的碳原子的数目不同于构成杂环烷基（即杂环烷基环的骨架原子）的原子（包括杂原子）的总数。除非在说明书中另外具体说明，杂环烷基可任选地被取代。

[0088] “杂芳基”指包含氢原子、1 至 13 个碳原子、1 至 6 个选自氮、氧、磷和硫的杂原子以及至少一个芳环的 5 至 14 元环系基团。为达到本发明的目的，杂芳基可以是单环、双环、三环或四环环系，可包括稠合或桥接的环系；且在杂芳基中的氮、碳或硫原子可任选地被氧化；氮原子可任选地被季铵化。实例包括但不限于氮杂萘基、吖啶基、苯并咪唑基、苯并噻唑基、苯并吲哚基 (benzindolyl)、苯并二氧戊环基 (benzodioxolyl)、苯并呋喃基、苯并噁唑基、苯并噻唑基、苯并噻二唑基、苯并 [b][1,4] 二氧杂萘基、1,4- 苯并二噁烷基、苯并萘并呋喃基 (benzonaphthofuranyl)、苯并噁唑基、苯并二氧戊环基、苯并二噁烯基 (benzodioxinyl)、苯并吡喃基、苯并吡喃酮基、苯并呋喃基、苯并呋喃酮基、苯并噻吩基 (benzothienyl 或 benzothiophenyl)、苯并三唑基、苯并 [4,6] 咪唑并 [1,2-a] 吡啶基、咔唑基、噌啉基、二苯并呋喃基、二苯并噻吩基、呋喃基、呋喃酮基、异噻唑基、咪唑基、吲唑基、吲哚基、吲唑基、异吲哚基、吲哚啉基、异吲哚啉基、异喹啉基、吲嗪基、异噁唑基、萘啶基、噁二唑基、2- 氧代氮杂萘基、噁唑基、环氧乙烷基、1- 氧代吡啶基、1- 氧代嘧啶基、1- 氧代吡嗪基、1- 氧代哒嗪基、1- 苯基 -1H- 吡咯基、吩嗪基、吩噻嗪基、吩噁嗪基、酞嗪基、蝶啶基、嘌呤基、吡咯基、吡唑基、吡啶基、吡嗪基、嘧啶基、哒嗪基、喹唑啉基、喹喔啉基、喹啉基、奎宁环基、异喹啉基、四氢喹啉基、噻唑基、噻二唑基、三唑基、四唑基、三嗪基和噻吩基 (thiophenyl)(即，噻吩基 (thienyl))。除非在说明书中另外具体说明，杂芳基可任选地被取代。

[0089] 上述所有基团可以是取代的或未取代的。如本文所使用的术语“取代的”指任何上述基团 (例如，烷基、亚烷基、烷氧基、芳基、环烷基、卤代烷基、杂环基和 / 或杂芳基) 可进一步被官能化，其中至少一个氢原子被连接非氢原子取代基的键所替代。除非在说明书中具体说明，被取代的基团可包括选自以下的一个或多个取代基：氧代、氨基、$-CO_2H$、腈、硝基、羟基、硫代氧基 (thiooxy)、烷基、亚烷基、烷氧基、芳基、环烷基、杂环基、杂芳基、二烷基胺、芳基胺、烷基芳基胺、二芳基胺、三烷基铵 ($-N^+R_3$)、N- 氧化物、酰亚胺和烯胺；在诸如三烷基甲硅烷基、二烷基芳基甲硅烷基、烷基二芳基甲硅烷基、三芳基甲硅烷基的基团中的硅原子，全氟烷基或全氟烷氧基，例如三氟甲基或三氟甲氧基。“取代的”还指其中一个或多个氢原子被连接杂原子的更高级的键 (例如，双键或三键) 所替代的任何上述基团，所述杂原子例如为在氧代、羰基、羧基和酯基团中的氧，和在诸如亚胺、肟、腙和腈的基团中的氮。例如，“取代的”包括其中一个或多个氢原子被 $-NH_2$、$-NR_gC(=O)NR_gR_h$、$-NR_gC(=O)OR_h$、$-NR_gSO_2R_h$、$-OC(=O)NR_gR_h$、$-OR_g$、$-SR_g$、$-SOR_g$、$-SO_2R_g$、$-OSO_2R_g$、$-SO_2OR_g$、$=NSO_2R_g$ 和 $-SO_2NR_gR_h$ 所替代的上述任何基团。在上文中，R_g 和 R_h 相同或不同，并且独立地为氢、烷基、烷氧基、烷基氨基、硫代烷基、芳基、芳烷基、环烷基、环烷基烷基、卤代烷基、杂环基、N- 杂环基、杂环基烷基、杂芳基、N- 杂芳基和 / 或杂芳基烷基。此外，上述取代基中的每一个还可任选地被一个或多个上述取代基所取代。此外，任何上述基团均可被取代，以包括一个或多个内部氧、硫或氮原子。例如，烷基可被一个或多个内部氧原子所取代，以形成醚或聚醚基团。相似地，烷基可被一个或多个内部硫原子所取代，以形成硫醚、二硫化物等。

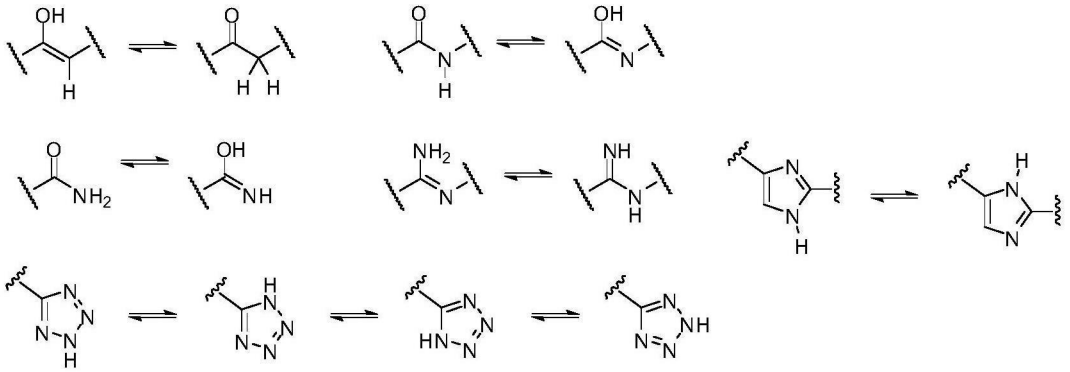
[0090] 术语“任选的”或“任选地”意指随后描述的事件或情况可能发生或可能不发生，并且该描述包括其中所述事件或情况发生的情形和所述事件或情况不发生的情形。例如，“任选取代的烷基”意指如上所定义的“烷基”或“被取代的烷基”。此外，任选取代的基团可

以是未取代的（例如，$-CH_2CH_3$）、完全取代的（例如，$-CF_2CF_3$）、单取代的（例如，$-CH_2CH_2F$），或以在完全取代和单取代之间的任一水平被取代的（例如，$-CH_2CHF_2$、$-CH_2CF_3$、$-CF_2CH_3$、$-CFHCHF_2$等）。本领域技术人员将会理解，对于含有一个或多个取代基的任何基团，这些基团并不旨在引入在空间上不能实现的和/或在合成上不可行的任何取代或取代模式（例如，被取代的烷基包括任选取代的环烷基，而该环烷基反过来又被定义为包括任选取代的烷基，如此可能无限循环）。因此，所述的任何取代基一般应理解为具有约 1,000 道尔顿，并且更典型地，高达约 500 道尔顿的最大分子量。

[0091] “有效量”或“治疗有效量”指作为单剂量或作为系列剂量的一部分施用于哺乳动物受试者并有效地产生所需治疗效果的化合物的量。

[0092] 对个体（例如，哺乳动物，如人）或细胞的“治疗（处理）”是在试图改变个体或细胞的自然进程中使用的任何类型的干预。在一些实施方案中，治疗包括在病理性事件或与病原体接触开始后施用药物组合物，并包括病况的稳定化（例如，病况不恶化）或病况的缓解。在其他实施方案中，治疗还包括预防性处理（例如当个体被怀疑为患有细菌感染时，施用本文所述的组合物）。

[0093] “互变异构体”指从分子的一个原子到同一分子的另一个原子的质子转移。本文提供的化合物可作为互变异构体存在。互变异构体为通过氢原子的迁移（伴随单键和相邻双键的转换）可相互转化的化合物。在可能发生互变异构的键合排列中，将存在互变异构体的化学平衡。考虑了本文所公开的化合物的所有互变异构形式。互变异构体的确切比例取决于若干因素，包括温度、溶剂和 pH。互变异构体相互转化的一些实例包括：



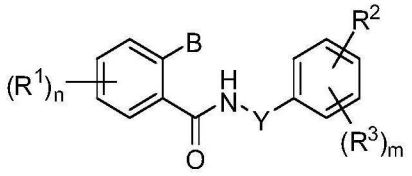
[0094] 本文所公开的化合物的“代谢物”为当化合物被代谢时所形成的该化合物的衍生物。术语“活性代谢物”指化合物被代谢时所形成的该化合物的生物活性衍生物。如本文所使用的，术语“代谢”指通过其使特定物质被生物体所改变的过程（包括但不限于，水解反应和由酶催化的反应，如氧化反应）的总和。因此，酶可产生化合物的特定结构改变。例如，细胞色素 P450 催化多种氧化和还原反应，而尿苷二磷酸葡糖醛酸基转移酶催化活化的葡糖醛酸分子转变为芳香醇、脂肪族醇、羧酸、胺和游离巯基。关于代谢的进一步信息可从 The Pharmacological Basis of Therapeutics, 第九版，McGraw-Hill(1996) 中获得。本文所公开的化合物的代谢物可通过以下方法来鉴定：将化合物施用于宿主并对来自该宿主的组织样品进行分析，或将化合物与肝细胞在体外温育并对所得化合物进行分析。这两种方法都是本领域公知的。在一些实施方案中，化合物的代谢物通过氧化过程形成，并对应于相应的含羟基化合物。在一些实施方案中，化合物被代谢成药理活性代谢物。

方法

[0095] 本文提供了一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用具有治疗有效量的本文公开的化合物的组合物。

[0096] 本文提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的本文公开的化合物，由此诱导干细胞分化为软骨细胞。

[0097] 在一方面，本文提供了一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 I 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 I)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NR^4R^{11}、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

m 为 1、2、3 或 4；

B 为 CO_2R^4、CH_2CO_2H、$CH_2CO_2R^4$或任选取代的苯基；

Y 为键、$-(CR^5R^6)-$、$-(CR^7R^8)(CR^9R^{10})-$ 或 $-(CR^7R^8)(CR^9R^{10})X-$；

X 为 O 或 CR^5R^6；

R^2为卤代、$C(O)R^4$、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或 $C(=NOR^4)R^4$；

各 R^3独立地选自 H、CN、卤代、$C(O)R^4$、CO_2H、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和 $C(=NOR^4)R^4$；

或者 R^3与相邻的 R^3或与 R^2一起形成环；

各 R^4独立地选自 H 和任选取代的烷基；

各 R^5、R^6、R^7、R^8、R^9和 R^{10}独立地选自 H、卤代、任选取代的烷基、OH、CO_2R^4、NR^4R^{11}和任选取代的烷氧基；且

R^{11}为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

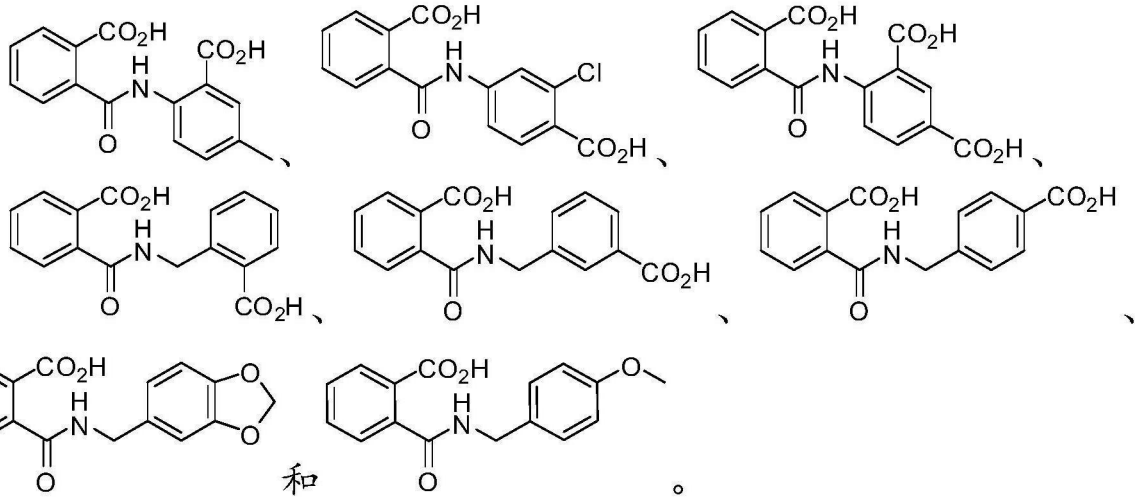
条件是

a) 如果 Y 为键且 m 为 0，则 R^2选自 $C(O)NR^4R^{11}$、$(CR^7R^8)OR^4$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、

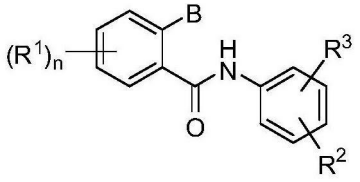
$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和 $C(=NOR^4)R^4$;且

R^2不是 $C(O)NH_2$、$p\text{-}CH_2OR^4$、$p\text{-}CH(OH)CH_2OH$、$p\text{-}CH_2CH_2OH$ 或 $p\text{-}CH_2CH_2CH_2OH$;且

b) 该化合物不选自



[0098] 在另一方面,本文提供了一种改善哺乳动物的关节炎或关节损伤的方法,该方法包括向哺乳动物的关节施用包含治疗有效量的式 Ia 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物:



(式 Ia)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NR^4R^{11}、CO_2H 或 CO_2R^4;

n 为 0、1、2、3 或 4;

B 为 CO_2R^4;

R^2为卤代、$C(O)R^4$、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或 $C(=NOR^4)R^4$;

各 R^3独立地选自 CN、卤代、$C(O)R^4$、CO_2H、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和 $C(=NOR^4)R^4$;

或者 R^3与相邻的 R^3或与 R^2一起形成环;

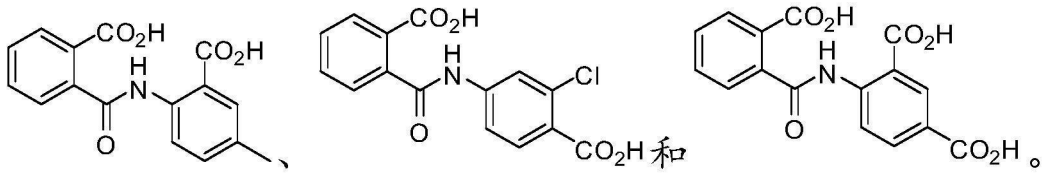
X 为 O 或 CR^5R^6；

各 R^4独立地选自 H 和任选取代的烷基；

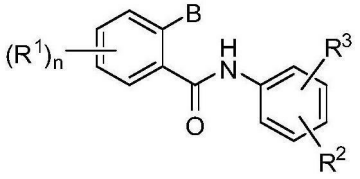
各 R^5、R^6、R^7、R^8、R^9和 R^{10}独立地选自 H、卤代、任选取代的烷基、OH、NR^4R^{11}和任选取代的烷氧基；且

R^{11}为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

条件是该化合物不选自



[0099] 在另一方面，本文提供了一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 Ib 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 Ib)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NR^4R^{11}、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 CO_2R^4；

R^2为 $C(O)NR^4R^{11}$、$(CR^7R^8)OR^4$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或 $C(=NOR^4)R^4$；

R^3为 H；

X 为 O 或 CR^5R^6；

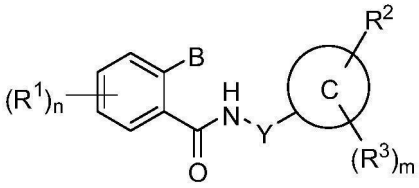
各 R^4独立地选自 H 和任选取代的烷基；

各 R^5、R^6、R^7、R^8、R^9和 R^{10}独立地选自 H、卤代、任选取代的烷基、OH、NR^4R^{11}和任选取代的烷氧基；且

R^{11}为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

条件是如果 n 为 0，则 R^2不是 $C(O)NH_2$、$p\text{-}CH_2OR^4$、$p\text{-}CH(OH)CH_2OH$、$p\text{-}CH_2CH_2OH$ 或 $p\text{-}CH_2CH_2CH_2OH$。

[0100] 在另一方面，本文提供了一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 Ic 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 Ic)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NR^4R^{11}、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

m 为 1、2、3 或 4；

B 为 CO_2R^4；

Y 为 $-(CR^5R^6)-$；

C 为芳基或杂芳基；

X 为 O 或 CR^5R^6；

R^2为卤代、$C(O)R^4$、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、SO_2NH_2、SO_3H、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或 $C(=NOR^4)R^4$；

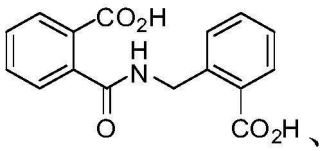
各 R^3独立地选自 H、CN、卤代、$C(O)R^4$、CO_2H、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和 $C(=NOR^4)R^4$；

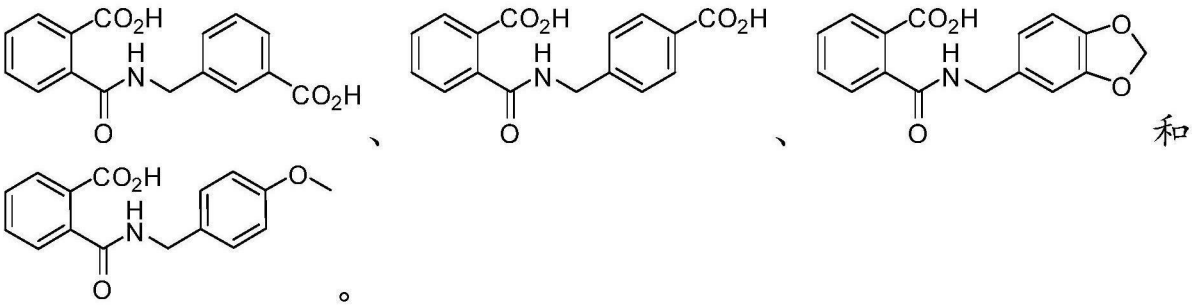
或者 R^3与相邻的 R^3或与 R^2一起形成环；

各 R^4独立地选自 H 和任选取代的烷基；

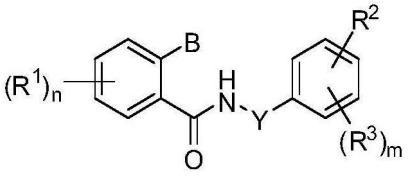
各 R^5、R^6、R^7、R^8、R^9和 R^{10}独立地选自 H、卤代、任选取代的烷基、OH、CO_2R^4、NR^4R^{11}和任选取代的烷氧基；且

R^{11}为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

条件是该化合物不选自  、



[0101] 在另一方面，本文提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 I 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 I)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NR^4R^{11}、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

m 为 1、2、3 或 4；

B 为 CO_2R^4、CH_2CO_2H、$CH_2CO_2R^3$或任选取代的苯基；

Y 为键、$-(CR^5R^6)-$、$-(CR^7R^8)(CR^9R^{10})-$ 或 $-(CR^7R^8)(CR^9R^{10})X-$；

X 为 O 或 CR^5R^6；

R^2为卤代、$C(O)R^4$、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或 $C(=NOR^4)R^4$；

各 R^3独立地选自 H、CN、卤代、$C(O)R^4$、CO_2H、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和 $C(=NOR^4)R^4$；

或者 R^3与相邻的 R^3或与 R^2一起形成环；

各 R^4独立地选自 H 和任选取代的烷基；

各 R^5、R^6、R^7、R^8、R^9和 R^{10}独立地选自 H、卤代、任选取代的烷基、OH、CO_2R^4、NR^4R^{11}和任选取代的烷氧基；且

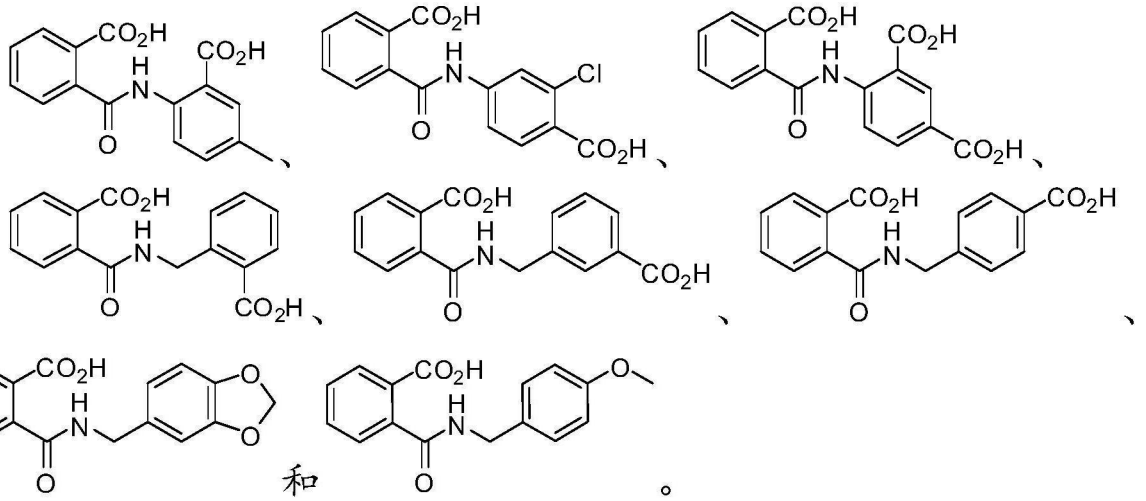
R^{11}为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

条件是

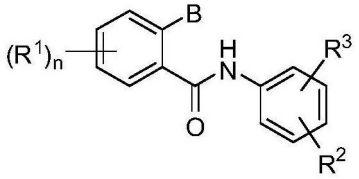
a) 如果 Y 为键且 m 为 0，则 R^2选自 $C(O)NR^4R^{11}$、$(CR^7R^8)OR^4$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和 $C(=NOR^4)R^4$；且

R^2不是 $C(O)NH_2$、$p\text{-}CH_2OR^4$、p-CH(OH)CH_2OH、$p\text{-}CH_2CH_2OH$ 或 $p\text{-}CH_2CH_2CH_2OH$；且

b) 该化合物不选自



[0102] 在另一方面，本文提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 Ia 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 Ia)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NR^4R^{11}、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 CO_2R^4；

R^2为卤代、$C(O)R^4$、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或 $C(=NOR^4)R^4$；

各 R^3独立地选自 CN、卤代、$C(O)R^4$、CO_2H、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)$

NR^4R^{11}、$(CR^7R^8)NR^4SO_2R^4$和 $C(=NOR^4)R^4$；

或者 R^3与相邻的 R^3或与 R^2一起形成环；

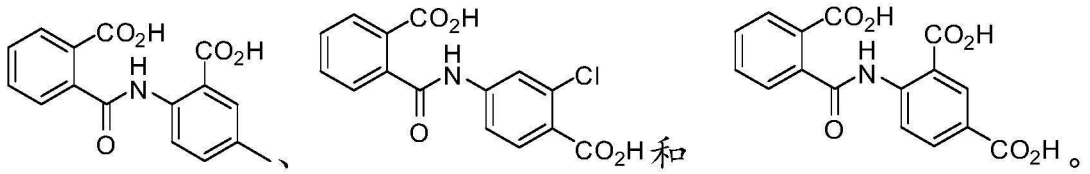
X 为 O 或 CR^5R^6；

各 R^4独立地选自 H 和任选取代的烷基；

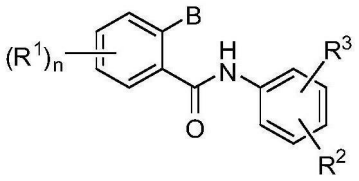
各 R^5、R^6、R^7、R^8、R^9和 R^{10}独立地选自 H、卤代、任选取代的烷基、OH、NR^4R^{11}和任选取代的烷氧基；且

R^{11}为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

条件是该化合物不选自



[0103] 在另一方面，本文提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 Ib 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 Ib)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NR^4R^{11}、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 CO_2R^4；

R^2为 $C(O)NR^4R^{11}$、$(CR^7R^8)OR^4$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或 $C(=NOR^4)R^4$；

R^3为 H；

X 为 O 或 CR^5R^6；

各 R^4独立地选自 H 和任选取代的烷基；

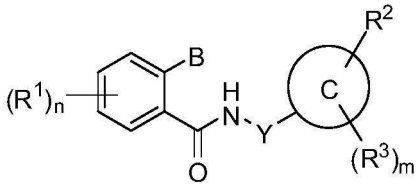
各 R^5、R^6、R^7、R^8、R^9和 R^{10}独立地选自 H、卤代、任选取代的烷基、OH、NR^4R^{11}和任选取代的烷氧基；且

R^{11}为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

条件是如果 n 为 4 且 R^1为 H，则 R^2不是 $C(O)NH_2$、$p\text{-}CH_2OR^4$、$p\text{-}CH(OH)CH_2OH$、$p\text{-}CH_2CH_2OH$或 $p\text{-}CH_2CH_2CH_2OH$。

[0104] 在另一方面，本文提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法

包括使间充质干细胞接触足量的式 Ic 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 Ic)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NR^4R^{11}、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

m 为 1、2、3 或 4；

B 为 CO_2R^4；

Y 为 $-(CR^5R^6)-$；

C 为芳基或杂芳基；

X 为 O 或 CR^5R^6；

R^2为卤代、$C(O)R^4$、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、SO_2NH_2、SO_3H、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或 $C(=NOR^4)R^4$；

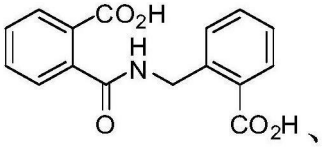
各 R^3独立地选自 H、CN、卤代、$C(O)R^4$、CO_2H、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和 $C(=NOR^4)R^4$

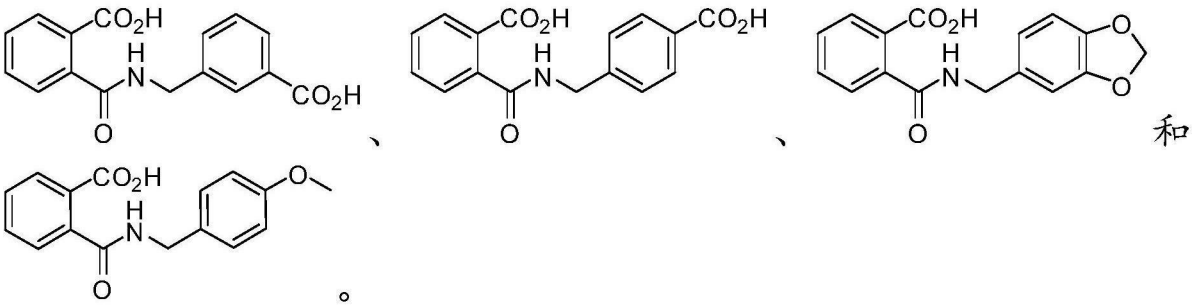
或者 R^3与相邻的 R^3或与 R^2一起形成环；

各 R^4独立地选自 H 和任选取代的烷基；

各 R^5、R^6、R^7、R^8、R^9和 R^{10}独立地选自 H、卤代、任选取代的烷基、OH、CO_2R^4、NR^4R^{11}和任选取代的烷氧基；且

R^{11}为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

条件是该化合物不选自  、



[0105] 在式 I 或 Ia 化合物的上文或下文描述的一些实施方案中：

R^2为卤代、C(O)R^4、烷基、任选取代的烷氧基、卤代烷基、$(CR^7R^8)OR^4$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)C(O)OR^4$或$X(CR^7R^8)C(O)NR^4R^{11}$；且

各 R^3独立地选自 CN、卤代、C(O)R^4、CO_2H、$C(O)NR^4R^{11}$、烷基或任选取代的烷氧基；

或者 R^3与相邻的 R^3或与 R^2一起形成环。

[0106] 在式 I 或 Ia 化合物的上文或下文描述的某些实施方案中：

R^2为 F、Cl、$C(O)CH_3$、CH_3、CF_3、OCH_3、OEt、OPr、OCF_3、$OCHF_2$、$(CR^7R^8)OR^4$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)C(O)OR^4$或$X(CR^7R^8)C(O)NR^4R^{11}$；且

各 R^3独立地选自 CN、F、Cl、$C(O)CH_3$、CO_2H、$C(O)NH_2$、CH_3、OCF_3或OCH_3；

或者 R^3与相邻的 R^3或与 R^2一起形成环。

在某些实施方案中，R^3独立地选自 CN、F、Cl、$C(O)CH_3$或CO_2H。在某些实施方案中，R^3为 CN 或CO_2H。在某些实施方案中，R^2为 F、Cl、$C(O)CH_3$、CH_3、CF_3、OCH_3、OEt、OPr、OCF_3或$CH_2CH_2CH_2OH$。在某些实施方案中，R^2为$CH_2CH_2CH_2OH$。在某些实施方案中，R^3与相邻的 R^3或与 R^2一起形成环。

[0107] 在某些实施方案中，R^2为 $(CR^7R^8)OR^4$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)C(O)OR^4$或$X(CR^7R^8)C(O)NR^4R^{11}$；且各 R^3独立地选自 CN、F、Cl、$C(O)CH_3$、CO_2H、$C(O)NH_2$、CH_3、OCF_3或OCH_3。在某些实施方案中，R^2为 F、Cl、$C(O)CH_3$、CH_3、CF_3、OCH_3、OEt、OPr、OCF_3或$CH_2CH_2CH_2OH$；且 R^3独立地选自 CN、F、Cl、$C(O)CH_3$或CO_2H。在某些实施方案中，R^2为 F、Cl、$C(O)CH_3$、CH_3、CF_3、OCH_3、OEt、OPr、OCF_3或$CH_2CH_2CH_2OH$；且 R^3独立地选自 CN 或CO_2H。在某些实施方案中，R^2为$CH_2CH_2CH_2OH$且 R^3独立地选自 CN、F、Cl、$C(O)CH_3$或CO_2H。

[0108] 在式 I 化合物的上文或下文描述的一些实施方案中：

R^2为卤代、C(O)R^4、CO_2R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或$C(=NOR^4)R^4$；且

各 R^3独立地选自 CN、卤代、C(O)R^4、$C(O)NR^4R^{11}$、烷基、任选取代的烷氧基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和$C(=NOR^4)R^4$。

[0109] 在式 Ia 化合物的上文或下文描述的一些实施方案中：

R^2为卤代、C(O)R^4、CO_2R^4、C(O)NR^4R^{11}、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或$C(=NOR^4)R^4$;且

各R^3独立地选自CN、卤代、C(O)R^4、C(O)NR^4R^{11}、烷基、任选取代的烷氧基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和$C(=NOR^4)R^4$。

[0110] 在式Ib化合物的上文或下文描述的一些实施方案中：

R^2为$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或$C(=NOR^4)R^4$;且

R^3为H。

在某些实施方案中，R^2为$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$或$(CR^7R^8)NR^4SO_2R^4$。在某些实施方案中，$R^2$为$CH_2CH_2OH$、$CH_2CH_2OCH_3$、$CH_2CHCH_3OH$、$CHCH_3CH_2OH$、$CH_2CH_2CH_2OH$、$CH_2CH_2CH_2NH_2$、$CH_2CH_2CHCH_3OH$、$C(CH_3)_2CH_2CH_2OH$、$CH_2CH_2C(CH_3)_2OH$、$OCH_2CH_2OH$、$OCH_2CH_2OCH_3$或$OCH_2CH_2NH_2$。在某些实施方案中，$R^2$为$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$或$X(CR^7R^8)C(O)NR^4R^{11}$。在某些实施方案中，$R^2$为$CH_2C(O)CH_3$、$CH_2C(O)NH_2$、$CH_2CH_2C(O)CH_3$或$CH_2CH_2C(O)NH_2$。

[0111] 在式Ic化合物的上文或下文描述的一些实施方案中，C为芳基。在某些实施方案中，C为苯基。在某些实施方案中，C为萘基。

[0112] 在式Ic化合物的上文或下文描述的一些实施方案中，C为杂芳基。在某些实施方案中，C为吡啶基、嘧啶基、哒嗪基或吡嗪基。在某些实施方案中，C为吡啶基。在某些实施方案中，C为嘧啶基。在某些实施方案中，C为哒嗪基。在某些实施方案中，C为5元杂芳基环。在某些实施方案中，C为噻吩、苯并呋喃、吡咯、噻唑、咪唑、噁唑、吡唑或三唑。

[0113] 在式Ic化合物的上文或下文描述的一些实施方案中：

R^2为卤代、C(O)R^4、CO_2R^4、C(O)NR^4R^{11}、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、SO_2NH_2、SO_3H、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$或$C(=NOR^4)R^4$;且

各R^3独立地选自H、CN、卤代、C(O)R^4、CO_2R^4、C(O)NR^4R^{11}、烷基、任选取代的烷氧基、卤代烷基、SO_2R^4、$(CR^7R^8)OR^4$、$(CR^7R^8)NR^4R^{11}$、$(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})OR^4$、$X(CR^7R^8)(CR^9R^{10})NR^4R^{11}$、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)R^4$、$X(CR^7R^8)C(O)OR^4$、$X(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)(CR^9R^{10})C(O)R^4$、$X(CR^7R^8)(CR^9R^{10})C(O)OR^4$、$X(CR^7R^8)(CR^9R^{10})C(O)NR^4R^{11}$、$(CR^7R^8)NR^4SO_2R^4$和$C(=NOR^4)R^4$;

条件是如果n＝0且C为苯基，R^2不是CO_2H或p-OCH_3。

[0114] 在式Ic化合物的上文或下文描述的一些实施方案中：

R^2为卤代、C(O)R^4、CO_2R^4、C(O)NR^4R^{11}、烷基、任选取代的烷氧基、卤代烷基、SO_2NH_2、SO_3H、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)OR^4$或$X(CR^7R^8)C(O)NR^4R^{11}$；且

各R^3独立地选自H、CN、卤代、CO_2H或卤代烷基。

[0115] 在式Ic化合物的上文或下文描述的某些实施方案中：

R^2为Cl、F、C(O)CH_3、CO_2H、C(O)NR^4R^{11}、CH_3、任选取代的烷氧基、CF_3、SO_2NH_2、SO_3H、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)OR^4$或$X(CR^7R^8)C(O)NR^4R^{11}$；且

各R^3独立地选自H、CN、Cl、F、CO_2H或CF_3。

在某些实施方案中，R^2为Cl、F、C(O)CH_3、CO_2H、CH_3、OCH_3、CF_3；且各R^3独立地选自H、CN或CO_2H。在某些实施方案中，R^2为$CH_2C(O)NH_2$、$CH_2C(O)CH_3$、$CH_2C(O)OH$、$CH_2CH_2C(O)OH$或$CH_2CH_2C(O)NH_2$。在某些实施方案中，R^2为CO_2H。在某些实施方案中，R^2为CO_2H且各R^3独立地选自H、CN、Cl、F或CF_3。

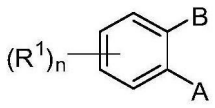
[0116] 在式Ic化合物的上文或下文描述的某些实施方案中：

R^2为Cl、F、C(O)CH_3、CO_2H、C(O)NR^4R^{11}、CH_3、任选取代的烷氧基、CF_3、SO_2NH_2、SO_3H、$(CR^7R^8)C(O)R^4$、$(CR^7R^8)C(O)OR^4$、$(CR^7R^8)C(O)NR^4R^{11}$、$X(CR^7R^8)C(O)OR^4$或$X(CR^7R^8)C(O)NR^4R^{11}$；且

各R^3独立地选自H、CN或CO_2H。

在某些实施方案中，R^2为$CH_2C(O)NH_2$、$CH_2C(O)CH_3$、$CH_2C(O)OH$、$CH_2CH_2C(O)OH$或$CH_2CH_2C(O)NH_2$；且各R^3独立地选自H、CN或CO_2H。

[0117] 在一方面，本文提供了一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式II化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N-氧化物、立体异构体或异构体的组合物：



(式II)

其中

各R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、S(O)R^4、SO_2R^4、NHR^5、NR^4R^5、CO_2H或CO_2R^4；

n为0、1、2、3或4；

B为$NHC(O)R^2$、$NR^3C(O)R^2$、$NHC(O)NH_2$、$NHC(O)NHR^2$、$NHC(O)NR^2R^4$、$NR^3C(O)NH_2$、$NR^3C(O)NHR^2$、$NR^3C(O)NR^2R^4$、$NHC(O)OR^2$、$NR^3C(O)OR^2$、$NHSO_2R^3$、$NR^3SO_2R^3$、$NHSO_2R^4$、$NR^3SO_2R^4$、$NHSO_2NH_2$、$NHSO_2NHR^2$、$NHSO_2NR^2R^4$、$NR^3SO_2NH_2$、$NR^3SO_2NHR^2$或$NR^3SO_2NR^2R^4$；

各R^2和R^4独立地为任选取代的苯基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳烷基或任选取代的烷基；

R^3为任选取代的烷基或任选取代的芳烷基；

R^5为H、任选取代的烷基、C(O)R^4、C(O)OR^4、C(O)NR^4R^4或SO_2R^4；

A为CO_2H、CO_2R^3、C(O)NH_2、C(O)NHR^2、C(O)NR^2R^4或$SO_2NR^aR^b$；且

各R^a和R^b独立地为任选取代的烷基或者与它们所连接的N一起形成环；

条件是

a) 如果 B 为 NHC(O)R^2或 $NR^3C(O)R^2$，则 A 不是 CO_2H；且

b) 该化合物不选自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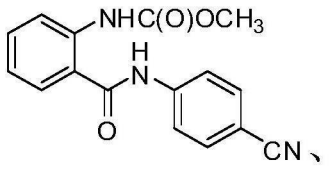
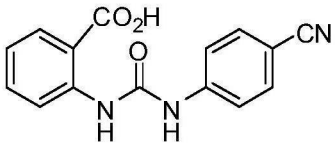

、

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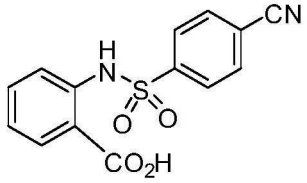
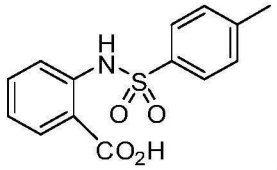
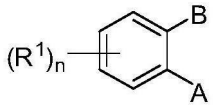

和

。

[0118] 在另一方面，本文提供了一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 IIa 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 IIa)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

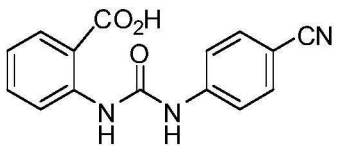
B 为 $NHC(O)NH_2$、$NHC(O)NHR^2$、$NHC(O)NR^2R^4$、$NR^3C(O)NH_2$、$NR^3C(O)NHR^2$或 $NR^3C(O)NR^2R^4$；

各 R^2和 R^4独立地为任选取代的苯基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳烷基或任选取代的烷基；

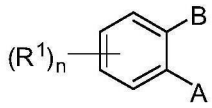
R^3为任选取代的烷基或任选取代的芳烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；且

A 为 CO_2H 或 CO_2R^3；

条件是该化合物不是 
。

[0119] 在另一方面，本文提供了一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 IIb 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 IIb)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 $NHC(O)R^2$或 $NR^3C(O)R^2$；

R^2为任选取代的苯基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳烷基或任选取代的烷基；

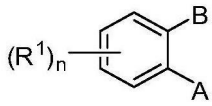
R^3为任选取代的烷基或任选取代的芳烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

A 为 $SO_2NR^aR^b$；且

各 R^a和 R^b独立地为任选取代的烷基或者与它们所连接的 N 一起形成环。

[0120] 在另一方面，本文提供了一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 IIc 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 IIc)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

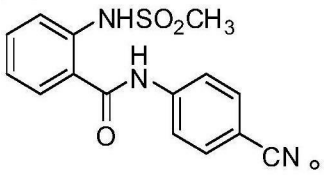
B 为 $NHSO_2R^3$、$NR^3SO_2R^3$、$NHSO_2R^4$、$NR^3SO_2R^4$、$NHSO_2NH_2$、$NHSO_2NHR^2$、$NHSO_2NR^2R^4$、$NR^3SO_2NH_2$、$NR^3SO_2NHR^2$或 $NR^3SO_2NR^2R^4$；

各 R^2和 R^4独立地为任选取代的苯基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳烷基或任选取代的烷基；

各 R^3独立地为任选取代的烷基或任选取代的芳烷基；

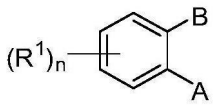
R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；且

A 为 $C(O)NHR^2$或 $C(O)NR^2R^4$；

条件是该化合物不是  。

[0121] 在另一方面，本文提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法

包括使间充质干细胞接触足量的式 II 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 II)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 $NHC(O)R^2$、$NR^3C(O)R^2$、$NHC(O)NH_2$、$NHC(O)NHR^2$、$NHC(O)NR^2R^4$、$NR^3C(O)NH_2$、$NR^3C(O)NHR^2$、$NR^3C(O)NR^2R^4$、$NHC(O)OR^2$、$NR^3C(O)OR^2$、$NHSO_2R^3$、$NR^3SO_2R^3$、$NHSO_2R^4$、$NR^3SO_2R^4$、$NHSO_2NH_2$、$NHSO_2NHR^2$、$NHSO_2NR^2R^4$、$NR^3SO_2NH_2$、$NR^3SO_2NHR^2$或 $NR^3SO_2NR^2R^4$；

各 R^2和 R^4独立地为任选取代的苯基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳烷基或任选取代的烷基；

R^3为任选取代的烷基或任选取代的芳烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

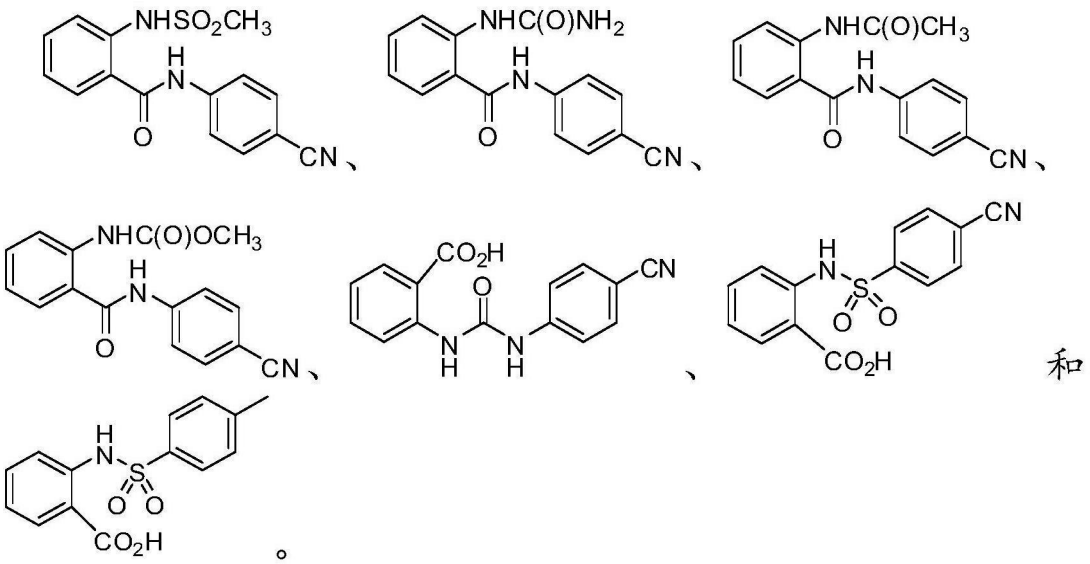
A 为 CO_2H、CO_2R^3、$C(O)NH_2$、$C(O)NHR^2$、$C(O)NR^2R^4$或 $SO_2NR^aR^b$；且

各 R^a和 R^b独立地为任选取代的烷基或者与它们所连接的 N 一起形成环；

条件是

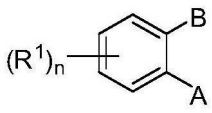
a) 如果 B 为 $NHC(O)R^2$或 $NR^3C(O)R^2$，则 A 不是 CO_2H；且

b) 该化合物不选自



。

[0122] 在另一方面，本文提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 IIa 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 IIa)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

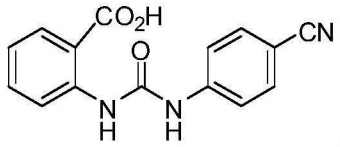
B 为 $NHC(O)NH_2$、$NHC(O)NHR^2$、$NHC(O)NR^2R^4$、$NR^3C(O)NH_2$、$NR^3C(O)NHR^2$或 $NR^3C(O)NR^2R^4$；

各 R^2和 R^4独立地为任选取代的苯基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳烷基或任选取代的烷基；

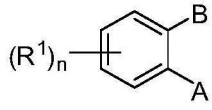
R^3为任选取代的烷基或任选取代的芳烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；且

A 为 CO_2H 或 CO_2R^3；

条件是该化合物不是  。

[0123] 在另一方面，本文提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 IIb 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 IIb)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 $NHC(O)R^2$或 $NR^3C(O)R^2$；

R^2为任选取代的苯基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳烷基或任选取代的烷基；

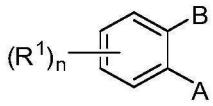
R^3为任选取代的烷基或任选取代的芳烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；

A 为 $SO_2NR^aR^b$；且

各 R^a和 R^b独立地为任选取代的烷基或者与它们所连接的 N 一起形成环。

[0124] 在另一方面，本文提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 IIc 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 IIc)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

B 为 $NHSO_2R^3$、$NR^3SO_2R^3$、$NHSO_2R^4$、$NR^3SO_2R^4$、$NHSO_2NH_2$、$NHSO_2NHR^2$、$NHSO_2NR^2R^4$、$NR^3SO_2NH_2$、$NR^3SO_2NHR^2$或 $NR^3SO_2NR^2R^4$；

各 R^2和 R^4独立地为任选取代的苯基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳烷基或任选取代的烷基；

各 R^3独立地为任选取代的烷基或任选取代的芳烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；且

A 为 $C(O)NHR^2$或 $C(O)NR^2R^4$；

条件是该化合物不是  。

[0125] 在式 IIa 化合物的上文或下文描述的一些实施方案中，B 为 $NHC(O)NHR^2$、$NHC(O)NR^2R^4$、$NR^3C(O)NHR^2$或 $NR^3C(O)NR^2R^4$。在某些实施方案中，B 为 $NHC(O)NHR^2$或 $NR^3C(O)NHR^2$。在某些实施方案中，B 为 $NHC(O)NR^2R^4$或 $NR^3C(O)NR^2R^4$。在某些实施方案中，B 为 $NHC(O)NHR^2$。

[0126] 在式 IIa 化合物的上文或下文描述的一些实施方案中，B 为 $NHC(O)NHR^2$、$NHC(O)NR^2R^4$、$NR^3C(O)NHR^2$或 $NR^3C(O)NR^2R^4$；且 A 为 CO_2H。在某些实施方案中，B 为 $NHC(O)NHR^2$或 $NR^3C(O)NHR^2$；且 A 为 CO_2H。在某些实施方案中，B 为 $NHC(O)NHR^2$且 A 为 CO_2H。在某些实施方案中，B 为 $NHC(O)NHR^2$且 A 为 CO_2H，其中 R^2为任选取代的苯基。

[0127] 在式 IIa 化合物的上文或下文描述的一些实施方案中，B 为 $NHC(O)NHR^2$、$NHC(O)NR^2R^4$、$NR^3C(O)NHR^2$或 $NR^3C(O)NR^2R^4$；且 A 为 CO_2R^3。在某些实施方案中，B 为 $NHC(O)NHR^2$或 $NR^3C(O)NHR^2$；且 A 为 CO_2R^3。在某些实施方案中，B 为 $NHC(O)NHR^2$且 A 为 CO_2R^3。在某些实施方案中，B 为 $NHC(O)NHR^2$且 A 为 CO_2R^3，其中 R^2为任选取代的苯基。

[0128] 在式 IIa 化合物的上文或下文描述的一些实施方案中，R^2为任选取代的苯基。在某些实施方案中，R^2的苯基为双取代的。在某些实施方案中，R^2的苯基为单取代的。在某些实施方案中，R^2的苯基上的取代独立地选自任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、卤代、CN、CO_2H、氨基、单烷基胺、二烷基胺、单芳基胺、烷基芳基胺、环烷基、羟基、C(O)-（任选取代的烷基）、$C(O)NH_2$、C(O)NH-（任选取代的烷基）、烷基硫醚、烷基亚砜、烷基砜、C(O)-（任选取代的芳基）、C(O)NH-（任选取代的芳基）、芳基硫醚、芳基亚砜或芳基砜。在某些实施方案中，R^2的苯基上的取代独立地选自 F、Cl、CO_2H、CN、OCH_3、$C(O)CH_3$、CF_3、CH_3、CH_2OH、CH_2CH_2OH 和 $CH_2CH_2CH_2OH$。在某些实施方案中，R^2的苯基上的双取代由 CN 和选自 F、Cl、CO_2H、OCH_3、$C(O)CH_3$、CF_3、CH_3、CH_2OH、CH_2CH_2OH 和 $CH_2CH_2CH_2OH$ 的基团组成。在某些实施方

案中，R^2的苯基上的双取代由 CO_2H 和选自 F、Cl、CN、OCH_3、$C(O)CH_3$、CF_3、CH_3、CH_2OH、CH_2CH_2OH 和 $CH_2CH_2CH_2OH$ 的基团组成。在某些实施方案中，R^2的苯基上的双取代由 $CH_2CH_2CH_2OH$ 和选自 F、Cl、CN、OCH_3、$C(O)CH_3$、CF_3、CH_3、CH_2OH、CH_2CH_2OH 和 CO_2H 的基团组成。

[0129] 在式 IIa 化合物的上文或下文描述的一些实施方案中，R^2为任选取代的萘基。

[0130] 在式 IIa 化合物的上文或下文描述的一些实施方案中，R^2为任选取代的杂芳基。在某些实施方案中，R^2为任选取代的吡啶基、任选取代的嘧啶基、任选取代的哒嗪基或任选取代的吡嗪基。在某些实施方案中，R^2为任选取代的 5 元杂芳基环。在某些实施方案中，该 5 元杂芳基环为噻吩、苯并呋喃、吡咯、噻唑、咪唑、噁唑、吡唑或三唑。在某些实施方案中，R^2为任选取代的双环杂芳基。在某些实施方案中，该双环杂芳基为苯并咪唑、苯并噻唑、苯并噁唑、吲唑、喹啉或萘啶。

[0131] 在式 IIb 化合物的上文或下文描述的一些实施方案中，B 为 $NHC(O)R^2$。在某些实施方案中，B 为 $NHC(O)R^2$且 R^2为任选取代的苯基。在某些实施方案中，B 为 $NHC(O)R^2$且 R^2为任选取代的杂芳基。

[0132] 在式 IIb 化合物的上文或下文描述的一些实施方案中，B 为 $NR^3C(O)R^2$。在某些实施方案中，R^3为任选取代的烷基。

[0133] 在式 IIb 化合物的上文或下文描述的一些实施方案中，各 R^a和 R^b独立地为任选取代的烷基。在某些实施方案中，各 R^a和 R^b独立地为烷基。在式 IIb 化合物的上文或下文描述的一些实施方案中，R^a和 R^b与它们所连接的 N 一起形成环。在某些实施方案中，该环为吗啉基、硫代吗啉基、哌啶基、吡咯烷基、氮杂环丁基、氮丙啶基、氮杂环庚基、高哌嗪基或哌嗪基。

[0134] 在式 IIb 化合物的上文或下文描述的一些实施方案中，R^2为任选取代的苯基。在某些实施方案中，R^2的苯基为双取代的。在某些实施方案中，R^2的苯基为单取代的。在某些实施方案中，R^2的苯基上的取代独立地选自任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、卤代、CN、CO_2H、氨基、单烷基胺、二烷基胺、单芳基胺、烷基芳基胺、环烷基、羟基、C(O)-（任选取代的烷基）、$C(O)NH_2$、C(O)NH-（任选取代的烷基）、烷基硫醚、烷基亚砜、烷基砜、C(O)-（任选取代的芳基）、C(O)NH-（任选取代的芳基）、芳基硫醚、芳基亚砜或芳基砜。在某些实施方案中，R^2的苯基上的取代独立地选自 F、Cl、CO_2H、CN、OCH_3、$C(O)CH_3$、CF_3、CH_3、CH_2OH、CH_2CH_2OH 和 $CH_2CH_2CH_2OH$。在某些实施方案中，R^2的苯基上的双取代由 CN 和选自 F、Cl、CO_2H、OCH_3、$C(O)CH_3$、CF_3、CH_3、CH_2OH、CH_2CH_2OH 和 $CH_2CH_2CH_2OH$ 的基团组成。在某些实施方案中，R^2的苯基上的双取代由 CO_2H 和选自 F、Cl、CN、OCH_3、$C(O)CH_3$、CF_3、CH_3、CH_2OH、CH_2CH_2OH 和 $CH_2CH_2CH_2OH$ 的基团组成。在某些实施方案中，R^2的苯基上的双取代由 $CH_2CH_2CH_2OH$ 和选自 F、Cl、CN、OCH_3、$C(O)CH_3$、CF_3、CH_3、CH_2OH、CH_2CH_2OH 和 CO_2H 的基团组成。

[0135] 在式 IIb 化合物的上文或下文描述的一些实施方案中，R^2为任选取代的萘基。

[0136] 在式 IIb 化合物的上文或下文描述的一些实施方案中，R^2为任选取代的杂芳基。在某些实施方案中，R^2为任选取代的吡啶基、任选取代的嘧啶基、任选取代的哒嗪基或任选取代的吡嗪基。在某些实施方案中，R^2为任选取代的 5 元杂芳基环。在某些实施方案中，该 5 元杂芳基环为噻吩、苯并呋喃、吡咯、噻唑、咪唑、噁唑、吡唑或三唑。在某些实施方案中，R^2为任选取代的双环杂芳基。在某些实施方案中，该双环杂芳基为苯并咪唑、苯并噻唑、苯并噁唑、吲唑、喹啉或萘啶。

[0137] 在式 IIc 化合物的上文或下文描述的一些实施方案中，B 为 $NHSO_2R^3$、$NR^3SO_2R^3$、$NHSO_2R^4$ 或 $NR^3SO_2R^4$。在某些实施方案中，B 为 $NHSO_2R^3$ 或 $NR^3SO_2R^3$。在某些实施方案中，B 为 $NHSO_2R^3$。在某些实施方案中，R^3 为任选取代的烷基。在某些实施方案中，R^3 为烷基。在某些实施方案中，R^3 为 CH_3。在某些实施方案中，B 为 $NHSO_2R^4$ 或 $NR^3SO_2R^4$。在某些实施方案中，R^4 为任选取代的苯基。在某些实施方案中，R^4 为任选取代的萘基。在某些实施方案中，R^4 为任选取代的杂芳基。在某些实施方案中，R^4 为任选取代的杂环基。

[0138] 在式 IIc 化合物的上文或下文描述的一些实施方案中，B 为 $NHSO_2R^3$、$NR^3SO_2R^3$、$NHSO_2R^4$ 或 $NR^3SO_2R^4$ 且 A 为 C(O)NHR^2。在某些实施方案中，B 为 $NHSO_2R^3$ 或 $NR^3SO_2R^3$ 且 A 为 C(O)NHR^2。在某些实施方案中，B 为 $NHSO_2R^3$ 且 A 为 C(O)NHR^2。在某些实施方案中，B 为 $NHSO_2R^3$ 且 A 为 C(O)NHR^2，其中 R^3 为任选取代的烷基。在某些实施方案中，B 为 $NHSO_2R^3$ 且 A 为 C(O)NHR^2，其中 R^3 为任选取代的烷基且 R^2 为任选取代的苯基。在某些实施方案中，B 为 $NHSO_2R^3$ 且 A 为 C(O)NHR^2，其中 R^3 为任选取代的烷基且 R^2 为任选取代的杂芳基。

[0139] 在式 IIc 化合物的上文或下文描述的一些实施方案中，B 为 $NHSO_2R^3$、$NR^3SO_2R^3$、$NHSO_2R^4$ 或 $NR^3SO_2R^4$ 且 A 为 C(O)NR^2R^4。在某些实施方案中，B 为 $NHSO_2R^3$ 或 $NR^3SO_2R^3$ 且 A 为 C(O)NR^2R^4。在某些实施方案中，B 为 $NHSO_2R^3$ 且 A 为 C(O)NR^2R^4。在某些实施方案中，B 为 $NHSO_2R^3$ 且 A 为 C(O)NR^2R^4，其中 R^3 为任选取代的烷基。在某些实施方案中，B 为 $NHSO_2R^3$ 且 A 为 C(O)NR^2R^4，其中 R^3 为任选取代的烷基且 R^2 为任选取代的苯基。在某些实施方案中，B 为 $NHSO_2R^3$ 且 A 为 C(O)NR^2R^4，其中 R^3 为任选取代的烷基且 R^2 为任选取代的杂芳基。

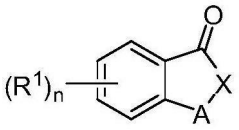
[0140] 在式 IIc 化合物的上文或下文描述的一些实施方案中，B 为 $NHSO_2NH_2$、$NHSO_2NHR^2$、$NHSO_2NR^2R^4$、$NR^3SO_2NH_2$、$NR^3SO_2NHR^2$ 或 $NR^3SO_2NR^2R^4$。在某些实施方案中，B 为 $NHSO_2NH_2$、$NHSO_2NHR^2$、$NHSO_2NR^2R^4$、$NR^3SO_2NH_2$、$NR^3SO_2NHR^2$ 或 $NR^3SO_2NR^2R^4$ 且 A 为 C(O)NHR^2。在某些实施方案中，B 为 $NHSO_2NH_2$、$NHSO_2NHR^2$、$NHSO_2NR^2R^4$、$NR^3SO_2NH_2$、$NR^3SO_2NHR^2$ 或 $NR^3SO_2NR^2R^4$ 且 A 为 C(O)NR^2R^4。

[0141] 在式 IIc 化合物的上文或下文描述的一些实施方案中，A 为 C(O)NHR^2。在式 IIc 化合物的上文或下文描述的一些实施方案中，A 为 C(O)NR^2R^4。在某些实施方案中，R^2 为任选取代的苯基。在某些实施方案中，R^2 的苯基为双取代的。在某些实施方案中，R^2 的苯基为单取代的。在某些实施方案中，R^2 的苯基上的取代独立地选自任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、卤代、CN、CO_2H、氨基、单烷基胺、二烷基胺、单芳基胺、烷基芳基胺、环烷基、羟基、C(O)-（任选取代的烷基）、C(O)NH_2、C(O)NH-（任选取代的烷基）、烷基硫醚、烷基亚砜、烷基砜、C(O)-（任选取代的芳基）、C(O)NH-（任选取代的芳基）、芳基硫醚、芳基亚砜或芳基砜。在某些实施方案中，R^2 的苯基上的取代独立地选自 F、Cl、CO_2H、CN、OCH_3、$C(O)CH_3$、CF_3、CH_3、CH_2OH、CH_2CH_2OH 和 $CH_2CH_2CH_2OH$。在某些实施方案中，R^2 的苯基上的双取代由 CN 和选自 F、Cl、CO_2H、OCH_3、$C(O)CH_3$、CF_3、CH_3、CH_2OH、CH_2CH_2OH 和 $CH_2CH_2CH_2OH$ 的基团组成。在某些实施方案中，R^2 的苯基上的双取代由 CO_2H 和选自 F、Cl、CN、OCH_3、$C(O)CH_3$、CF_3、CH_3、CH_2OH、CH_2CH_2OH 和 $CH_2CH_2CH_2OH$ 的基团组成。在某些实施方案中，R^2 的苯基上的双取代由 $CH_2CH_2CH_2OH$ 和选自 F、Cl、CN、OCH_3、$C(O)CH_3$、CF_3、CH_3、CH_2OH、CH_2CH_2OH 和 CO_2H 的基团组成。在某些实施方案中，R^2 为任选取代的萘基。

[0142] 在式 IIc 化合物的上文或下文描述的一些实施方案中，R^2 为任选取代的杂芳基。在某些实施方案中，R^2 为任选取代的吡啶基、任选取代的嘧啶基、任选取代的哒嗪基或任选

取代的吡嗪基。在某些实施方案中，R^2为任选取代的 5 元杂芳基环。在某些实施方案中，该 5 元杂芳基环为噻吩、苯并呋喃、吡咯、噻唑、咪唑、噁唑、吡唑或三唑。在某些实施方案中，R^2为任选取代的双环杂芳基。在某些实施方案中，该双环杂芳基为苯并咪唑、苯并噻唑、苯并噁唑、吲唑、喹啉或萘啶。

[0143] 在另一方面，本文提供了一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 III 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 III)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

X 为 O、NH 或 NR^6；

A 为 C(O)、CH_2或 $CH\text{-}CR^3R^4\text{-}C(O)R^2$；

R^2为任选取代的芳基或任选取代的杂芳基；

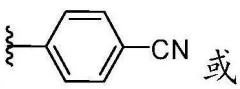
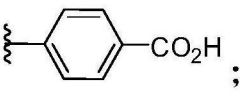
各 R^3和 R^4独立地为 H 或任选取代的烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；且

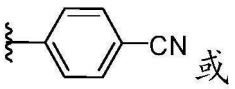
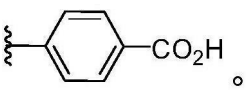
R^6为任选取代的苯基；

条件是

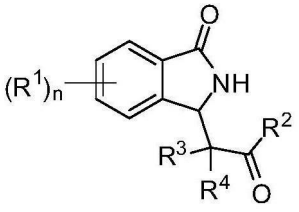
a) 如果 A 为 $CH\text{-}CR^3R^4\text{-}C(O)R^2$，则 X 为 O 或 NH；

b) 如果 n 为 0，A 为 $CHCH_2C(O)R^2$且 X 为 O，则 R^2不是  或  ；

且

c) 如果 A 为 C(O) 或 CH_2，则 X 为 NR^6且 R^6不是  或  。

[0144] 在另一方面，本文提供了一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的式 IIIa 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物：



(式 IIIa)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

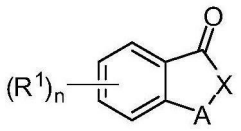
n 为 0、1、2、3 或 4；

R^2为任选取代的芳基或任选取代的杂芳基；

各 R^3和 R^4独立地为 H 或任选取代的烷基；且

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4。

[0145] 在另一方面，本文提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 III 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 III)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

X 为 O、NH 或 NR^6；

A 为 C(O)、CH_2或 $CH-CR^3R^4-C(O)R^2$；

R^2为任选取代的芳基或任选取代的杂芳基；

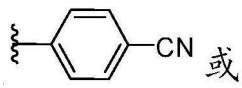
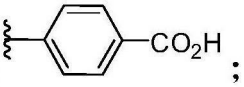
各 R^3和 R^4独立地为 H 或任选取代的烷基；

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4；且

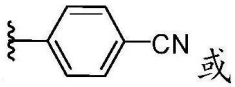
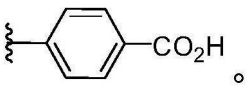
R^6为任选取代的苯基；

条件是

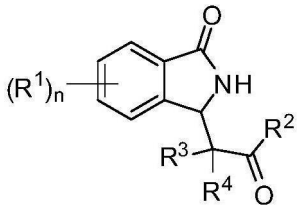
d) 如果 A 为 $CH-CR^3R^4-C(O)R^2$，则 X 为 O 或 NH；

e) 如果 n 为 0，A 为 $CHCH_2C(O)R^2$且 X 为 O，则 R^2不是  或  ；

且

如果 A 为 C(O) 或 CH_2，则 X 为 NR^6且 R^6不是  或  。

[0146] 在另一方面，本文提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的式 IIIa 化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体：



(式 IIIa)

其中

各 R^1独立地为卤代、任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、CN、NO_2、SR^4、$S(O)R^4$、SO_2R^4、NHR^5、NR^4R^5、CO_2H 或 CO_2R^4；

n 为 0、1、2、3 或 4；

R^2为任选取代的芳基或任选取代的杂芳基；

各 R^3和 R^4独立地为 H 或任选取代的烷基；且

R^5为 H、任选取代的烷基、$C(O)R^4$、$C(O)OR^4$、$C(O)NR^4R^4$或 SO_2R^4。

[0147] 在式 III 化合物的上文或下文描述的一些实施方案中，X 为 NR^6且 A 为 C(O)。在式 III 化合物的上文或下文描述的一些实施方案中，X 为 NR^6且 A 为 CH_2。在式 III 化合物的上文或下文描述的一些实施方案中，X 为 O 且 A 为 $CH\text{-}CR^3R^4\text{-}C(O)R^2$。在式 III 化合物的上文或下文描述的一些实施方案中，X 为 NH 且 A 为 $CH\text{-}CR^3R^4\text{-}C(O)R^2$。

[0148] 在式 III 或 IIIa 化合物的上文或下文描述的一些实施方案中，R^3和 R^4均为氢。在式 III 或 IIIa 化合物的上文或下文描述的一些实施方案中，R^3为任选取代的烷基且 R^4为氢。在式 III 或 IIIa 化合物的上文或下文描述的一些实施方案中，R^3和 R^4独立地为任选取代的烷基。

[0149] 在式 III 或 IIIa 化合物的上文或下文描述的一些实施方案中，R^2为杂芳基。在某些实施方案中，R^2为任选取代的任选取代的吡啶基、任选取代的嘧啶基、任选取代的哒嗪基或任选取代的吡嗪基。在某些实施方案中，R^2为 5 元杂芳基。在某些实施方案中，该 5 元杂芳基为噻吩、苯并呋喃、吡咯、噻唑、咪唑、噁唑、吡唑或三唑。在某些实施方案中，R^2为双环杂芳基。在某些实施方案中，该双环杂芳基为苯并咪唑、苯并噻唑、苯并噁唑、吲唑、喹啉或萘啶。

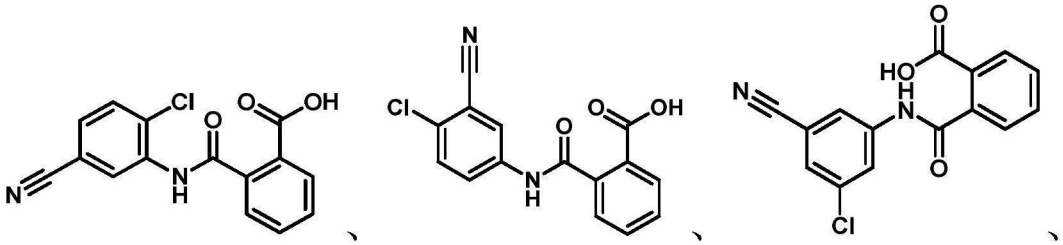
[0150] 在式 III 或 IIIa 化合物的上文或下文描述的一些实施方案中，R^2为苯基。在某些实施方案中，R^2的苯基为双取代的。在某些实施方案中，R^2的苯基为单取代的。在某些实施方案中，R^2的苯基上的取代独立地选自任选取代的烷基、任选取代的烷氧基、任选取代的芳氧基、卤代、CN、CO_2H、氨基、单烷基胺、二烷基胺、单芳基胺、烷基芳基胺、环烷基、羟基、C(O)-（任选取代的烷基）、$C(O)NH_2$、C(O)NH-（任选取代的烷基）、烷基硫醚、烷基亚砜、烷基砜、C(O)-（任选取代的芳基）、C(O)NH-（任选取代的芳基）、芳基硫醚、芳基亚砜或芳基砜。在某些实施方案中，苯基上的取代独立地选自 F、Cl、CO_2H、CN、OCH_3、$C(O)CH_3$、CF_3、CH_3、CH_2OH、CH_2CH_2OH 和 $CH_2CH_2CH_2OH$。在某些实施方案中，R^2的苯基上的双取代由 CN 和选自 F、Cl、CO_2H、OCH_3、$C(O)CH_3$、CF_3、CH_3、CH_2OH、CH_2CH_2OH 和 $CH_2CH_2CH_2OH$ 的基团组成。在某些实施方案中，R^2的苯基上的双取代由 CO_2H 和选自 F、Cl、CN、OCH_3、$C(O)CH_3$、CF_3、CH_3、CH_2OH、CH_2CH_2OH 和 $CH_2CH_2CH_2OH$ 的基团组成。在某些实施方案中，R^2的苯基上的双取代由 $CH_2CH_2CH_2OH$ 和选自 F、Cl、CN、OCH_3、$C(O)CH_3$、CF_3、CH_3、CH_2OH、CH_2CH_2OH 和 CO_2H 的基团组成。

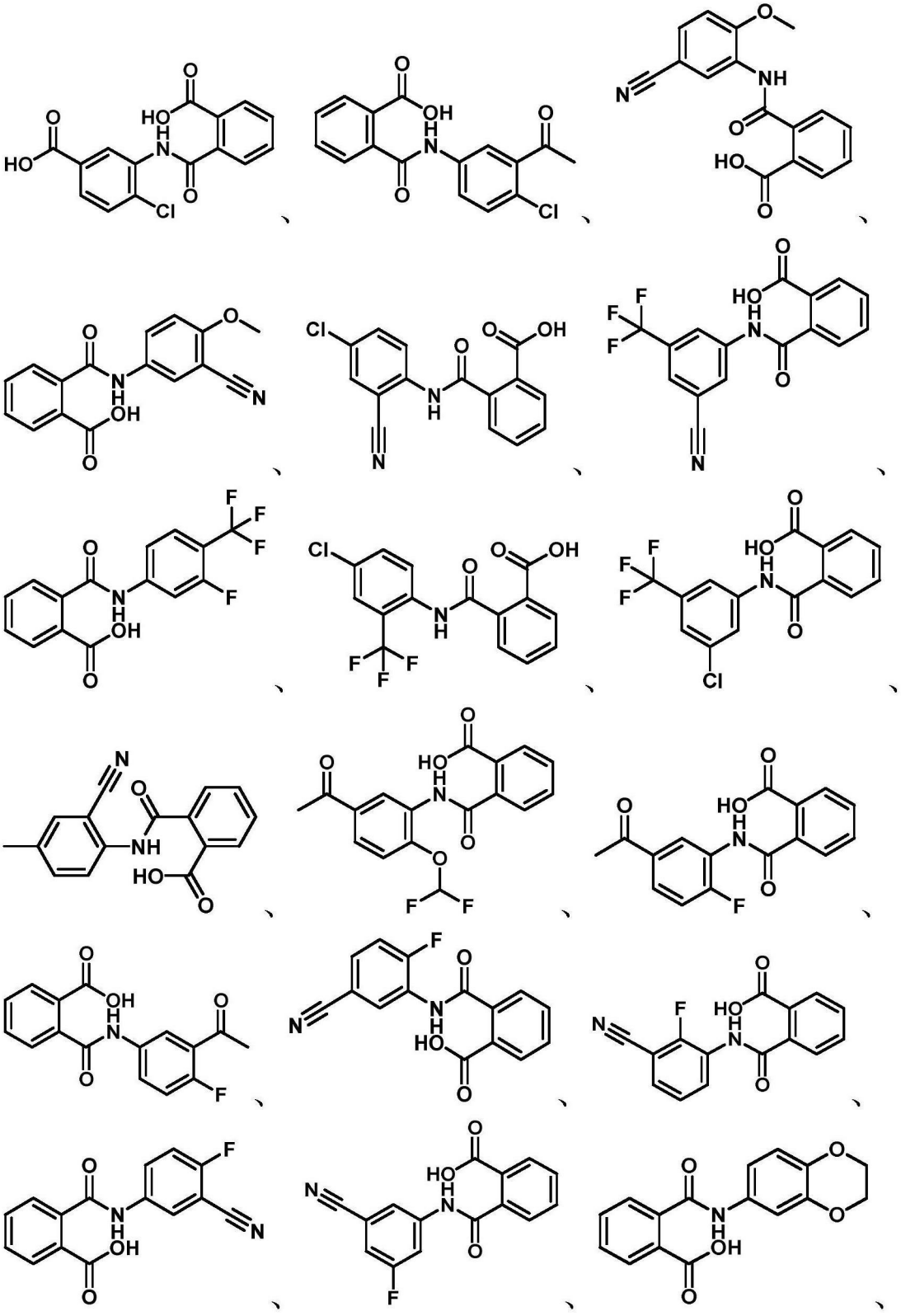
[0151] 在式 III 或 IIIa 化合物的上文或下文描述的一些实施方案中，R^2为萘基。

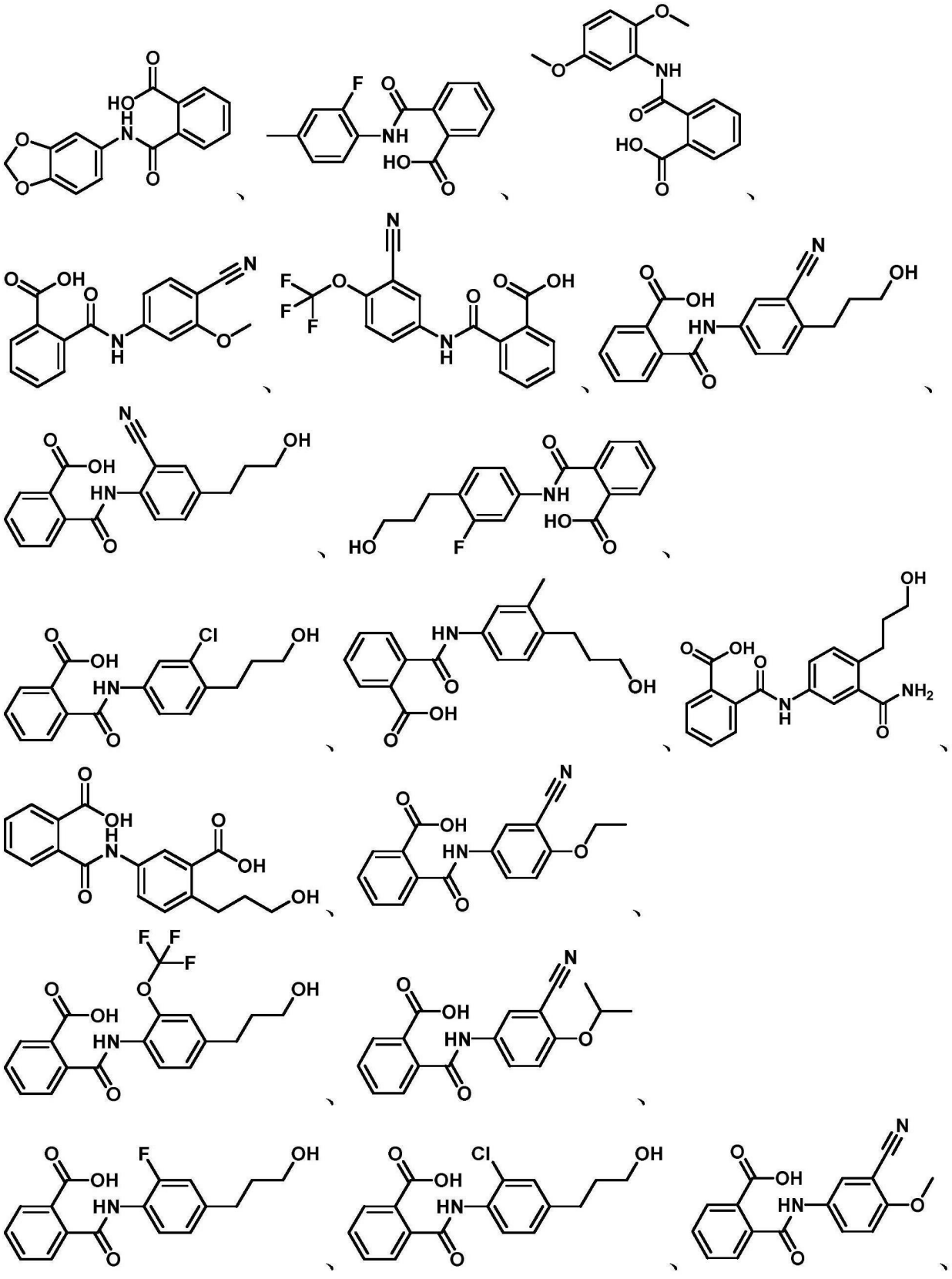
[0152] 在本文公开的化合物的上文或下文描述的一些实施方案中，B 为 CO_2R^4且 R^4为任选取代的烷基。在本文公开的化合物的上文或下文描述的一些实施方案中，B 为 CO_2R^4且 R^4为氢。

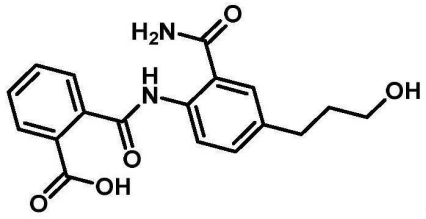
[0153] 在本文公开的化合物的上文或下文描述的一些实施方案中，n 为 0、1 或 2。在某些实施方案中，n 为 0。在某些实施方案中，n 为 1。在某些实施方案中，R^1独立地选自 Cl、F、CH_2OH、CH_2NH_2、OCH_3、OCF_3、$OCHF_2$、CN、NO_2、CO_2H 和 CO_2CH_3。

[0154] 在式 I 化合物的上文或下文描述的一些实施方案中，该化合物选自：





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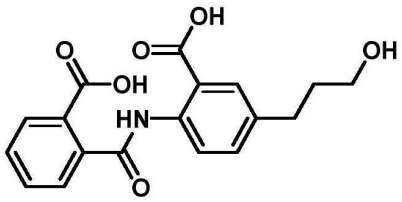
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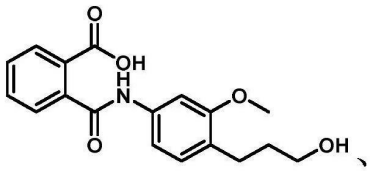
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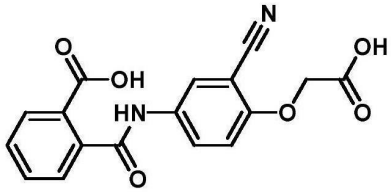
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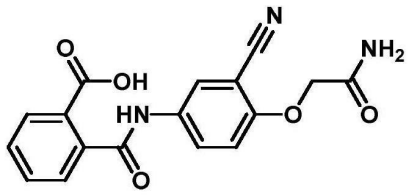
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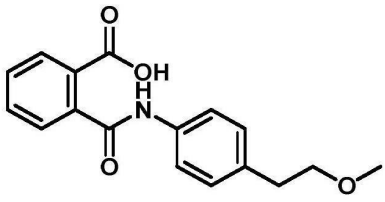
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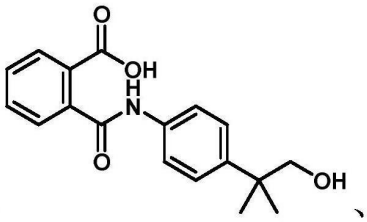
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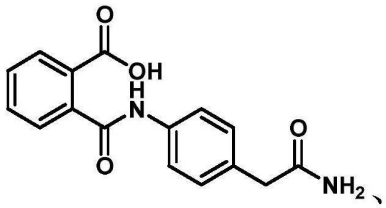
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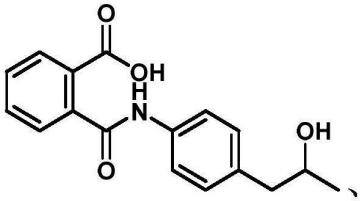
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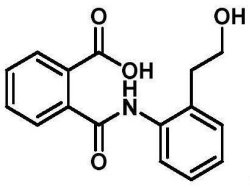
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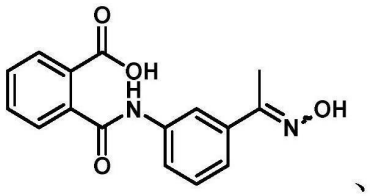
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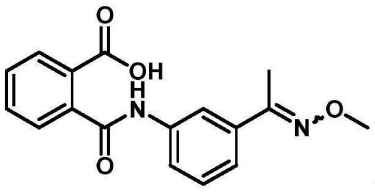
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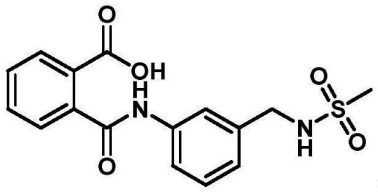
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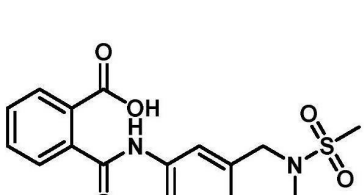
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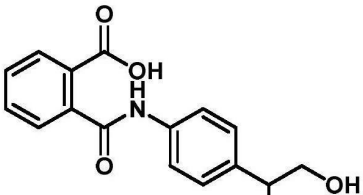
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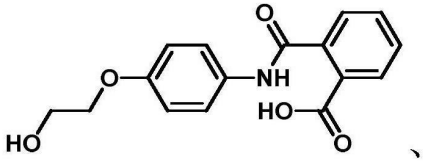
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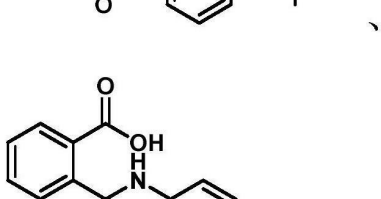
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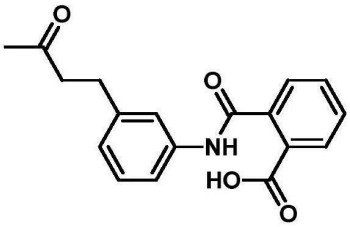
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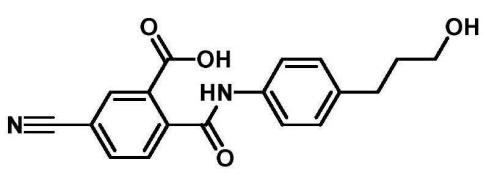
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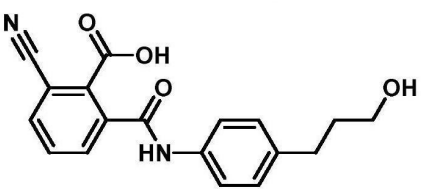
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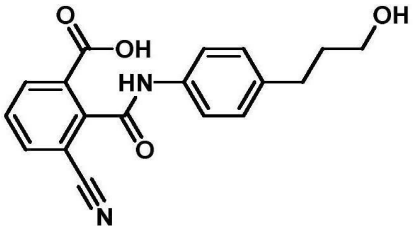
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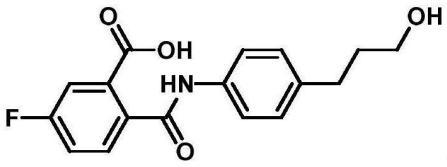
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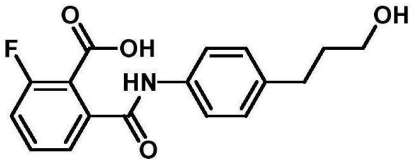
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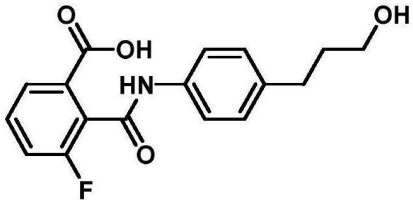
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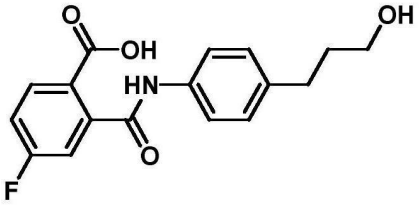
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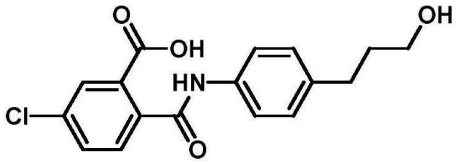
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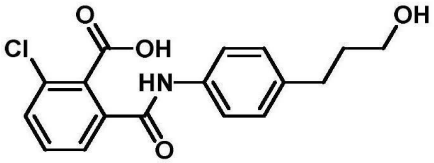
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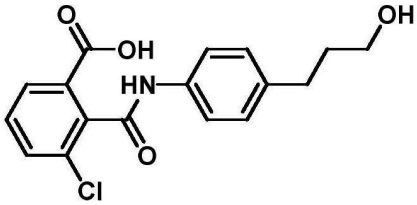
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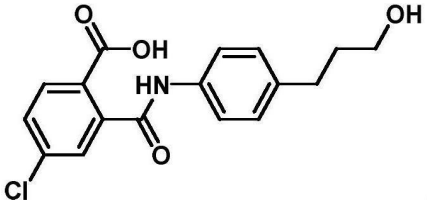
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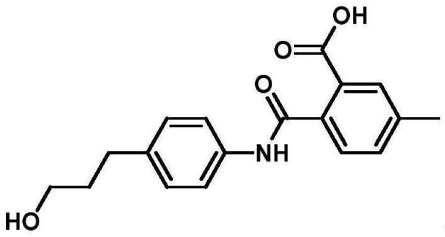
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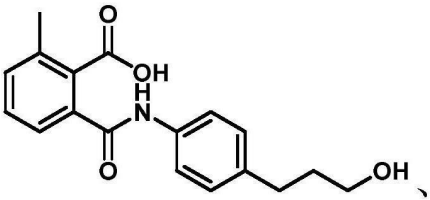
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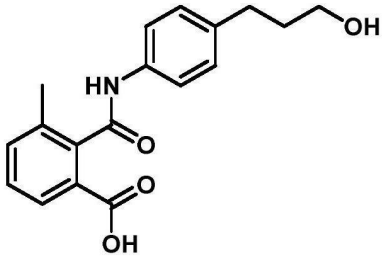
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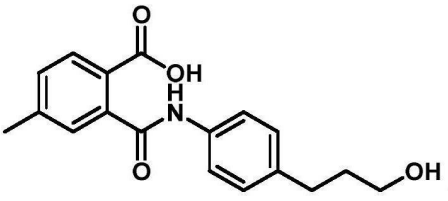
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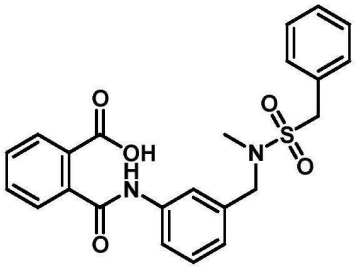
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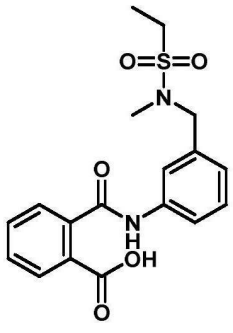
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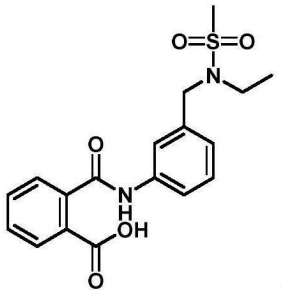
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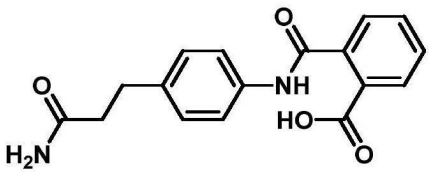
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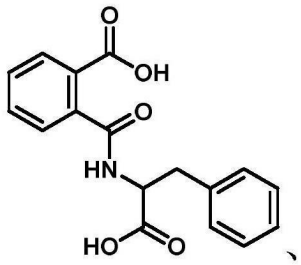
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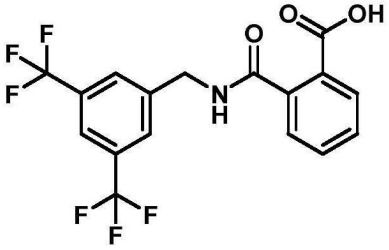
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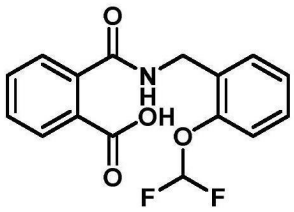
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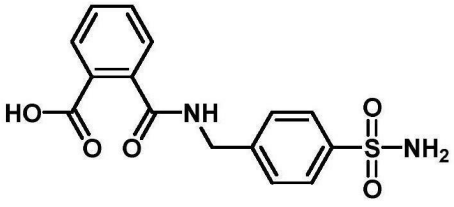
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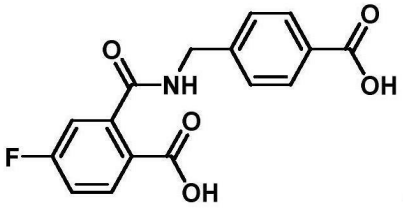
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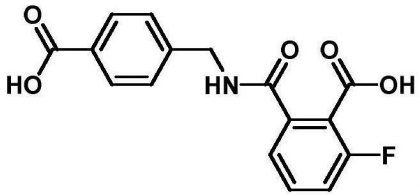
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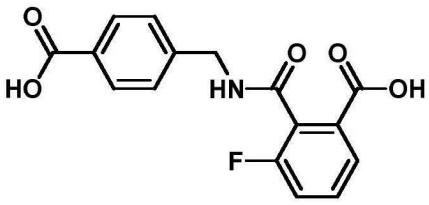
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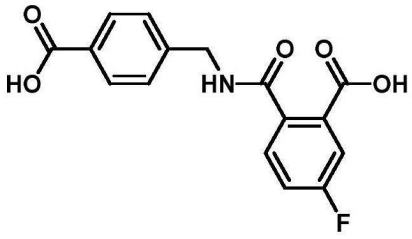
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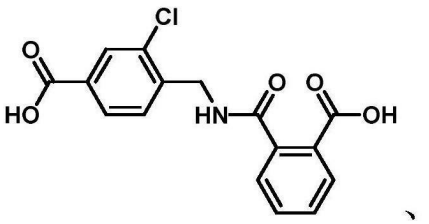
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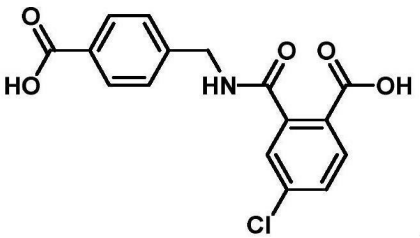
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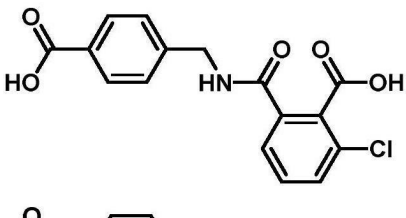
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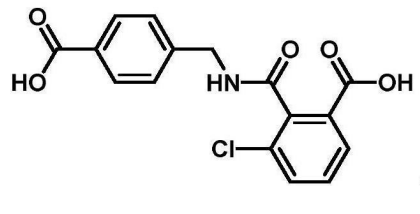
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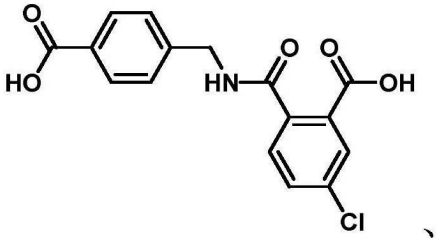
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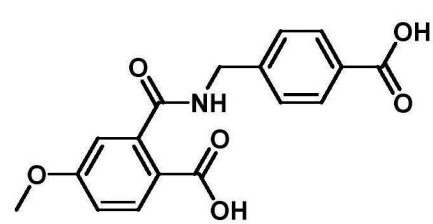
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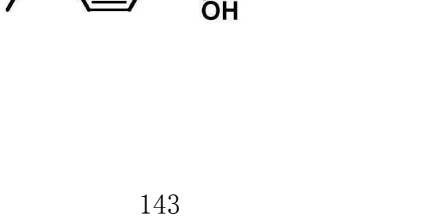
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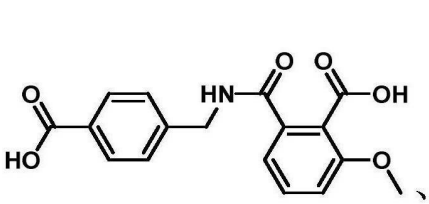
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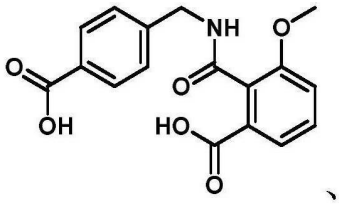
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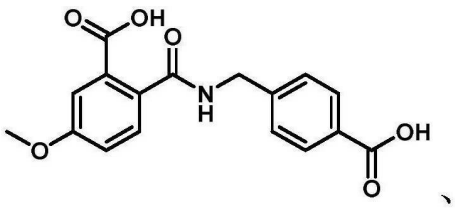
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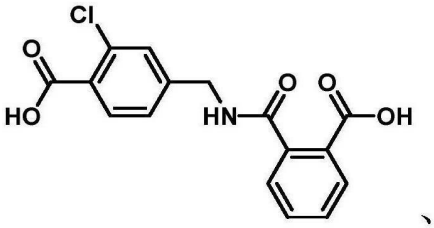
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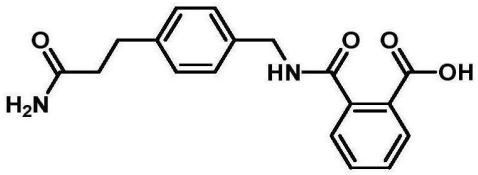
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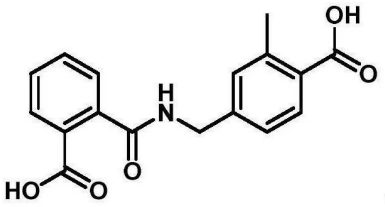
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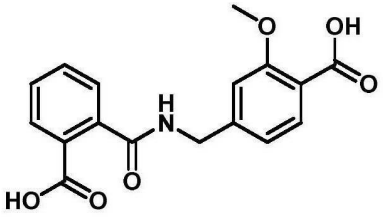
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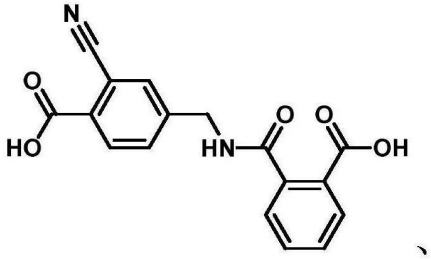
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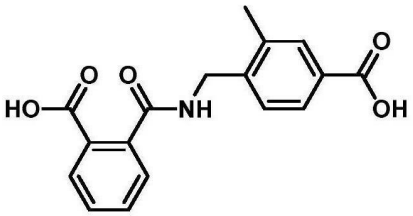
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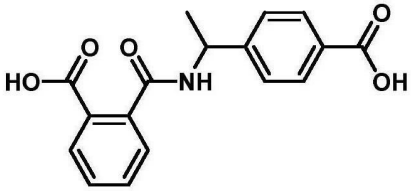
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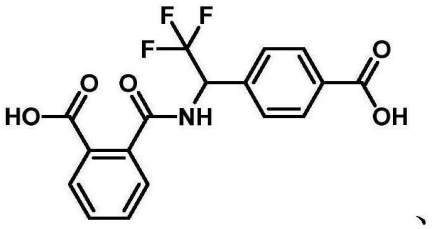
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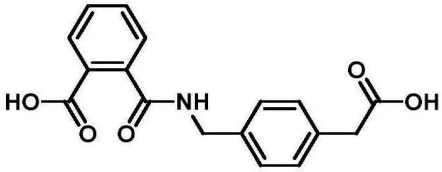
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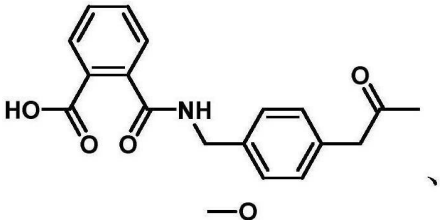
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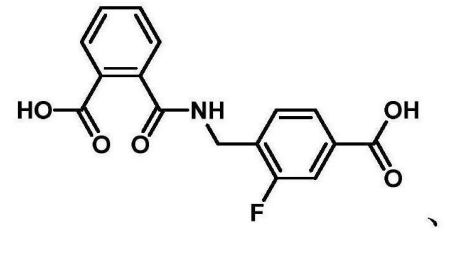
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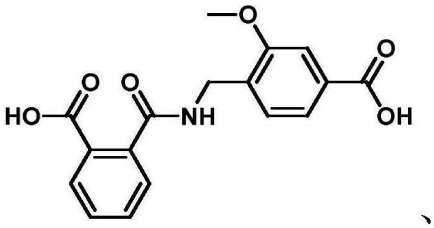
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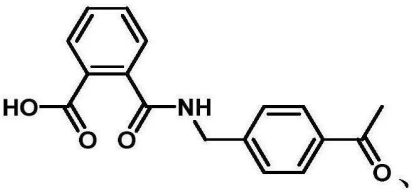
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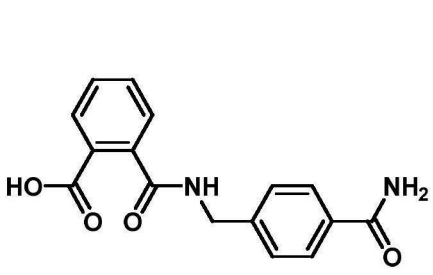
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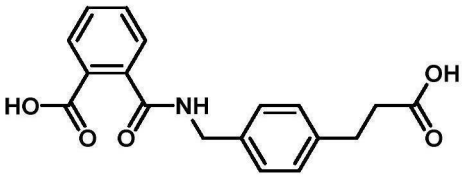
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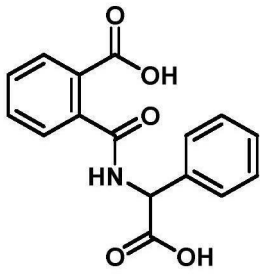
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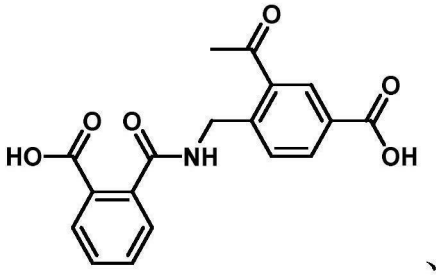
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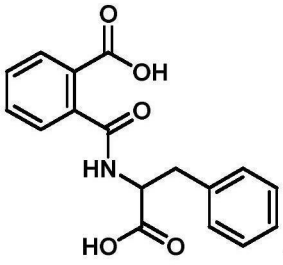
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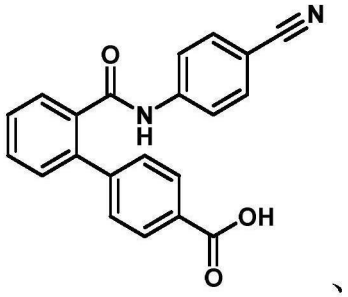
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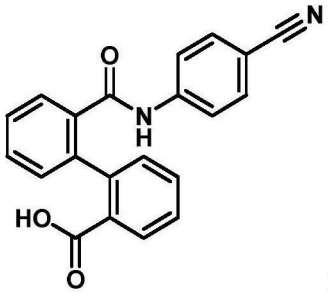
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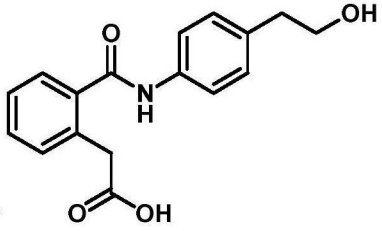
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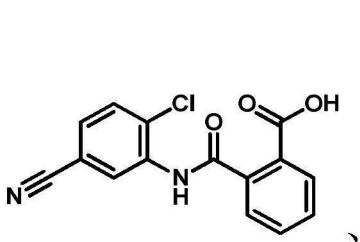
或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

[0155] 在式 Ia 化合物的上文或下文描述的一些实施方案中，该化合物选自：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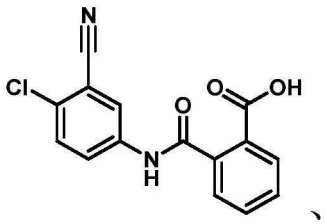
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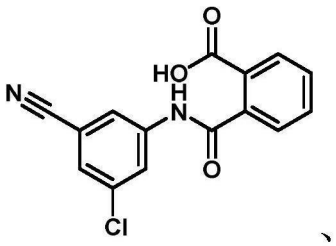
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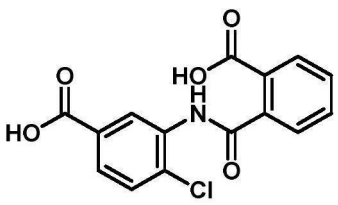
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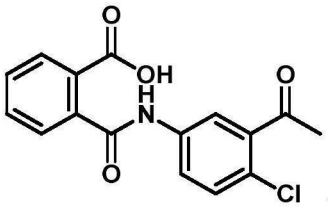
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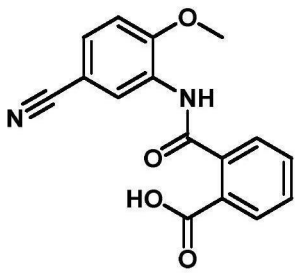
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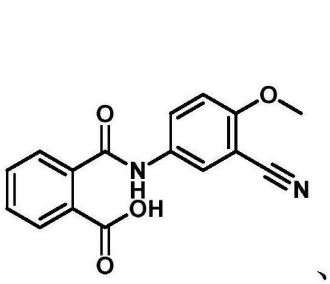
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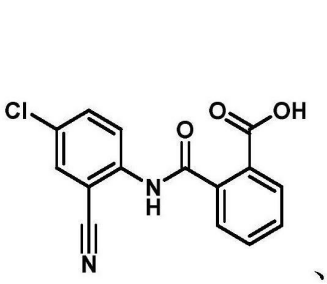
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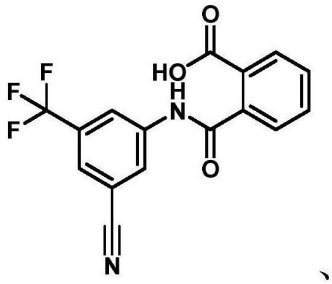
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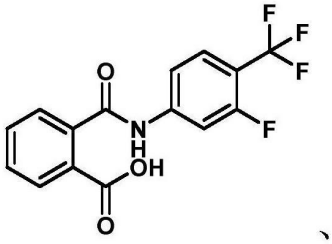
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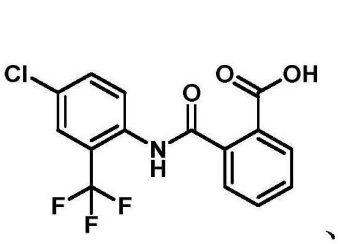
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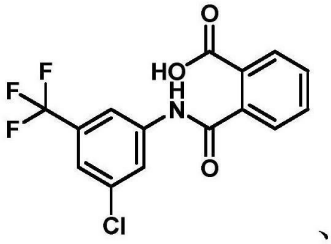
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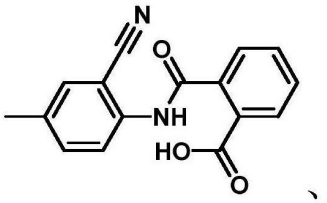
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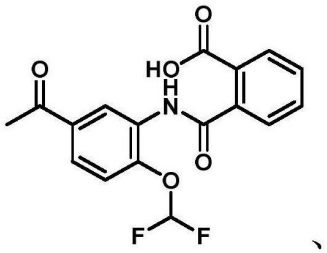
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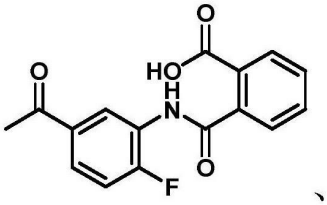
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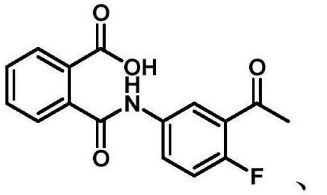
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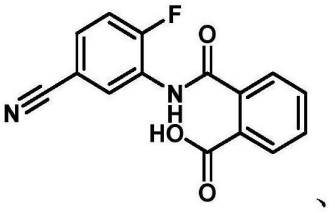
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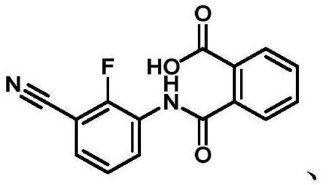
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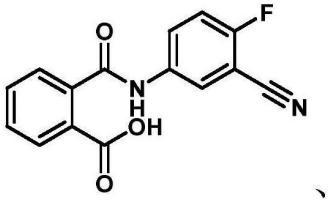
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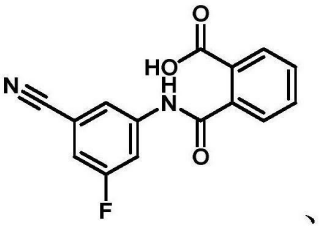
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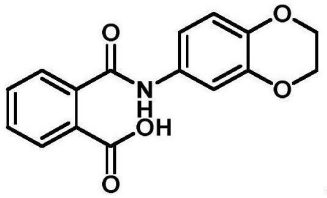
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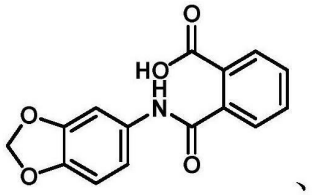
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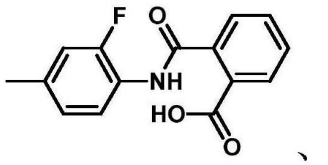
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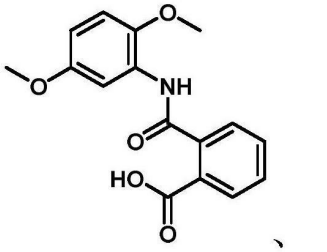
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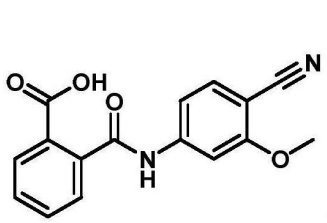
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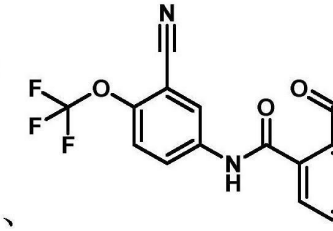
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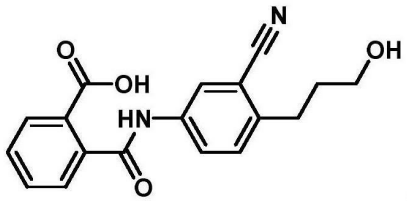
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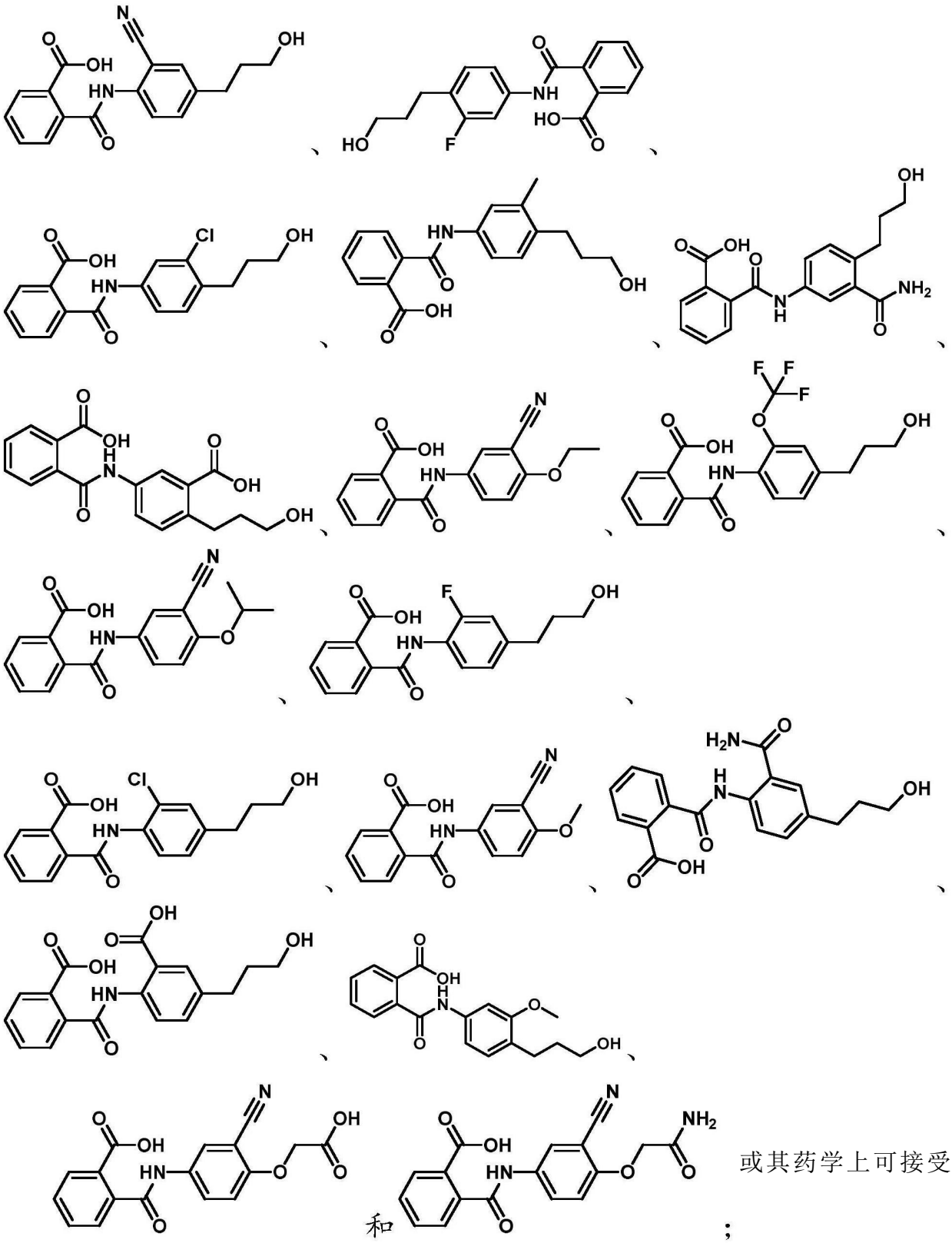
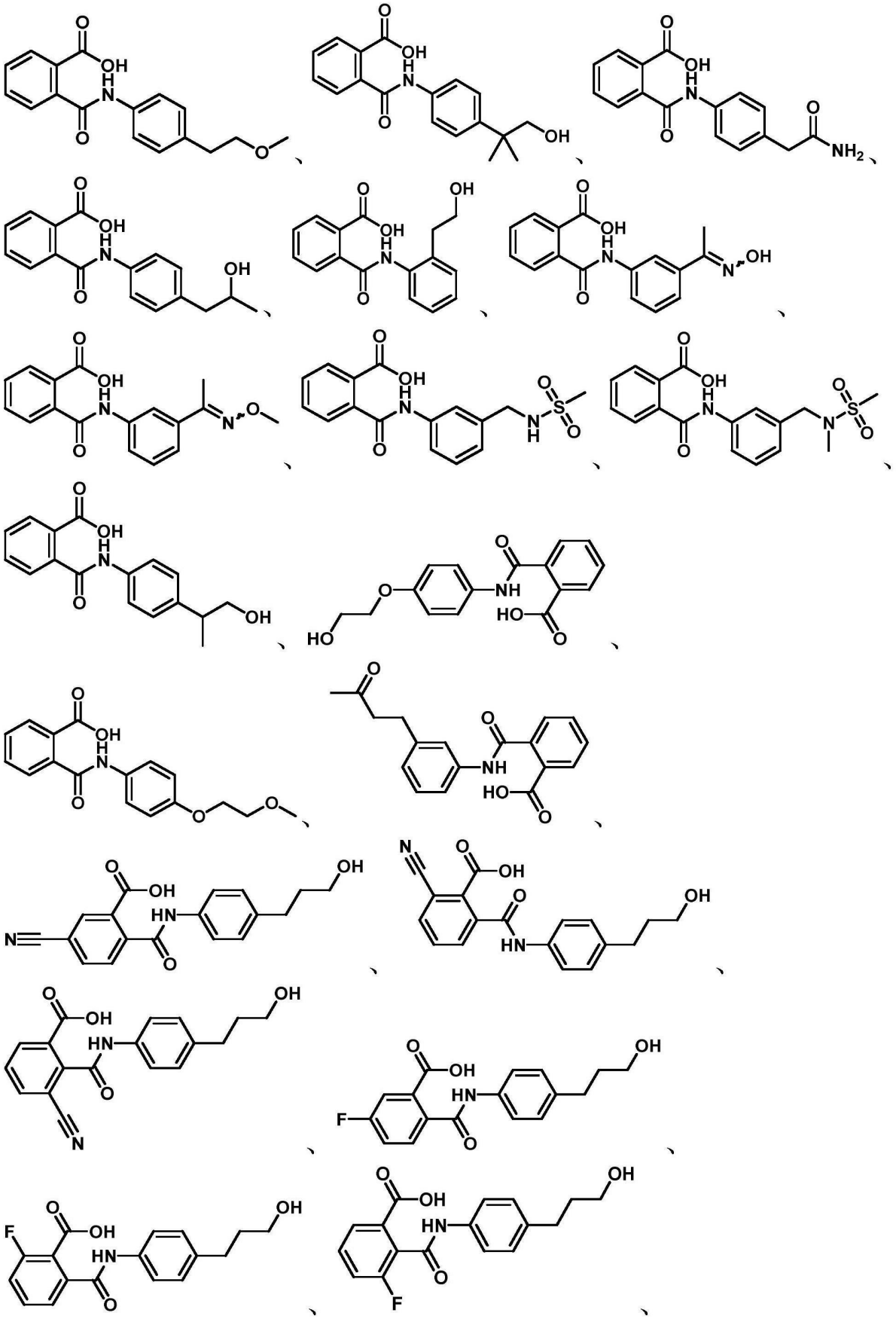
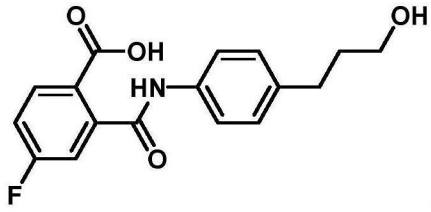


或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

[0156] 在式 Ib 化合物的上文或下文描述的一些实施方案中，该化合物选自：

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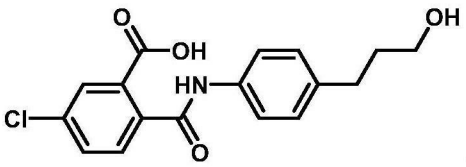
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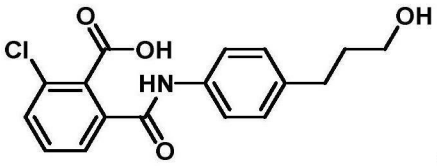
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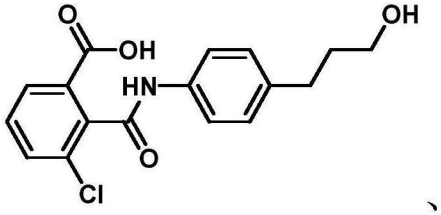
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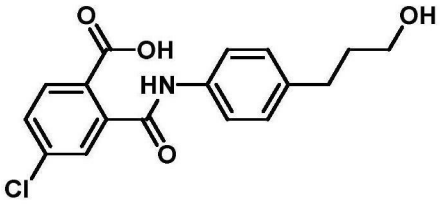
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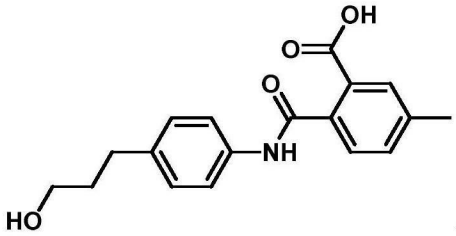
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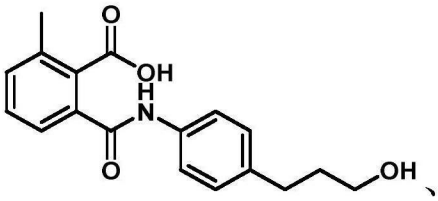
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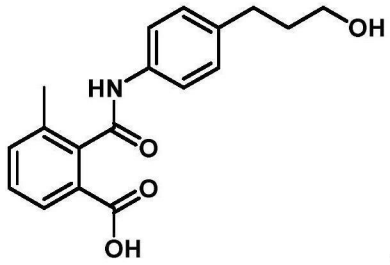
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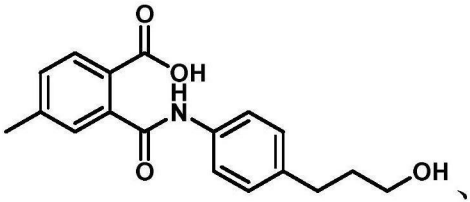
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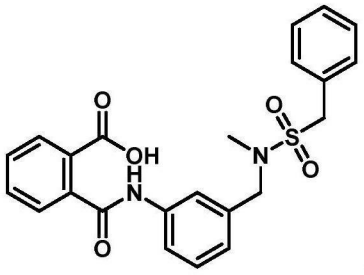
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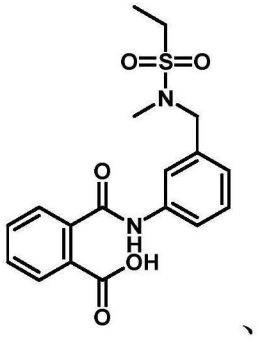
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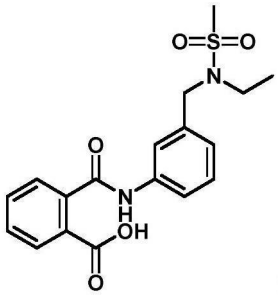
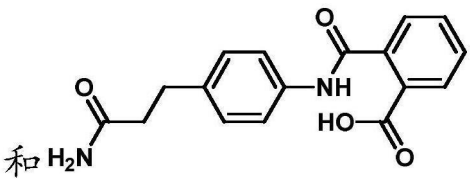
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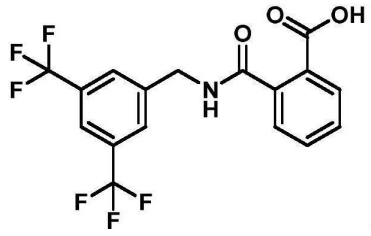
或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

[0157] 在式 Ic 化合物的上文或下文描述的一些实施方案中，该化合物选自：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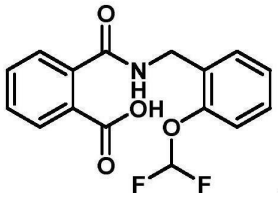
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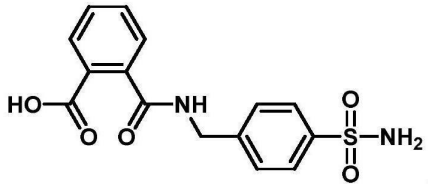
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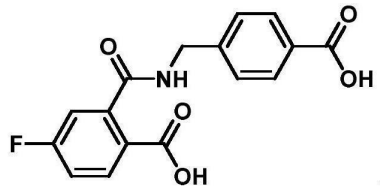
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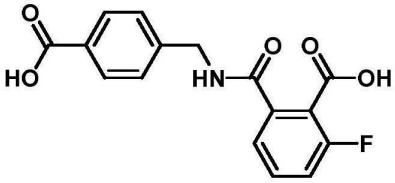
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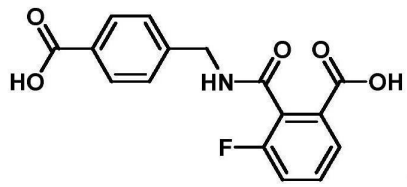
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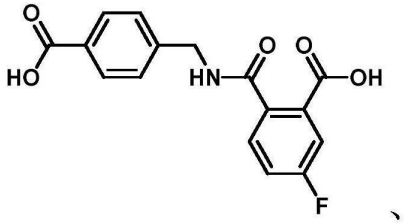
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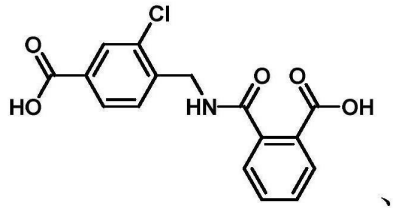
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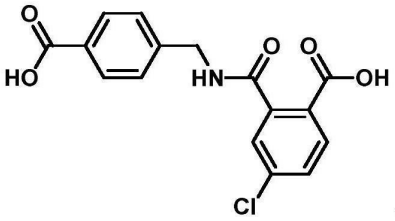
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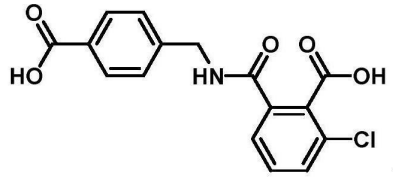
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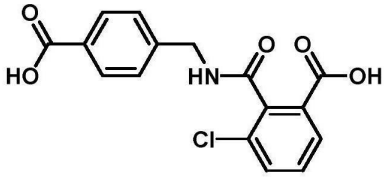
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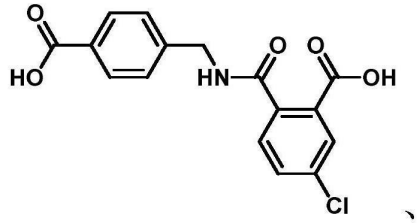
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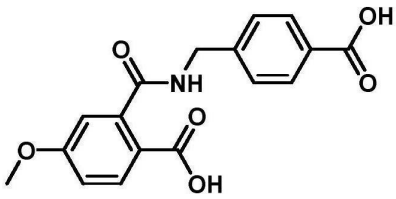
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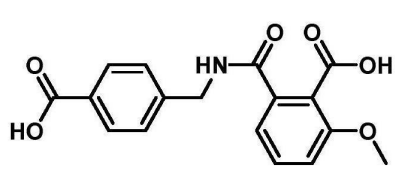
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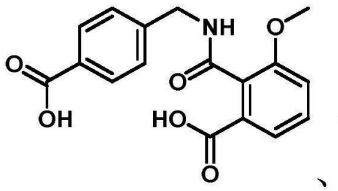
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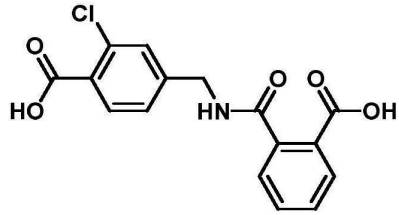
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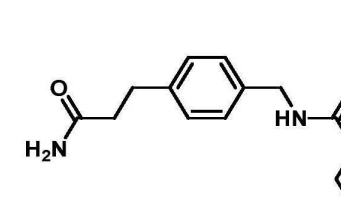
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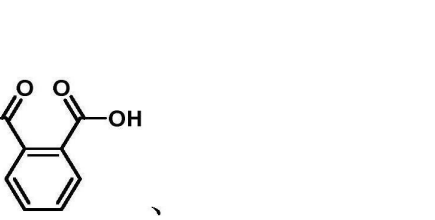
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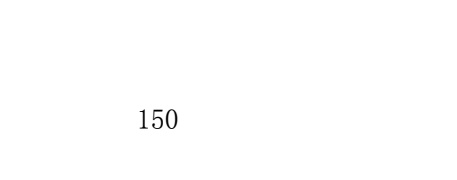
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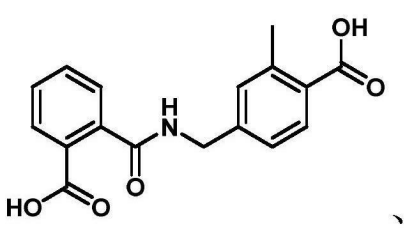
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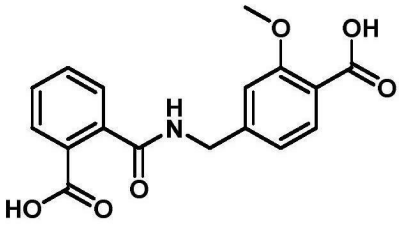
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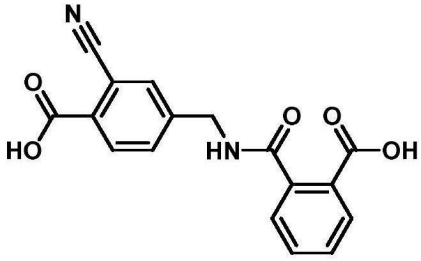
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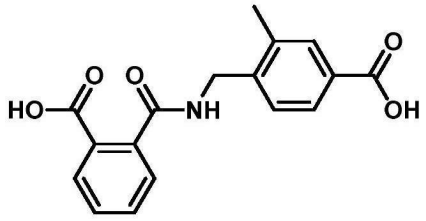
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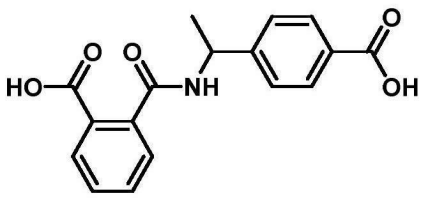
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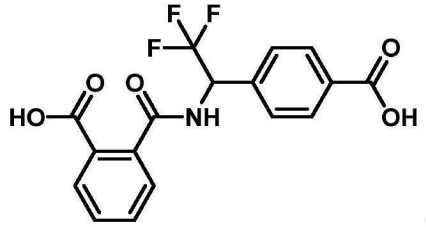
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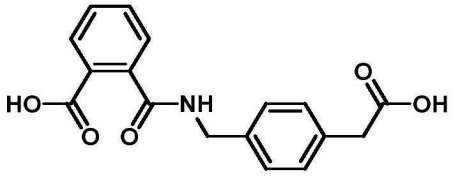
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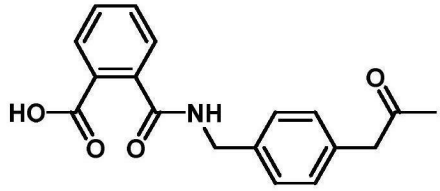
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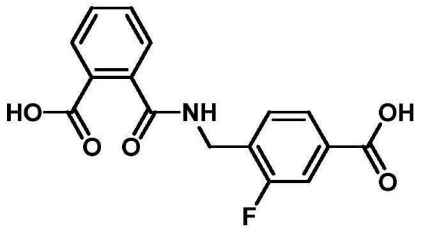
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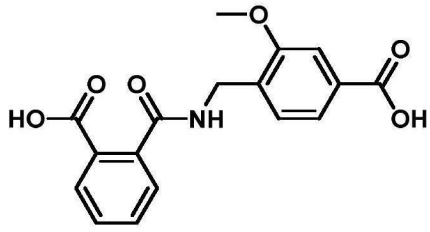
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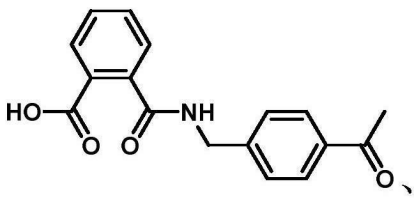
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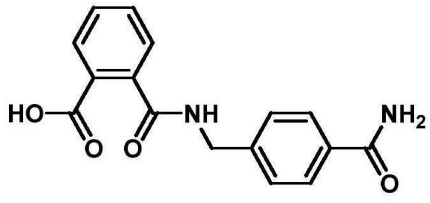
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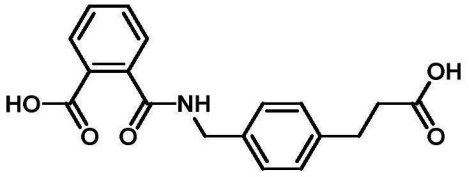
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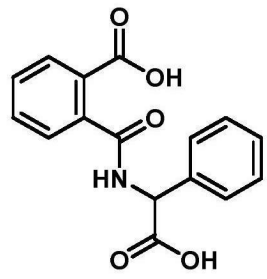
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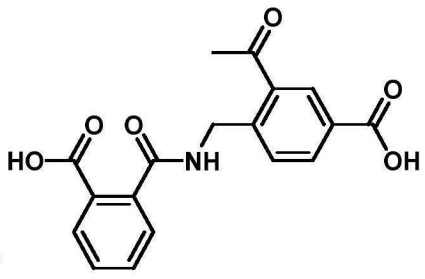
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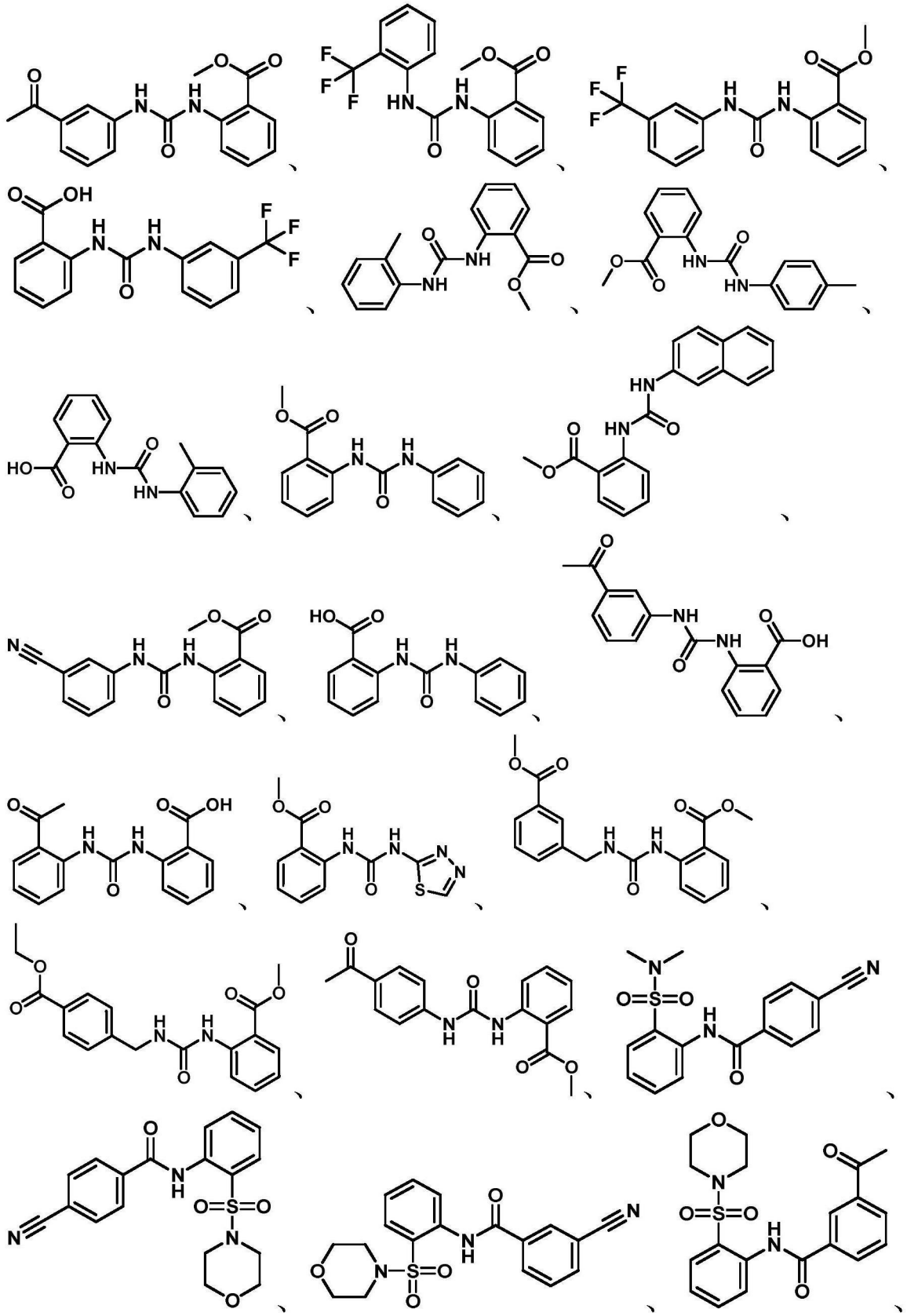
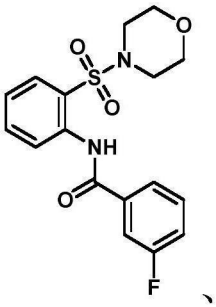
或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

[0158] 在式 II 化合物的上文或下文描述的一些实施方案中，该化合物选自：

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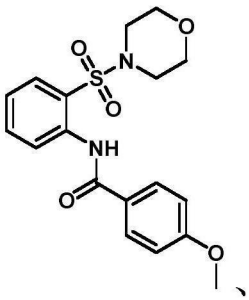
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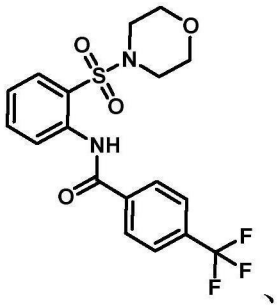
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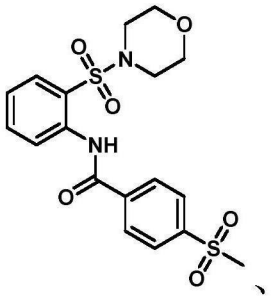
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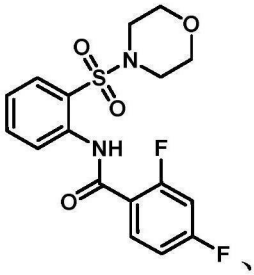
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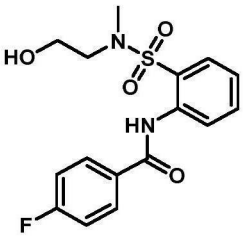
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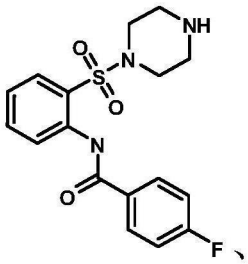
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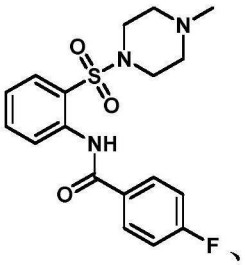
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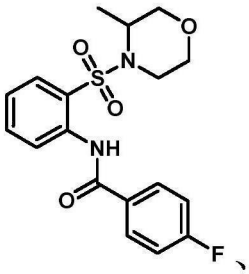
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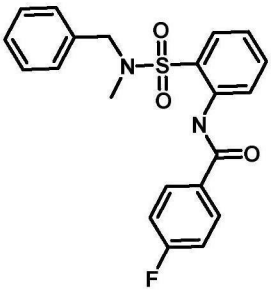
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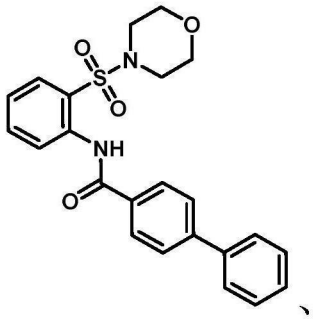
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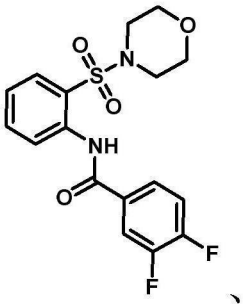
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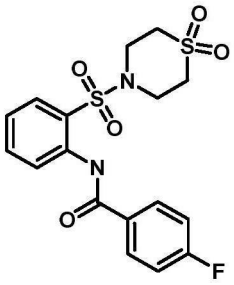
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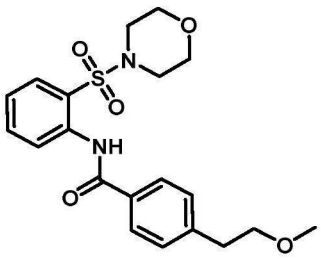
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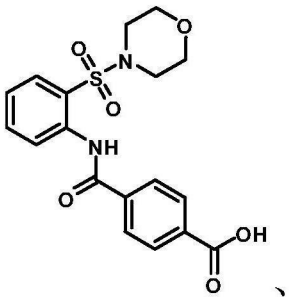
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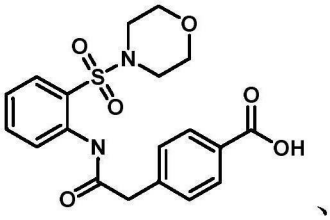
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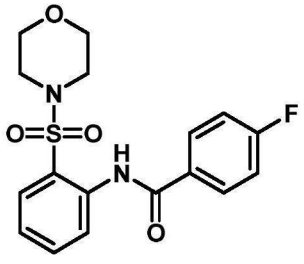
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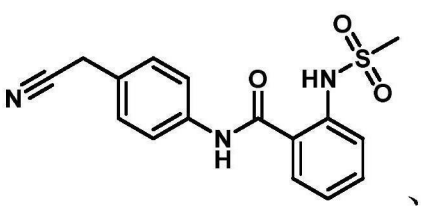
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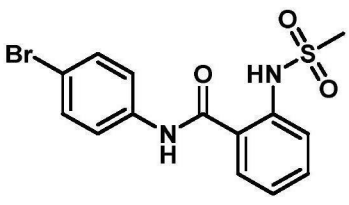
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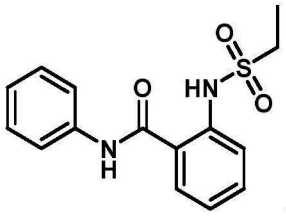
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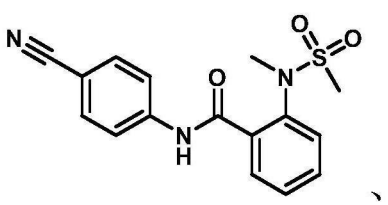
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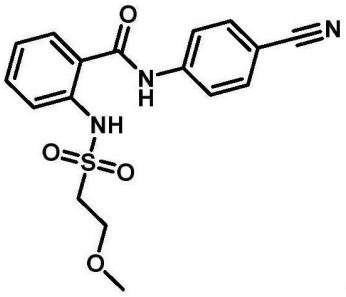
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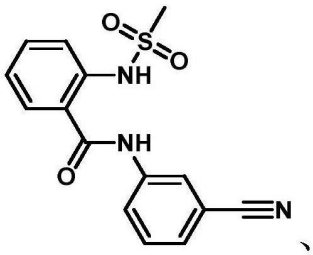
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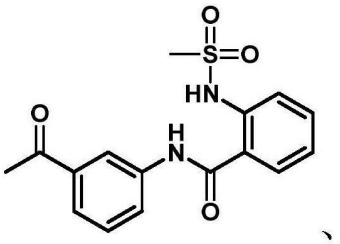
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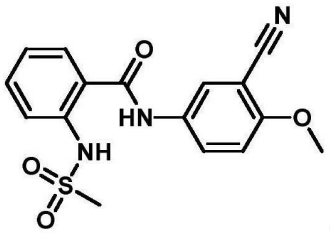
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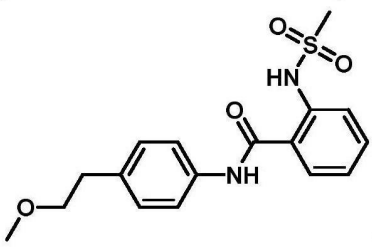
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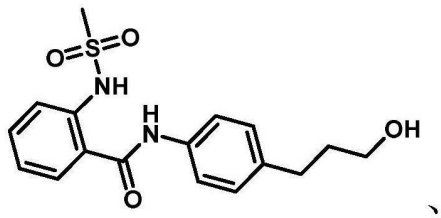
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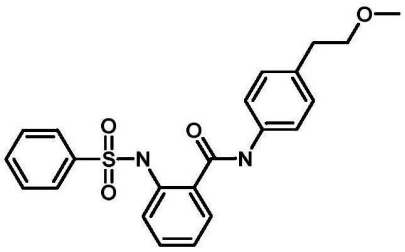
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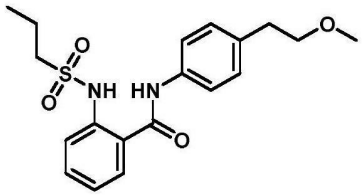
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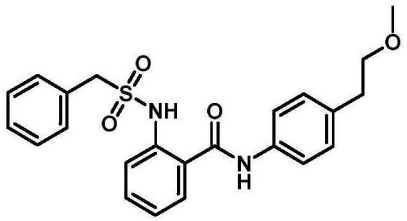
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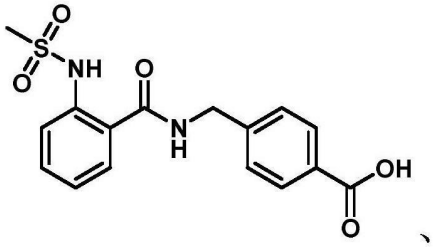
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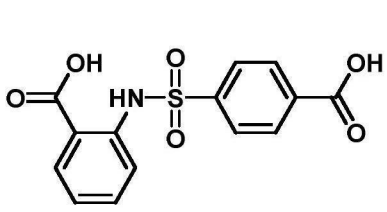
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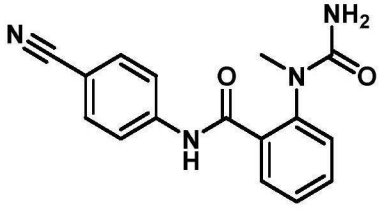
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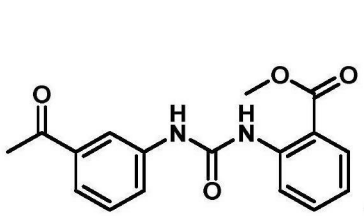
或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

[0159] 在式 IIa 化合物的上文或下文描述的一些实施方案中，该化合物选自：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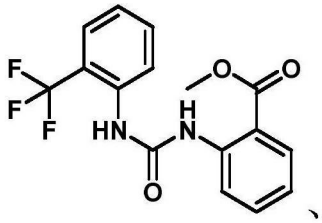
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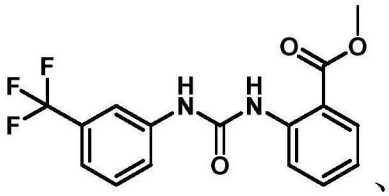
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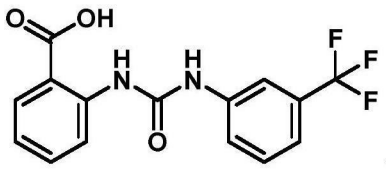

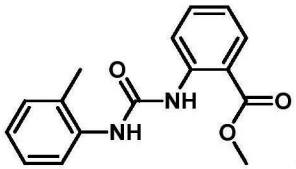

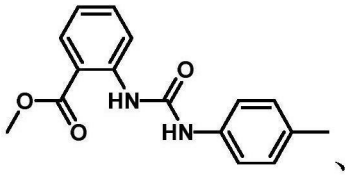

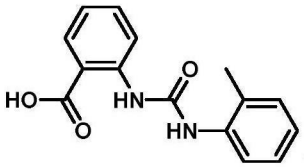

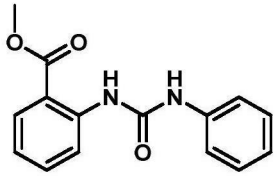

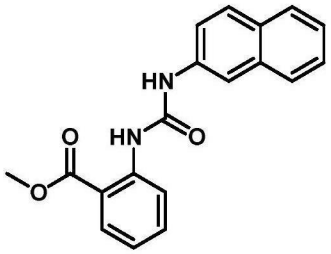

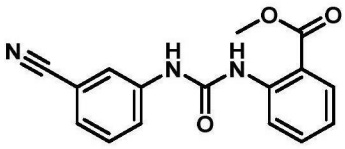

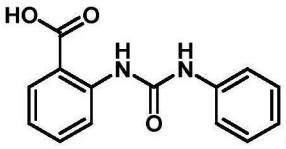

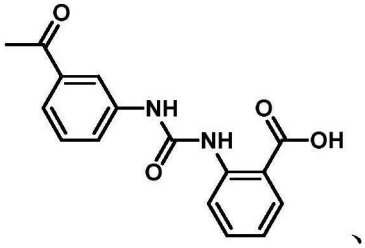

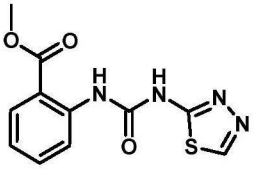

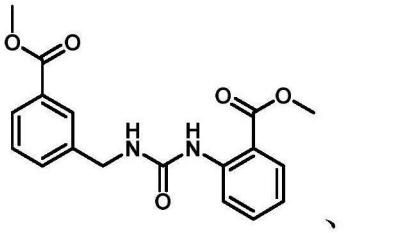

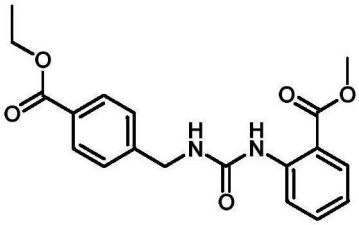

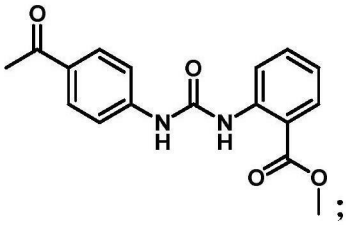

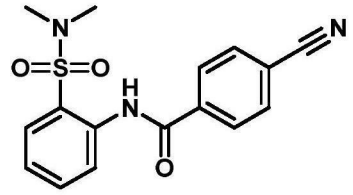

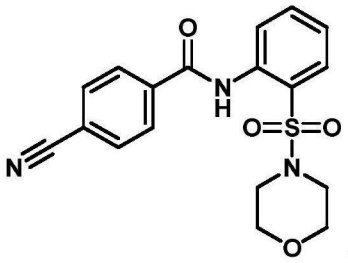

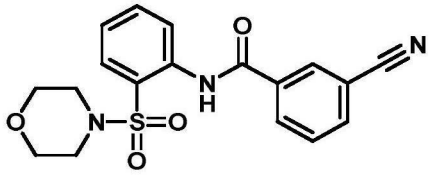

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和或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

[0160] 在式 IIb 化合物的上文或下文描述的一些实施方案中，该化合物选自：

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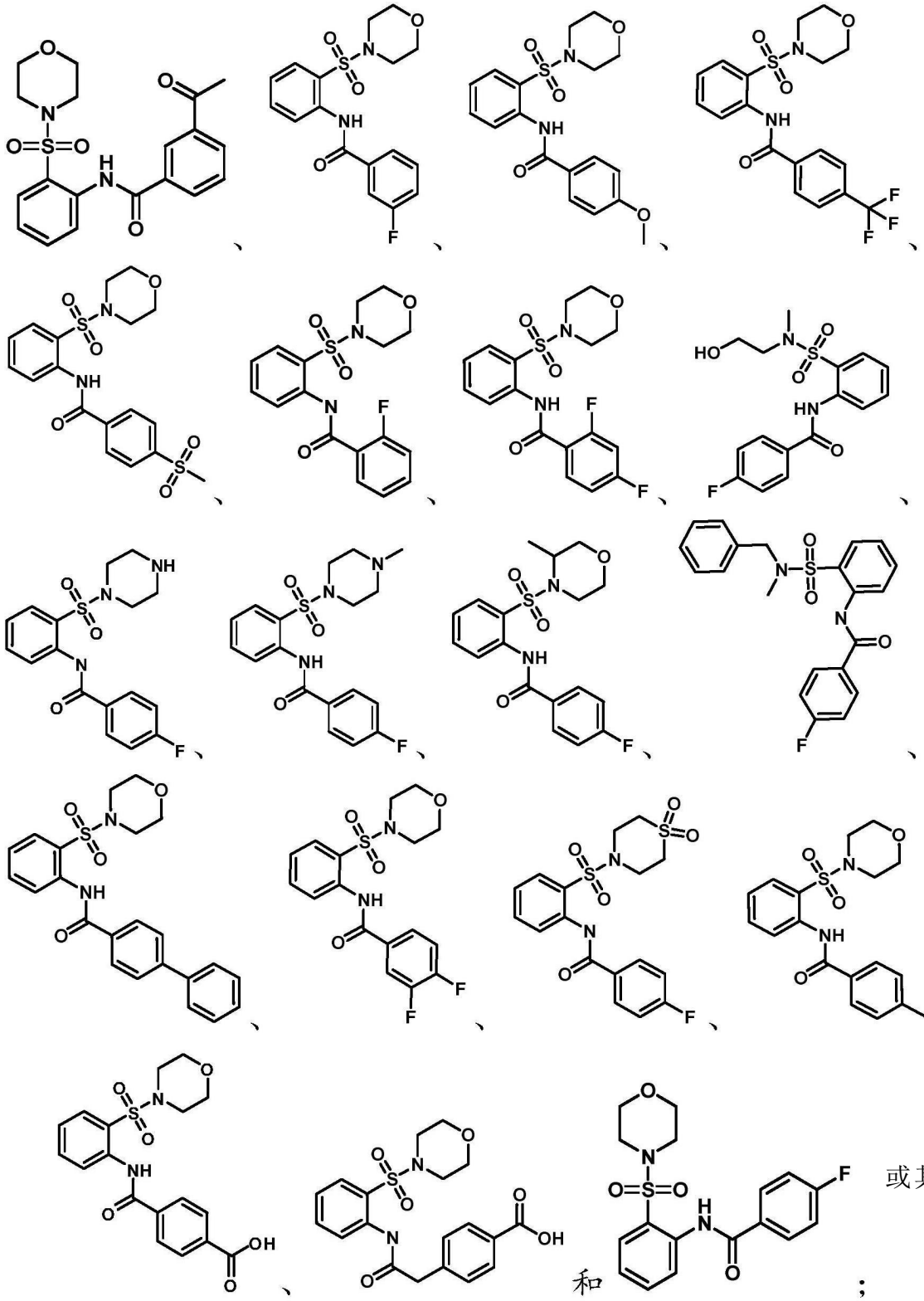
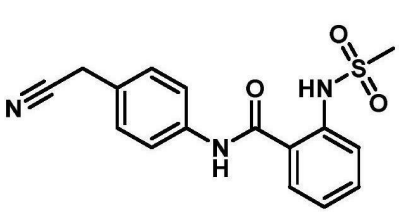


或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

[0161] 在式 IIc 化合物的上文或下文描述的一些实施方案中，该化合物选自：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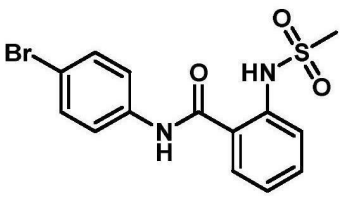
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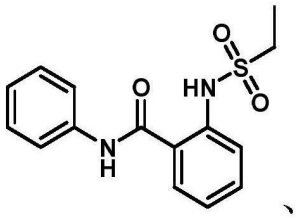
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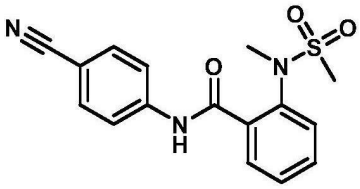
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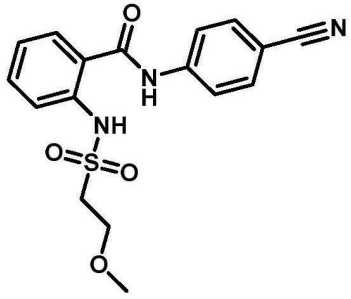
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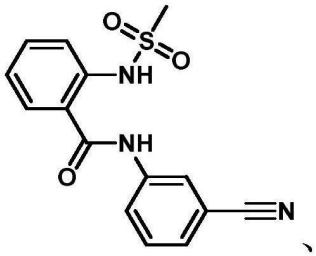
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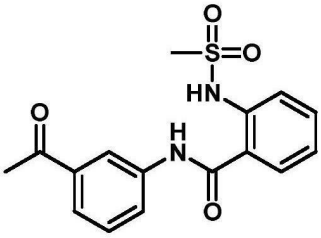
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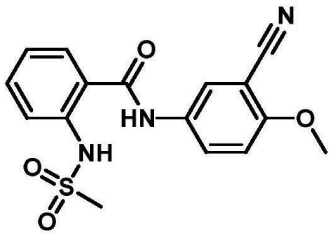
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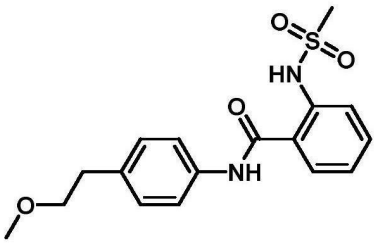
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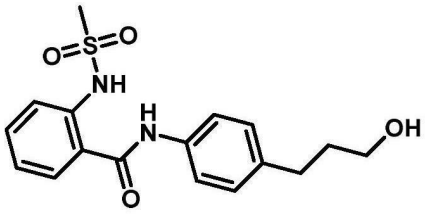
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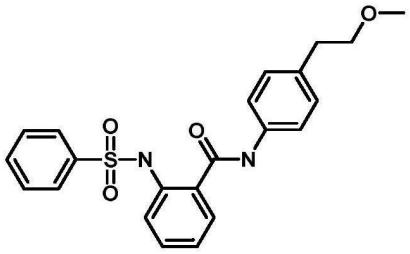
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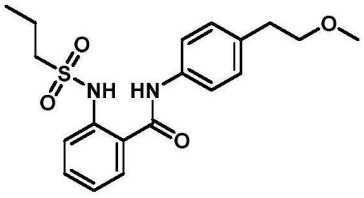
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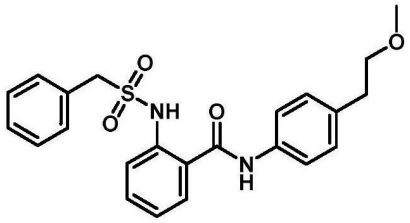
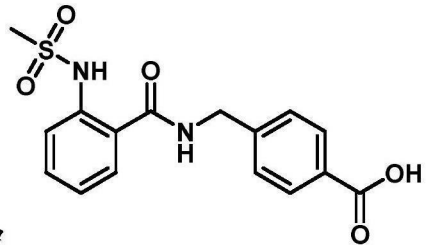
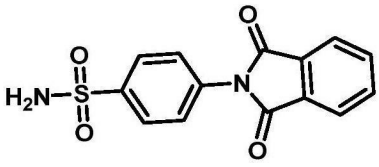
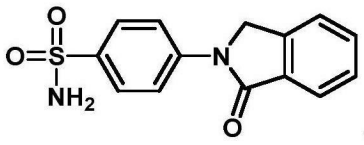
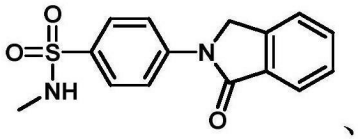
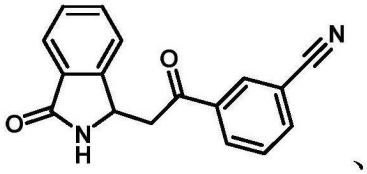
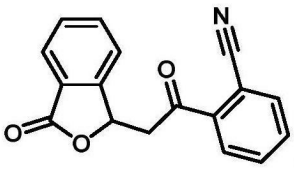
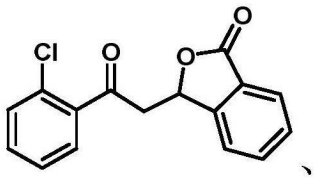
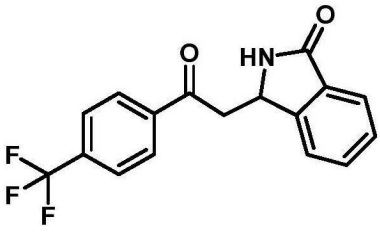
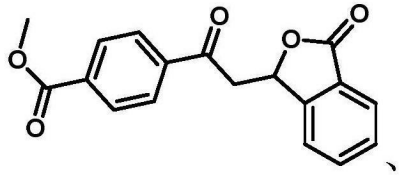
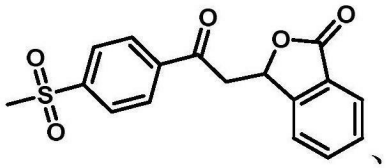
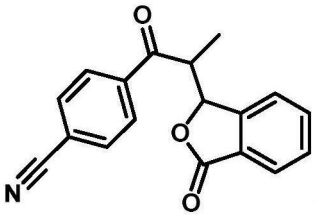
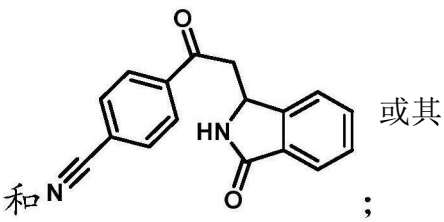
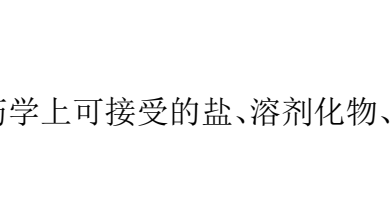

、

和 ；

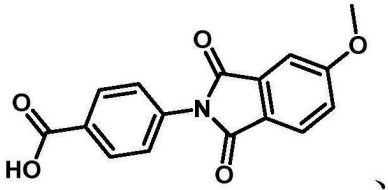
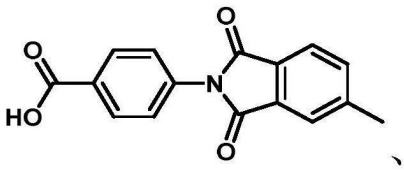
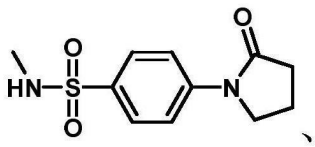
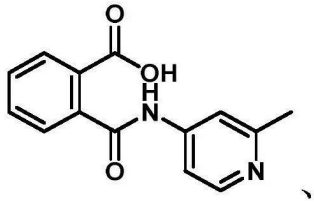
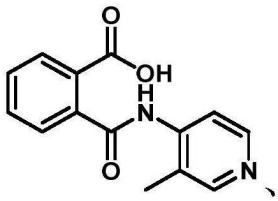
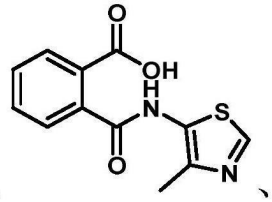
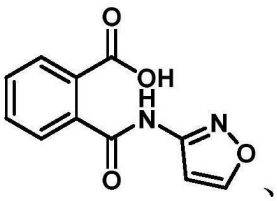
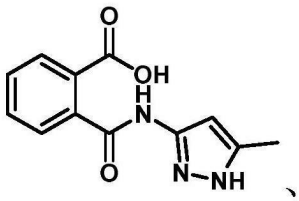
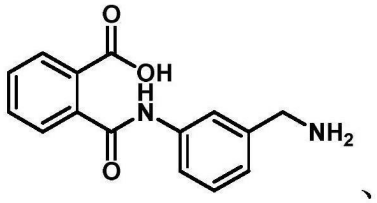
或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

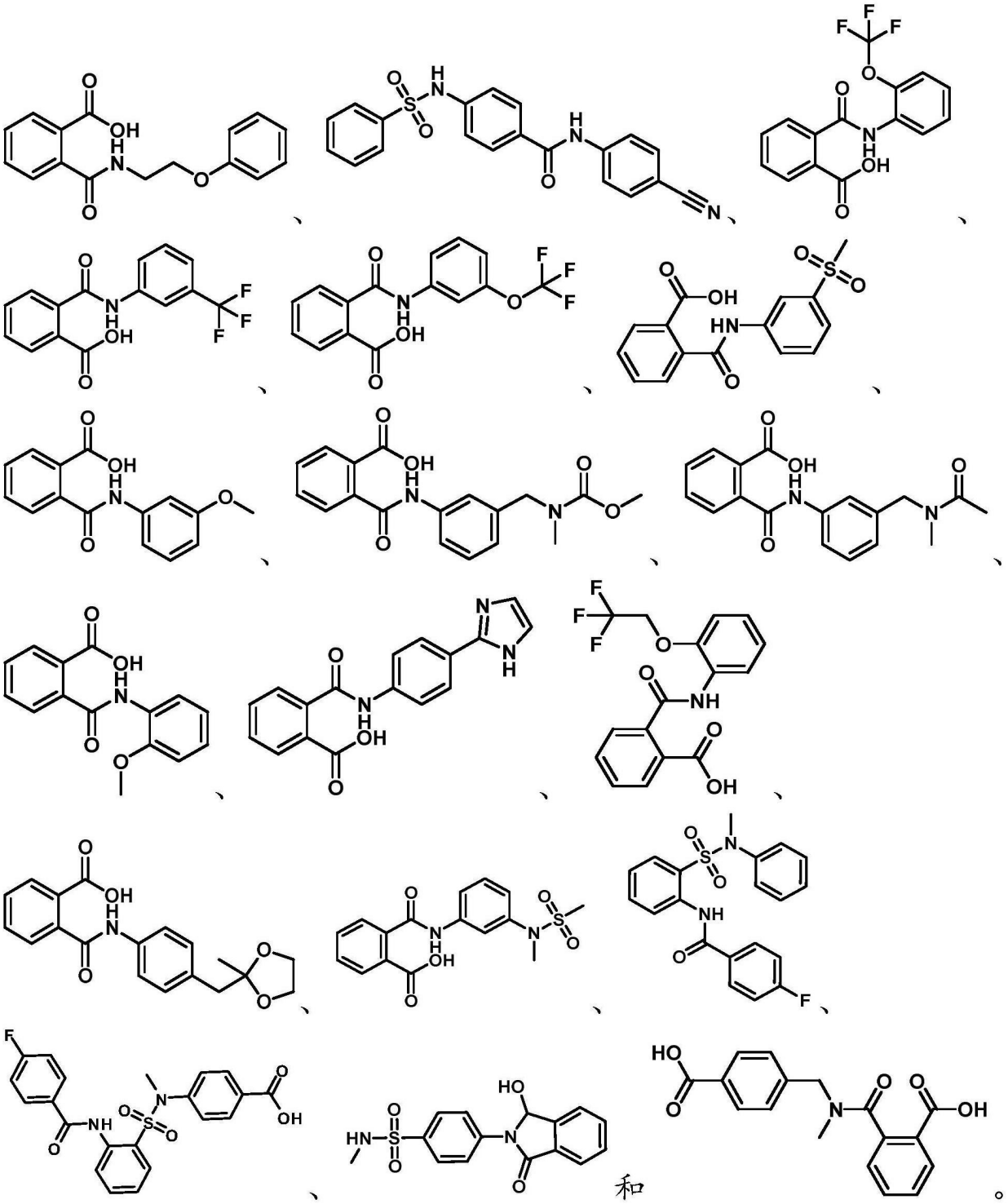
[0162] 在式 III 化合物的上文或下文描述的一些实施方案中，该化合物选自：

 、  、  、  、  、  、  、  、  、  、  、  、、；

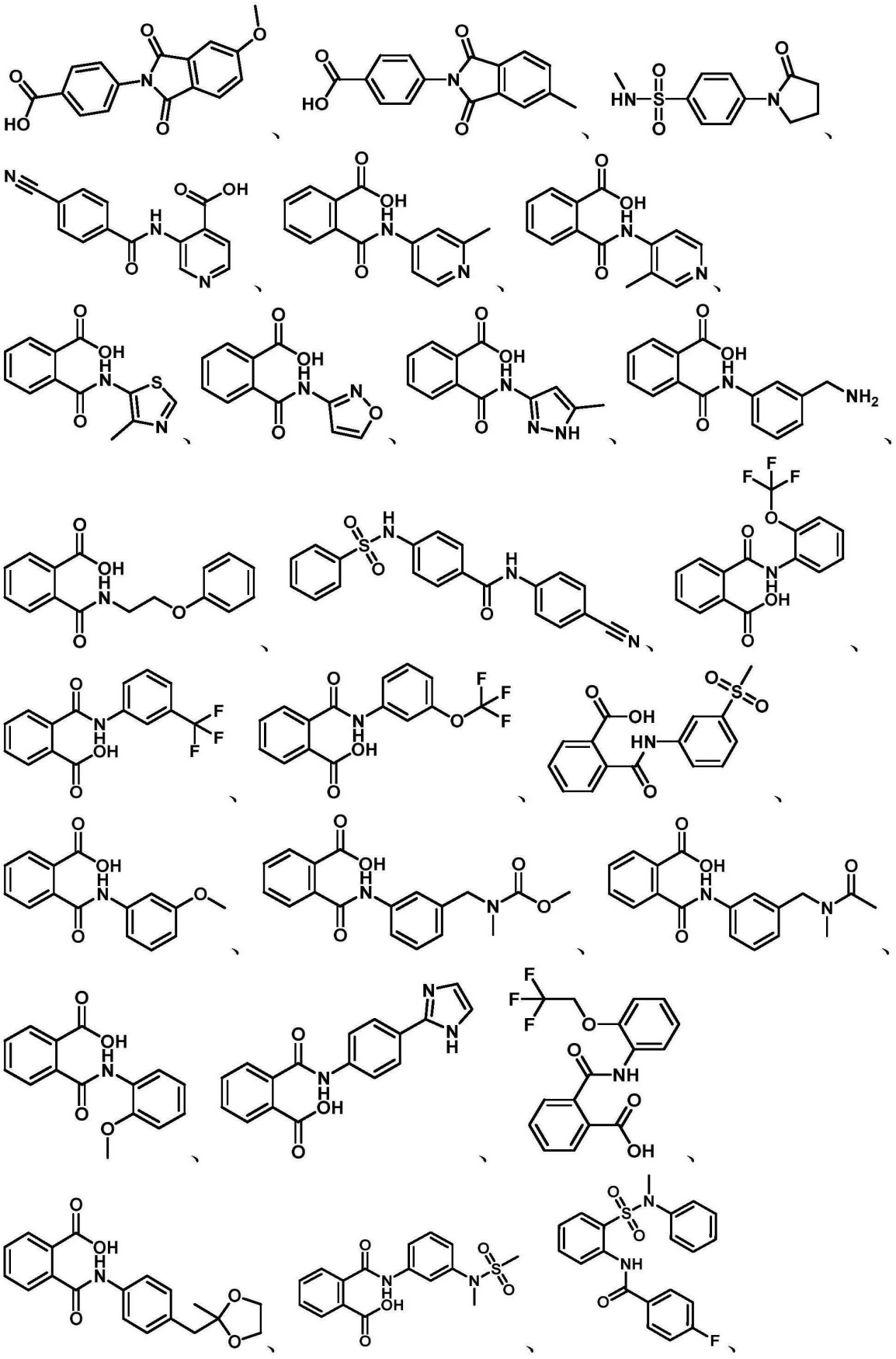
或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

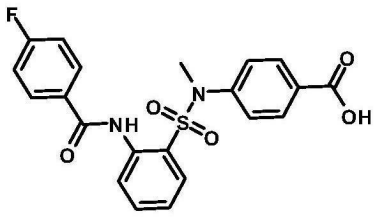
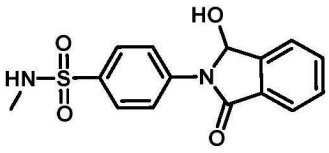
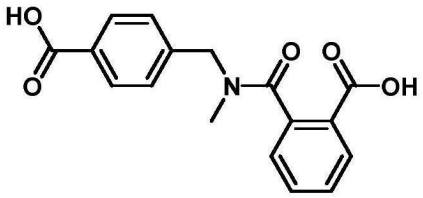
[0163] 在一方面，本文提供了一种改善哺乳动物的关节炎或关节损伤的方法，该方法包括向哺乳动物的关节施用包含治疗有效量的化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体的组合物，该化合物选自：

 、  、  、  、  、  、  、  、  、 



[0164] 在另一方面，本文提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体，该化合物选自：




、

和

。

[0165] 在一些实施方案中，所述哺乳动物没有患有关节炎或关节损伤，但其患关节炎或关节损伤的风险增加。

[0166] 预期本发明的化合物、组合物和方法可以用于改善任何类型的关节炎或关节损伤。进一步预期本发明的化合物、组合物和方法可以用于改善各种软骨病症。在一些实施方案中，施用本发明的化合物和组合物以预防关节炎或关节损伤，例如在存在关节炎或关节损伤的遗传或家族史或先前的或过程中的关节手术的情况下，或在关节炎或关节损伤风险增加的其他情况下。将要用本发明的化合物、组合物和方法治疗或预防的示例性的病况或病症包括但不限于系统性类风湿性关节炎、幼年型慢性关节炎、骨关节炎、椎间盘退变性疾病、脊椎关节病和系统性硬化症（硬皮病）。在本发明的一些实施方案中，本发明的化合物、组合物和方法可以用于治疗骨关节炎。在一些实施方案中，所述关节炎可以是骨关节炎、创伤性关节炎、椎间盘退变性疾病、迪皮特朗病（dupuytren disease）或腱疾病。

[0167] 在一些实施方案中，本发明的化合物、组合物和方法提供了一种用于刺激已经由于创伤性损伤或软骨病而损伤的软骨组织中的软骨细胞增殖和软骨产生的方法。创伤性损伤可以包括但不限于关节的钝伤或韧带的损伤，如前交叉韧带、内侧副韧带撕裂或半月板撕裂。展现出关节联接表面，因此对治疗特别敏感的组织的实例包括但不限于脊柱、肩、肘、腕、手指关节、髋、膝、踝和足关节。可以受益于治疗的疾病的实例包括骨关节炎、类风湿性关节炎、其他自身免疫性疾病或分离性骨软骨炎。另外，软骨畸形在人类侏儒形式中常见，提示该化合物、组合物和方法在这些患者中将是有用的。

[0168] 预期本发明的化合物、组合物和方法可以用于治疗哺乳动物。如本文所用的，“哺乳动物”是指被分类为哺乳动物的任何哺乳动物，包括人，驯养动物和农畜，以及动物园、竞技或宠物动物，如牛（例如母牛）、马、狗、绵羊、猪、兔、山羊、猫等。在一些实施方案中，该哺乳动物可以是人、狗、猫或马。在本发明的一些实施方案中，该哺乳动物是人。在一些实施方案中，该哺乳动物是狗、猫或马。在一些实施方案中，该哺乳动物是牛、绵羊、猪、山羊或兔。在一些实施方案中，该哺乳动物是驯养动物或家畜。在进一步的实施方案中，该驯养动物或家畜是狗、猫或马。在一些实施方案中，该哺乳动物是陪伴动物。如本文所用的，“陪伴动物”是指狗、猫、啮齿动物和兔。在一些实施方案中，该哺乳动物是陪伴动物或家畜。在一些实施方案中，该哺乳动物是家畜。

[0169] 本发明的化合物还可用于诱导间充质干细胞（MSC）分化为软骨细胞。在一些实施方案中，本发明提供了一种诱导间充质干细胞分化为软骨细胞的方法，该方法包括使间充质干细胞接触足量的本发明的化合物，由此诱导干细胞分化为软骨细胞。

[0170] MSC 是多能干细胞，其能够分化成数种不同类型的细胞，包括但不限于成骨细胞、软骨细胞和脂肪细胞。分化是由特化程度较低的细胞类型形成特化的细胞类型，例如由MSC形成软骨细胞的过程。在一些实施方案中，所述方法在体外进行。在一些实施方案中，所述方法在哺乳动物的体内进行，并且所述干细胞存在于该哺乳动物中。在某些实施方案中，该

哺乳动物是人、狗、猫或马。在某些实施方案中，该哺乳动物是人。在某些实施方案中，该哺乳动物是狗、猫或马。

[0171] 诱导 MSC 分化为软骨细胞可以使用任何适量的本发明的化合物来完成。在一些实施方案中，根据活性组分的特定应用和效力，本发明的化合物可以以约 0.1mg 至约 10000mg，例如 1.0mg 至 1000mg，例如 10mg 至 500mg 的量存在。在一些实施方案中，本发明的化合物可以以 0.1μM－100μM 的浓度存在于针对膝盖的关节内注射液中。

用于鉴定化合物的试验

[0172] 本发明的化合物使用多种试验来鉴定。最初的筛选鉴定了刺激人间充质干细胞(hMSC)以发展成软骨细胞结节的化合物。进行了另外的试验来确定软骨细胞分化的毒性和特异性。

化合物

[0173] 本文描述了诱导间充质干细胞分化为软骨细胞的化合物。在一些实施方案中，本文所述的化合物改善哺乳动物的关节炎或关节损伤。在一些实施方案中，本文所述的化合物治疗哺乳动物的关节炎或关节损伤。

[0174] 在一方面，本文提供了式 I 的化合物，或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

[0175] 在另一方面，本文提供了式 Ia 的化合物，或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

[0176] 在另一方面，本文提供了式 Ib 的化合物，或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

[0177] 在另一方面，本文提供了式 Ic 的化合物，或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

[0178] 在另一方面，本文提供了式 II 的化合物，或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

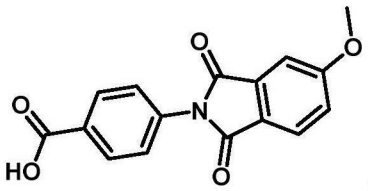
[0179] 在另一方面，本文提供了式 IIa 的化合物，或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

[0180] 在另一方面，本文提供了式 IIb 的化合物，或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

[0181] 在另一方面，本文提供了式 IIc 的化合物，或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

[0182] 在另一方面，本文提供了式 III 的化合物，或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体。

[0183] 在另一方面，本文提供了化合物或其药学上可接受的盐、溶剂化物、多晶型物、前药、酯、代谢物、N- 氧化物、立体异构体或异构体，该化合物选自：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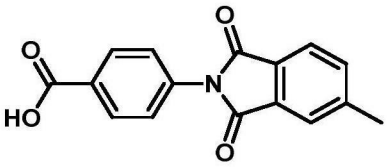
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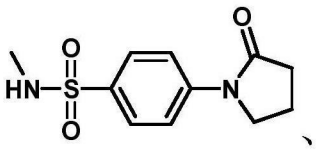
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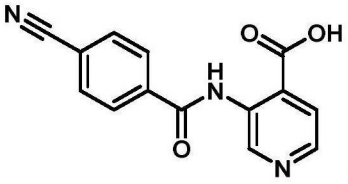
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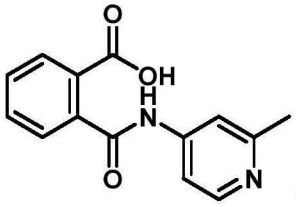
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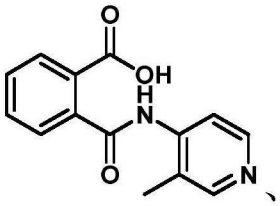
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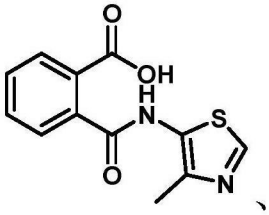
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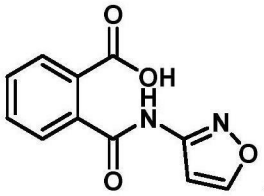
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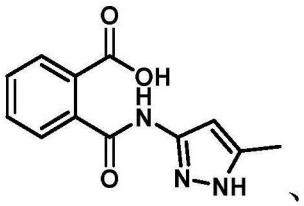
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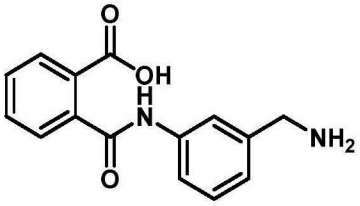
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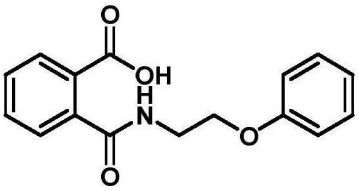
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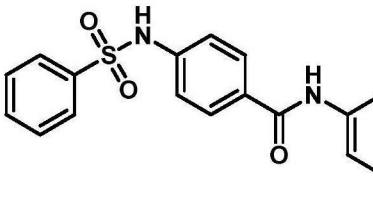
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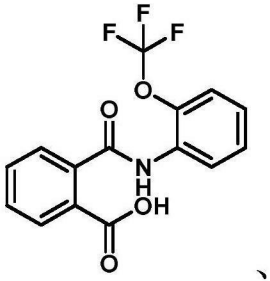
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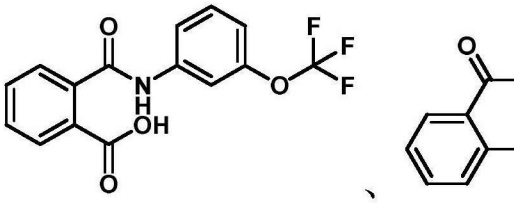
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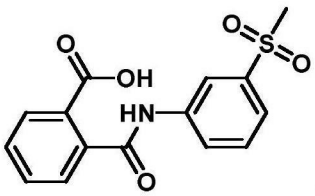
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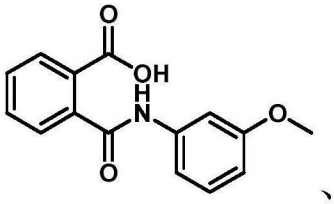
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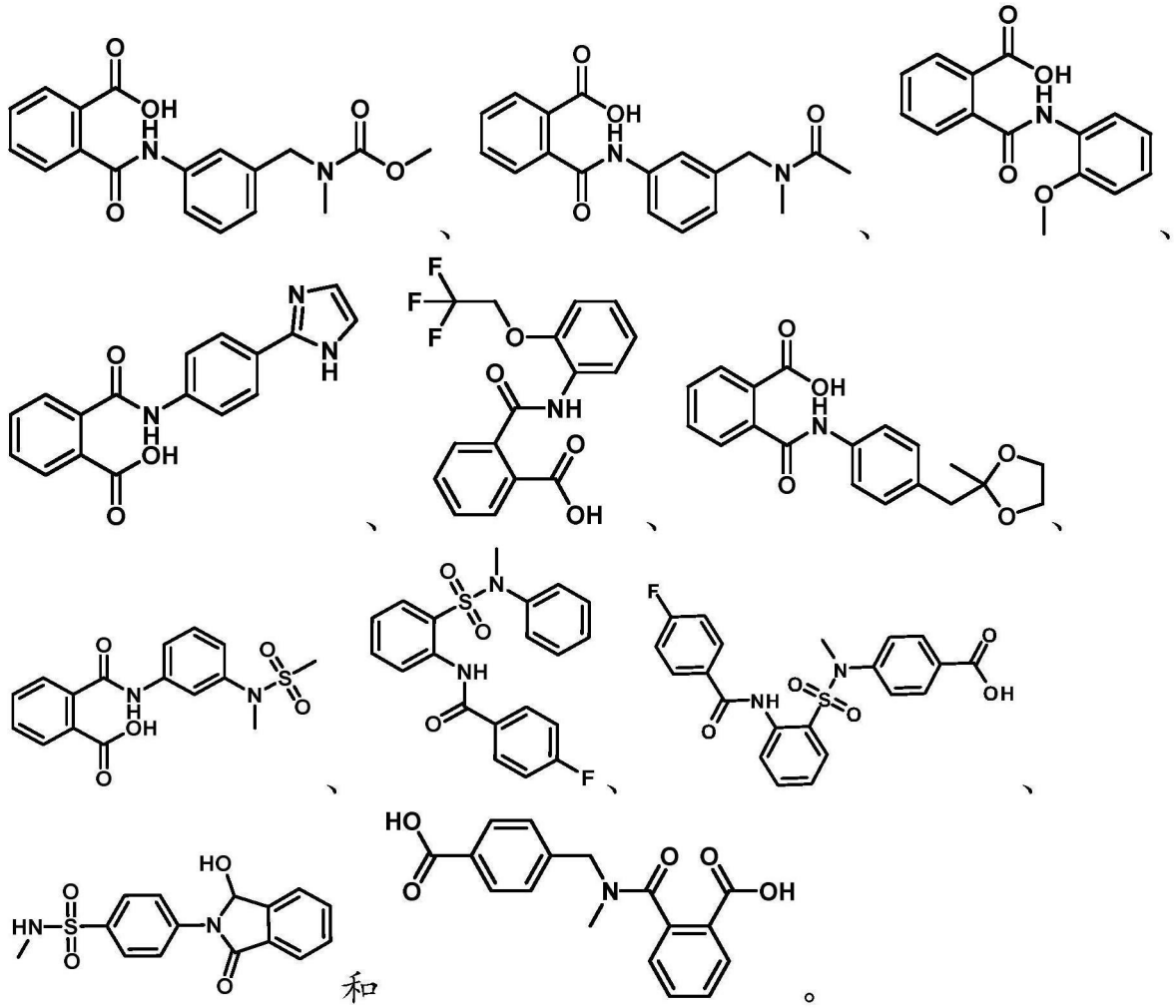


化合物的制备

[0184] 本文描述了用于诱导间充质干细胞分化为软骨细胞以及用于改善哺乳动物的关节炎或关节损伤的化合物以及这些化合物的制备方法。本文还描述了这些化合物的药学上可接受的盐、药学上可接受的溶剂化物、药学活性代谢物以及药学上可接受的前药。还提供了包含至少一种这样的化合物或该化合物的药学上可接受的盐、药学上可接受的溶剂化物、药学活性代谢物或药学上可接受的前药以及药学上可接受的赋形剂的药物组合物。

[0185] 本文描述的化合物可使用本领域技术人员已知的标准合成反应或使用本领域已知的方法来合成。可以以线性顺序采用反应来提供所述化合物，或者可使用这些反应来合成片段，随后通过本领域已知的方法进行连接。

[0186] 用于合成本文所述的化合物的起始材料可以合成或可从商业来源获得，该商业来源例如是但不限于Aldrich Chemical Co.(Milwaukee,Wisconsin)、Bachem(Torrance,California)或Sigma Chemical Co.(St.Louis,Mo.)。本文所述的化合物及其他具有不同取代基的相关化合物可使用本领域技术人员已知的技术和材料来合成，例如使用描述于诸如以下的技术和材料：March,ADVANCED ORGANIC CHEMISTRY,第4版.,(Wiley 1992)；Carey和Sundberg,ADVANCED ORGANIC CHEMISTRY,第4版.,Vols.A和B(Plenum 2000,2001)；Green和Wuts,PROTECTIVE GROUPS IN ORGANIC SYNTHESIS,第3版.,(Wiley 1999)；Fieser and Fieser's Reagents for Organic Synthesis,Volumes 1-17(John Wiley and Sons,1991)；Rodd's Chemistry of Carbon

Compounds,Volumes 1-5and Supplementals(Elsevier Science Publishers,1989)；Organic Reactions,Volumes 1-40(John Wiley and Sons,1991)；以及 Larock's Comprehensive Organic Transformations(VCH Publishers Inc.,1989)。(所有这些均通过引用整体并入本文)。用于合成本文所述的化合物的其他方法可见于国际专利公开号 WO 01/01982901,Arnold 等,Bioorganic&Medicinal Chemistry Letters 10(2000)2167-2170;Burchat 等,Bioorganic&Medicinal Chemistry Letters 12(2002)1687-1690。用于制备本文所公开的化合物的一般方法可从本领域已知的反应得到,并且为了引入在如本文所提供的通式中所见的各个部分,如本领域技术人员所公认的,可通过使用适当的试剂和条件对该反应进行修改。

[0187] 如果需要,可使用包括但不限于过滤、蒸馏、结晶及色谱法等常规技术来分离和纯化反应产物。这类材料可使用包括物理常数和波谱数据在内的常规手段来表征。

[0188] 本文所述的化合物可制备成单一异构体或异构体的混合物。

本文公开的化合物的其他形式

异构体

[0189] 在一些实施方案中,本文所述的化合物以几何异构体形式存在。在一些实施方案中,本文所述的化合物具有一个或多个双键。本文提供的化合物包括所有顺式、反式、同侧、对侧、E 型 (E) 和 Z 型 (Z) 异构体以及其相应混合物。在一些情况下,化合物以互变异构体形式存在。本文所述的化合物包括在本文所述的通式内的所有可能的互变异构体。在一些情况下,本文所述的化合物具有一个或多个手性中心且各中心以 R 构型或 S 构型存在。本文所述的化合物包括所有非对映异构、对映异构和差向异构形式以及其相应混合物。在本文提供的化合物和方法的其他实施方案中,由单一制备步骤、组合或相互转化得到的对映异构体和/或非对映异构体的混合物可用于本文所述的应用。在一些实施方案中,通过使化合物的外消旋混合物与旋光拆分剂反应形成一对非对映异构化合物、分离非对映异构体并回收光学纯的对映异构体,将本文所述的化合物制备为其单独的立体异构体。在一些实施方案中,优选可分离的复合物(例如结晶的非对映异构盐)。在一些实施方案中,非对映异构体具有不同的物理性质(例如熔点、沸点、溶解度、反应性等),并且利用这些差异进行分离。在一些实施方案中,通过手性色谱法或优选地通过基于溶解度差异的分离/拆分技术来分离非对映异构体。在一些实施方案中,然后通过不会引起外消旋的任何实用方式回收光学纯的对映异构体以及拆分剂。

标记的化合物

[0190] 在一些实施方案中,本文所述的化合物以其同位素标记的形式存在。在一些实施方案中,本文公开的方法包括通过施用此类同位素标记的化合物来治疗疾病的方法。在一些实施方案中,本文公开的方法包括通过以药物组合物形式施用此类同位素标记的化合物来治疗疾病的方法。因此,在一些实施方案中,本文公开的化合物包括同位素标记的化合物,除了其中一个或多个原子被替换成具有与在自然界中通常发现的原子质量或质量数不同的原子质量或质量数的原子的事实以外,该同位素标记的化合物与本文所述化合物相同。可引入本发明化合物的同位素的实例包括氢、碳、氮、氧、磷、硫、氟和氯的同位素,分别如 ^{2}H、^{3}H、^{13}C、^{14}C、^{15}N、^{18}O、^{17}O、^{31}P、^{32}P、^{35}S、^{18}F 和 ^{36}Cl。含有上述同位素和/或其他原子的其他同位素的本文所述的化合物及其代谢物、药学上可接受的盐、酯、前药、溶剂化物、水合物或

衍生物在本发明的范围内。某些同位素标记的化合物，例如其中引入了放射性同位素如 ^{3}H 和 ^{14}C 的那些化合物，可用于药物和 / 或基质组织分布分析。氚标记 (即 ^{3}H) 和碳 -14(即 ^{14}C) 同位素由于其容易制备和可检测性而尤其优选。此外，用重同位素如氘 (即 ^{2}H) 取代产生了由较高代谢稳定性引起的某些治疗优势，例如体内半衰期的延长或剂量需求的减少。在一些实施方案中，同位素标记的化合物、其药学上可接受的盐、酯、前药、溶剂化物、水合物或衍生物通过任何合适的方法制备。

[0191] 在一些实施方案中，本文所述的化合物通过其他方式标记，包括但不限于使用发色团或荧光部分、生物发光标记或化学发光标记。

药学上可接受的盐

[0192] 在一些实施方案中，本文所述的化合物以其药学上可接受的盐的形式存在。在一些实施方案中，本文公开的方法包括通过施用此类药学上可接受的盐来治疗疾病的方法。在一些实施方案中，本文公开的方法包括通过以药物组合物形式施用此类药学上可接受的盐来治疗疾病的方法。

[0193] 在一些实施方案中，本文所述的化合物具有酸性或碱性基团，并因此与多种无机或有机碱和无机与有机酸中的任一种反应形成药学上可接受的盐。在一些实施方案中，这些盐在本发明化合物的最终分离和纯化期间原位制备，或通过使处于游离形式的经纯化的化合物分别与合适的酸或碱反应并分离由此形成的盐来制备。

[0194] 药学上可接受的盐的实例包括通过使本文所述的化合物与无机酸、有机酸或无机碱反应制备的那些盐，此类盐包括乙酸盐、丙烯酸盐、己二酸盐、藻酸盐、天冬氨酸盐、苯甲酸盐、苯磺酸盐、硫酸氢盐、亚硫酸氢盐、溴化物、丁酸盐、丁炔 -1,4- 二酸盐、樟脑酸盐、樟脑磺酸盐、己酸盐、辛酸盐、氯苯甲酸盐、氯化物、柠檬酸盐、环戊烷丙酸盐、癸酸盐、二葡糖酸盐、磷酸二氢盐、二硝基苯甲酸盐、十二烷基硫酸盐、乙烷磺酸盐、甲酸盐、反丁烯二酸盐、葡糖庚酸盐、甘油磷酸盐、乙醇酸盐、半硫酸盐、庚酸盐、己酸盐、己炔 -1,6- 二酸盐、羟基苯甲酸盐、γ- 羟基丁酸盐、盐酸盐、氢溴酸盐、氢碘酸盐、2- 羟基乙烷磺酸盐、碘化物、异丁酸盐、乳酸盐、顺丁烯二酸盐、丙二酸盐、甲烷磺酸盐、扁桃酸盐、偏磷酸盐、甲烷磺酸盐、甲氧基苯甲酸盐、甲基苯甲酸盐、磷酸单氢盐、1- 萘磺酸盐、2- 萘磺酸盐、烟酸盐、硝酸盐、双羟萘酸盐、果胶酸盐、过硫酸盐、3- 苯基丙酸盐、磷酸盐、苦味酸盐、三甲基乙酸盐、丙酸盐、焦硫酸盐、焦磷酸盐、丙炔酸盐、邻苯二甲酸盐、苯基乙酸盐、苯基丁酸盐、丙烷磺酸盐、水杨酸盐、丁二酸盐、硫酸盐、亚硫酸盐、丁二酸盐、辛二酸盐、癸二酸盐、磺酸盐、酒石酸盐、硫氰酸盐、甲苯磺酸盐、十一烷酸盐和二甲苯磺酸盐。

[0195] 此外，本文所述的化合物可制备为通过化合物的游离碱形式与药学上可接受的无机或有机酸反应而形成的药学上可接受的盐，此类药学上可接受的无机或有机酸包括但不限于无机酸，诸如盐酸、氢溴酸、硫酸、硝酸、磷酸、偏磷酸等；和有机酸，诸如乙酸、丙酸、己酸、环戊烷丙酸、乙醇酸、丙酮酸、乳酸、丙二酸、丁二酸、苹果酸、顺丁烯二酸、反丁烯二酸、Q- 甲苯磺酸、酒石酸、三氟乙酸、柠檬酸、苯甲酸、3-(4- 羟基苯甲酰基) 苯甲酸、肉桂酸、扁桃酸、芳基磺酸、甲烷磺酸、乙烷磺酸、1,2- 乙烷二磺酸、2- 羟基乙烷磺酸、苯磺酸、2- 萘磺酸、4- 甲基双环 -[2.2.2] 辛 -2- 烯 -1- 甲酸、葡糖庚酸、4,4'- 亚甲基双 -(3- 羟基 -2- 烯 -1- 甲酸)、3- 苯基丙酸、三甲基乙酸、叔丁基乙酸、月桂基硫酸、葡糖酸、谷氨酸、羟基萘甲酸、水杨酸、硬脂酸和粘康酸。在一些实施方案中，诸如草酸的其他酸虽然本身并

非药学上可接受的，但用于制备可用作获得本发明化合物及其药学上可接受的酸加成盐中的中间体的盐。

[0196] 在一些实施方案中，包含游离酸基团的本文所述的那些化合物与以下化合物反应：合适的碱，诸如药学上可接受的金属阳离子的氢氧化物、碳酸盐、碳酸氢盐、硫酸盐，氨，或药学上可接受的有机伯胺、仲胺、叔胺或季胺。代表性的盐包括碱金属盐或碱土金属盐，如锂盐、钠盐、钾盐、钙盐和镁盐和铝盐等。碱的说明性实例包括氢氧化钠、氢氧化钾、胆碱氢氧化物、碳酸钠、$N^+(C_{1-4}$烷基$)_4$等。

[0197] 可用于形成碱加成盐的代表性有机胺包括乙胺、二乙胺、乙二胺、乙醇胺、二乙醇胺、哌嗪等。应当理解，本文所述的化合物也包括其所含有的任何碱性含氮基团的季铵化。在一些实施方案中，通过此类季铵化获得水溶性或油溶性或可分散性产物。

溶剂化物

[0198] 在一些实施方案中，本文所述的化合物以溶剂化物的形式存在。本发明提供通过施用此类溶剂化物来治疗疾病的方法。本发明进一步提供通过以药物组合物形式施用此类溶剂化物来治疗疾病的方法。

[0199] 溶剂化物含有化学计量或非化学计量的量的溶剂，并且在一些实施方案中，在与药学上可接受的溶剂如水、乙醇等结晶的过程中形成。当溶剂是水时形成水合物，或者当溶剂是醇时形成醇化物。本文所述化合物的溶剂化物可方便地在本文所述的过程中制备或形成。仅举例来说，可方便地使用包括但不限于二氧杂环己烷、四氢呋喃或甲醇的有机溶剂，通过从水性/有机溶剂混合物中再结晶来制备本文所述化合物的水合物。此外，本文提供的化合物可以以非溶剂化以及溶剂化的形式存在。一般而言，对于本文提供的化合物和方法而言，溶剂化形式被视为与非溶剂化形式等同。

多晶型物

[0200] 在一些实施方案中，本文所述的化合物以多晶型物的形式存在。本发明提供通过施用此类多晶型物来治疗疾病的方法。本发明进一步提供通过以药物组合物形式施用此类多晶型物来治疗疾病的方法。

[0201] 因此，本文所述的化合物包括其所有结晶形式，称为多晶型物。多晶型物包括化合物的具有相同元素组成的不同晶体堆积排列。在某些情况下，多晶型物具有不同的X-射线衍射图案、红外光谱、熔点、密度、硬度、晶体形状、光学和电学性质、稳定性和溶解度。在某些情况下，诸如再结晶溶剂、结晶速率和储存温度等各种因素使单一晶体形式占优势。

前药

[0202] 在一些实施方案中，本文所述的化合物以前药的形式存在。本发明提供通过施用此类前药来治疗疾病的方法。本发明进一步提供以药物组合物形式施用此类前药来治疗疾病的方法。

[0203] 前药一般为药物前体，其在施用于个体且随后吸收后经由诸如通过代谢途径转化的某一过程转化为具有活性或活性更强的物质。一些前药在前药上具有使其活性较低和/或赋予药物溶解性或一些其他性质的化学基团。一旦化学基团从前药上裂解和/或修饰，即产生活性药物。因为在一些情况下前药比母体药物更易于施用，前药通常为可用的。例如，它们可通过口服施用而可生物利用，而母体药物则不能。在某些情况下，前药在药物组合物中也具有比母体药物改善的溶解度。前药的一个实例是但不限于如本文所述的化合

物，其以酯的形式（“前药”）施用以促进跨过其中水溶性对移动性不利的细胞膜输送，但其随后一旦在水溶性有利的细胞内部则代谢水解成羧酸（活性实体）。前药的另一实例可以是与酸基团键合的短肽（聚氨基酸），其中该肽经代谢以显露活性部分。（参见例如 Bundgaard，“Design and Application of Prodrugs”，A Textbook of Drug Design and Development，Krosgaard-Larsen 和 Bundgaard 编，1991，第 5 章，113-191，其通过引用并入本文）。

[0204] 在一些实施方案中，前药被设计成可逆性药物衍生物，以用作提高药物向位点特异性组织输送的调节剂。迄今为止，前药的设计是为了提高靶向以水为主要溶剂的区域的治疗性化合物的有效水溶性。

[0205] 在一些实施方案中，前药是本文公开的化合物的 C_1-C_6烷基酯。

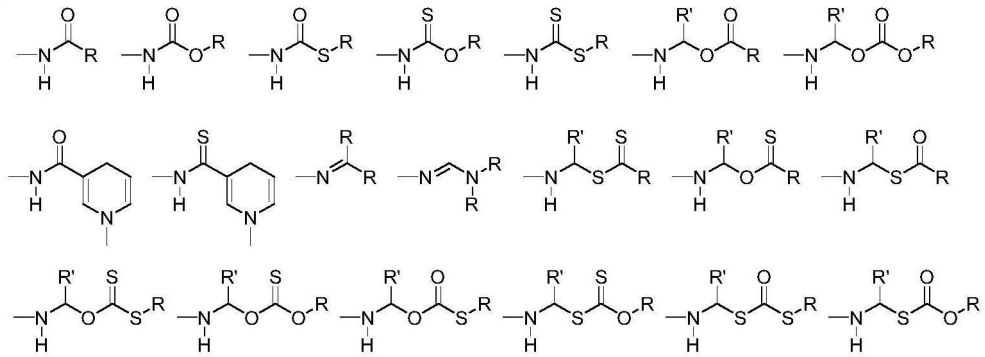
[0206] 另外，本文所述化合物的前药衍生物可通过本文所述或本领域已知的方法制备（关于更多细节，请参见 Saulnier 等人，Bioorganic and Medicinal Chemistry Letters，1994，4，1985）。仅举例而言，可通过使未衍生化的化合物与诸如但不限于氯甲酸 1，1- 酰氧基烷基酯、碳酸对硝基苯基酯等合适的氨基甲酰化试剂反应来制备适当的前药。本文所述化合物的前药形式（其中前药在体内代谢产生如本文所述的衍生物）包括在权利要求书的范围内。实际上，一些本文所述的化合物为另一衍生物或活性化合物的前药。

[0207] 在一些实施方案中，前药包括其中氨基酸残基或具有两个或两个以上（例如 2、3 或 4 个）氨基酸残基的多肽链经由酰胺键或酯键共价连接至本发明化合物的游离氨基、羟基或羧酸基团的化合物。氨基酸残基包括但不限于 20 种天然存在的氨基酸，并且也包括 4- 羟基脯氨酸、羟赖氨酸、锁链赖氨酸 (demosine)、异锁链赖氨酸、3- 甲基组氨酸、正缬氨酸、β - 丙氨酸、γ - 氨基丁酸、瓜氨酸、高半胱氨酸、高丝氨酸、鸟氨酸和甲硫氨酸砜。在其他实施方案中，前药包括其中核酸残基或具有两个或两个以上（例如 2、3 或 4 个）核酸残基的寡核苷酸共价连接至本发明化合物的化合物。

[0208] 本文所述化合物的药学上可接受的前药也包括但不限于酯、碳酸酯、硫代碳酸酯、N- 酰基衍生物、N- 酰氧基烷基衍生物、叔胺的季铵化衍生物、N- 曼尼希碱、席夫碱、氨基酸偶联物、磷酸酯、金属盐和磺酸酯。具有游离氨基、酰胺基、羟基或羧基的化合物可转化为前药。例如，游离羧基可衍生为酰胺或烷基酯。在某些情况下，所有这些前药部分中引入包括但不限于醚、胺和羧酸官能团的基团。

[0209] 羟基前药包括酯，诸如但不限于酰氧基烷基（例如酰氧基甲基、酰氧基乙基）酯、烷氧基羰氧基烷基酯、烷基酯、芳基酯、磷酸酯、磺酸酯、硫酸酯和含有二硫化物的酯；醚、酰胺、氨基甲酸酯、半琥珀酸酯、二甲基氨基乙酸酯和磷酰基氧基甲氧基羰基，如 Advanced Drug Delivery Reviews 1996，19，115 中所概述的。

[0210] 胺衍生的前药包括但不限于以下基团和基团的组合：



以及磺酰胺和磷酰胺。

[0211] 在某些情形下，在任何芳香环部分上的位点易发生各种代谢反应，因此在芳香环结构上并入合适的取代基可减少、最小化或消除该代谢途径。

代谢物

[0212] 在一些实施方案中，本文描述的化合物易发生各种代谢反应。因此在一些实施方案中，将合适的取代基并入结构中将减少、最小化或消除代谢途径。在具体的实施方案中，仅举例而言，减少或消除芳香环对代谢反应的敏感性的合适的取代基为卤素或烷基。

[0213] 在另外的或进一步的实施方案中，本文所述的化合物在施用于有需要的生物体后被代谢以产生代谢物，该代谢物随后用于产生所期望的效果，包括所期望的治疗效果。

药物组合物 / 制剂

[0214] 在另一方面，本文提供了包含本文描述的化合物或其药学上可接受的盐、多晶型物、溶剂化物、前药、N- 氧化物或异构体以及药学上可接受的赋形剂的药物组合物。

[0215] 在一些实施方案中，将本文所述的化合物配制为药物组合物。药物组合物以常规方式使用一种或多种药学上可接受的非活性成分进行配制，该非活性成分便于将活性化合物加工成可在药学上使用的制剂。适当的制剂取决于所选择的给药途径。本文所述的药物组合物的概述可见于，例如，Remington:The Science and Practice of Pharmacy, 第十九版 (Easton,Pa.:Mack Publishing Company,1995) ;Hoover,John E.,Remington's Pharmaceutical Sciences,Mack Publishing Co.,Easton,Pennsylvania 1975 ; Liberman,H.A. 和 Lachman,L. 编著 ,Pharmaceutical Dosage Forms,Marcel Decker,New York,N.Y.,1980 ;以及Pharmaceutical Dosage Forms and Drug Delivery Systems, 第七版 (Lippincott Williams&Wilkins 1999)，这些公开文献通过引用并入本文。

[0216] 本文提供了包含本文描述的化合物以及至少一种药学上可接受的非活性成分的药物组合物。在一些实施方案中，本文所述的化合物作为药物组合物施用，在该药物组合物中本文描述的化合物与其他活性成分混合，如在联合治疗中。在其他实施方案中，药物组合物包含其他医学或药学制剂、载体、佐剂、防腐剂、稳定剂、润湿剂或乳化剂、溶解促进剂 (solution promoter)、用于调节渗透压的盐和 / 或缓冲液。在又一些实施方案中，药物组合物包含其他有治疗价值的物质。

[0217] 本文所使用的药物组合物指本文描述的化合物与其他化学组分 (即，药学上可接受的非活性成分) 的混合物，所述其他化学组分例如是载体、赋形剂、粘合剂、填充剂、悬浮剂、矫味剂、甜味剂、崩解剂、分散剂、表面活性剂、润滑剂、着色剂、稀释剂、增溶剂、湿润剂、增塑剂、稳定剂、渗透促进剂、润湿剂、消泡剂、抗氧化剂、防腐剂或它们的一种或多种组合。

药物组合物有利于将化合物施用于生物体。在实施本文提供的治疗方法或应用的过程中，将治疗有效量的本文所述的化合物以药物组合物的形式施用于待治疗的患有疾病、病症或病况的哺乳动物。在一些实施方案中，该哺乳动物是人、狗、猫或马。在一些实施方案中，该哺乳动物是人。在一些实施方案中，该哺乳动物是狗、猫或马。治疗有效量可根据疾病的严重程度、受试者的年龄和相对健康、所用化合物的效力和其他因素而发生较大变化。化合物可以单独使用或作为混合物的组分与一种或多种治疗剂组合使用。

[0218] 本文所述的药物制剂通过适当的给药途径施用于受试者，该给药途径包括但不限于，口服、肠胃外（例如，静脉内、皮下、肌肉内、关节内）、鼻内、颊部、局部、直肠或经皮给药途径。本文所述的药物制剂包括但不限于：水性液体分散剂、液体、凝胶剂、糖浆、酏剂、浆液、悬浮液、自乳化分散剂、固溶体、脂质体分散剂、气雾剂、固体口服剂型、粉剂、立即释放制剂、控制释放制剂、快速熔解制剂（fast melt formulation）、片剂、胶囊、丸剂、粉剂、锭剂、泡腾制剂、冻干制剂、延迟释放制剂、延长释放制剂、脉冲释放制剂、多颗粒制剂以及立即和控制释放混合制剂。

[0219] 包含本文描述的化合物的药物组合物以常规方法进行制备，诸如，仅举例而言，通过常规的混合、溶解、制粒、制锭、磨细、乳化、包封、包埋或压制方法。

[0220] 所述药物组合物将包含以游离酸或游离碱的形式或以药学上可接受的盐的形式作为活性成分的至少一种本文描述的化合物。此外，本文所述的方法和药物组合物包括使用具有相同类型活性的这些化合物的N-氧化物（如果合适的话）、结晶形式、无定形相以及活性代谢物。在一些实施方案中，本文所述的化合物以非溶剂化形式存在或与药学上可接受的溶剂诸如水、乙醇等以溶剂化形式存在。本文提供的化合物的溶剂化形式也被认为在本文中公开。

[0221] 用于口服使用的药物制剂通过以下方法获得：将一种或多种固体赋形剂与本文所述的一种或多种化合物混合，任选地研磨所得混合物，并在加入合适的助剂（如果需要）后对颗粒混合物进行加工，以得到片剂或锭剂核芯。合适的赋形剂包括，例如，填充剂，诸如糖，包括乳糖、蔗糖、甘露醇或山梨糖醇；纤维素制剂，例如，玉米淀粉、小麦淀粉、大米淀粉、马铃薯淀粉、明胶、黄蓍胶、甲基纤维素、微晶纤维素、羟丙基甲基纤维素、羧甲基纤维素钠；或其他赋形剂，诸如：聚乙烯吡咯烷酮（PVP 或聚维酮）或磷酸钙。如果需要，加入崩解剂，诸如交联羧甲基纤维素钠、聚乙烯吡咯烷酮、琼脂或海藻酸或其盐如海藻酸钠。在一些实施方案中，将染料或色素加入到片剂或锭剂包衣中，用于辨识或表征活性化合物剂量的不同组合。

[0222] 口服给药的药物制剂包括由明胶制成的推入配合式（push-fit）胶囊以及由明胶和增塑剂（诸如甘油或山梨糖醇）制成的软密封胶囊。推入配合式胶囊含有与填充剂诸如乳糖、粘合剂诸如淀粉和/或润滑剂诸如滑石或硬脂酸镁以及任选的稳定剂混合的活性成分。在软胶囊中，活性化合物溶解或悬浮于合适的液体如脂肪油、液体石蜡或液体聚乙二醇中。在一些实施方案中，加入稳定剂。

[0223] 在某些实施方案中，可采用药物化合物的递送系统，例如，脂质体和乳剂。在某些实施方案中，本文提供的组合物还可包括选自例如羧甲基纤维素、卡波姆（丙烯酸聚合物）、聚（甲基丙烯酸甲酯）、聚丙烯酰胺、聚卡波非、丙烯酸/丙烯酸丁酯共聚物、海藻酸钠和葡聚糖的粘膜粘着聚合物。

联合治疗

[0224] 本发明的化合物和组合物可以与适合于改善关节炎或关节损伤的其他组分联合使用。在一些实施方案中，该组合物可以进一步包含对于治疗哺乳动物的关节炎或关节损伤和/或与关节炎或关节损伤相关的症状在治疗上有效的额外的化合物。在一些实施方案中，该组合物还可以包含非甾体抗炎药(NSAID)、镇痛药、糖皮质激素、血管生成素样3蛋白(ANGPTL3)或其软骨形成变体、口服鲑降钙素、SD-6010(iNOS抑制剂)、维生素D3(胆骨化醇)、胶原水解物、FGF18、BMP7、鳄梨大豆不皂化物(ASU)或透明质酸。ANGPTL3在WO2011/008773(整体并入本文)中更详细地描述。在一些实施方案中，该组合物包含具有抗炎活性的药剂。在一些实施方案中，该组合物包含凋亡调节剂。在某些实施方案中，该凋亡调节剂是胱天蛋白酶抑制剂。凋亡/胱天蛋白酶抑制剂的一个非限制性实例是恩利卡生。在一些实施方案中，该组合物包含iNOS抑制剂。iNOS抑制剂的一个非限制性实例是SD-6010。

[0225] NSAID包括但不限于阿司匹林、二氟尼柳、双水杨酯、布洛芬、右布洛芬、萘普生、非诺洛芬、酮洛芬、右酮洛芬、氟比洛芬、奥沙普秦、洛索洛芬、吲哚美辛、托美丁、舒林酸、依托度酸、酮咯酸、萘丁美酮、双氯芬酸、吡罗昔康、美洛昔康、替诺昔康、屈噁昔康、氯诺昔康、伊索昔康、甲芬那酸、甲氯芬那酸、氟芬那酸、托芬那酸、塞来考昔、帕瑞考昔、艾托考昔、鲁米考昔和非罗考昔。

[0226] 镇痛药包括但不限于醋氨酚和阿片类药物(麻醉剂)。阿片类药物包括但不限于右丙氧芬、可待因、曲马朵、他喷他多、阿尼利定、阿法罗定、哌替啶、氢可酮、吗啡、羟可酮、美沙酮、二乙酰吗啡、氢吗啡酮、羟吗啡酮、左啡诺、7-羟基帽柱木碱、丁丙诺啡、芬太尼、舒芬太尼、bromadol、埃托啡、二氢埃托啡和卡芬太尼。

[0227] 糖皮质激素包括但不限于氢化可的松、可的松、泼尼松、泼尼松龙、甲泼尼龙、地塞米松、倍他米松、曲安西龙、倍氯米松或氟氢可的松。

[0228] 本文所述的化合物可以与对于治疗关节炎或关节损伤和/或与关节炎或关节损伤相关的症状在治疗上有效的一种或多种化合物联合使用。这样的额外化合物可以通过常用的途径并以常用的量与本文公开的化合物同时或顺序施用。当本文公开的化合物与一种或多种这样的额外化合物同时使用时，含有这样的其他药物和本发明的化合物的单位剂型中的药物组合物是优选的。然而，联合疗法还可以包括其中本文公开的化合物和一种或多种额外的化合物按照不同的重叠时间表施用的疗法。还考虑到，当与一种或多种额外的化合物联合使用时，该化合物可以比各自单独使用时以更低的剂量使用。

[0229] 上述组合包括本文公开的化合物不仅与一种对于治疗关节炎或关节损伤和/或与关节炎或关节损伤相关的症状在治疗上有效的化合物的组合，而且与两种或更多种这样的化合物的组合。同样，本文公开的化合物本身或与对于治疗关节炎或关节损伤和/或与关节炎或关节损伤相关的症状在治疗上有效的化合物组合，可以与在预防、治疗、控制或改善骨关节炎或关节损伤或与骨关节炎或关节损伤相关的病况中使用的其他药物联合使用。这样的其他药物可以通过常用的途径并以常用的量与本文公开的化合物同时或顺序施用。当本文公开的化合物与一种或多种其他药物同时使用时，除本发明的化合物外还含有这样的其他药物的药物组合物是优选的。因此，本发明的药物组合物还包括除本文公开的化合物外还含有一种或多种其他活性成分的那些药物组合物。本文公开的化合物与第二活性成分的重量比可以变化，并且将取决于每种成分的有效剂量。通常，将使用其各自的有效剂

量。

药物组合物的给药

[0230] 合适的给药途径包括但不限于，口服、静脉内、关节内、直肠、喷雾、肠胃外、眼、肺、经粘膜、经皮、阴道、耳、鼻和局部给药。此外，仅举例而言，肠胃外递送包括肌肉内、皮下、静脉内、髓内注射，以及鞘内、直接心室内、腹膜内、淋巴管内、关节内和鼻内注射。

[0231] 在一些实施方案中，本文公开的化合物及其组合物以任何合适的方式进行给药。给药方式可基于例如是期望进行局部治疗还是全身治疗以及待治疗的区域来进行选择。例如，所述组合物可以口服、肠胃外（例如，静脉内、皮下、腹膜内、关节内或肌肉内注射）、通过吸入、体外、局部（包括经皮、眼、阴道、直肠、鼻内）等进行施用。在一些实施方案中，该组合物可以通过微针施用。在一些实施方案中，该组合物可以通过能够进行皮内药物递送的贴片形式的微针阵列施用。在一些实施方案中，该组合物可以通过透皮微针贴片递送来施用。

[0232] 如果使用的话，组合物的肠胃外施用通常以注射为特征。注射剂可以制备为常规形式，作为液体溶液或者悬浮液，适合于在注射前在液体中溶解或悬浮的固体形式，或作为乳剂。用于胃肠外施用的最近修订的方法包括使用缓慢释放或延迟释放系统以保持恒定剂量。

实施例

缩写列表

[0233] 如上所使用的，并且在本发明的整篇说明书中，除非另有说明，否则下列缩写应理解为具有以下含义：

ACN	乙腈
Bn	苯基
BOC 或 Boc	氨基甲酸叔丁酯
BOP	苯并三唑 -1- 基 - 氧基三（二甲基氨基）鏻
t-Bu	叔丁基
Cbz	氨基甲酸苄酯
Cy	环己基
DBU	1,8- 二氮杂双环 [5.4.0] 十一碳 -7- 烯
DCC	二环己基碳二亚胺
DCM	二氯甲烷 (CH2CI2)
DIC	1,3- 二异丙基碳二亚胺
DEAD	偶氮二甲酸二乙酯
DIAD	偶氮二甲酸二异丙酯
DIPEA	二异丙基乙胺
DMAP	4-(N,N- 二甲基氨基）吡啶
DMP 试剂	戴斯 - 马丁氧化剂 (Dess-Martin Periodinane reagent)
DMF	二甲基甲酰胺
DMA	N,N- 二甲基乙酰胺
DME	1,2- 二甲氧基 - 乙烷

DMSO	二甲基亚砜
Dppf	1,1'-双(二苯基膦基)二茂铁
EDCI	1-乙基-3-(3-二甲基氨基丙基)碳二亚胺 HCl
eq	当量
Et	乙基
Et2O	二乙醚
EtOH	乙醇
EtOAc	乙酸乙酯
HOAt	1-羟基-7-氮杂苯并三唑
HOBT	1-羟基苯并三唑
HOSu	N-羟基琥珀酰胺
HPLC	高效液相色谱法
LAH	酸酐锂铝
Me	甲基
MeI	碘甲烷
MeOH	甲醇
MOMCl	甲氧基甲基氯
MOM	甲氧基甲基
MS	质谱法
NMP	N-甲基-吡咯烷-2-酮
NMR	核磁共振
PyBOP	苯并三唑-1-基-氧基三-吡咯烷基-鏻六氟磷酸盐
SPHOS	2-二环己基膦基-2',6'-二甲氧基联苯基
TBD	1,5,7-三氮杂双环[4.4.0]-癸-5-烯
RP-HPLC	反相高压液相色谱法
TBS	叔丁基二甲基硅烷基
TBSCl	叔丁基二甲基硅烷基氯化物
TBTU	O-(苯并三唑-1-基)-N,N,N',N'-四甲基鎓
TEOC	2-三甲基硅烷基乙基氨基甲酸酯
TFA	三氟乙酸
Tf_2O	三氟甲磺酸酐
TMG	1,1,3,3-四甲基胍
THF	四氢呋喃
THP	四氢吡喃
TLC	薄层色谱法
XPHOS	2-二环己基膦基-2′,4′,6′-三异丙基联苯基

用于制备本发明的化合物的通用实施例

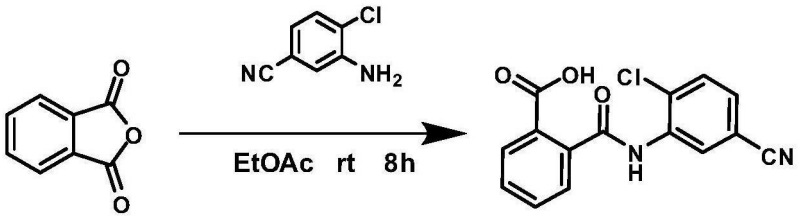
[0234] 用于本发明的化合物的起始材料和中间体可以通过应用或修改以下描述的方法来制备,其明显的化学等同物,或者,例如,如以下文献中所述:The Science of

Synthesis, 第 1-8 卷 .E.M.Carreira 等 人 编 .Thieme publishers(2001-2008)。 试 剂和反应选项的细节也可以通过使用商业计算机搜索引擎如 Scifinder(www.cas.org) 或 Reaxys(www.reaxys.com) 进行结构和反应搜索而获得。

合成实施例

[0235] 给出以下的本文公开的化合物和中间体的制备以使本领域技术人员能够更清楚地理解和实施本发明。它们不应被认为是限制本发明的范围,而仅作为其示例和代表。

合成流程 A :用于化合物 1 的实验样品

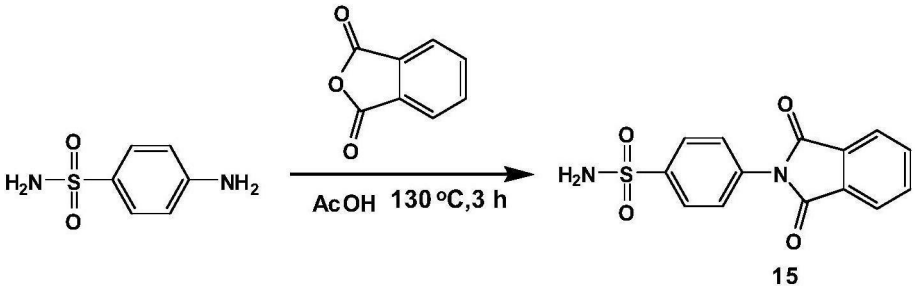


1

[0236] 向邻苯二甲酸酐 (1.0eq) 的 EtOAc 溶液中加入 3- 氨基 -4- 氯苄腈 (1eq),然后在 20-30℃下搅拌 1-8h。TLC 指示起始材料已经消失。过滤反应混合物,并且将固体通过在 EtOAc 中重结晶而纯化,得到化合物 1(12mg)。终产物 1 通过 ^{1}H NMR 和 LCMS 来证实。LCMS :实测 301.0[M+H]。^{1}H NMR(400MHz,MeOD-d4):8.35(s,1H),8.09(d,J = 7.7Hz,1H),7.71(dd,J = 8.0,4.1Hz,1H),7.67(d,J = 8.4Hz,1H),7.61(t,J = 7.4Hz.2H),7.57(dd,J = 8.4,2.0Hz,1H)。

[0237] 表 1 中的选择化合物使用与以上给出的反应流程类似的条件获得,其中将 3- 氨基 -4- 氯苄腈替换为合适的苯胺或胺。基于分离的产物的反应产率范围为 20%至 80%。

合成流程 B-1 :用于化合物 15 的实验样品

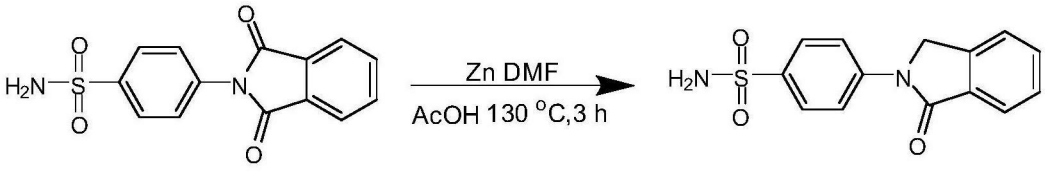


15

[0238] 向 4- 氨基苯磺酰胺 (100mg,0.58mmol) 的 AcOH(20mL) 溶液中加入邻苯二甲酸酐 (82mg,0.55mmol)。在 130℃下搅拌该混合物 3h。该混合物用 H_2O(30mL) 稀释,并搅拌 2h。过滤后得到呈白色固体的化合物 15(44mg,产率 :26%)。终产物 15 通过 ^{1}H NMR 和 LCMS 来证实。LCMS :实测 303.0[M+H]。^{1}H NMR(400MHz,DMSO-d_6):7.10-7.36(m,6H),6.56-6.70(m,2H),6.62(br s,2H)。

[0239] 表 1 中的选择化合物使用与以上给出的反应流程类似的条件获得,其中将 4- 氨基苯磺酰胺替换为合适的苯胺。在化合物 33 的情况下,反应时间为 3h,且反应混合物用 H_2O 稀释并搅拌 12h 以供结晶。

合成流程 B-2 :用于化合物 26 的实验样品



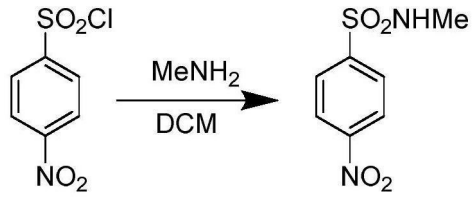
15 26

[0240] 向化合物 15(276mg,0.913mmol) 的 AcOH(5mL) 溶液中加入 Zn(596.91mg,9.13mmol) 和 DMF(0.1mL)。该混合物在 130℃下搅拌 3h,然后冷却至室温并浓缩,得到呈无色油的粗产物。残余物通过制备型 HPLC(0.1% TFA 作为添加剂) 纯化,通过减压蒸发除去大多数 CH_3CN,并且通过冻干除去其余的溶剂,以得到呈白色固体的化合物 26(80mg,产率 :30%)。LCMS :实测 289.1[M+H]。

[0241] 化合物 27(表 1) 使用与以上给出的反应流程类似的条件获得。在化合物 27 的制备中,不使用 DMF。

[0242] 产物 27 的起始材料通过以下程序制备。

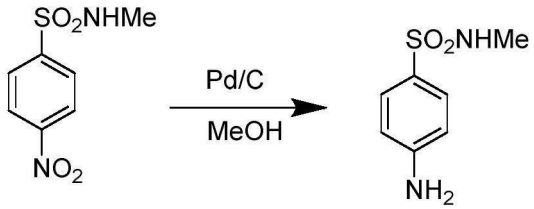
化合物 27-2 的制备



27-1 27-2

[0243] 向化合物 27-1(3.8g,17mmol) 的 DCM(50ml) 溶液中加入在醇中的 $MeNH_2$(5.3g,51mmol)。将混合物在室温下搅拌 2h。该混合物用 DCM(30ml) 稀释,并用 H_2O(30ml) 洗涤。有机层经无水 Na_2SO_4干燥,过滤,并浓缩,得到化合物 27-2(3.3g,产率 :90%)。

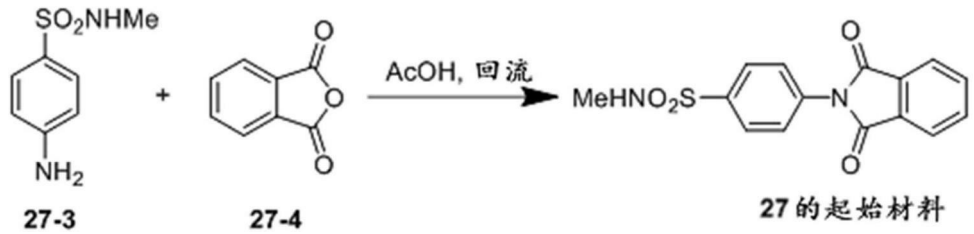
化合物 27-3 的制备



27-2 27-3

[0244] 在室温下向化合物 27-2(3.3g,15.3mol) 的 CH_3OH(50mL) 溶液中加入 Pd/C(0.16g)。该混合物在 H_2(30psi) 下于室温搅拌 12h。过滤该混合物并除去溶剂,得到呈灰色固体的化合物 27-3(2.3g,产率 :80%)。

化合物 27 的起始材料的制备

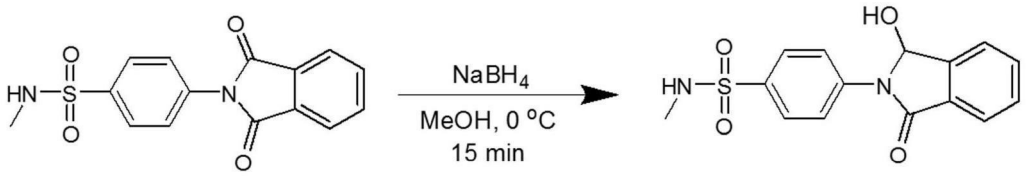


27-3 27-4 27 的起始材料

[0245] 向 27-3(0.5g,2.68mmol) 的 AcOH(40mL) 溶液中加入 27-4(0.433g,2.92mmol)。将

反应混合物在130℃下搅拌3h。冷却反应混合物，并除去溶剂以得到粗产物，其直接用于下一步。

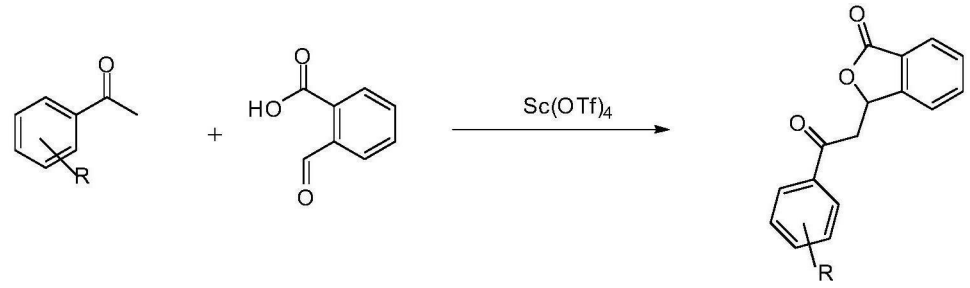
合成流程B-3：用于化合物177的实验样品



27的起始材料 177

[0246] 向0℃下的化合物27的起始材料(1.0g，3.16mmol)在CH_3OH(20mL)中的溶液中加入$NaBH_4$(239mg，6.32mmol)。该混合物在0℃下搅拌15min，之后减压除去溶剂。向粗残余物中加入水(20mL)和饱和NH_4Cl水溶液(20mL)。将混合物在室温下搅拌30min。过滤提供呈灰白色固体的化合物177(840mg，产率：83％)。

合成流程C：用于化合物C的通用程序

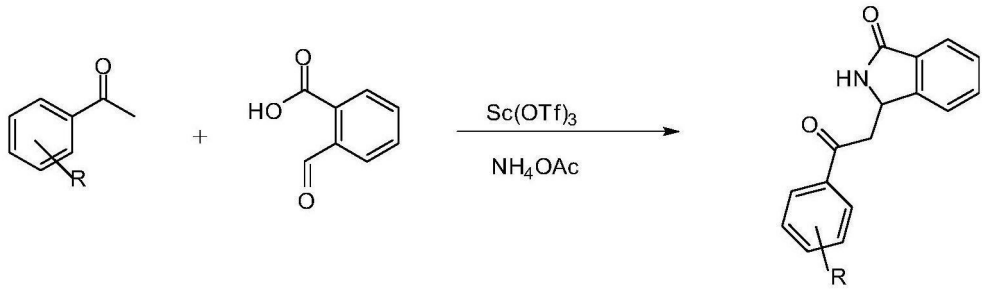


sm-1 sm-2 C

[0247] 向酮sm-1(1.0eq)的二氧杂环己烷(V/M＝10:1)溶液中加入羧基苯甲醛sm-2(1.2eq)，随后加入$Sc(OTf)_4$。将混合物加热至回流12h。冷却至室温后，浓缩该混合物并通过制备型HPLC纯化以得到化合物C。

[0248] 表1中的选择化合物使用合成流程C获得。基于分离的产物的反应产率范围为5％至50％。

合成流程D：用于化合物D的通用程序



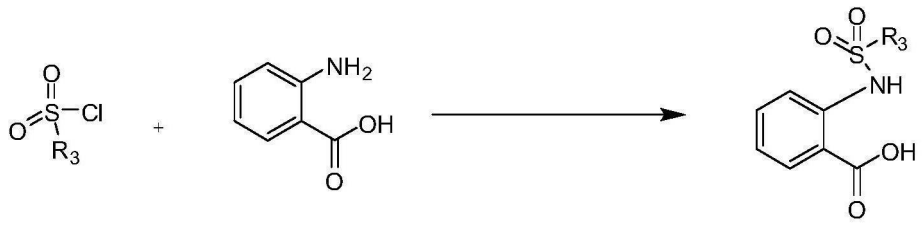
sm-1 sm-2 D

[0249] 向酮sm-1(1.0eq)的二氧杂环己烷(V/M＝15:1)溶液中加入羧基苯甲醛sm-2(1.2eq)，随后加入$Sc(OTf)_4$(2eq)。将混合物加热至回流12h。加入NH_4OAc(5eq)，并将反应混合物加热至回流另外12h。冷却至室温后，将该混合物浓缩并通过制备型HPLC纯化以得到化合物D。

[0250] 表1中的选择化合物使用合成流程D获得。基于分离的产物的反应产率范围为

3%至 20%。

合成流程 E :用于化合物 E 的通用程序

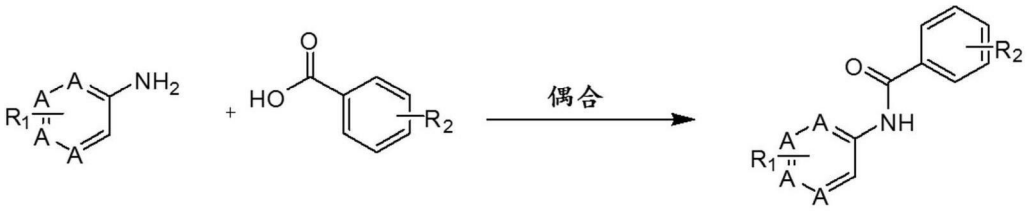


sm-3 sm-4 E

[0251] 向 2- 氨基苯甲酸 sm-4(1eq) 在 2M $NaHCO_3$(V = 10eq) 中的溶液中加入磺酰氯 sm-3(1.0eq),并将混合物在室温下搅拌 2h。TLC 指示起始材料已经消失。用 EtOAc 萃取该混合物。有机层经无水 Na_2SO_4干燥、浓缩并通过制备型 HPLC 纯化以得到纯产物 E。

[0252] 化合物 53(表 1) 使用合成流程 E 获得。基于分离的产物的反应产率范围为 60%至 80%。

合成流程 F :用于化合物 F 的通用程序

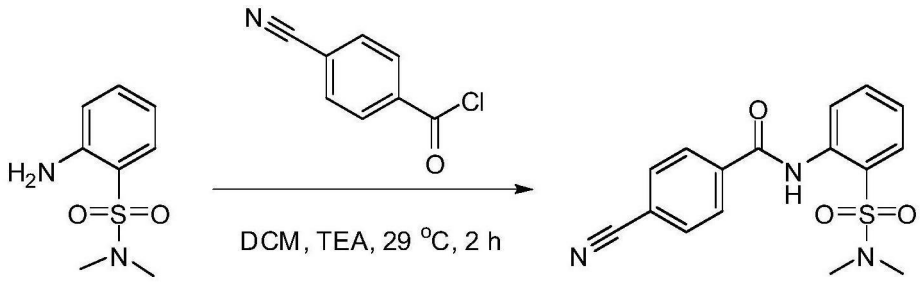


sm-5 sm-6 F

[0253] 在 0 ℃ 下向苯甲酸 sm-6(1eq) 的 DMF(10eq) 溶液中加入 EDCI(1.5eq) 和 HOBT(1.5eq),之后在室温下搅拌约 2h。向反应混合物中加入胺 sm-5(1.5eq),在室温下再搅拌 12h。加水,并将混合物用 EtOAc 萃取,经无水 Na_2SO_4干燥并浓缩。残余物通过柱色谱法纯化以得到产物 F。

[0254] 表 1 中的选择化合物使用合成流程 F 获得。基于分离的产物的反应产率范围为 20%至 40%。

合成流程 G :用于化合物 56 的实验样品



56

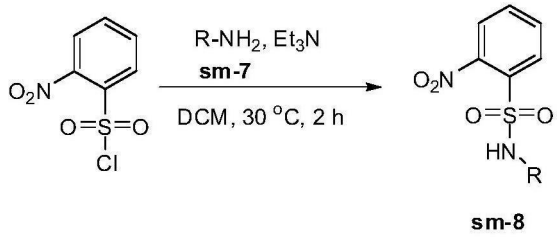
[0255] 向 2- 氨基 -N,N- 二甲基苯磺酰胺 (1.0eq) 和 TEA(1.5eq) 在 DCM 中的溶液中加入 4- 氰基苯甲酰氯 (1.0eq)。反应混合物在 29℃下搅拌约 2h。TLC 指示起始材料已经消失。将反应混合物用饱和 $NaHCO_3$水溶液猝灭,用 DCM 萃取,经无水 Na_2SO_4干燥并浓缩。残余物通过制备型 HPLC 纯化以得到化合物 56(产率 :70%)。LCMS :实测 330.1[M+H]。

[0256] 化合物 62(表 1) 使用与以上给出的反应流程类似的条件获得。基于分离的产物

的反应产率范围为 70％至 80％。

[0257] 化合物 56 和 62 必需的苯胺起始材料 I 通过以下程序制成。

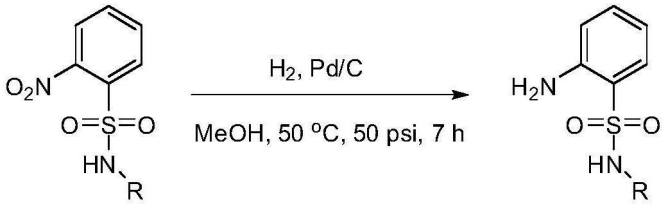
中间体 sm-8 的制备



sm-8

[0258] 将 2- 硝基苯 -1- 磺酰氯 (1.0eq) 和胺 sm-7(1.0eq) 在 DCM 中的溶液在 30℃下搅拌约 2h。TLC 指示起始材料已经消失。反应混合物用盐水洗涤、经无水 Na_2SO_4干燥并浓缩以得到中间体 sm-8(产率 :72-91％)。

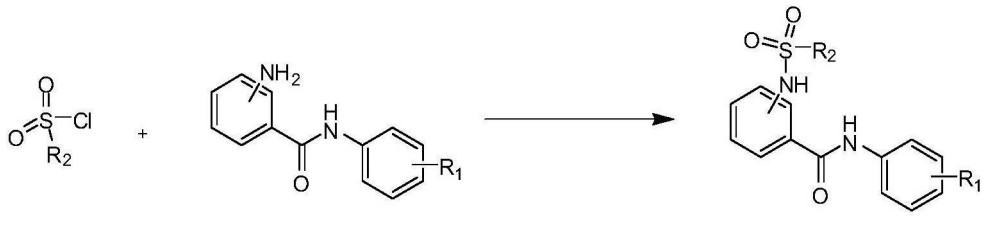
苯胺起始材料 I 的制备



sm-8 I

[0259] 向中间体 sm-8(1.0eq) 的 MeOH 溶液中加入 Pd/C。反应混合物在 50psi H_2下于 50℃搅拌 7h。TLC 指示起始材料已经消失。过滤该混合物，并浓缩滤液以得到化合物 I(产率 :89 ～ 91％)。

合成流程 H :用于化合物 H 的通用程序

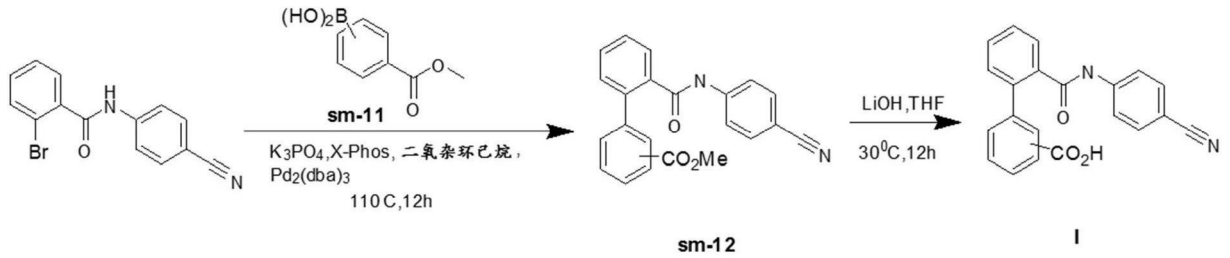


sm-9 sm-10 H

[0260] 在 0℃下向酰胺 sm-10(1eq) 的 THF(V ＝ 10eq) 溶液中逐滴加入 LiHMDS(1eq)。30min 后，加入磺酰氯 sm-9(1.0eq)，并将混合物在室温下搅拌 2h。TLC 指示起始材料已经消失。混合物用 EtOAc 萃取。有机层经无水 Na_2SO_4干燥，浓缩，并通过制备型 HPLC 纯化以得到化合物 H。

[0261] 表 1 中的选择化合物使用合成流程 H。基于分离的产物的反应产率范围为 50％至 80％。

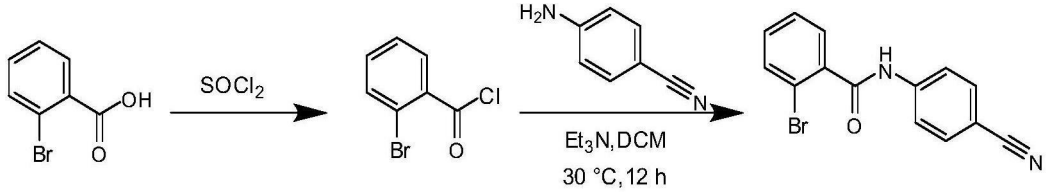
合成流程 I :用于化合物 I 的通用程序



[0262] 向搅拌的2-溴-N-(4-氰基苯基)苯甲酰胺(1.66mmol)和硼酸sm-11(3.32mmol)在二氧杂环己烷(10mL)中的混合物中加入K_3PO_4(1.06g,4.98mmol)。在N_2下加入$Pd_2(dba)_3$(45.61mg,49.81umol)和X-Phos(39.58mg,83.02umol)。最后将混合物加热至110℃并搅拌12h。过滤后,将混合物浓缩以得到呈棕色油的中间体sm-12。向sm-12(770mg,2.16mmol)的THF(30mL)溶液中逐滴加入LiOH(4.32mL,4.32mmol)并搅拌12h。在10℃下将溶液酸化至pH 4,用EtOAc(30mL)萃取,用H_2O(50mL)和盐水(50mL)洗涤,浓缩,并通过制备型HPLC(0.1%TFA作为添加剂)纯化。通过减压蒸发和冻干除去溶剂以得到呈白色固体的化合物I。

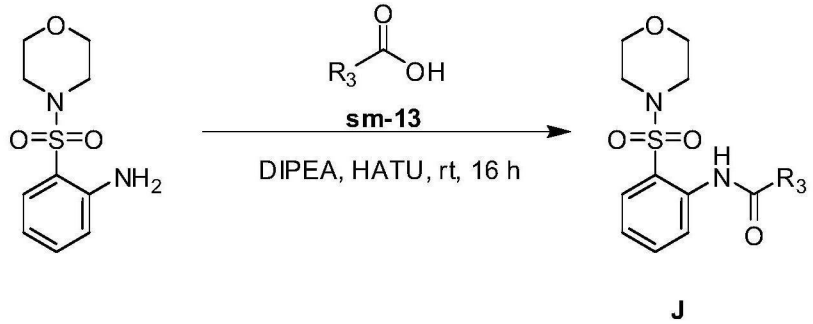
[0263] 表1中的选择化合物使用合成流程I获得。基于分离的产物的反应产率范围为15%至30%。

[0264] 2-溴-N-(4-氰基苯基)苯甲酰胺通过以下程序制备。



[0265] 将2-溴苯甲酸(4.4g,21.89mmol)的$SOCl_2$(45mL)溶液加热至70℃ 2h。将其蒸发以获得呈黄色油的2-溴苯甲酰氯,将其用DCM(90mL)稀释。在10℃下向4-氨基苯甲腈(2.59g,21.92mmol)的DCM(10mL)溶液和Et_3N(4.43g,43.78mmol)中逐滴加入所得混合物。最后使混合物升温至30℃并搅拌12h。混合物用DCM(100mL)稀释,用HCl(100mL)、$NaHCO_3$(50mL)、H_2O(50mL)和盐水(50mL)洗涤。有机层经Na_2SO_4干燥,浓缩,并通过硅胶柱色谱法(PE:EtOAc=5:1)纯化以提供呈白色固体的2-溴-N-(4-氰基苯基)苯甲酰胺(4.7g,产率:72%)。

合成流程J:用于化合物J的通用程序

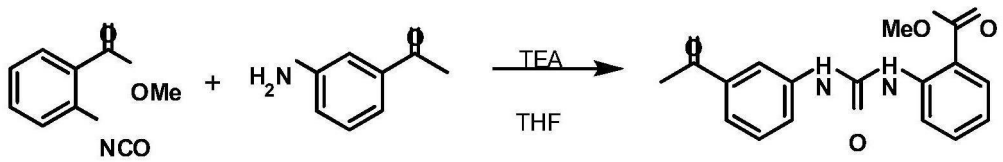


J

[0266] 向2-(吗啉基磺酰基)苯胺(1.0eq)的DMF溶液中加入羧酸sm-13(1.0eq)、DIPEA(1.5eq)和HATU(1.3eq)。所得混合物在10-15℃下搅拌16-24h。TLC指示起始材料已经消失。将反应混合物浓缩,固体通过硅胶柱色谱法纯化以得到化合物J。

[0267] 表 1 中的选择化合物使用合成流程 J 获得。

合成流程 K-1 :用于化合物 193 的实验样品



193

[0268] 将 2- 异氰酸苯甲酸甲酯 (200mg 1.13mmol) 和 1-(3- 氨基苯基) 乙酮 (167mg, 1.24mmol) 溶解在 THF(2.5ml) 中,并使用微波在 100℃下加热 15min。反应混合物用饱和 $NaHCO_3$水溶液洗涤,通过柱色谱法 (EtOAc: 己烷) 纯化以提供终产物 193(262mg,产率 : 75%),这通过 ^1H NMR 和 LCMS 来证实。

[0269] 表 1 中的选择化合物使用与以上给出的反应流程类似的条件获得。在这些反应中,使用 DIPEA 代替 TEA,并且将温度升高至 120℃。基于分离的产物的反应产率范围为 47-90%。

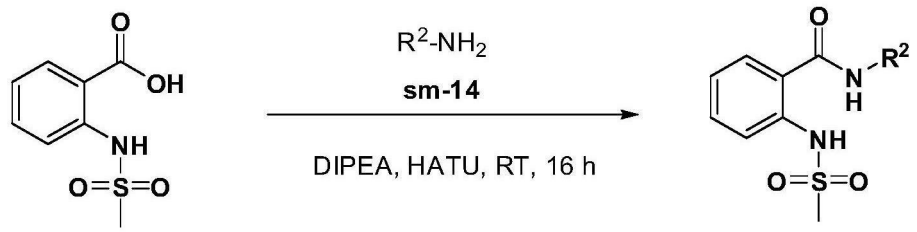
合成流程 K-2 :用于化合物 196 的实验样品

195 196

[0270] 将化合物 195 溶解在 THF(2mL) 和 1N NaOH(1mL) 中。反应混合物在室温下搅拌 15h。混合物用 EtOAc(20mL) 稀释,之后在恒定搅拌下逐滴加入 1N HCl(3mL)。将有机层萃取,干燥,并浓缩。粗产物从 EtOAc 中重结晶以提供化合物 196(25mg)。

[0271] 表 1 中的选择化合物使用与以上给出的反应流程类似的条件获得。基于分离的产物的反应产率范围为 80-90%。

合成流程 L :用于化合物 L 的通用程序

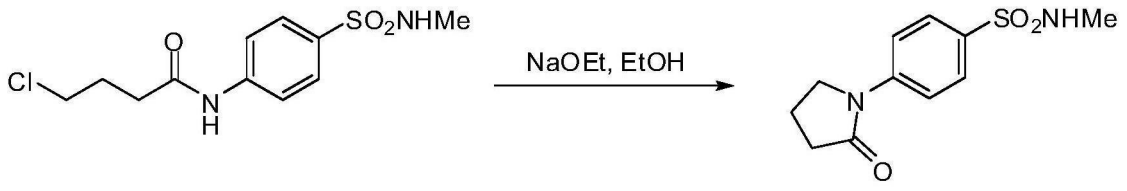


L

[0272] 向 2-(甲基磺酰胺基) 苯甲酸 (1.0eq) 的 DMF 溶液中加入 sm-14(1.0eq)、DIPEA(1.5eq) 和 HATU(1.3eq)。混合物在 10-15℃下搅拌 16-24h。通过 TLC 指示反应完全后,对反应混合物进行浓缩,并将固体通过硅胶色谱法纯化以得到化合物 L。

[0273] 表 1 中的选择化合物使用合成流程 L 获得。

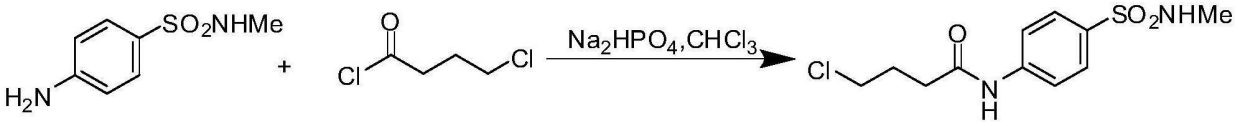
用于化合物 28 的合成流程 :



sm-15 28

[0274] 在 0 ℃ 下，化合物 I(320g,1.1mmol) 在 EtOH(10mL) 中的溶液逐滴加入 NaOEt(571.6mg,8.4mmol) 持续 3h。该反应用 1N HCl 酸化并除去溶剂以得到粗产物。残余物通过制备型 HPLC(0.1% TFA 作为添加剂）纯化，通过减压蒸发除去大多数 CH_3CN，并通过冻干除去剩余的溶剂以得到呈白色固体的化合物 28(17mg,6%产率）。LCMS :实测 255.0[M+H]。^1H NMR(400MHz,$CDCl_3$):7.50-7.72(m,4H),4.85(br s,1H),3.90(t,2H,J = 7.2Hz),2.53-2.72(m,5H),2.14-2.28(m,2H)。

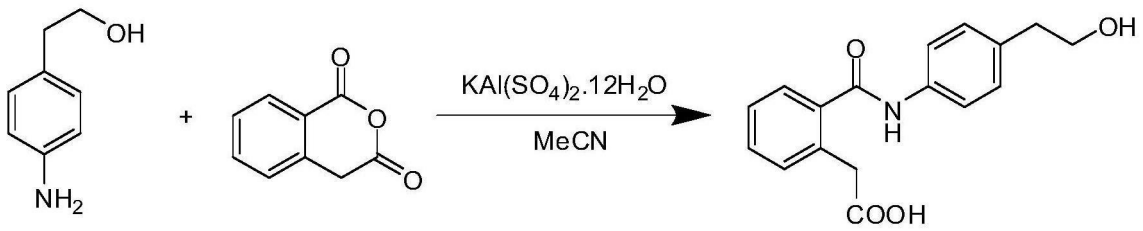
[0275] 中间体 sm-15 通过以下程序制成。



sm-15

[0276] 在 0 ℃ 下向 4- 氨基 -N- 甲基苯磺酰胺 (200mg,1.1mmol) 和 Na_2HPO_4(300mg,2.2mmol) 在 $CHCl_3$(10mL) 中的溶液中逐滴加入 4- 氯丁酰基氯 (151mg,1.1mol)。添加试剂后，将混合物在室温下搅拌。浓缩该混合物以得到粗 sm-15，其无需进一步纯化而直接用于下一步。

用于化合物 47 的合成流程：



47

[0277] 将 2-(4- 氨基苯基）乙醇 (300mg,2.2mmol)、异色满 -1,3- 二酮 (355mg,2.2mmol) 和 $KAl(SO_4)_2$-$12H_2O$(522mg,11mmol) 在 MeCN(10mL) 中的溶液在室温下搅拌 1-1.5h。除去溶剂以获得粗产物。残余物通过制备型 HPLC(0.1% TFA 作为添加剂）纯化。通过减压蒸发除去溶剂并冻干，得到呈白色固体的化合物 47(25mg,5.5%产率）。LCMS :实测 300.1[M+H]。

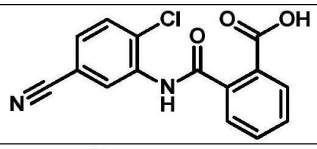
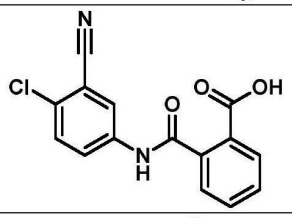
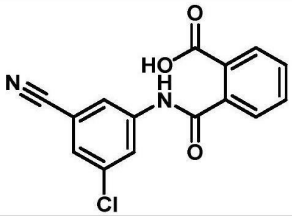
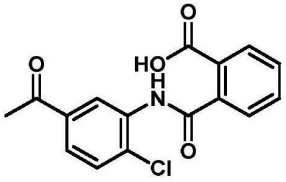
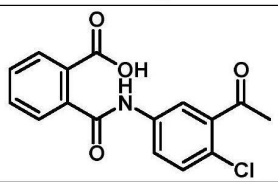
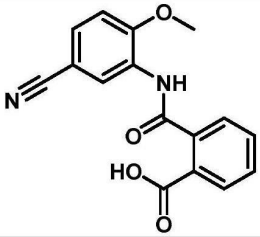
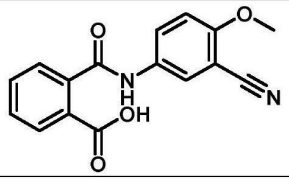
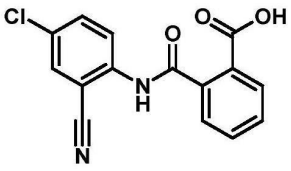
生物实施例

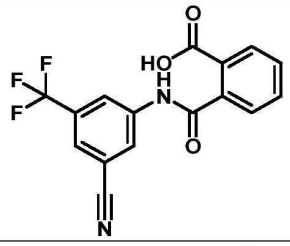
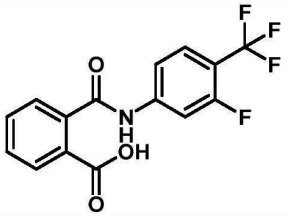
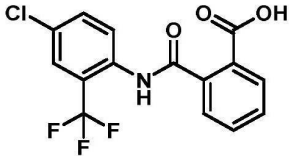
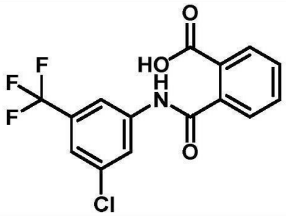
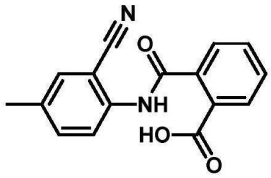
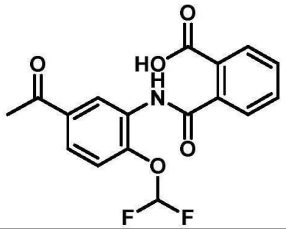
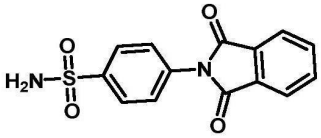
实施例 1 :人软骨细胞分化试验

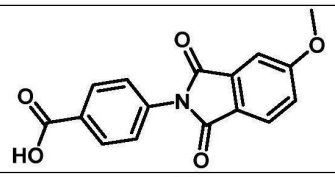
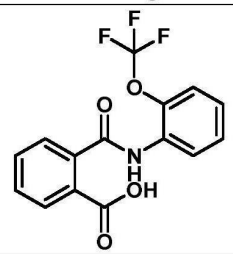
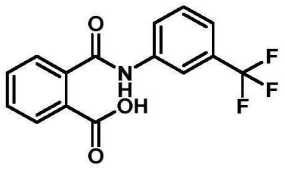
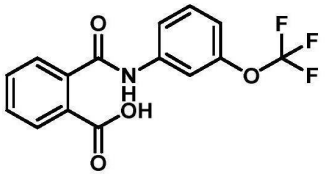
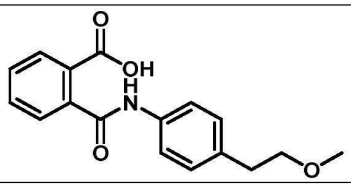
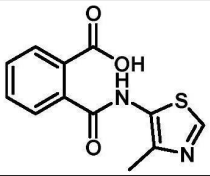
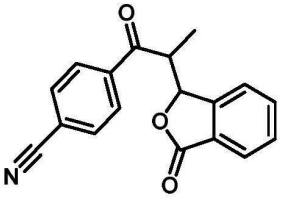
[0278] 将人 MSC(50,000) 接种到 96 孔板的每个孔中，并培养过夜。以 1 μM 的终浓度向细胞中加入化合物（在 DMSO 溶液中），并在 5% CO_2、37℃下培养细胞 7 天。将细胞在室温下用 10%福尔马林溶液固定 10min，并使用针对 II 型胶原蛋白 (Abcam)、Sox9(Santa Cruz) 和软骨寡聚基质蛋白 (COMP,Santa Cruz) 的特异性抗体和荧光标记的第二抗体 (Li-Cor) 进行免疫染色。染色的总强度使用 Oddyssey CLx 成像系统 (Li-Cor) 测量。使用载体 (DMSO)

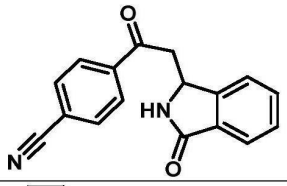
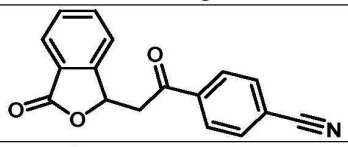
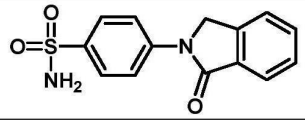
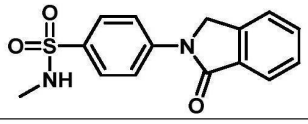
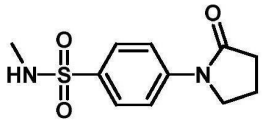
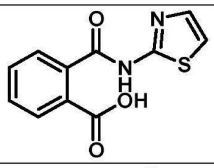
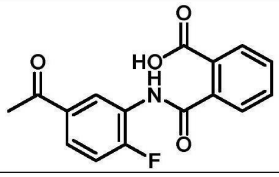
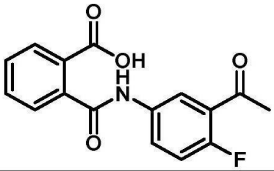
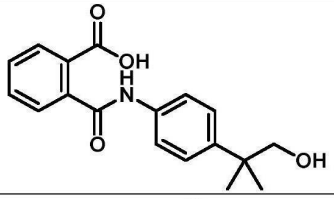
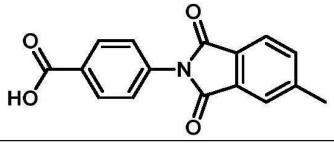
作为对照来确定软骨细胞分化的基础水平。选择显示出染色强度相比载体对照增加30％或更多的化合物作为活性命中物 (active hits)。代表性数据在表 1 中示出 [A :与载体对照相比染色强度增加 >50％ ;B :与载体对照相比染色强度增加 30-50％]。

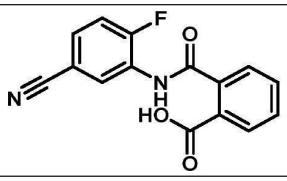
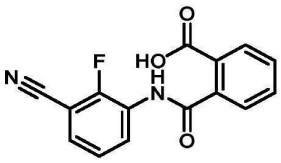
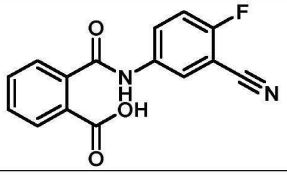
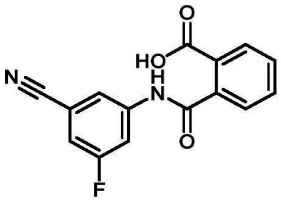
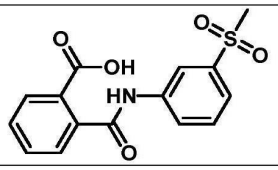
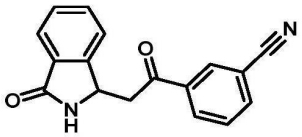
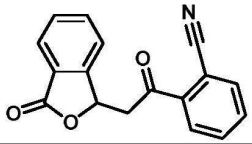
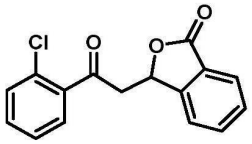
表 1

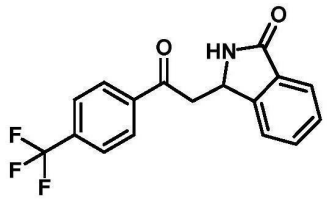
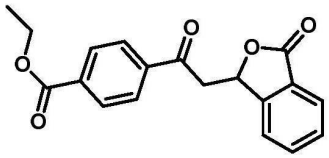
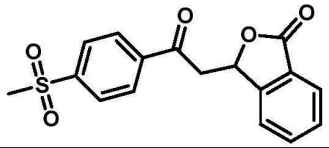
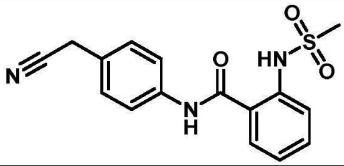
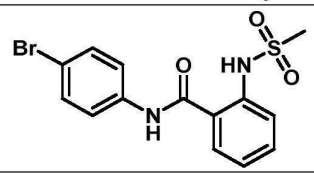
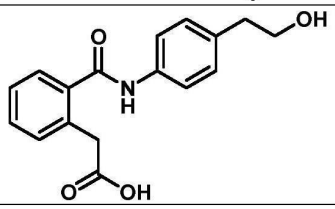
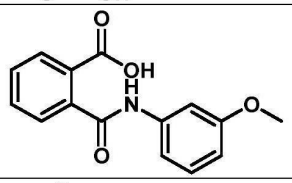
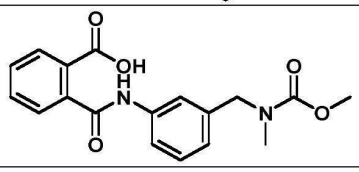
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
1		A	LCMS：实测 301.0 [M+H]	B
2		A	LCMS：实测 301.0 [M+H] LCMS：实测 323.0 [M+Na]	B
3		A	LCMS：实测 301.0 [M+H]	A
4		A	LCMS：实测 318.0 [M+H] LCMS：实测 340.0 [M+Na]	A
5		A	LCMS：实测 318.0 [M+H] LCMS：实测 340.0 [M+Na]	B
6		A	LCMS：实测 297.0 [M+H] LCMS：实测 615.2 [2M+Na]	A
7		A	LCMS：实测 297.0 [M+H] LCMS：实测 615.2 [2M+Na]	A
8		A	LCMS：实测 301.1 [M+H] LCMS：实测 322.9 [M+Na] ^{1}H NMR (400 MHz, DMSO-d_6): 13.19 (S, 1H), 10.72 (S, 1H), 8.05 (D, J=2.5Hz, 1H), 7.94 (DD, J=7.7, 1.3Hz, 1H), 7.84 (DD, J=8.8, 2.5Hz, 1H), 7.72-7.55 (M,	B

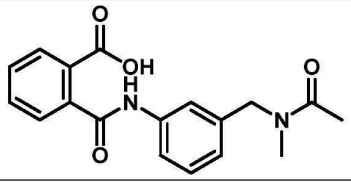
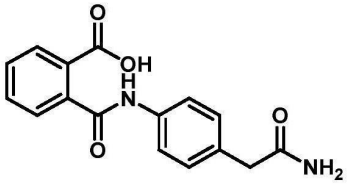
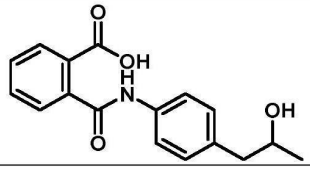
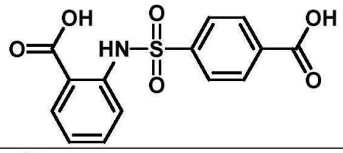
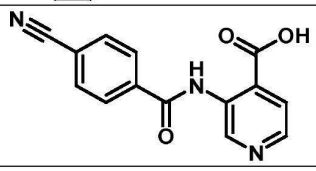
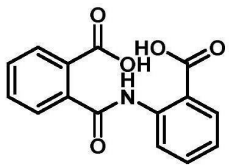
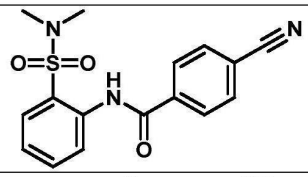
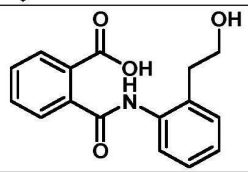
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
			4H)	
9		A	LCMS：实测 335.0 [M+H] LCMS：实测 691.0 [2M+Na] LCMS：实测 357.0 [M+Na]	A
10		A	LCMS：实测 328 [M+H] LCMS：实测 350 [M+Na] LCMS：实测 677 [2M+Na]	B
11		A	LCMS：实测 344 [M+H] LCMS：实测 366 [M+Na] ^{1}H NMR (400 MHz, DMSO-d_6): 13.19 (S, 1H), 10.19 (S, 1H), 7.93-7.86 (M, 3H), 7.71- 7.58(M, 4H)	B
12		A	LCMS：实测 344 [M+H]	B
13		A	LCMS：实测 281.0 [M+H]	B
14		A	LCMS：实测 350 [M+H] LCMS：实测 372 [M+Na]	B
15		B-1	LCMS：实测 303.0 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 7.10-7.36 (M, 6H), 6.56-6.70 (M, 2H), 6.62 (br s, 2H)	B

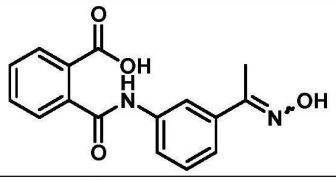
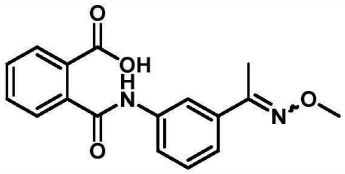
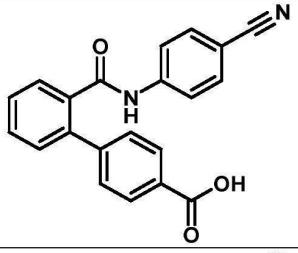
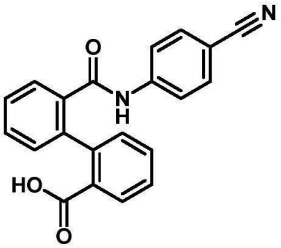
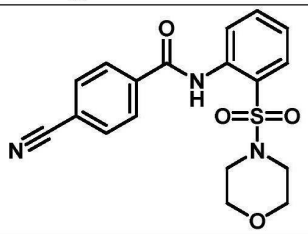
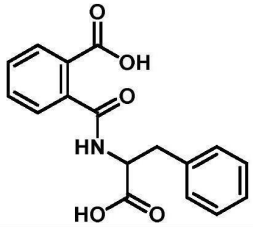
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
16		B-1	LCMS：实测 298.0 [M+H]	A
17		A	LCMS：实测 326 [M+H] LCMS：实测 348 [M+Na]	B
18		A	LCMS：实测 308.0 [M-H] NEG ^{1}H NMR (400 MHz, DMSO-d_6): 13.12 (S, 1H), 10.69 (S, 1H), 8.21 (S, 1H), 7.93-7.85 (M, 2H), 7.71-7.67 (M, 1H), 7.63-7.61 (M 3H), 7.46-7.44 (M, 1H)	A
19		A	LCMS：实测 326 [M+H] LCMS：实测 348 [M+Na] LCMS：实测 673 [2M+Na] ^{1}H NMR (400 MHz, DMSO-d_6): 13.05 (S, 1H), 10.65 (S, 1H), 7.92-7.87 (M, 2H), 7.69-7.45 (M, 5H), 7.09-7.07 (D, J=8 Hz, 1H)	A
21		A	LCMS：实测 300 [M+H] LCMS：实测 322 [M+Na] LCMS：实测 622 [2M+Na]	A
22		A	LCMS：实测 263.1 [M+H] LCMS：实测 571.1 [2M+Na]	B
23		C	LCMS：实测 314.0 [M+Na] LCMS：实测 292.0 [M+H]	A

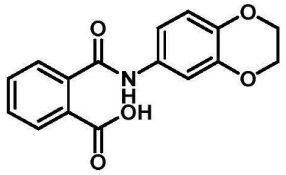
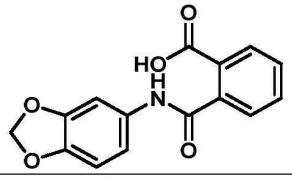
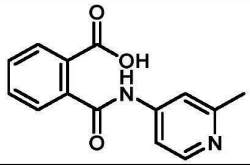
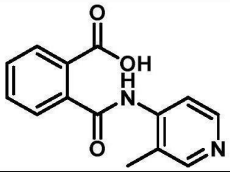
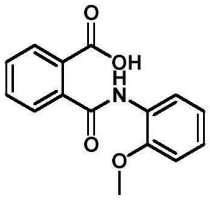
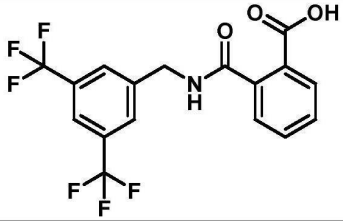
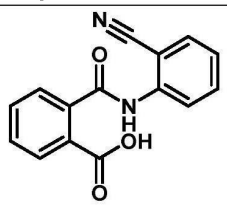
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
24		D	LCMS：实测 277.2 [M+H] LCMS：实测 299.1 [M+Na]	A
25		C	LCMS：实测 278.0 [M+H] LCMS：实测 300.0 [M+Na]	B
26		B-2	LCMS：实测 289.1 [M+H]	B
27		B-2	LCMS：实测 303.1 [M+H]	A
28		28	LCMS：实测 255.0 [M+H] ^{1}H NMR (400 MHz, $CDCl_3$): 7.50-7.72 (M, 4H), 4.85 (br s, 1H), 3.90 (T, 2H, J = 7.2 Hz), 2.53-2.72 (M, 5H), 2.14-2.28 (M, 2H)	B
29		A	LCMS：实测 249 [M+H] LCMS：实测 271 [M+Na]	B
30		A	LCMS：实测 302 [M+H] LCMS：实测 324 [M+Na] LCMS：实测 625 [2M+Na]	B
31		A	LCMS：实测 302 [M+H] LCMS：实测 324 [M+Na] LCMS：实测 625 [2M+Na]	B
32		A	LCMS：实测 314 [M+H]	B
33		B-1	LCMS：实测 282.2 [M+H]	B

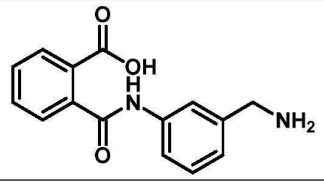
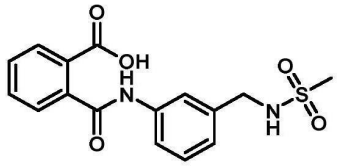
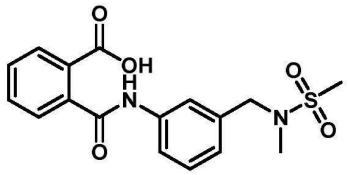
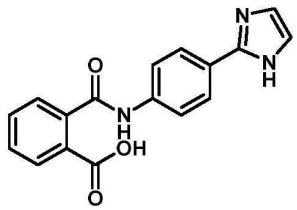
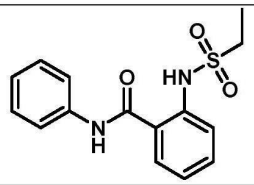
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
34		A	LCMS：实测 307 [M+Na] LCMS：实测 591 [2M+Na]	B
35		A	LCMS：实测 307 [M+Na] LCMS：实测 591 [2M+Na] ^{1}H NMR (400 MHz, DMSO-d_6): 13.15 (S, 1H), 10.54 (S, 1H), 8.21-8.19 (D, J=7.6 Hz, 1H), 7.92-7.90 (D, J=7.6 Hz, 1H), 7.72-7.44 (M, 5H)	B
36		A	LCMS：实测 284 [M+H] LCMS：实测 307 [M+Na] LCMS：实测 591 [2M+Na]	B
37		A	LCMS：实测 284 [M+H] LCMS：实测 307 [M+Na] LCMS：实测 591 [2M+Na] ^{1}H NMR (400 MHz, DMSO-d_6): 13.23 (S, 1H), 10.91 (S, 1H), 7.95-7.88 (S, 3H), 7.71-7.69 (M, 1H), 7.65-7.58 (M, 3H)	A
38		A	LCMS：实测 320.0 [M+H] LCMS：实测 342.0 [M+Na] LCMS：实测 661.0 [2M+Na]	B
39		D	LCMS：实测 277.1 [M+H] LCMS：实测 299.1 [M+Na] ^{1}H NMR (400 MHz, DMSO-d_6): 8.60 (S, 1H), 8.47 (S, 1H), 8.29 (D, 1H), 8.13 (D, 1 H), 7.78-7.49 (M, 5H), 5.13-5.10 (M, 1H), 3.80 (DD, 1H), 3.41 (DD, 1H)	B
40		C	LCMS：实测 278.1 [M+H]	B
41		C	LCMS：实测 287.1 [M+H] LCMS：实测 309.0 [M+Na] ^{1}H NMR (400 MHz, DMSO-d_6): 7.87-7.75 (M, 4H), 7.64-7.45 (M, 4H),	A

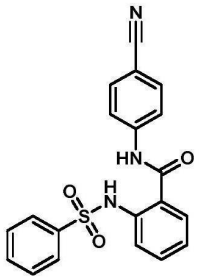
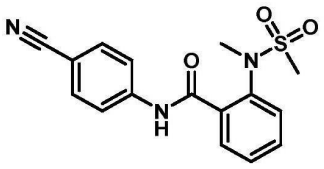
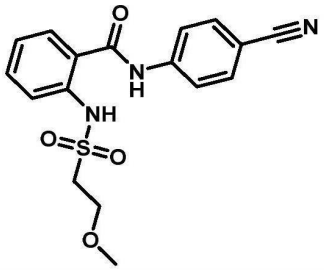
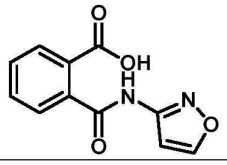
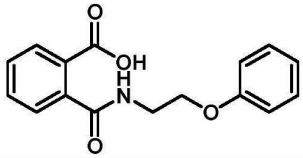
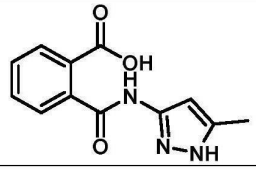
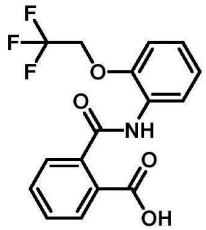
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
			6.09 (M, 1H), 3.86 (DD, 1 H), 3.62 (DD, 1H)	
42		D	LCMS：实测 320.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 8.61 (S, 1H), 8.20 (D, J=8.1Hz, 2H), 7.92 (D, J=8.2Hz, 2H), 7.69-7.59 (M, 3H), 7.50 (TD, J=7.3, 1.3Hz, 1H), 5.13(DD, J=8.0, 4.4Hz, 1H), 3.80(DD, J=18.1, 4.4Hz, 1H), 3.43(DD, J=18.1, 8.1Hz, 1H)	B
43		C	LCMS：实测 311.0 [M+H] LCMS：实测 333.0 [M+Na]	B
44		C	LCMS：实测 331.0 [M+H] LCMS：实测 353.0 [M+Na]	B
45		H	LCMS：实测 330.0 [M+H] LCMS：实测 352.0 [M+Na]	B
46		H	LCMS：实测 369.0 [M+H] LCMS：实测 391.0 [M+Na]	B
47		47	LCMS：实测 300.1 [M+H]	B
48		A	LCMS：实测 272.0 [M+H] LCMS：实测 294.0 [M+Na] LCMS：实测 565.1 [2M+Na]	B
49		A	LCMS：实测 365.0 [M+Na] LCMS：实测 707.2 [2M+Na]	B

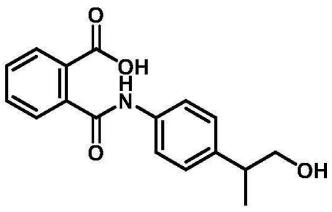
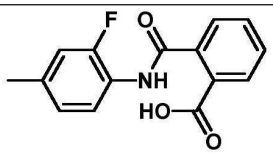
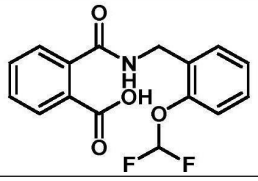
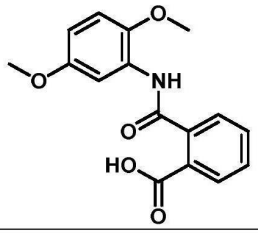
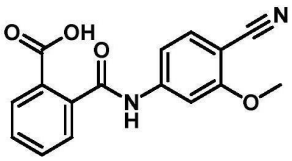
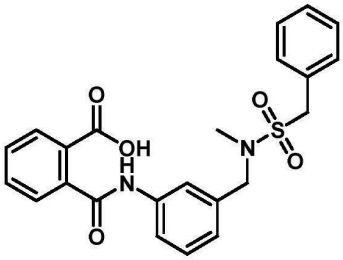
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
50		A	LCMS：实测 349.1 [M+Na]	B
51		A	LCMS：实测 299.1 [M+H] LCMS：实测 321.0 [M+Na] ^{1}H NMR (400 MHz, DMSO-d_6): 13.03 (S, 1H), 10.29 (S, 1H), 7.88 (T, 1H), 7.62 (M, 5 H), 7.43 (S, 1H), 7.22 (D, J = 8.4 Hz, 1H), 6.86 (S, 1H), 3.17 (S, 2H)	B
52		A	LCMS：实测 300.1 [M+H] LCMS：实测 322.0 [M+Na]	B
53		E	LCMS：实测 322.0 [M+H] LCMS：实测 344.0 [M+Na]	B
54		F	LCMS：实测 268.1 [M+H]	B
55		A	LCMS：实测 289.0 [M+H] LCMS：实测 308.0 [M+Na] LCMS：实测 593.0 [2M+Na] ^{1}H NMR (400 MHz, MeOD): 8.71 (D, J = 8 Hz, 1H), 8.13 (M, 1H), 8.01 (D, J = 8 Hz, 1H), 7.65 (M, 4H), 7.20 (M, 1H)	A
56		G	LCMS：实测 330.1 [M+H]	A
57		A	LCMS：实测 286.2 [M+H] LCMS：实测 308.1 [M+Na] LCMS：实测 593.3 [2M+Na]	B

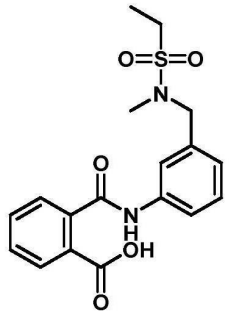
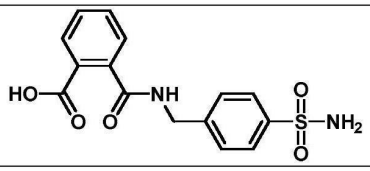
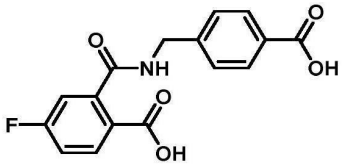
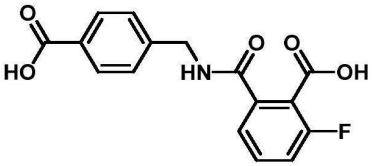
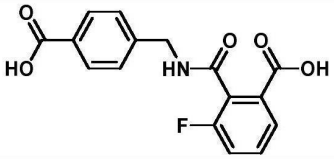
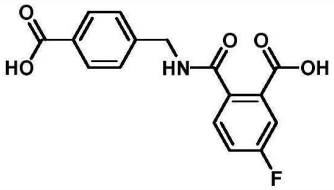
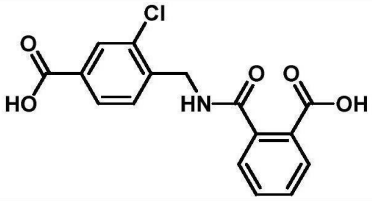
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
58		A	LCMS：实测 299.2 [M+H] LCMS：实测 321.2 [M+Na] LCMS：实测 619.1 [2M+Na]	B
59		A	LCMS：实测 313.1 [M+H] LCMS：实测 335.0 [M+Na] LCMS：实测 647.1 [2M+Na]	B
60		I	LCMS：实测 343.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.00 (br s, 1H), 10.72 (br s, 1H), 8.03 (S, 1H), 7.82-7.91 (M, 1H), 7.58-7.80 (M, 7H), 7.42-7.58 (M, 3H)	A
61		I	LCMS：实测 343.1 [M+H]	A
62		G	LCMS：实测 372.2 [M+H] LCMS：实测 394.1 [M+Na]	A
63		A	LCMS：实测 249 [M+H] LCMS：实测 271 [M+Na]	A

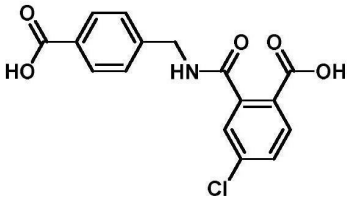
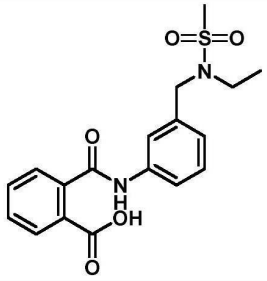
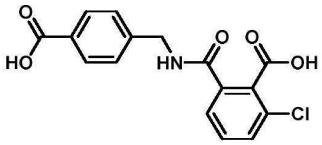
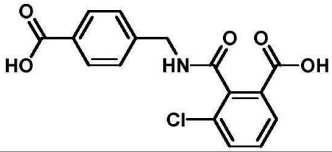
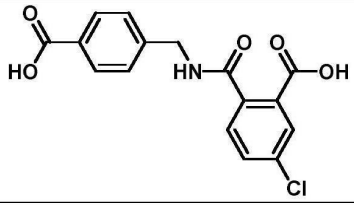
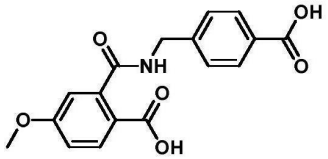
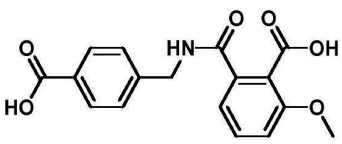
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
64		A	LCMS：实测 300.2 [M+H] LCMS：实测 621.2 [2M+Na] ^{1}H NMR (400 MHz, DMSO-d_6): 12.99 (S, 1H), 10.13 (S, 1H), 7.86 (M, 1H), 7.63 (M, 1H), 7.51 (M, 2H), 7.31 (S, 1H), 7.07 (M, 1H), 6.80 (D, J = 8.4 Hz, 1H), 4.23 (M, 4H)	B
65		A	LCMS：实测 286.2 [M+H] LCMS：实测 593.2 [2M+Na]	A
66		A	LCMS：实测 257.0 [M+H]	B
67		A	LCMS：实测 257.0 [M+H]	A
68		A	LCMS：实测 272.0 [M+H] LCMS：实测 294.0 [M+Na] LCMS：实测 565.1 [2M+Na] ^{1}H NMR (400 MHz, DMSO-d_6): 9.37 (S, 1H), 7.98 (D, J = 7.6 Hz, 1H), 7.85 (D, J = 7.6 Hz, 1H), 7.65 (M, 1H), 7.58 (M, 2H), 7.15 (M, 1H), 7.07 (M, 1H), 6.98 (M, 1H)	A
69		A	LCMS：实测 392.1 [M+H] LCMS：实测 414.1 [M+Na]	B
70		A	LCMS：实测 267.1 [M+H]	A

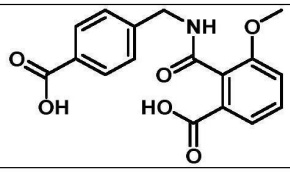
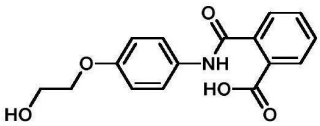
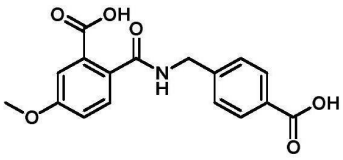
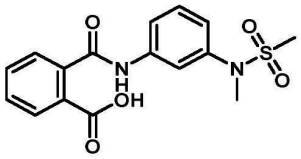
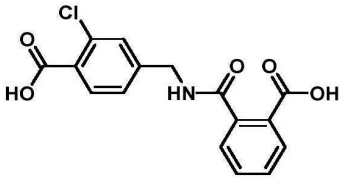
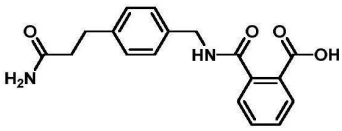
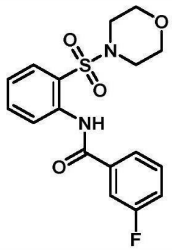
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
71		A	LCMS：实测 271.0 [M+H]	A
72		A	LCMS：实测 349.0 [M+H] LCMS：实测 371.0 [M+Na] ^{1}H NMR (400 MHz, DMSO-d_6): 10.38 (S, 1H), 7.89 (T, 1H), 7.23 (S, 1H), 7.66 (M, 1H), 7.58 (M, 4H), 7.07 (D, J = 7.6 Hz, 1H), 4.15 (D, J = 6 Hz, 2H), 2.89 (S, 3H)	A
73		A	LCMS：实测 363.0 [M+H] LCMS：实测 385.0 [M+Na] LCMS：实测 747.0 [2M+Na] ^{1}H NMR (400 MHz, DMSO-d_6): 13.02 (S, 1H), 10.41 (S, 1H), 7.87 (D, J = 7.2 Hz, 1H), 7.65 (M, 3H), 7.35 (T, 1H), 7.04 (D, J = 7.6 Hz, 1H), 4.21 (S, 1H), 2.96 (S, 1H), 2.67 (S, 1H)	A
74		A	LCMS：实测 308.2 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.53 (S, 1H), 7.88 (D, J = 8.4 Hz, 3H), 7.56 (D, J = 8.8 Hz, 2H), 7.65 (M, 1H), 7.59 (M, 2H), 7.10 (S, 1H)	B
75		F	LCMS：实测 295.1 [M+H] LCMS：实测 317.1 [M+Na] ^{1}H NMR (400 MHz, $CDCl_3$):) 9.47 (br s, 1 H), 7.86 (D, 1H), 7.79 (D, 2H), 7.57 - 7.66 (M, 3H), 7.48 - 7.54 (M, 1H), 7.31 (D, 1H), 4.74 (br s, 2H), 3.25 (S, 3H)	B
76		H	LCMS：实测 330.1 [M+H]	B

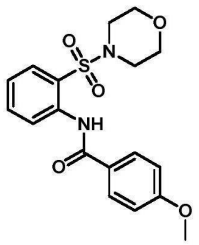
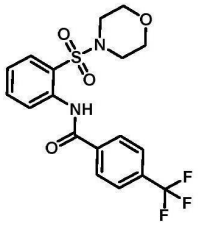
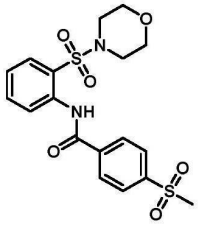
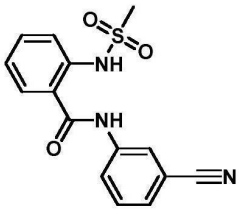
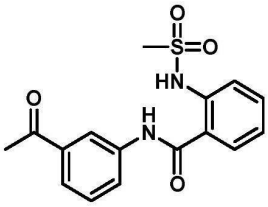
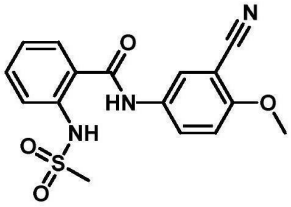
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
77		H	LCMS：实测 378.1 [M+H]	A
78		H	LCMS：实测 330.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.70 (S, 1H), 7.90 (D, 2H), 7.82 (D, 2H), 7.64-7.49 (M, 4H), 3.26 (S, 3H), 3.00 (S, 3H)	B
79		H	LCMS：实测 360.1 [M+H] ^{1}H NMR (400 MHz, CDCl3) 10.85 (S, 1H), 9.97 (S, 1H), 7.94 (D, 2H), 7.84 (D, 2H), 7.59 – 7.63 (M, 2H), 7.30 - 7.32 (M, 1H), 3.61 - 3.64 (M, 2H), 3.44 - 3.47 (M, 2H), 3.06 (S, 3H)	B
80		A	LCMS：实测 233.1 [M+H] LCMS：实测 255.1 [M+Na] LCMS：实测 487.0 [2M+Na]	B
81		A	LCMS：实测 286.0 [M+H] LCMS：实测 308.0 [M+Na]	B
82		A	LCMS：实测 246.2 [M+H] LCMS：实测 513.2 [2M+Na]	A
83		A	LCMS：实测 340.0 [M+H] LCMS：实测 362.0 [M+Na] LCMS：实测 701.1 [2M+Na]	A

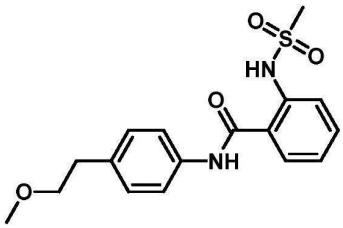
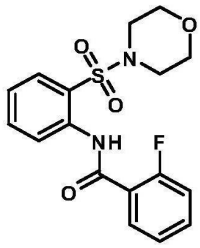
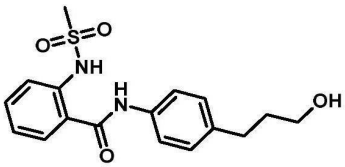
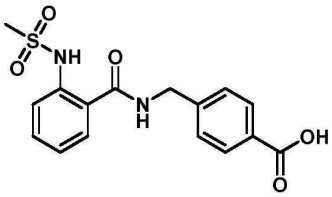
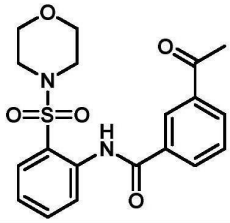
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
84		A	LCMS：实测 300.2 [M+H] LCMS：实测 322.1 [M+Na] ^{1}H NMR (400 MHz, DMSO-d_6): 10.24 (S, 1H), 7.84 (D, J = 6.8 Hz, 1H), 7.56 (M, 4H), 7.15 (D, J = 8.8 Hz, 1H), 4.61 (T, 1H), 3.47 (M, 1H), 2.75 (M, 1H), 1.14 (D, J = 6.8 Hz, 3H)	A
85		A	LCMS：实测 274.2 [M+H] LCMS：实测 296.1 [M+Na]	B
86		A	LCMS：实测 322.1 [M+H] LCMS：实测 344.0 [M+Na]	B
87		A	LCMS：实测 302.0 [M+H] LCMS：实测 625.1 [2M+Na]	B
88		A	LCMS：实测 297.1 [M+H] LCMS：实测 316.0 [M+Na] ^{1}H NMR (400 MHz, CD_3OD): 8.06-8.04 (D, 1H), 7.75-7.65 (M, 2H), 7.61-7.53 (M, 3H), 7.24-7.24 (D, 2H), 3.95 (S, 3H)	-
89		A	LCMS：实测 461.0 [M+Na] ^{1}H NMR (400 MHz, CD_3OD): 8.05 (D,1H), 7.69-7.57 (M, 5H), 7.46-7.35 (M, 6H), 7.20 (D, 1H), 4.45 (S, 2H), 4.16 (S, 2H), 2.69 (S, 3H).	-

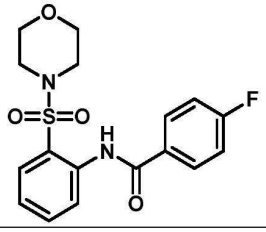
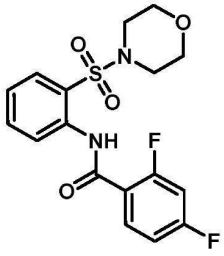
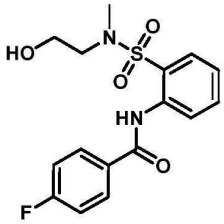
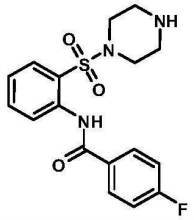
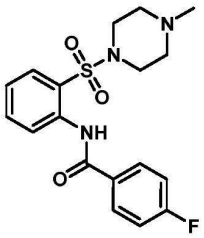
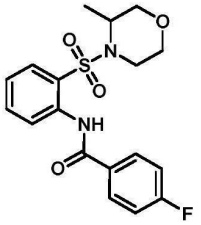
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
90		A	LCMS：实测 377.0 [M+H], LCMS：实测 399.0 [M+Na] ^{1}H NMR (400 MHz, CD_3OD): 8.05 (D,1H), 7.72-7.57 (M, 5H), 7.37 (T, 1H), 7.18 (D, 1H), 4.39 (S, 2H), 3.15 (Q, 2H), 2.81 (S, 3H), 1.38 (T, 3H).	-
91		A	LCMS：实测 335.1 [M+H]	-
92		A	LCMS：实测 318.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.05 (br s, 2H), 9.04-8.98 (M, 1H), 7.92-7.88 (D, 2H), 7.58-7.45 (M, 3H), 7.37-7.33 (M, 1H), 4.50(D, 2H)	-
93		A	LCMS：实测 318.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.20 (br s, 2H), 9.03 (S, 1H), 7.90 (D, 2H), 7.74 (D, 1H), 7.55-7.50 (M, 4H), 4.52(D, 2H)	B
94		A	LCMS：实测 318.1 [M+H]	B
95		A	LCMS：实测 318.1 [M+H]	-
96		A	LCMS：实测 334.0 [M+H]	B

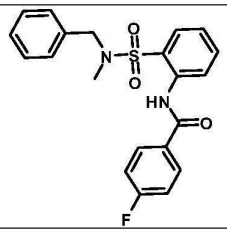
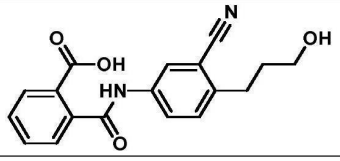
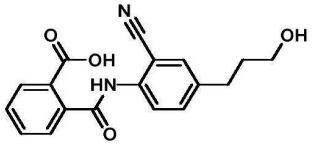
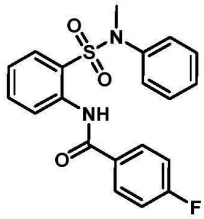
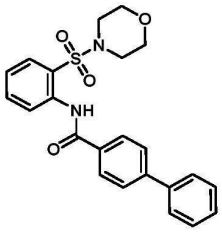
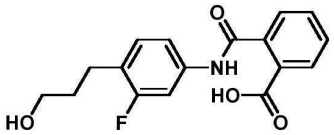
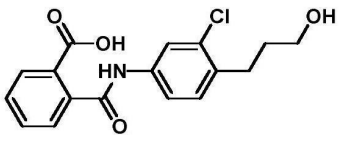
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
97		A	LCMS：实测 334.0 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 9.74 (br s, 1H), 9.39 (br s, 1H), 7.90 (D, 2H), 7.59-7.56(M, 3H), 7.51-7.47 (M, 2H), 4.50(D, 2H)	-
98		A	LCMS：实测 377.0 [M+H], LCMS：实测 399.0 [M+Na] ^{1}H NMR (400 MHz, CD_3OD): 8.05 (D,1H), 7.76-7.57 (M, 5H), 7.37 (T, 1H), 7.20 (D, 1H), 4.43 (S, 2H), 3.32-3.27 (M, 2H), 2.96 (S, 3H), 1.15 (T, 3H).	-
99		A	LCMS：实测 334.0 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.10 (br s, 2H), 8.93-8.90(M, 1H), 7.90 (D, 2H), 7.74 (D, 1H), 7.56-7.51 (M, 3H), 4.51(D, 2H)	B
100		A	LCMS：实测 334.0 [M+H]	B
101		A	LCMS：实测 334.1 [M+H]	-
102		A	LCMS：实测 330.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.96 (br s, 2H), 7.90 (D, 2H), 7.51-7.47 (M, 3H), 7.19 (D, 1H), 7.10 (DD, 1H), 4.49 (D, 2H), 3.82 (S,3H)	-
103		A	LCMS：实测 330.0 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.90 (br s, 2H), 8.65(T, 1H), 7.91 (D, 2H), 7.54 (D, 2H), 7.45 (D, 2H), 7.32 (DD, 1H), 4.48 (D, 1H), 3.83 (S,3H)	A

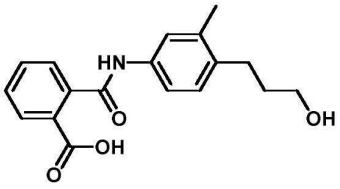
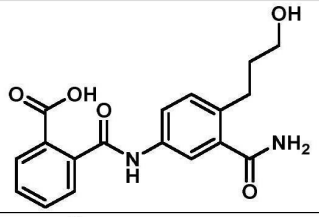
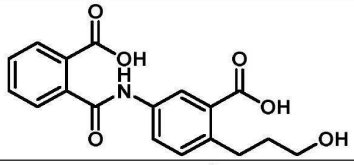
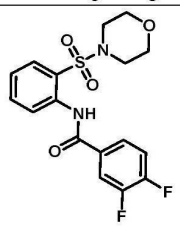
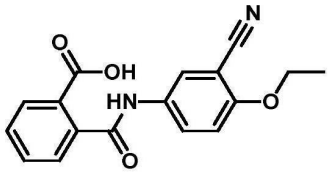
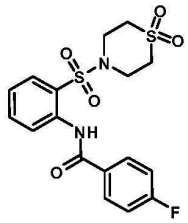
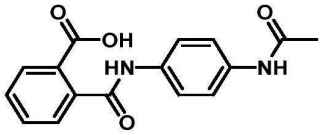
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
104		A	LCMS：实测 330.0 [M+H]	A
105		A	LCMS：实测 302.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.98 (br s, 1H), 10.19 (S, 1H), 7.86 (D, 1H), 7.67-7.52 (M, 5H), 6.91 (D, 2H), 4.87(br s, 1H), 3.96 (T, 2H), 3.71 (Q, 2H)	B
106		A	LCMS：实测 330.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.80 (br s, 2H), 7.90 (D, 2H), 7.81 (D, 1H), 7.52 (D, 2H), 7.05 (DD, 1H), 6.95(D, 1H), 4.49(D, 2H), 3.85(S,3H)	B
107		A	LCMS：实测 349.0 [M+H], LCMS：实测 371.0 [M+Na] ^{1}H NMR (400 MHz, CD_3OD): 8.06 (D,1H), 7.83 (S, 1H), 7.69-7.56 (M, 4H), 7.39 (T, 1H), 7.23 (D, 1H), 3.32 (S, 3H), 2.95 (S, 3H).	B
108		A	LCMS：实测 334.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.18 (br s, 2H), 9.01 (S, 1H), 7.92 (D, 1H), 7.88 (DD, 1H), 7.80 (DD, 1H), 7.71 (D,1H), 7.63-7.53(M, 3H), 4.53(D, 2H)	-
109		A	LCMS：实测 327.2 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.98 (br s, 1H), 8.81 (S, 1H), 7.76 (D, 2H), 7.58-7.44 (M, 3H), 7.28 (D, 2H), 7.15 (D, 2H), 4.40(D, 2H), 2.77(Q, 2H), 2.34(Q,2H)	-
110		G	LCMS：实测 365.2 [M+H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.50 (S, 1H), 8.76 (D, 1H), 7.82-7.70 (M, 4H), 7.54-7.53 (M, 1H), 7.34 - 7.30 (m, 2H), 3.71 - 3.69 (m, 4H), 3.05-3.03 (m, 4H).	B

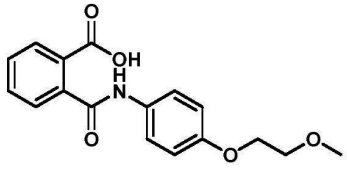
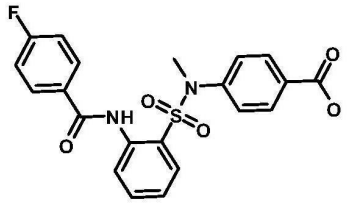
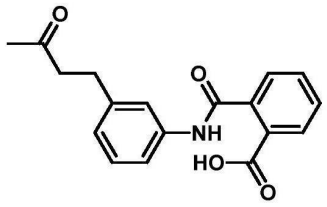
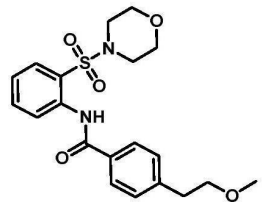
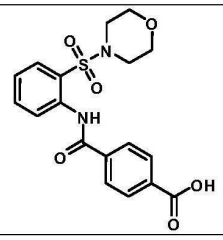
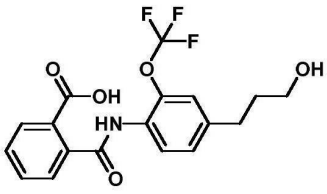
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
111		G	LCMS：实测 377.2 [M+H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.38 (S, 1H), 8.74 (D, 1H), 7.94-8.07 (M, 2H), 7.80 (D, 1H), 7.68 (D, 1H), 7.25 - 7.31 (M, 1H), 6.95-7.14 (M, 2H), 3.91 (S, 3H), 3.62 - 3.72 (M, 4H), 2.96-3.11 (M, 4H).	-
112		G	LCMS：实测 415.1 [M+H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.62 (S, 1H), 8.78 (D, 1H), 8.14 (D, 2H), 7.84-7.82 (M, 3H), 7.51-7.46 (M, 1H), 7.36-7.32 (M, 1H), 3.72 - 3.69 (M, 4H), 3.05-3.03 (M, 4H).	-
113		G	LCMS：实测 425.1 [M+H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.68 (S, 1H), 8.78 (D, 1H), 8.22 (D, 2H), 8.14 (D, 2H), 7.81 (D, 1H), 7.76-7.68 (M, 1H), 7.37-7.33 (M, 1H), 3.73 - 3.70 (M, 4H), 3.05-3.03 (M, 4H).	A
114		L	LCMS：实测 316.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.76 (S, 1H), 9.98 (S, 1H), 8.21 (S, 1H), 7.98 (T, 1H), 7.83 (D, 1H), 7.62-7.57 (M,4H), 7.32(T, 1H), 3.12(S, 3H)	-
115		L	LCMS：实测 333.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.70 (br s, 1H), 10.18 (br s, 1H), 8.33 (S, 1H), 7.99 (D, 1H), 7.89 (D, 1H), 7.76 (D, 1H), 7.58-7.52 (M, 3H), 7.30(T, 1H), 3.13(S, 3H), 2.60(S, 3H)	-
116		L	LCMS：实测 346.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.60 (S, 1H), 10.16 (S, 1H), 8.07 (S, 1H), 7.90 (DD, 2H), 7.59-7.57 (M, 2H), 7.31-7.29 (M, 2H), 3.92(S, 3H), 3.12(S, 3H)	-

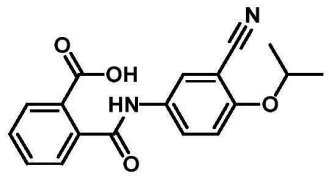
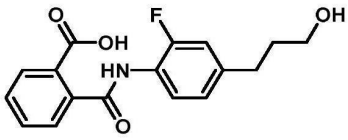
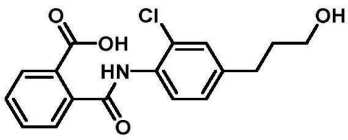
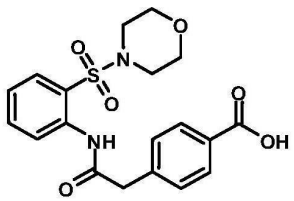
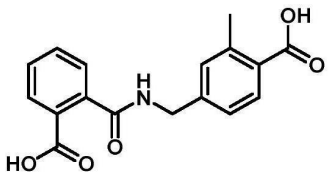
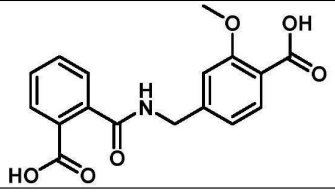
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
117		L	LCMS：实测 349.2 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.44 (S, 1H), 10.29 (S, 1H), 7.88 (D, 1H), 7.64-7.55 (M, 4H), 7.31-7.22 (M, 3H), 3.52 (Q, 2H), 3.25 (S, 3H), 3.13 (S, 3H), 2.79 (Q,2H)	A
118		G	LCMS：实测 365.1 [M+H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.40 (D, 1H), 8.67 (D, 1H), 8.14-8.10 (M, 2H), 7.87 (D, 1H), 7.72-7.68 (M, 1H), 7.61-7.55 (M, 1H), 7.36-7.30 (M, 4H), 3.71 - 3.68 (M, 4H), 3.10-3.07 (M, 4H).	B
119		L	LCMS：实测 349.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.31 (br s, 2H), 7.90 (D, 1H), 7.62 (D, 2H), 7.53 (S, 2H), 7.20-7.18 (M, 3H), 4.49-4.46 (M, 1H), 3.43-3.39(M, 2H), 3.08(S, 3H), 2.65-2.55(M, 2H), 1.74-1.67 (M, 2H)	-
120		L	LCMS：实测 349.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.91 (br s, 1H), 11.13 (br s, 1H), 9.51 (T, 1H), 7.94-7.91 (M, 3H), 7.57 (S, 2H), 7.46 (D, 2H), 7.24-7.21 (M, 1H), 4.56(D, 2H), 3.12(S, 3H)	B
121		J	LCMS：实测 372.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.37 (S, 1H), 8.37 (S, 1H), 8.26 (M, 1H), 8.14-8.12 (M, 2H), 7.86-7.79 (M, 3H), 7.52 (M, 1H), 3.56-3.54 (T, 4H), 2.83-2.86 (T, 4H)	-
122		J	LCMS：实测 389.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.42 (S, 1H), 8.51 (S, 1H), 8.30 (D, 1H), 8.23-8.19 (M, 2H), 7.87-7.74 (M, 3H), 7.50 (T, 1H), 3.57-3.55 (M, 4H),	A

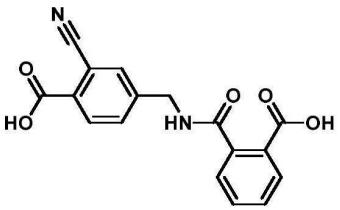
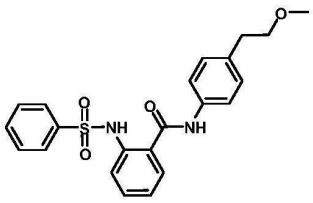
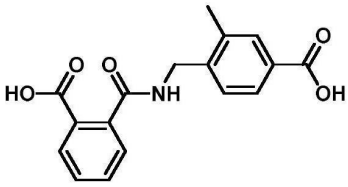
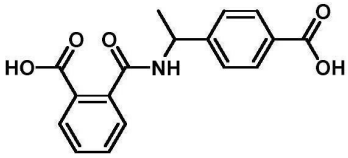
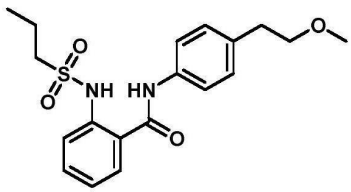
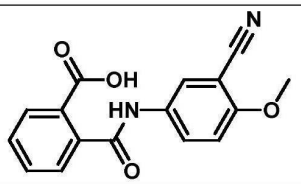
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
			2.92-2.89 (M, 4H), 2.67 (S,3H)	
123		J	LCMS：实测 365.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.27 (S, 1H), 8.30 (D, 1H), 8.05-8.01 (M, 2H), 7.84-7.80 (M, 2H), 7.47-7.41 (M, 3H), 3.62-3.55 (M, 4H), 2.95-2.88 (M, 4H)	A
124		G	LCMS：实测 383.1 [M+H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.36 (D, 1H), 8.64 (D, 1H), 8.20-8.14 (M, 1H), 7.85 (D, 1H), 7.69 (T, 1H), 7.35-7.29 (M, 2H), 7.10-6.95 (M, 2H), 3.71 - 3.69 (M, 4H), 3.09-3.06 (M, 4H).	-
125		G	LCMS：实测 353.1 [M+H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.40 (S, 1H), 8.66 (D, 1H), 8.07-8.04 (M, 2H), 7.85 (D, 1H), 7.60 (T, 1H), 7.32-7.20 (M, 3H), 3.73 - 3.71 (M, 2H), 3.25-3.23 (M, 2H), 2.86 (S, 3H).	B
126		G	LCMS：实测 364.2 [M+H] ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD): 8.60 (D, 1H), 7.97-7.94 (M, 2H), 7.80 (D, 1H), 7.70 (T, 1H), 7.32-7.16 (M, 3H), 3.37 - 3.33 (M, 4H), 3.18-3.15 (M, 4H).	-
127		G	LCMS：实测 378.2 [M+H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.17 (S,1H), 8.73 (D, 1H), 8.03-8.00 (M, 2H), 7.80 (D, 1H), 7.74 (T, 1H), 7.35-7.22 (M, 3H), 3.81 (br s, 2H), 3.56 (br s, 2H), 3.29 (br s, 2H), 2.90 (br s, 2H), 2.81 (S, 3H).	-
128		G	LCMS：实测 379.2 [M+H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.28 (S,1H), 8.64 (D, 1H), 8.06-8.03 (M, 2H), 7.89 (D, 1H), 7.65 (T, 1H), 7.30-7.21 (M, 3H), 3.87-3.85 (M, 1H), 3.75 (D, 1H), 3.55-3.26 (M, 5H), 1.19 (D, 3H).	A

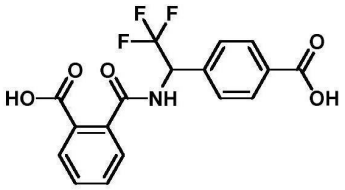
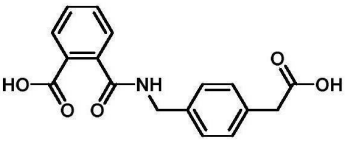
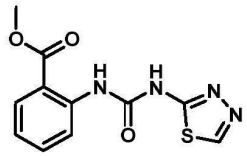
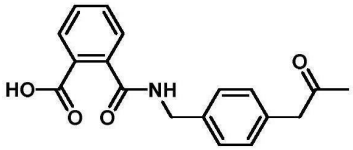
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
129		G	LCMS：实测 399.2 [M+H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.55 (S,1H), 8.76 (D, 1H), 8.05-8.02 (M, 2H), 7.90 (D, 1H), 7.69 (T, 1H), 7.33-7.17 (M, 8H), 4.19 (S, 2H), 2.63 (S, 3H).	-
130		A	LCMS：实测 325.1 [M+H]	-
131		A	LCMS：实测 325.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.15 (br s, 1H), 10.58 (S, 1H), 7.92 (D, 1H), 7.72-7.53 (M, 6H), 4.54 (T,1H), 4.42-4.39 (M, 2H), 2.68-2.65 (M, 2H), 1.76-1.69 (M, 2H)	-
132		G	LCMS：实测 385.1 [M+H] ^{1}H NMR (400 MHz, $CDCl_3$): 9.84 (S,1H), 8.63 (D, 1H), 7.89 (D, 1H), 7.67-7.59 (M, 3H), 7.30-7.28 (M, 1H), 7.11-7.05 (M, 6H), 6.95-6.93 (M, 1H), 3.19 (S, 3H).	-
133		G	LCMS：实测 423.1 [M+H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.54 (S,1H), 8.79 (D, 1H), 8.10 (D, 2H), 7.83-7.66 (M, 6H), 7.54-7.42 (M, 3H), 7.33-7.29 (M, 1H), 3.71-3.69 (M, 4H), 3.07-3.05 (M, 4H).	B
134		A	LCMS：实测 318.2 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.10 (br s, 1H), 10.49 (S, 1H), 7.89 (D, 1H), 7.63-7.53 (M, 4H), 7.31(D, 2H), 7.23 (T, 1H), 4.51 (T, 1H), 3.45-3.42 (M, 2H), 2.62-2.58 (M, 2H), 1.71-1.65 (M, 2H)	-
135		A	LCMS：实测 334.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.09 (br s, 1H), 10.44 (S, 1H), 7.90-7.84 (M, 2H), 7.67-7.49 (M, 4H), 7.28(D, 2H), 4.53 (T, 1H), 3.46-3.42 (M, 2H),	-

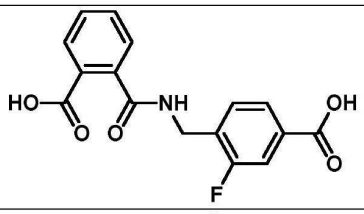
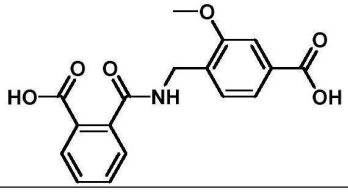
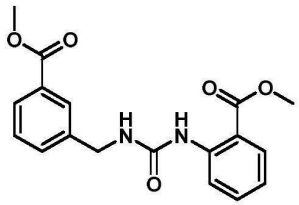
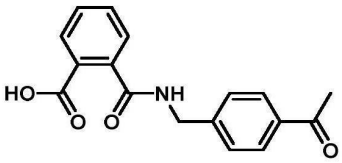
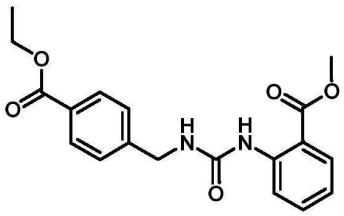
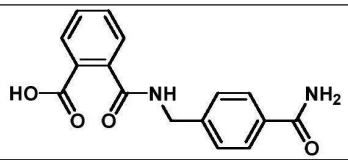
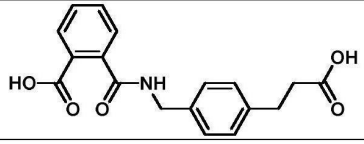
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
			2.70-2.66 (M, 2H), 1.73-1.66 (M, 2H)	
136		A	LCMS：实测 314.1 [M+H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.17 (S, 1H), 7.86-7.84 (D, 1H), 7.63-7.62 (D, 1H), 7.55-7.47 (M, 3H), 7.40-7.35 (D, 1H), 7.06-7.04 (D, 1H), 4.49-4.47 (T, 1H), 3.45-3.41 (M, 2H), 2.57-2.53 (M, 2H), 2.24 (S, 3H), 1.67-1.60 (M, 2H)	-
137		A	LCMS：实测 343.0 [M+H]	-
138		A	LCMS：实测 344.1 [M+H]	-
139		G	LCMS：实测 383.2 [M+H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.50 (S,1H), 8.73 (D, 1H), 7.92 (T, 1H), 7.82-7.70 (M, 3H), 7.40-7.29 (M, 2H), 3.72-3.70 (M, 4H), 3.05-3.02 (M, 4H).	-
140		A	LCMS：实测 311.2 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.10 (br s, 1H), 10.51 (S, 1H), 8.02 (S, 1H), 7.90-7.82 (M, 2H), 7.67-7.55(M, 3H), 7.26 (D, 1H), 4.18 (Q, 2H),1.37 (T, 3H)	-
141		G	LCMS：实测 412.9 [M+H] ^{1}H NMR (400 MHz, CD_3OD): 8.33 (D,1H), 8.11-8.08 (M, 2H), 7.98 (D, 1H), 7.79 (T,1H), 7.49 (T, 1H), 7.36-7.31 (M, 2H), 3.68-3.66 (M, 4H), 3.28-3.16 (M, 4H).	B
142		A	LCMS：实测 299.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.99 (br s, 1H), 10.27 (S, 1H), 9.89(S,1H), 7.87 (D, 1H), 7.67-7.50 (M, 7H), 2.03(S,	B

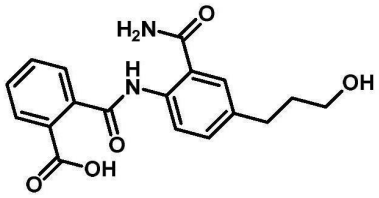
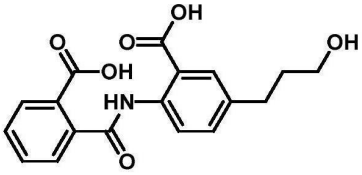
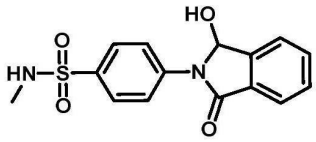
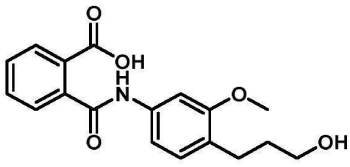
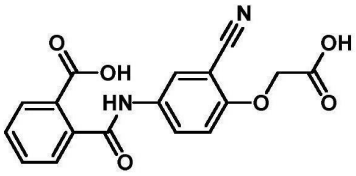
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
			3H)	
143		A	LCMS：实测 316.1 [M+H] ^{1}H NMR (400 MHz, CD_3OD): 8.03-8.01 (T, 1H), 7.66-7.63 (T, 1H), 7.58-7.52 (M, 4H), 6.94-6.92 (M, 2H), 4.12-4.10 (M, 2H), 3.75-3.73 (M, 2H), 3.42 (S, 3H)	-
144		G	LCMS：实测 429.0 [M+H] ^{1}H NMR (400 MHz, CD_3OD): 8.40 (D,1H), 7.99 (D, 1H), 7.74 (T, 1H), 7.65-7.57 (M, 4H), 7.42 (T, 1H), 7.20-7.11 (M, 4H), 3.19 (S, 3H).	-
145		A	LCMS：实测 312.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 11.18 (br s, 1H), 7.80 (D, 1H), 7.62-7.50 (M, 5H), 7.22(T, 1H), 6.91 (D, 1H), 2.75 (S, 3H),2.12-2.09 (M, 2H)	B
146		G	LCMS：实测 405.0 [M+H], LCMS：实测 427.0 [M+Na] ^{1}H NMR (400 MHz, CD_3OD): 8.53 (D,1H), 7.93 (D, 2H), 7.88 (D, 1H), 7.76 (T, 1H), 7.47 (D, 2H), 7.42 (D, 1H), 3.68 (T, 2H), 3.64-3.62 (M, 4H), 3.36 (S, 3H), 3.01-2.96 (M, 6H).	-
147		G	LCMS：实测 391.0 [M+H] ^{1}H NMR (400 MHz, CD_3OD): 8.53 (D,1H), 8.22 (D, 2H), 8.12 (D, 2H), 7.92 (D, 1H), 7.80 (T, 1H), 7.44 (T, 1H), 3.65-3.63 (M, 4H), 3.02-3.00 (M, 4H).	B
148		A	LCMS: 384.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 11.18 (br s, 1H), 7.80 (D, 1H), 7.62-7.50 (M, 5H), 7.22(T, 1H), 6.91 (D, 1H), 2.75 (S, 3H),2.12-2.09 (M, 2H)	B

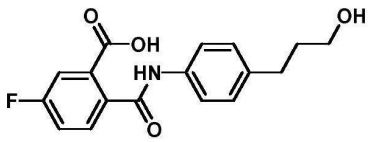
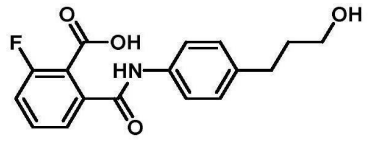
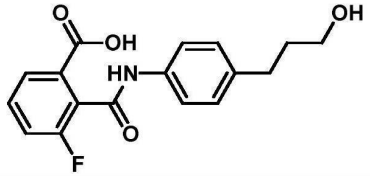
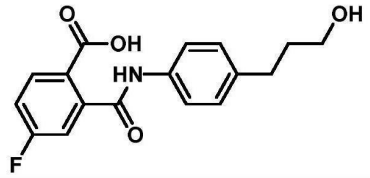
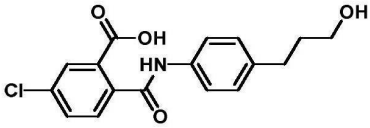
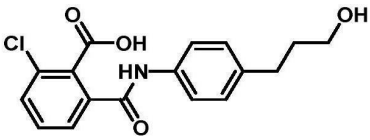
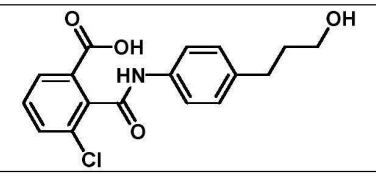
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
149		A	LCMS：实测 325.2 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.09 (S, 1H), 10.48 (S, 1H), 8.01-8.01 (D, 1H), 7.90-7.88 (D, 1H), 7.81-7.80 (D, 1H), 7.67 (S,1H), 7.59-7.56 (D, 2H), 7.31-7.28 (D, 2H), 4.77-4.72 (M, 1H), 1.32-1.31 (D, 6H)	-
150		A	LCMS：实测 318.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.03 (S, 1H), 10.05 (S, 1H), 7.88-7.86 (D, 2H), 7.07-7.65 (M, 2H), 7.57-5.52 (M, 2H), 7.11-7.03 (M, 2H), 4.50 (S, 1H), 3.42-3.41 (D, 2H), 2.64-2.60 (T, 2H), 1.76-1.69 (M, 2H)	-
151		A	LCMS：实测 334.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.13 (S, 1H), 9.93 (S, 1H), 7.88-7.86 (D, 1H), 7.66-7.65 (M, 1H), 7.59-7.54 (M, 3H), 7.35 (S, 1H), 7.22-7.20 (D, 1H), 4.50 (S, 1H), 3.43-3.39 (M, 2H), 2.64-2.60 (T, 2H), 1.74-1.68 (M, 2H)	-
152		G	LCMS：实测 405.0 [M+H] ^{1}H NMR (400 MHz, CD_3OD): 8.36 (D,1H), 8.05 (D, 2H), 7.76 (D, 1H), 7.67 (T, 1H), 7.53 (D, 2H), 7.35 (T, 1H), 3.88 (S, 2H), 3.51-3.48 (M, 4H), 2.64-2.62 (M, 4H).	-
153		A	LCMS：实测 314.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.91 (br s, 2H), 8.98 (S, 1H), 7.80-7.75 (M, 2H), 7.58-7.50(M, 3H), 7.31-7.28 (M, 2H), 4.46-4.04 (M, 2H)	-
154		A	LCMS：实测 330.0 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.95 (br s, 1H), 12.55(br s, 1H), 8.93 (S, 1H), 7.78 (D, 1H), 7.62-7.49(M, 4H), 7.16 (D,	B

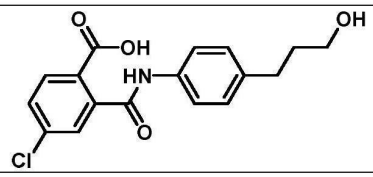
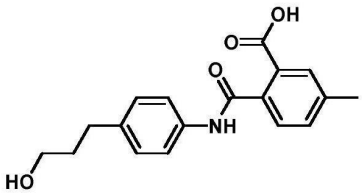
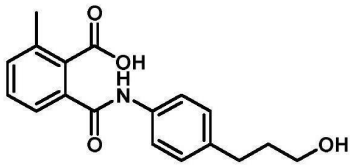
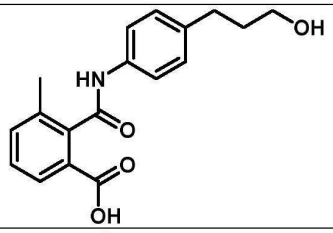
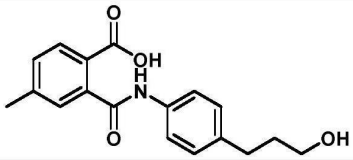
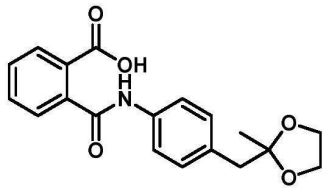
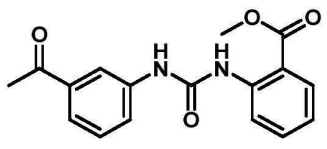
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
			1H), 4.47 (D, 2H), 3.84 (S, 3H)	
155		A	LCMS：实测 325.0 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.37 (br s, 1H), 8.99(T, 1H), 8.07 (D, 1H), 7.97 (S, 1H), 7.83-7.80(M, 2H), 7.62-7.51 (M, 3H), 4.54 (D, 2H)	A
156		H	LCMS：实测 455.1 [M+2Na-H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.36 (S,1H), 7.82-7.75 (M, 3H), 7.51-7.43 (M, 5H), 7.37-7.33 (M, 2H), 7.29-7.27 (M, 2H), 7.16 (T,1H), 4.38 (T, 2H), 3.81 (S, 3H), 3.02 (T, 2H).	A
157		A	LCMS：实测 314.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.92 (br s, 2H), 8.86 (T, 1H), 7.79-7.73 (M, 3H), 7.60-7.48(M, 4H), 4.45 (D, 2H), 2.38 (S, 3H)	-
158		A	LCMS: 314.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.97 (br s, 2H), 8.83(D, 1H), 8.02 (D, 1H), 7.91 (D, 1H), 7.79 (D,1H), 7.61-7.55(M, 3H), 7.44 (D, 1H), 5.18-5.11 (M,1H), 1.44 (D, 3H)	-
159		H	LCMS：实测 421.2 [M+2Na-H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.36 (S,1H), 7.96 (S, 1H), 7.79 (D, 1H), 7.67 (D, 1H), 7.56-7.51 (M, 3H), 7.29-7.27 (M, 1H), 7.19 (T, 1H), 4.36 (T, 2H), 3.80 (S, 3H), 3.14 (T, 2H), 3.01 (T, 2H), 1.91-1.85 (M, 2H), 1.02 (T, 3H).	B
160		A	LCMS：实测 297.1 [M+H]	-

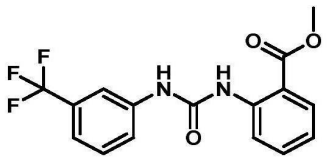
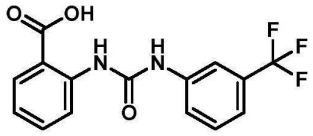
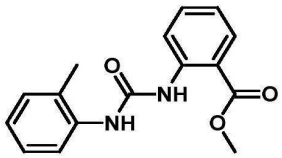
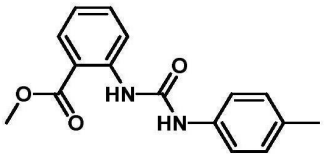
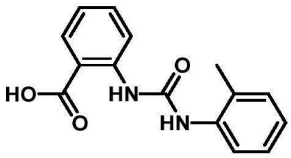
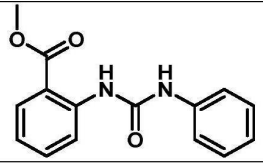
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
161		A	LCMS：实测 368.1 [M+H] ^{1}H NMR (400 MHz, CD_3OD): 8.08-8.06 (D, 2H), 8.01-7.99 (D, 1H), 7.68-7.64 (M, 3H), 7.56-7.56 (D, 1H), 7.42-7.40 (D, 1H), 6.03-5.97 (M, 1H)	-
162		H	LCMS：实测 421.2 [M+2Na-H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.35 (S,1H), 7.95 (S, 1H), 7.85 (D, 1H), 7.65 (D, 1H), 7.56-7.48 (M, 3H), 7.31-7.27 (M, 1H), 7.16 (T, 1H), 4.36 (T, 2H), 3.80 (S, 3H), 3.37-3.32 (M, 1H), 3.01 (T, 2H), 1.41 (S, 6H).	B
163		H	LCMS：实测 469.2 [M+2Na-H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.42 (S,1H), 7.80 (S, 1H), 7.67 (D, 1H), 7.61 (D, 1H), 7.50-7.44 (M, 3H), 7.29-7.24 (M, 6H), 7.16 (T, 1H), 4.42 (S, 2H), 4.37 (T, 2H), 3.80 (S, 3H), 3.01 (T, 2H).	-
164		A	LCMS：实测 314.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.70 (br s, 2H), 8.83 (T, 1H), 7.76 (D, 1H), 7.59-7.45(M, 3H), 7.32 (D, 2H), 7.20 (D, 2H), 4.41 (D, 2H), 3.55 (S,2H)	A
165		K-1	LCMS：实测 279.0 [M+H] ^{1}H NMR (400MHz,$CDCl_3$): 10.98 (S, 1H), 8.80 (S, 1H), 8.46 (D, 1H), 8.03 (D, 1H), 7.61-7.56 (M, 1H), 7.28 – 7.11 (M, 1H), 3.92 (S, 3H)	-
166		A	LCMS：实测 312.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.99 (br s, 1H), 8.84 (T, 1H), 7.76 (D, 1H), 7.59-7.47(M, 3H), 7.33 (D, 2H), 7.14 (D, 2H), 4.41 (D, 2H), 3.74 (S,2H), 2.12 (S,3H)	B

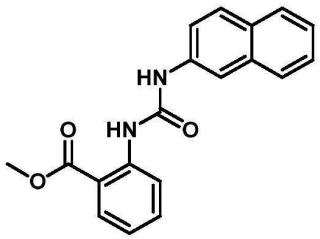
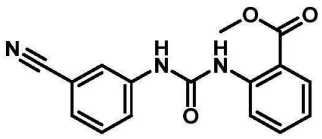
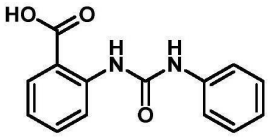
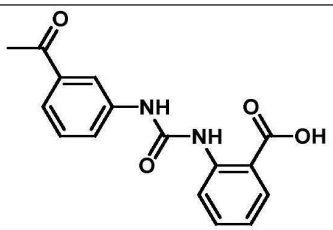
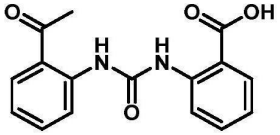
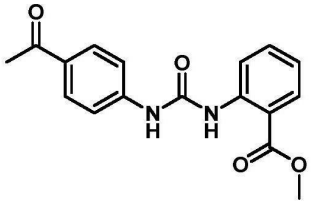
化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
167		A	LCMS：实测 318.1 [M+H]	-
168		A	LCMS：实测 330.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 9.39 (br s, 2H), 7.71 (D, 1H), 7.59-7.47(M, 6H), 4.43 (D, 2H), 3.55 (S,2H)	-
169		K-1	LCMS：实测 343.0 [M+H] LCMS：实测 365.0 [M+Na] ^{1}H NMR (400MHz,$CDCl_3$): 10.48 (S, 1H), 8.56 (D, 1H), 8.04-7.79 (M, 3H), 7.60 (D, 1H), 7.53 (T, 1H), 7.45 (T, 1H), 7.02-6.98 (M,1H), 5.11 (br s, 1H), 4.56 (D, 2H), 3.94 (S, 3H), 3.91 (S, 3H)	-
170		A	LCMS：实测 298.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.03 (br s, 1H), 8.94 (T, 1H), 7.92(D, 2H), 7.78 (D, 2H), 7.61-7.49 (M, 5H), 4.50 (D,2H), 2.58 (S, 3H)	-
171		K-1	LCMS：实测 357.0 [M+H] LCMS：实测 379.0 [M+Na] ^{1}H NMR (400MHz,$CDCl_3$): 10.50 (S, 1H), 8.56 (D, 1H), 8.05-8.01 (M, 3H), 7.53 (T, 1H), 7.44 (D, 1H), 7.00 (T,1H), 5.10 (br s, 1H), 4.57 (D, 2H), 4.38 (Q, 2H), 3.91 (S, 3H), 1.41 (T, 3H)	-
172		A	LCMS：实测 299.1 [M+H]	B
173		A	LCMS：实测 328.2 [M+H]	-

化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
174		A	LCMS：实测 300.1 [M+H] ^{1}H NMR (400 MHz, CD_3OD): 7.98-7.97 (D, 1H), 7.63-7.51 (M, 5H), 7.39-7.36 (T, 3H), 5.68 (S, 1H)	-
175		A	LCMS：实测 365.1 [M+Na] ^{1}H NMR (400 MHz, DMSO-d_6): 13.09 (br s, 1H), 12.09 (S, 1H), 8.49(D, 1H), 8.30 (S, 1H), 7.82 (D, 1H), 7.7-7.61 (M, 4H), 7.36 (D, 1H), 4.52 (T,1H), 3.44-3.41 (M, 2H), 2.63-2.60 (M,2H), 1.78-1.71 (M, 2H)	-
176		A	LCMS：实测 344.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.12 (S, 1H), 11.42 (S, 1H), 8.52-8.50 (D, 1H), 7.86-7.83 (M, 2H), 7.70-7.64 (M, 3H), 7.62 (D, 1H), 4.49 (S, 1H), 3.41 (M, 2H), 2.65-2.62 (T, 2H), 1.75-1.68 (M, 2H)	B
177		B-3	LCMS：实测 318.9 [M+H] LCMS：实测 301.0 [M-H_2O] ^{1}H NMR (400 MHz, DMSO-d_6): 8.07 (D,2H), 7.84 (D, 2H), 7.83-7.71 (M, 3H), 7.64 (T, 1H), 7.42 (br s, 1H), 7.03 (br s, 1H), 6.66 (S, 1H), 2.44 (S, 3H).	-
178		A	LCMS：实测 330.2 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.03 (S, 1H), 10.26 (S, 1H), 7.88 (D, 1H), 7.64 (D, 1H), 7.59-7.52 (M, 2H), 7.41 (S, 1H), 7.17 (D, 1H), 7.06 (D, 1H), 4.43 (T, 1H), 3.75 (S, 3H), 3.43-3.38 (M, 2H), 2.51-2.50 (M, 2H), 1.67-1.65 (M, 2H)	B
179		A	LCMS：实测 341.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.21 (br s, 1H), 10.56 (S, 1H), 8.03(D, 1H), 7.90 (D, 1H), 7.80(D, 1H), 7.69-7.55 (M, 3H),7.17 (D, 1H), 4.87 (S, 2H)	-

化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
180		A	LCMS：实测 318.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.13 (br s, 1H), 10.31 (S, 1H), 7.96 (D, 1H), 7.63-7.39(M, 5H), 7.15 (D, 2H), 4.47 (T, 1H), 3.42-3.40 (M, 2H), 2.59-2.53 (M, 2H), 1.73-1.66 (M, 2H)	B
181		A	LCMS：实测 318.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.25 (br s, 1H), 10.46 (S, 1H), 7.64-7.45(M, 6H), 7.15 (D, 2H), 4.47 (T, 1H), 3.43-3.37 (M, 2H), 2.60-2.56 (M, 2H), 1.74-1.66 (M, 2H)	B
182		A	LCMS：实测 318.1 [M+H]	B
183		A	LCMS：实测 318.1 [M+H]	B
184		A	LCMS：实测 334.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.30 (br s, 1H), 10.31 (S, 1H), 7.90-7.55(M, 6H), 7.15 (D, 2H), 4.47 (br s, 1H), 3.43-3.38 (M, 2H), 2.60-2.55 (M, 2H), 1.73-1.68 (M, 2H)	B
185		A	LCMS：实测 334.1 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.46 (S, 1H), 7.727.68 (M, 2H), 7.61-7.54 (M, 3H), 7.16 (D, 2H), 4.47 (S, 1H), 3.43-3.39 (M, 2H), 2.60-2.50 (M, 2H), 1.74-1.66 (M, 2H)	B
186		A	LCMS：实测 334.1 [M+H]	B

化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
187		A	LCMS：实测 334.1 [M+H]	B
188		A	LCMS：实测 314.2 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 12.85 (br s, 1H), 10.19 (S, 1H), 7.79-7.56 (M, 3H), 7.44-7.33(M, 2H), 7.13 (D, 2H), 4.47 (T, 1H), 3.42-3.39 (M, 2H), 2.59-2.51 (M, 2H), 1.73-1.66 (M, 2H)	-
189		A	LCMS：实测 314.2 [M+H] ^{1}H NMR (400 MHz, MeOD): 7.59-7.53 (M, 3H), 7.48-7.41 (M, 2H), 7.18-7.14 (M, 2H), 3.60-3.57 (T, 2H), 2.72-2.67 (M, 2H), 2.47 (S, 3H), 1.88-1.81 (M, 2H)	A
190		A	LCMS：实测 314.2 [M+H]	A
191		A	LCMS：实测 314.2 [M+H]	-
192		A	LCMS：实测 342.2 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 13.04 (br s, 1H), 10.28 (S, 1H), 7.86 (D, 1H), 7.65-7.53 (M, 5H), 7.19 (D, 2H), 3.86-3.77 (M, 4H), 2.81 (S, 2H), 1.19 (S, 3H)	-
193		K-1	LCMS：实测 313.2 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6):10.63 (S, 1H), 8.53 (D, 1H), 8.03 (M, 2H), 7.75 (D, 1H), 7.68 (D, 1H), 7.53 (T, 1H), 7.42 (T, 1H), 7.04 (M, 1H), 3.90 (S, 3H), 2.30 (S, 3H)	B

化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
194		K-1	LCMS：实测 339.2 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.70 (S, 1H), 8.50 (D, 1H), 8.00 (T, 2H), 7.65 (D, 1H), 7.55 (M, 2H), 7.26 (M, 1H), 6.67 (S, 1H), 3.88 (S, 3H)	B
195		K-1	LCMS：实测 339.2 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.65 (S, 1H), 8.55 (D, 1H), 8.02 (D, 1H), 7.81 (S, 1H), 7.62 (D, 1H), 7.55 (T, 1H), 7.45 (T, 1H), 7.26 (D, 1H), 7.05 (T, 1H), 6.95 (S, 1H), 3.91 (S, 3H)	B
196		K-2	LCMS：实测 307.1 [M-H_2O+H] ^{1}H NMR (400 MHz, DMSO-d_6): 11.63 (S, 1H), 7.95 (D, 1H), 7.82 (M, 1H), 7.81 (S, 1H), 7.73 (M, 2H), 7.68 (M, 1H), 7.24 (M, 2H)	B
197		K-1	LCMS：实测 285.2 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 9.96 (S, 1H), 9.01 (S, 1H), 8.29 (D, 1H), 7.92 (DD, 1H), 7.55 (T, 1H),7.46 (DD, 1H), 7.22-7.16 (M, 2H), 7.07-7.04 (M, 2H), 3.87 (S, 3H), 2.25 (S, 3H)	B
198		K-1	LCMS：实测 285.2 [M+H] ^{1}H NMR (400 MHz, $CDCl_3$): 10.47 (S, 1H), 8.55 (D, 1H), 7.99 (D, 1H), 7.51 (T, 1H), 7.30 (D, 2H),7.16 (D, 2H), 7.0 (T, 1H), 6.68 (S,1H), 3.87 (S, 3H), 2.33 (S, 3H)	B
199		K-2	LCMS：实测 253.2 [M-H_2O+H] ^{1}H NMR (400 MHz, DMSO-d_6): 11.60 (S, 1H), 7.96 (D, 1H), 7.72 (T, 1H), 7.35 (M, 2H), 7.30 (M, 1H), 7.22 (M, 3H), 3.32 (S, 3H)	B
200		K-1	LCMS：实测 271.2 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.50 (S, 1H), 8.55 (D, 1H, J=6Hz), 7.97 (D,	B

化合物编号	结构	合成流程	表征数据 (NMR 和/或 LCMS)	生物活性
			1H, J=7.8Hz), 7.52 (M, 1H), 7.44 (M, 1H), 7.34 (M, 2H), 7.11 (M, 1H), 7.00 (M, 1H), 6.84 (S, 1H), 3.88 (S, 3H)	
201		K-1	LCMS：实测 321.2 [M+H] ^{1}H NMR (400 MHz,$CDCl_3$): 10.64 (S, 1H), 8.60 (DD, 1H), 8.08 – 7.98 (M, 2H), 7.83 – 7.74 (M, 3H), 7.55 (DD, 1H), 7.49 – 7.34 (M, 3H), 7.06 – 6.97 (M, 1H), 6.95 (S, 1H), 3.89 (S, 3H)	B
202		K-1	LCMS：实测 296.2 [M+H] ^{1}H NMR (400 MHz,$CDCl_3$): 10.70 (S, 1H), 8.52 (DD, 1H), 8.02 (DD, 1H), 7.89 (T, 1H), 7.64 (DD, 1H), 7.56 (DD, 1H), 7.45 – 7.33 (M, 2H), 7.05 (DD, 1H), 6.92 (S, 1H), 3.93 (S, 3H)	A
203		K-2	LCMS：实测 238.07 [M-H_2O+H] ^{1}H NMR (400 MHz, DMSO-d_6): 11.56 (S, 2H), 7.94 (D, 1H, J=8Hz), 7.70 (T, 1H, J=6Hz), 7.48 (M, 2H), 7.42 (M, 1H), 7.32 (M, 2H), 7.22 (M, 2H)	B
204		K-2	LCMS：实测 280.08 [M-H_2O+H] ^{1}H NMR (400 MHz, DMSO-d_6): 11.60 (S, 2H), 8.03 (D, 2H, J=6Hz), 7.95 (M, 2H), 7.72 (T, 2H, J=6Hz), 7.25 (D, 2H, J=6.4Hz), 3.32 (S, 3H)	B
205		K-2	LCMS：实测 281.2 [M-H_2O+H] ^{1}H NMR (400 MHz, DMSO-d_6): 11.55 (S, 1H), 8.05 (D, 1H), 7.90 (D, 1H), 7.70 (M, 2H), 7.61 (M, 1H), 7.42 (D, 1H), 7.23 (M, 2H), 2.46 (S, 3H)	B
206		K-1	LCMS：实测 313.2 [M+H] ^{1}H NMR (400 MHz, DMSO-d_6): 10.67 (S, 2H), 8.52 (D, 1H, J=7.8Hz), 8.00 (D, 1H), 7.94 (D, 2H, J=8Hz), 7.55 (M, 3H), 7.03 (T, 1H, J=6Hz), 3.88 (S, 3H), 2.58 (S, 3H)	B

实施例 2：细胞活力试验

[0279] 以每孔 10,000 个细胞的密度将人 MSC、软骨细胞、成骨细胞和滑膜细胞接种到

384 孔板中。以 100μM 的终浓度加入化合物。将细胞培养 48h。使用 EnVision 读板仪 (PerkinElmer) 通过 Cell Titer-Glo(Promega) 试验分析细胞活力。使用 EnVision 读板仪 (PerkinElmer) 通过胱天蛋白酶 3/7-Glo(Promega) 试验分析凋亡活性。

实施例 3 :在大鼠中经由关节内注射的 PK 研究

[0280] 将 30μl 化合物溶液 (100μM,在含有 0.1% DMSO 的 PBS 中) 注射到每只大鼠的右膝的关节间隙内。动物在注射后 1、3、4、6、7、8、9 和 10 小时放血。给药后 2 或 12 小时处死动物。收集所注射的膝的血浆和关节灌洗液。使用 LCMS 分析所注射的化合物的量。

实施例 4 :大鼠内侧半月板撕裂 (MMT) 骨关节炎 (OA) 模型

[0281] 经手术撕裂每只动物的右膝的内侧半月板以诱发 OA。化合物溶液 (30μl, 100μM,在含有 0.1% DMSO 的 PBS 中) 的给药在手术后 7 天开始,每周一次剂量,持续三周。就在给药前每周监测体重和步态缺陷。在手术后第 28 天处死动物。对经手术的膝关节进行处理,并对软骨进行组织化学染色,并评价软骨。

[0282] 在 5% 甲酸脱钙剂中 4-6 天后,将经手术的关节沿额面切成两个大致相等的半部并在石蜡中包埋。以大约 200μm 的步级从每个经手术的右膝 (g1-8) 切成三个切片,并用甲苯胺蓝染色。第 1 组的左膝和第 9 组的右膝制备单一切片并用甲苯胺蓝染色。

[0283] 通过显微术分析每个经手术的膝的所有三个切片。针对总体软骨退化、蛋白聚糖损失、胶原损伤和骨赘形成,确定对于每一个载片上的两个半部而言最坏的情形。然后将每个参数的值在三个切片之间进行平均,以确定整体主观得分。

[0284] 另外,对于一些参数 (以下指出),通过将每个切片分成三个区带 (1- 外部,2- 中部,3- 内部) 考虑跨胫骨坪的区域性差异。在手术 OA 模型中,外部 (z1) 和中部 (z2) 各三分之一受到最严重的影响,而在内部三分之一 (z3) 上存在较轻的变化。当单独对区带进行评分时,基于受影响区带的面积百分比分配得分。使用目镜测微计描绘区带面积。

[0285] 对以下参数进行测量和 / 或评分 :

[0286] 总体软骨退化包括软骨细胞死亡 / 损失、蛋白聚糖损失和胶原损失或纤颤 (fibrillation) 的重要参数。对于每个区带,使用以下标准将胫骨中的软骨退化评分为从无到重度的 (数值 0-5) :

• 0 = 无退化

• 1 = 最小的退化,在该区带内,5-10% 的基质由于显著的软骨细胞损失 (大于正常细胞密度的 50%) 而呈现为非存活的。PG 损失通常存在于细胞损失的这些区域中,且可能存在胶原基质损失。

•2 = 轻度退化,在该区带内,11-25% 的基质由于显著的软骨细胞损失 (大于正常细胞密度的 50%) 而呈现为非存活的。PG 损失通常存在于细胞损失的这些区域中,且可能存在胶原基质损失。

•3 = 中度退化,在该区带内,26-50% 的基质由于显著的软骨细胞损失 (大于正常细胞密度的 50%) 而呈现为非存活的。PG 损失通常存在于细胞损失的这些区域中,且可能存在胶原基质损失。

•4 = 明显退化,在该区带内,51-75% 的基质由于显著的软骨细胞损失 (大于正常细胞密度的 50%) 而呈现为非存活的。PG 损失通常存在于细胞损失的这些区域中,且可能存在胶原基质损失。

• 5 ＝重度退化，在该区带内，76-100％的基质由于显著的软骨细胞损失（大于正常细胞密度的 50％）而呈现为非存活的。PG 损失通常存在于细胞损失的这些区域中，且可能存在胶原基质损失。

在一些情况下，可以使用图像分析来确定每个区带或所选的区带中确切的基质活力和 / 或损失％，以使得可以比较绝对％而不是得分 (0-5)。除了表示每个区带的数据外，还计算了软骨退化的 3 区带总和。

[0287] 相同的过程应用于对股骨软骨的评价，不同之处是不基于区带分析病变，因为病变通常不以区带模式分布在整个表面上。确定承载负荷的表面的总宽度（对于股骨为约 2000μm) 并将上述标准应用于受到最严重影响的 1/3、2/3 或 3/3。例如，如果总面积的 1/3（病变可以处于覆盖约 667μm 的坪的中心）具有最小的退化（总面积的 5-10％具有软骨细胞和 / 或基质的损失），则分配得分 1。如果该最小的退化在整个表面上延伸 (3/3)，则分配得分 3。如果整个股骨软骨由于严重的扩散退化而不存在，则得分为 15。

[0288] 除这种整体软骨退化得分外，还单独对胶原基质损伤进行了评分，以便确定药剂的更具体的影响。跨内侧胫骨坪的胶原损伤（两个半部的受到最严重影响的切片）通过测量以下的总宽度来量化：

• 任意损伤（从浅表到完全厚度损失的纤颤）

• 重度损伤（胶原全部损失或接近全部损失至潮标 (tidemark)，>90％厚度）

• 明显损伤（延伸穿过软骨厚度的 61-90％）

• 中度损伤（延伸穿过软骨厚度的 31-60％）

• 轻度损伤（延伸穿过软骨厚度的 11-30％）

• 最小损伤（极浅表，仅影响上面 10％）

[0289] 除了以上的主观总体软骨评分外，还进行了两个软骨退化宽度测量：

• 总胫骨软骨退化宽度（μm)是胫骨坪受到任何类型的退化（细胞损失、蛋白聚糖损失或胶原损伤）影响的总程度的测微计测量值。该测量从具有相邻软骨退化的骨赘的起点（外部 1/3) 跨过表面延伸到切向层和下方软骨在组织学上表现为正常处的点。

• 实质软骨退化宽度（μm)反映软骨细胞和蛋白聚糖损失都延伸穿过大于软骨厚度的 50％的胫骨软骨退化区域。通常，对于该参数，胶原损伤是轻度的 (25％深度）或更大的，但是软骨细胞和蛋白聚糖损失延伸到软骨深度的至少 50％或更大。

[0290] 任何类型的病变（软骨细胞和蛋白聚糖两者的损失，但是可具有胶原基质的良好保留且没有纤颤）的测微计深度，表示为变化的区域深度相对于至潮标的深度的比值，在区带中点处跨过胫骨表面的三个区带中每一个的最大病变严重程度的区域中获得。该测量是对存在的任何类型的微观变化的最关键分析。在区带的中点进行测量时，分母可充当三个区带中的每一个的软骨厚度的平均量度以用于比较合成代谢。

[0291] 骨赘的评分以及分类（分类为小、中和大）使用目镜测微计进行。为了能够测量并指定为骨赘，边缘区增生变化必须≥ 200μm。根据以下标准向每个切片中的最大骨赘（一般在胫骨中发现）分配得分：

• 1 ＝小，可达 299μm

• 2 ＝中度，300-399μm

• 3 ＝大，400-499μm

• 4 ＝极大，500-599

• 5 ＝极大，≥ 600

还记录了实际的骨赘测量（潮标至朝向滑膜延伸的最远距离点）。

[0292] 将股骨软骨退化得分和胫骨软骨退化得分的三区带总和（三个水平的平均值）加起来以形成总软骨退化得分。向该值增加每个关节的平均骨赘得分以产生总关节得分。

图像分析

[0293] 为了量化和比较软骨基质保持，从每只动物的受到最严重影响的切片进行软骨面积测量。用 CoolSNAP-Pro 显微照相机拍摄显微照片并加载到 ImagePro Plus 软件中。从这些显微照片的描记进行下列测量，每页四个，其包括在报告中：

• 在 9cm（显微照片）胫骨坪上从潮标到表面（或退化的区域中凸出的表面）的总面积，从骨赘的内缘测量

• 总面积内非存活基质（具有少于 50％软骨细胞、蛋白聚糖和完整胶原的软骨）和无基质的面积

• 总面积内无基质的面积

从总面积中减去非存活基质的面积以得到活基质的面积，并且从总面积中减去无基质的面积以得到任何基质（含有或不含软骨细胞和蛋白聚糖的胶原基质）的面积。这两个值然后回过来与总面积进行比较，以得出活基质面积百分比和任何基质面积百分比，它们在组间进行比较。该过程中包括来自载体组的五个左膝作为正常对照。该过程可以用来根据病变的严重程度和明显的治疗效果来分析整个表面或选择的区带。

[0294] 滑液反应如果是异常的，则在炎症类型和程度方面进行描述（应当主要是纤维化）和表征，但不包括在 OA 得分中。

[0295] 钙化的软骨层和软骨下骨的损伤（对于所有切片最坏的情形）使用以下标准来评分：

• 0 ＝无变化

• 1 ＝在潮标处增加的嗜碱性粒细胞增多，潮标无破碎，无骨髓改变或者如果存在则是最小的和局灶性的

• 2 ＝在潮标处增加的嗜碱性粒细胞增多，潮标的钙化软骨有最小到轻度的局灶性破碎，骨髓中的间质变化涉及总面积的 1/4，但通常局限于病变下的软骨下区域

•3 ＝在潮标处增加的嗜碱性粒细胞增多，钙化软骨有轻度到明显的局灶性或多灶性破碎（多灶性），骨髓中的间质变化涉及总面积的最多 3/4，骨髓软骨形成的面积可以是明显的，但关节软骨没有大量瓦解为骨骺骨（表面中明确的凹陷）

• 4 ＝在潮标处增加的嗜碱性粒细胞增多，钙化软骨有明显的到重度的破碎，骨髓间质变化涉及面积的最多3/4，且关节软骨已经瓦解为骨骺，距潮标的深度为250μm或更少（表面软骨中可见明确的凹陷）

• 5 ＝在潮标处增加的嗜碱性粒细胞增多，钙化软骨有明显的到重度的破碎，骨髓间质变化涉及面积的最多 3/4，且关节软骨已经瓦解为骨骺，距潮标的深度大于 250μm

另外，对切片的非切向区中的内侧滑液 / 侧副韧带修复的厚度进行了测量。

[0296] 所有膝在内侧和侧面上 (2 次测量 / 关节)，在内侧和侧面骨骺的近似中点处测量了生长面厚度（假定切片的非切向区）。

实施例 5 :关节和血浆大鼠样品中软骨形成化合物的提取和量化

[0297] 针对软骨形成化合物的 LC-MS/MS 分析使用配备有 Agilent 1100HPLC 和 Leap Technologies 自动进样器的 API 3000 来进行。使用 HPLC Phenomenex 5 微米,100A Luna C18(2) 分析柱,尺寸为 2.0x 50mm(货号 00B-4252-B0),温度为 30℃,流速为 0.6mL/min,注入体积为 10uL,运行时间为 6.0min。流动相 A1 为 0.1% 甲酸水溶液,流动相 B1 为 0.1% 甲酸的乙腈溶液。梯度在时间 0 时为 90% A1/10% B1 ;时间 1.0min 时为 90% A1/10% B1 ;时间 2.0min 时为 10% A1/90% B1 ;时间 4.0min 时为 10% A1/90% B1 ;时间 4.10min 时为 90% A1/10% B1 ;时间 6.0min 时为 90% A1/10% B1。分析物和内部标准的量化使用多反应监测 (Multiple Reaction Monitoring)(MRM) 定量法来进行。以下列出了用来给药并测量血浆中的暴露的具体方法以及观察到的在关节提取物中的浓度。

[0298] 大鼠血浆样品 :通过在对照大鼠血浆中连续稀释浓缩的、掺加的化合物溶液来制作校准标准曲线。通过向标准和样品的每个等分试样中添加乙腈和内部标准的等分试样经蛋白质沉淀制备校准标准和大鼠血浆样品。在涡旋混合和离心后,来自每个标准和样品的上清液的等分试样用甲酸水溶液稀释,混合并注入。在 IA 给药后采集的所有血浆样品 (在 t = 0、0.5、1、2、4 和 6h 开始) 都表明,对于表 2 中列出的任何化合物没有全身性暴露。

[0299] 大鼠膝关节样品 :通过在内部标准稀释剂中连续稀释浓缩的、掺加的化合物溶液来制作校准标准曲线。内部标准稀释剂通过将内部标准化合物以特定浓度溶解在乙腈中来制备。单独压碎每个时间点的大鼠膝关节样品并将其转移到每个离心管中,并添加 1.0-mL 内部标准稀释剂。将每个离心管涡旋并离心 30 分钟。从每个管中移取上清液并注入到柱上以供分析。另外,通过眼眶后放血到肝素涂覆的管中获得血浆样品并储存在 -80℃,稍后与以上针对大鼠血浆样品所述的方案类似地进行处理。

[0300] 化合物施用与组织处理 :将 30 μL 的 100 μM 化合物溶液 (含有 0.1% DMSO 的 PBS) 注射到每只动物的右后膝的关节内间隙中。在所示的时间点 (0hr、0.5hr、1hr、2hr、4hr 和 6hr) 对动物施以安乐死。每个时间点使用四只动物。收获经注射的膝关节,在液氮中骤冻。将整个关节在冷冻下研磨成粉末,与 1mL 含有内部标准的乙腈混合,并在 4℃下温育过夜,涡旋,并离心 30min。使用 LC-MS/MS 分析每个样品的上清液。表 2 中显示的数据表示了在膝提取物中观察到的浓度。ND = 未测定。

表 2

化合物编号	在提取物中观察到的浓度(ng/mL)					
	T = 0 h	T = 0.5 h	T = 1 h	T=2 h	T = 4 h	T = 6 h
21	433.5	9.1	4.9	0	ND	ND
27	592	35.4	6.3	2.5	ND	ND
62	411	108.75	52.6	15.7	ND	ND
73	587	28.5	9.41	2.6	ND	ND
113	565.5	25.3	4.2	0	ND	ND
117	925.5	50.6	4.4	0	ND	ND
123	4430	1102	741.25	337.5	38	0
128	7280	2942.5	1365	546	ND	ND
156	108.8	3.5	0	0	ND	ND

实施例 6:本文提出的化合物的肠胃外组合物

[0179] 为了制备适于通过注射施用的肠胃外药物组合物,将 100mg 的本文提出的化合物或其水溶性药学上可接受的盐溶解于 DMSO,然后与 10ml 的 0.9%无菌盐水溶液混合。将混合物组入适于通过注射施用的剂量单位。

实施例 7:本文提出的化合物的口服组合物

[0180] 为了制备用于经口递送的药物组合物,将 400mg 的本文提出的化合物和下述成分紧密混合,并压入单个刻痕的片剂内。

片剂配方

成分	每片含量 mg
化合物	400
玉米淀粉	50
交联羧甲纤维素钠	25
乳糖	120
硬脂酸镁	5

[0181] 将下述成分紧密混合并加载于硬壳的明胶胶囊内。

胶囊配方

成分	每个胶囊的含量 mg
化合物	200
乳糖, 喷雾干燥	148
硬脂酸镁	2