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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 November 2009 (26.11.2009)

PCT

(10) International Publication Number
WO 2009/143404 A1

(51) International Patent Classification:
C07D 213/74 (2006.01) *C07D 295/192* (2006.01)
C07D 241/20 (2006.01) *A61K 31/496* (2006.01)
C07D 401/12 (2006.01) *A61P 25/00* (2006.01)

(21) International Application Number:
PCT/US2009/044938

(22) International Filing Date:
22 May 2009 (22.05.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/055,671 23 May 2008 (23.05.2008) US

(71) Applicant *(for all designated States except US)*: **WYETH** [US/US]; Five Giralda Farms, Madison, NJ 07940 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BURSAVICH, Matthew, Gregory** [US/US]; 864 East 200 South, Salt Lake City, UT 84102 (US). **GILBERT, Adam, Matthew** [US/US]; 2 Plainview Court, Congers, NY 10920 (US). **STOCK, Joseph, Raymond** [US/US]; 439 High Street, Monroe, NY 10950 (US).

(74) Agents: **MAZZARESE, Joseph M.** et al.; Wyeth, Patent Law Department, Five Giralda Farms, Madison, NJ 07940 (US).

(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, BR, BW, BY, BZ, CA, CH, 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, IS, JP, KE, KG, KM, 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, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, 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, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (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, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

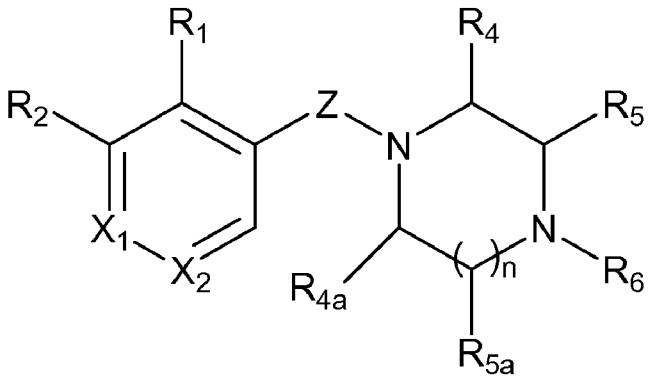
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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))*

(54) Title: PIPERAZINE METABOTROPIC GLUTAMATE RECEPTOR 5 (MGLUR5) NEGATIVE ALLOSTERIC MODULATORS FOR ANXIETY/DEPRESSION



(I)

(57) Abstract: The present teachings relate to piperazine metabotropic glutamate receptor 5 (mGluR5) negative allosteric modulators having Formula (I); wherein the constituent variables are as defined herein. The present teachings further relate to methods for the preparation of the compounds, and to methods for using the compounds for treatment of diseases and disorders including schizophrenia, paranoia, depression, manic-depressive illness and anxiety.

WO 2009/143404 A1

PIPERAZINE METABOTROPIC GLUTAMATE RECEPTOR 5 (MGLUR5) NEGATIVE ALLOSTERIC MODULATORS FOR ANXIETY/DEPRESSION

FIELD OF THE INVENTION

In one aspect, this invention relates to piperazine metabotropic glutamate receptor 5 (mGluR5) negative allosteric modulators, and methods for their preparation. In a further aspect, the invention provides methods for using the mGluR5 negative allosteric modulators for treatment of diseases and disorders including schizophrenia, paranoia, depression, manic-depressive illness, anxiety (including panic disorders, social anxiety, obsessive compulsive disorders, generalized anxiety disorders, phobias), post-traumatic stress disorder, bipolar disorder, Asperger's syndrome, pervasive developmental disorders, gastrointestinal disorders such as gastroesophageal reflux disease, dyspepsia, irritable bowel syndrome, functional bloating, functional diarrhea, chronic constipation, functional disturbances of the biliary tract, migraine, chronic pain, fibromyalgia, neuropathic pain, post-herpatic neuropathic pain, addiction, Parkinson's disease, senile dementia, levadopa-induced dyskinesia, Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis, multiple sclerosis, Down Syndrome, fragile-X syndrome, autistic spectrum disorders, attention deficit hyperactivity disorder, stroke, ischemic injury, epilepsy, hypoglycemia and obesity.

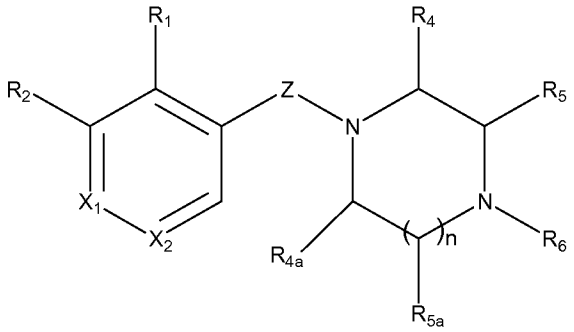
BACKGROUND OF THE INVENTION

The metabotropic glutamate 5 receptor (mGluR5) is a G-protein-coupled metabolic glutamate receptor that plays a role as a modulator of synaptic plasticity, ion channel activity, and excitotoxicity (Bach et al., Metabotropic Glutamate Receptor 5 Modulators and their Potential Therapeutic Applications, Department of Med. Chemistry, AstraZeneca R and D Moelndal, Moelndal, Sweden, Expert Opinion on Therapeutic Patents **2007**, 17(4), 371-384 and references therein).

Recent evidence indicates that current mGluR5 negative allosteric modulators are not sufficiently selective, and cause off-target effects, such as inhibition of NMDA receptors. Thus, there exists an ongoing need for compounds that more selectively bind to mGluR5, and that are useful in repressing and/or treating disorders such as schizophrenia, paranoia, depression, manic-depressive illness and anxiety. This invention is directed to these, as well as other, important ends.

SUMMARY OF THE INVENTION

In one aspect, the invention provides compounds of Formula I:



I

wherein the constituent variables are as defined herein.

In another aspect, the invention provides pharmaceutical compositions containing a compound of the invention, and a pharmaceutically acceptable carrier.

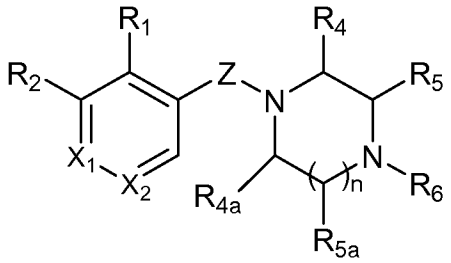
In a further aspect, the invention provides methods for the treatment of a patient suffering from a chronic condition such as, schizophrenia, paranoia, manic-depressive illness, depression, or anxiety (including panic disorders, social anxiety, obsessive compulsive disorders, generalized anxiety disorders, phobias), post-traumatic stress disorder, bipolar disorder, Asperger's syndrome, pervasive developmental disorders, gastrointestinal disorders such as gastroesophageal reflux disease, dyspepsia, irritable bowel syndrome, functional bloating, functional diarrhea, chronic constipation, functional disturbances of the biliary tract, migraine, chronic pain, fibromyalgia, neuropathic pain, post-herpatic neuropathic pain, addiction, Parkinson's disease, senile dementia, levadopa-induced dyskinesia, Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis, multiple sclerosis, Down Syndrome, fragile-X syndrome, autistic spectrum disorders, attention deficit hyperactivity disorder, stroke, ischemic injury, epilepsy, hypoglycemia and obesity.

In yet another aspect, the invention provides methods for producing compounds of Formula I.

Other aspects of the present teachings are described further in the following detailed description.

DETAILED DESCRIPTION

In accordance with the invention, there are provided A compound of Formula I:



I

wherein:

R_1 is each independently selected from H, C_{1-6} alkyl, halogen, OH, and OC_{1-6} alkyl;

R_2 is selected from $-(L_1)_a-(Y)_c-(L_2)_b-Q_3$, $-L_3-Q_4$ and $-L_4-Q_5$;

L_3 is C_{2-12} alkynyl optionally substituted with 1-3 substituents selected from OH and halogen;

L_1 and L_2 are each independently C_{1-3} alkyl;

L_4 is C_{2-12} alkenyl optionally substituted with 1-3 substituents selected from OH and halogen;

n is 1 or 2

R_4, R_{4a}, R_5, and R_{5a} are each independently selected from H, (=O) and C_{1-6} alkyl; or R_4 and one of R_{5a} together can form a bridging methylene; or R_5 can be together with the carbon to which it is attached –C(=O)

R_6 is selected from H, CH_3, $-(L_5)-$(3- to 14-membered heterocycle), $-(L_5)-$(5 to 14 membered heteroaromatic), $(L_5)-$(3- to 10-membered cycloalkyl), $(L_5)-(C_{6-14}$ aryl) and $-(L_5)-C_{1-6}$ alkyl each of which except H can be optionally substituted with 1 to 3 substituents independently selected from H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, $-C(=O)O-(C_{1-6}$ alkyl), NO_2, C_{1-3} haloalkyl, $-S-C_{1-6}$ alkyl, CN, (5- to 14-membered heteroaromatic), NR_1R_1, SO_2C_{1-6} alkyl, SO_2, $SO_2NR_1R_1$, C_{1-6}alkylaryl, COC_{1-6} alkyl, and (3- to 14-membered heterocycle) optionally substituted with NO_2.

L_5 is selected from a bond, C_{1-3} alkyl, -C(=O)-, SO_2, (3- to 6-membered heterocycle) and (5- to 14-membered heteroaromatic).

X_1, X_2 are independently CR_3 or N;

each R_3 is independently H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, SO_2, 3- to 14-membered heterocycle or 5- to 14-membered heteroaromatic, wherein each of C_{1-6} alkyl or OC_{1-6} alkyl can be optionally substituted with 1 to 3 substituents independently selected from halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), cycloalkyl, NR_1R_1, or CN;

Z is CO;

Y is CR_7R_8, NR_9, O, or S;

R_7, R_8, R_9 are independently H, C_{1-6} alkyl, halogen, OH, or OC_{1-6} alkyl

a, b, c are independently 0 or 1; and

Q_3 is C_{6-14} aryl, 5 to 14 membered heterocyclic, 5 to 14 membered heteroaromatic, or 4 to 9 membered carbocyclic; each of which can be optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), OC_{1-3} haloalkyl, OC_{1-6} alkylaryl and CN;

Q_4 is H, C_{6-14} aryl, 5 to 14 membered heterocyclic, 5 to 14 membered heteroaromatic, or 4 to 9 membered carbocyclic; each of which except H can be optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), -C(=O)C_{1-6} alkyl, NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), OC_{1-3}haloalkyl, OC_{1-6}alkylaryl and CN;

Q_5 is C_{6-14} aryl, 5 to 14 membered heterocyclic, 5 to 14 membered heteroaromatic, or 4 to 9 membered carbocyclic; each of which can be optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), OC_{1-3}haloalkyl, OC_{1-6}alkylaryl and CN.

In some embodiments of formula I, n is 1.

In some embodiments, R_2 is -L_3-Q_4. In some embodiments, Z is CO. In some embodiments, R_1, R_4, R_{4a}, R_5, R_{5a}, and R_6 are each H. In some embodiments, R_3 is H, methyl, methoxy or halogen.

In some embodiments, R_2 is $-L_3-Q_4$, and Z is CO. In some such embodiments, R_1, R_4, R_{4a}, R_5, and R_{5a}, are each H. In some further such embodiments, R_1, R_4, R_{4a}, R_5, and R_{5a}, are each H; and R_3 is H, methyl, methoxy or halogen. In some further such embodiments, Q_4 is H. In some further such embodiments, Q_4 is phenyl optionally substituted with 1 to 3 substituents independently selected from H, C_{1-6} alkyl, halogen, OH, and OC_{1-6} alkyl. In some further such embodiments, Q_4 is 5 to 14 membered heterocyclic optionally substituted with 1 to 3 substituents independently selected from H, C_{1-6} alkyl, halogen, OH, and OC_{1-6} alkyl. In some further such embodiments, Q_4 is 5 to 14 membered heteroaromatic optionally substituted with 1 to 3 substituents independently selected from H, C_{1-6} alkyl, halogen, OH, and OC_{1-6} alkyl.

In some embodiments R_2 is $-L_3-Q_4$, Z is CO, and R_6 is $-(L_5)$-2-pyridyl, $-(L_5)$-4-pyridyl, $-(L_5)$-pyrazinyl, $-(L_5)$-phenyl, $-(L_5)$-(tetrazole-5-yl), pyrimidin-2-yl, -(4-phenyl)-pyrimidin-2-yl or $-(L_5)$-1,2,5-diathiazole-3-yl, each of which can be optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, $-C(=O)O-(C_{1-6}$ alkyl), NO_2, C_{1-3} haloalkyl, $-S-C_{1-6}$ alkyl and CN. In some such embodiments, L_5 is a bond.

In some embodiments of the compounds of Formula I, X_1 and X_2 are each independently CR_3 or N.

In some embodiments of the compounds of Formula I, one of X_1 and X_2 is CR_3, and the other of X_1 and X_2 is N. In some such embodiments, Z is CO. In some further such embodiments, Z is CO; R_2 is $-L_3-Q_4$, and L_3 is C_2 alkynyl. In some further such embodiments, Z is CO; R_2 is $-L_3-Q_4$, L_3 is C_2 alkynyl, and Q_4 is phenyl optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, $-C(=O)O-(C_{1-6}$ alkyl), NO_2, C_{1-3} haloalkyl, $-S-C_{1-6}$ alkyl $-NH_2$, $-NH-(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)(C_{1-6} alkyl) and CN. In some such embodiments, R_4, R_{4a}, R_5, and R_{5a}, are each H. In some such embodiments, R_6 is 5 to 14 membered heteroaromatic, each of which is optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, $-C(=O)O-(C_{1-6}$ alkyl), NO_2, C_{1-3} haloalkyl, $-S-C_{1-6}$ alkyl and CN.

In some embodiments of the compounds of Formula I, X_1 and X_2 are each independently CR_3. In some such embodiments, R_6 is H.

In some embodiments of the compounds of Formula I, X_1 is CR_3, X_2 is CH, and R_6 is H. In some such embodiments, Z is CO.

In some embodiments of the compounds of Formula I, X_1 is CR_3, X_2 is CH, R_6 is H, Z is CO and R_1, R_4, R_{4a}, R_5, and R_{5a}, are each H.

In some embodiments of the compounds of formula I, X_1 is CR_3, X_2 is CH, R_6 is –(L_5)-phenyl optionally substituted with halogen or C_{1-6} alkyl, wherein L_5 is a bond, Z is CO and R_{4a} and R_5 form a bridging methylene, R_2 is -L_3-Q_4, L_3 is C_2 alkynyl, and Q_4 is 2-pyridyl or phenyl optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl) and CN. In some such further embodiments R_3 is OC_{1-6} alkyl.

In some other embodiments of the compounds of formula I, R_6 is H, CH_3, -(L_5)-2-pyridyl, -(L_5)-4-pyridyl, -(L_5)-pyrazinyl, -(L_5)-phenyl, -(L_5)-(3-14-membered heterocycle), -(L_5)-(5- to 14-membered heteroaromatic), (L_5)-cycloalkyl, (L_5)-(3- to 10-membered cycloalkyl), (L_5)-(C_{6-14} aryl) or –(L_5)-C_{1-6} alkyl each of which except H can be optionally substituted with 1 to 3 substituents independently selected from H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl, CN, a 3- to 14-membered heterocycle or 5- to 14-membered heteroaromatic, NR_1, SO_2, $SO_2NR_1R_1$ or C_{1-6} alkylaryl.

In other embodiments of the compounds of formula I, R_6 is –(L_5)-(3- to 14-membered heterocycle), –(L_5)-(5 to 14 membered heteroaromatic) or (L_5)-(C_{6-14} aryl), wherein L_5 can be a bond, SO_2
or –C(=O)-.

In some embodiments of the compounds of Formula I, X_1 is CR_3, X_2 is CH, R_6 is H, Z is CO, R_1, R_4, R_{4a}, R_5, and R_{5a}, are each H, and R_2 is -$(L_1)_a$-$(Y)_c$-$(L_2)_b$-Q_3 or -L_4-Q_5. In some such embodiments, Y is O. In some further such embodiments, Y is O, and Q_3 and Q_5 are each phenyl optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl) and CN. In some further such embodiments, R_2 is –CH=CH-, –CH_2-O- or –O-CH_2-; Y is O; and Q_3 and Q_5 are each phenyl optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl) and CN.

In some embodiments of the compounds of Formula I, Z is CH_2. In some such embodiments, X_1 and X_2 are each CH.

In some embodiments of the compounds of Formula I, Z is CH_2, X_1 and X_2 are each CH, and R_6 is -(L_5)-(5 to 14 membered heteroaromatic), optionally substituted with 1 to 3 substituents independently selected from H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl and CN.

In some embodiments of the compounds of Formula I, Z is CH_2, X_1 and X_2 are each CH, and R_2 is -L_3-Q_4; wherein Q_4 is phenyl or 4 to 9 membered carbocyclic, each of which is optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl) and CN.

In some embodiments of the compounds of Formula I, Z is CH_2, X_1 and X_2 are each CH, and R_2 is -L_3-Q_4; wherein Q_4 is phenyl or 4 to 9 membered carbocyclic, each of which is optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl) and CN; and R_6 is -(L_5)-(5 to 14 membered heteroaromatic), optionally substituted with 1 to 3 substituents independently selected from H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl and CN.

In some embodiments of the compounds of Formula I, Z is CH_2, X_1 and X_2 are each CH, and R_2 is -L_3-Q_4; wherein Q_4 is phenyl or 4 to 9 membered carbocyclic, each of which is optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl) and CN; and R_6 is (L_5)-(C_{6-14} aryl), optionally substituted with 1 to 3 substituents independently selected from H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl and CN.

In some embodiments of the compounds of Formula I, Z is CH_2, X_1 and X_2 are each CH, and R_2 is -L_3-Q_4; wherein Q_4 is phenyl, cyclopentyl, cyclohexyl, cyclopentenyl or cyclohexenyl, each of which is optionally substituted with 1 or 2 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl and -NH_2; and R_6 is pyrid-2-yl. In some such embodiments, R_1, R_4, R_{4a}, R_5, and R_{5a}, are each H, and L_3 is C_{2-3} alkynyl.

In some embodiments of the compounds of Formula I, Z is SO_2. In some such embodiments, X_1 and X_2 are each CH.

In some embodiments of the compounds of Formula I, Z is SO_2, X_1 and X_2 are each CH, and R_6 is -(L_5)-(5 to 14 membered heteroaromatic), optionally substituted with 1 to 3 substituents independently selected from H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl and CN.

In some embodiments of the compounds of Formula I, Z is SO_2, X_1 and X_2 are each CH, and R_2 is -L_3-Q_4; wherein Q_4 is phenyl or 4 to 9 membered carbocyclic, each of which is optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl and CN.

In some embodiments of the compounds of Formula I, Z is SO_2, X_1 and X_2 are each CH, and R_2 is -L_3-Q_4; wherein Q_4 is phenyl or 4 to 9 membered carbocyclic, each of which is optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl and CN; and R_6 is -(L_5)-(5 to 14 membered heteroaromatic), optionally substituted with 1 to 3 substituents independently selected from H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl and CN.

In some embodiments of the compounds of Formula I, Z is SO_2, X_1 and X_2 are each CH, and R_2 is -L_3-Q_4; wherein Q_4 is phenyl, cyclopentyl, cyclohexyl, cyclopentenyl or cyclohexenyl, each of which is optionally substituted with 1 or 2 substituents independently selected from C_{1-6} alkyl, halogen, OH, and OC_{1-6} alkyl; and R_6 is pyrid-2-yl. In some such embodiments, R_1, R_4, R_{4a}, R_5, and R_{5a}, are each H, and L_3 is C_{2-3} alkynyl.

In some embodiments of the compounds of Formula I, R_2 is -L_3-Q_4; Q_4 is 5 to 14 membered heteroaromatic optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl) and CN; and R_6 is -(L_5)-(5 to 14 membered heteroaromatic) optionally substituted with 1 to 3 substituents independently selected from H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl and CN.

In some embodiments of the compounds of Formula I, R_2 is -L_3-Q_4; Q_4 is 5 to 14 membered heteroaromatic optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl) and CN; and R_6 is -(L_5)-(5 to 14 membered

heteroaromatic) optionally substituted with 1 to 3 substituents independently selected from H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl and CN.

In some such embodiments, Q_4 is pyridyl, preferably pyrid-2-yl, optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl) and CN.

In some further such embodiments, R_6 is -(L_5)-(pyridyl), preferably -(L_5)-(pyrid-2-yl), optionally substituted with 1 to 3 substituents independently selected from H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl and CN.

In some further such embodiments, Z is CO. In some further such embodiments, X_1 is CR_3 and X_2 is CH. In some further such embodiments, R_1 is H. In some further such embodiments, R_4, R_{4a}, R_5, and R_{5a} are each H, and in some further such embodiments, R_1 is H.

In some embodiments of the compounds of Formula I, one or more of the following conditions a-g exist:

(a) if R_2 is -L_3-Q_4, L_3 is C_2 alkynyl, Q_4 is cyclohexanol-1-yl, Z is CO, R_1, R_4, R_{4a}, R_5, and R_{5a}, are each H, and X_1 and X_2 are each CH, then R_6 is not 2-methoxyphenyl;

(b) if R_2 is -L_3-Q_4, L_3 is C_2 alkynyl, Q_4 is phenyl, Z is CO, R_1, R_4, R_{4a}, R_5, and R_{5a}, are each H, and X_1 and X_2 are each CH, then R_6 is not pyrimidin-2-yl;

(c) if R_2 is -L_3-Q_4, L_3 is C_2 alkynyl, Q_4 is phenyl, Z is CO, R_1, R_4, R_{4a}, R_5, and R_{5a}, are each H, and X_1 and X_2 are each CH, then R_6 is not 3-trifluoromethylphenyl;

(d) if R_2 is -L_3-Q_4, L_3 is C_2 alkynyl, Q_4 is phenyl, Z is CO, R_1, R_4, R_{4a}, R_5, and R_{5a}, are each H, and X_1 and X_2 are each CH, then R_6 is not 2-methoxyphenyl;

(e) if R_2 is -L_3-Q_4, L_3 is C_2 alkynyl, Q_4 is phenyl, Z is CO, R_1, R_4, R_{4a}, R_5, and R_{5a}, are each H, and X_1 and X_2 are each CH, then R_6 is not pyrid-2-yl;

(f) if R_2 is -L_3-Q_4, L_3 is C_2 alkynyl, Q_4 is phenyl, Z is CO, R_1, R_4, R_{4a}, R_5, and R_{5a}, are each H, and X_1 and X_2 are each CH, then R_6 is not 2-fluorophenyl;

(g) if R_2 is -L_3-Q_4, L_3 is C_2 alkynyl, Q_4 is cyclohexanol-1-yl, Z is CO, R_1, R_4, R_{4a}, R_5, and R_{5a}, are each H, and X_1 and X_2 are each CH, then R_6 is not 4-nitrophenyl.

In some embodiments of the compounds of Formula I, all of the foregoing conditions a-g exist. In some embodiments of the compounds of Formula I, none of the foregoing conditions a-g exist. In some embodiments of the compounds of Formula I, one or more, but less than all of the foregoing conditions a-g exist.

Prodrugs of the compounds of Formula I are also embraced by the present invention. The term "prodrug", as used herein, means a compound which is convertible in vivo by metabolic means (e.g. by hydrolysis) to a compound of formula I. Various forms of prodrugs are known in the art, for example, as discussed in, for example, Bundgaard, (ed.), Design of Prodrugs, Elsevier (1985); Widder, et al. (ed.), Methods in Enzymology, vol. 4, Academic Press (1985); Krogsgaard-Larsen, et al. (ed.), "Design and Application of Prodrugs", Textbook of Drug Design and Development, Chapter 5, 113-191 (1991), Bundgaard, et al., Journal of Drug Deliver reviews, 8:1-38 (1992), Bundgaard, J. of Pharmaceutical Sciences, 77:285 et seq. (1988); and Higuchi and Stella (eds.) Prodrugs as Novel Drug Delivery Systems, American Chemical Society (1975), each of which is incorporated by reference in its entirety.

The mGluR5 negative allosteric modulators disclosed herein are useful for treating diseases and disorders including schizophrenia, paranoia, depression, including manic-depressive illness, anxiety (including panic disorders, social anxiety, obsessive compulsive disorders, generalized anxiety disorders, phobias), post-traumatic stress disorder, bipolar disorder, Asperger's syndrome, pervasive developmental disorders, gastrointestinal disorders such as gastroesophageal reflux disease, dyspepsia, irritable bowel syndrome, functional bloating, functional diarrhea, chronic constipation, functional disturbances of the biliary tract, migraine, chronic pain, fibromyalgia, neuropathic pain, post-herpatic neuropathic pain, addiction, Parkinson's disease, senile dementia, levadopa-induced dyskinesia, Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis, multiple sclerosis, Down Syndrome, fragile-X syndrome, autistic spectrum disorders, attention deficit hyperactivity disorder, stroke, ischemic injury, epilepsy, hypoglycemia and obesity.. Accordingly, in some embodiments, the invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a compound of Formula I, or a pharmaceutically acceptable salt, hydrate or prodrug thereof. In further embodiments, the invention provides methods of treating a patient suffering from a chronic condition such as schizophrenia, paranoia, manic-depressive illness or anxiety, comprising providing a therapeutically effective amount of compound of Formula I, or a pharmaceutically acceptable salt, hydrate, solvate or prodrug thereof.

Some compounds of the present invention can contain an asymmetric atom (also referred as a chiral center), and some of the compounds can contain one or more asymmetric atoms or centers, which can thus give rise to optical isomers (enantiomers) and diastereomers (geometric isomers). The present invention includes such optical isomers and diastereomers, as well as, the racemic and resolved, enantiomerically pure *R* and *S* stereoisomers, as well as, other mixtures of the *R* and *S* stereoisomers and pharmaceutically acceptable salts, hydrates, solvates, metabolites and prodrugs thereof. Optical isomers can be obtained in pure form by standard procedures known to those skilled in the art, and include, but are not limited to, chiral chromatography, diastereomeric salt formation, kinetic resolution, and asymmetric synthesis. The present teachings also encompass cis and trans or E/Z isomers of compounds containing alkenyl moieties (e.g., alkenes and imines). It is also understood that this invention encompasses all possible regioisomers, and mixtures thereof, which can be obtained in pure form by standard separation procedures known to those skilled in the art, and include, but are not limited to, column chromatography, thin-layer chromatography, and high-performance liquid chromatography.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium.

Compounds of the invention can also include tautomeric forms, such as keto-enol tautomers. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

As used herein, the term “alkyl” as a group or part of a group is intended to denote hydrocarbon groups including straight chain, branched and cyclic saturated hydrocarbons. Alkyl groups can contain 1-20, or 1-12, or 1-6 carbon atoms. The term “lower alkyl” is intended to mean an alkyl group having up to 6 carbon atoms. Nonlimiting examples of straight chain and branched alkyl groups include methyl (Me), ethyl (Et), propyl (e.g., n-propyl and isopropyl), butyl (e.g., n-butyl, isobutyl, s-butyl, and t-butyl), pentyl groups (e.g., n-pentyl, isopentyl, and neopentyl), hexyl groups, and the like.

The term “cycloalkyl” is intended to mean a monocyclic or bicyclic saturated hydrocarbon group having the indicated number of carbon atoms. For example, a C_3-C_8 cycloalkyl group would include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl groups, as well as polycyclic systems (e.g., containing fused, bridged, and/or spiro ring systems). Any

suitable ring position of a cyclic alkyl group can be covalently linked to the defined chemical structure. Unless otherwise indicated, alkyl groups are unsubstituted. However, where indicated, alkyl groups may be substituted with one or more independently selected substituents as described herein.

As used herein, the term "alkenyl" as a group or part of a group is intended to denote an alkyl group that contains at least one carbon-carbon double bond. Alkenyl groups can contain 2-20, or 2-12, or 2-6 carbon atoms. The term "lower alkenyl" is intended to mean an alkenyl group having up to 6 carbon atoms. Nonlimiting examples of straight chain and branched alkenyl groups include ethenyl, propenyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, vinyl, allyl, 2-methyl-allyl, 4-but-3-enyl, 4-hex-5-enyl, 3-methyl-but-2-enyl, cyclohex-2-enyl, and the like. The one or more carbon-carbon double bonds can be internal (such as in 2-butene) or terminal (such as in 1-butene). Additionally, hydrocarbon alkenyl moieties may be mono or polyunsaturated, and may exist in the E or Z configurations. The compounds of this invention are meant to include all possible E and Z configurations. Alkenyl groups may be substituted with one or more independently selected substituents as described herein.

The term "cycloalkenyl" is intended to mean a cycloalkyl group that contains at least one carbon-carbon double bond. Examples of cycloalkenyl groups include, but are not limited to, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, and the like. Alkenyl groups may be substituted with one or more independently selected substituents as described herein. Any suitable ring position of a cycloalkenyl group can be covalently linked to the defined chemical structure. Unless otherwise indicated, alkenyl groups are unsubstituted. However, where indicted, alkenyl groups may be substituted with one or more independently selected substituents as described herein.

As used herein, the term "alkynyl" is intended to denote an alkyl group that contains at least one carbon-carbon triple bond. Alkynyl groups can contain 2-20, or 2-12, or 2-6, or 2-3 carbon atoms. Examples of alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, pent-2-yne, ethynyl-cyclohexyl, and the like. The one or more carbon-carbon triple bonds can be internal (such as in 2-butyne) or terminal (such as in 1-butyne). Alkynyl groups may be substituted with one or more independently selected substituents as described herein.

As used herein, the term "aryl" as a group or part of a group refers to an aromatic monocyclic hydrocarbon ring system or a polycyclic ring system (e.g., bicyclic or tricyclic), e.g., of

6-14 carbon atoms where at least one of the rings present in the ring system is an aromatic hydrocarbon ring and any other aromatic rings present in the ring system include only hydrocarbons. Any suitable ring position of the aryl group can be covalently linked to the defined chemical structure. In some embodiments, an aryl group can have only aromatic carbocyclic rings e.g., phenyl, 1-naphthyl, 2-naphthyl, anthracenyl, phenanthrenyl groups, and the like. In other embodiments, an aryl group can be a polycyclic ring system in which at least one aromatic carbocyclic ring is fused (i.e., having a bond in common with) to one or more cyclic alkyl or heterocyclic alkyl rings, provided that the group is attached to the remainder of the molecule through the aromatic portion thereof. Examples of such aryl groups include, among others, benzo derivatives of cyclopentane (i.e., an indanyl group, which is a 5,6-bicyclic cyclic alkyl/aromatic ring system), cyclohexane (i.e., a tetrahydronaphthyl group, which is a 6,6-bicyclic cyclic alkyl/aromatic ring system), imidazoline (i.e., a benzimidazolinyl group, which is a 5,6-bicyclic heterocyclic alkyl/aromatic ring system), and pyran (i.e., a chromenyl group, which is a 6,6-bicyclic heterocyclic alkyl/aromatic ring system). Other examples of aryl groups include, but are not limited to, benzodioxanyl, benzodioxolyl, chromanyl, indolinyl groups, and the like.

In some embodiments, an aryl group can be substituted with one or more (e.g., up to 4) independently selected substituents as described herein.

As used herein, the terms, “carbocyclyl”, “carbocycle” or “carbocyclic” refer to (1) a non-aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms. In some embodiments ("C_{3-8} carbocyclyl"), a carbocyclyl group can have from 3 to 8 ring carbon atoms. In some embodiments ("C_{3-6} carbocyclyl"), a carbocyclyl group can have from 3 to 6 ring carbon atoms. Examples of such C_{3-6} carbocyclyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cyclohexadienyl and the like. Examples of such C_{3-8} carbocyclyl groups include the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl, cycloheptadienyl, cycloheptatrienyl, cyclooctyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl and the like. Examples of such C_{3-10} carbocyclyl groups include the aforementioned C_{3-8} carbocyclyl groups as well as octahydro-1*H*-indenyl, decahydronaphthalenyl, spiro[4.5]decanyl and the like. As the foregoing examples illustrate, in some embodiments a carbocyclyl group can be monocyclic ("monocyclic carbocyclyl") or bicyclic (e.g., containing a fused, bridged or spiro ring system), and can be saturated or can contain one or more carbon-carbon double or triple bonds. "Carbocyclyl" also refers to (2) a phenyl group; (3) an aryl group (as defined herein); and (4) a 5- or 6-membered heteroaryl group (as defined herein) fused to a monocyclic carbocyclyl group,

where the point of attachment is on the carbocyclyl portion of the group. Examples of such carbocyclyl groups include 1,2,3,4-tetrahydronaphthalen-1-yl, 1,2,3,4-tetrahydronaphthalen-2-yl, 2,3-dihydro-1H-inden-1-yl, 2,3-dihydro-1H-inden-2-yl, 1H-inden-1-yl, 5,6,7,8-tetrahydroquinolin-5-yl, 5,6,7,8-tetrahydroquinolin-7-yl, 4,5,6,7-tetrahydro-1H-indol-4-yl, 4,5,6,7-tetrahydro-1H-indol-6-yl, 4,5,6,7-tetrahydrobenzofuran-7-yl and the like.

The term "heterocyclic" or "heterocyclic group" or "heterocycle" is used herein to describe a 3-14 membered monocyclic or polycyclic, ring system having at least 1, and up to 4, ring heteroatoms independently selected from N, O and S. Heterocyclic groups can be saturated, partially unsaturated, or wholly unsaturated, but cannot be aromatic. When the heterocyclic ring contains nitrogen or sulfur atoms in the backbone of the ring, the nitrogen or sulfur atoms can be oxidized, for example, N-oxides, SO or SO_2. Heterocyclic groups include, without limitation, oxygen-containing rings, nitrogen-containing rings, sulfur-containing rings, and mixed heteroatom-containing rings. Nonlimiting examples of heterocyclic groups include aziridinyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothienyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, dihydro-1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydroquinolinyl, and tetrahydroisoquinolinyl.

The term "heteroaromatic" as used herein is intended to denote 3-14 membered monocyclic or polycyclic ring systems having at least one aromatic ring that contains at least 1, and up to 4, ring heteroatoms independently selected from N, O and S. Heteroaromatic groups can contain one or more non-aromatic rings fused to (i.e., sharing a bound in common with) the monocyclic or polycyclic heteroatom-containing ring described above, provided that the group is attached to the remainder of the molecule through the aromatic portion thereof. Thus, the term "heteroaromatic" includes groups such as 5,6,7,8-tetrahydroquinolin-2-yl groups. Further examples of heteroaromatic groups include furyl, thienyl, pyridyl, pyrrolyl, oxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, isoxazolyl, triazolyl, oxadiazolyl, pyrimidinyl, pyrazinyl, indolyl, benzimidazolyl, benzothiophenyl, quinolinyl, isoquinolinyl, quinoxalinyl, and benzothiazolyl.

The term “optionally substituted” is used herein to refer to the optional substitution of one or more protons with a named substituent or substituents.

The term “alkoxy” as used herein refers to a group of formula –O-alkyl. Examples of alkoxy groups include but are not limited to methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, neopentoxy, tertiary pentoxy, hexoxy, isohexoxy, heptoxy, octoxy, prop-2-oxy, but-2-oxy and methylprop-2-oxy.

The term “halogen” refers to Cl, Br, F, and I.

The term “haloalkyl” is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen atom. Haloalkyl groups include perhaloalkyl groups, wherein all hydrogens of an alkyl group have been replaced with halogens (e.g., $-CF_3$, $-CF_2CF_3$). The halogens can be the same (e.g., CHF_2, $-CF_3$) or different (e.g., CF_2Cl). Haloalkyl groups can optionally be substituted with one or more substituents in addition to halogen. Examples of haloalkyl groups include, but are not limited to, fluoromethyl, dichloroethyl, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl groups.

Methods of treating the diseases and syndromes listed herein are understood to involve administering to an individual in need of such treatment a therapeutically effective amount of a compound of the invention, or a salt, hydrate or solvate thereof, or a composition comprising one or more of the same. Accordingly, methods are provided in accordance with the invention for treating disorders involving the mGluR5 receptor, such as anxiety and depression diseases and/or disorders, including those specifically listed above, comprising the administration to a patient in need thereof a compound of the invention, or a pharmaceutically acceptable salt, hydrate or solvate thereof. Such methods comprise administering to the patient in need of such treatment a pharmaceutically or therapeutically effective amount of a compound of this invention. In the instances of combination therapies described herein, it will be understood the administration further includes a pharmaceutically or therapeutically effective amount of the second pharmaceutical agent in question. The second or additional pharmacological agents described herein may be administered in the doses and regimens known in the art.

As used herein, the phrase “therapeutically effective amount” refers to the amount of active compound or pharmaceutical agent that is effective to treat the condition of interest – i.e., the amount of active compound or pharmaceutical agent that is effective to elicit a biological or

medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following:

(1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease;

(2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting or slowing further development of the pathology and/or symptomatology); and

(3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

When administered for the treatment or inhibition of a particular disease state or disorder, it is understood that the effective dosage may vary depending upon the particular compound utilized, the mode of administration, the condition, and severity thereof, of the condition being treated, as well as the various physical factors related to the individual being treated. Effective administration of the compounds (including the salts) and the compositions of the present invention may be given at an oral dose of from about 0.1 mg/day to about 1,000 mg/day. Preferably, administration will be from about 10 mg/day to about 600 mg/day, more preferably from about 50 mg/day to about 600 mg/day. The dosing regimen can be adjusted to provide the optimal therapeutic response, and the projected daily dosages are expected to vary with route of administration. Several divided doses can be delivered daily or a single daily dosage can be delivered. The dose can be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation.

As used herein, the term “individual” or “patient,” used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

Therapeutic doses of compounds or compositions of the invention can be administered in any manner useful in directing the active compounds herein to the recipient's bloodstream. For example, compounds and compositions of the invention can be delivered by a route such as oral,

via implants, dermal, transdermal, intrabronchial, intranasal, parental (including intravenous, intraperitoneal, intraarticularly and subcutaneous injections), intraperitoneal, sublingual, intracranial, epidural, intratracheal, vaginal, rectal, topical, ocular (via eye drops) or by sustained release. Optionally, one or more of the compounds of Formula I can be mixed with other active agents.

When the compound is delivered orally, it can be sub-divided in a dose containing appropriate quantities of the active ingredient. The unit dosage forms can be packaged compositions, for example, packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form. The powders and tablets can contain up to 99% of the active ingredient.

The compounds of Formula I can be combined with one or more pharmaceutically acceptable carriers or excipients including, without limitation, solid and liquid carriers, which are compatible with the compounds of Formula I. Oral formulations containing the active compounds (including the salts, hydrates and solvates thereof) and the compositions of the present invention may comprise any conventionally used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. Such carriers can include adjuvants, syrups, elixirs, diluents, binders, lubricants, surfactants, granulating agents, disintegrating agents, emollients, solubilizers, suspending agents, fillers, glidants, compression aids, encapsulating materials, emulsifiers, buffers, preservatives, thickening agents, colors, viscosity regulators, stabilizers, osmoregulators, and combinations thereof. Optionally, one or more of the compounds of Formula I can be mixed with other active agents.

Adjuvants can include, without limitation, flavoring agents, sweeteners, coloring agents, preservatives, and supplemental antioxidants, which can include vitamin E, ascorbic acid, butylated hydroxytoluene (BHT) and butylated hydroxyanisole (NHA).

Elixirs and syrups can be prepared from acceptable sweeteners such as sugar, saccharine or a biological sweetener, a flavoring agent, and/or solvent.

Capsules and tablets may contain mixtures of the active compound(s) with inert fillers, diluents, binders, lubricants, granulating agents, disintegrating agents, emolients, surface modifying agents (including surfactants), suspending or stabilizing agents, and the like. Nonlimiting examples of diluents and fillers include materials in which the compound can be

dispersed, dissolved, or incorporated, such as water, lower monovalent alcohols, polyhydric alcohols, and low molecular weight glycols and polyols, including, for example, propylene glycol, glycerol, butylenes glycol, 1,2,4-butanetriol, sorbitol esters, 1,2,6-hexanetriol, ethanol, isopropanol, butanediol, ethyl oleate, isopropyl myristate, ether propanol, ethoxylated ethers, propoxylated ethers, oils such as corn, peanut, fractionated coconut, arachis, sesame oils, dimethylsulfoxide (DMSO), dimethylformamide (DMF), waxes, dextrin, and combinations thereof. Examples of binders include, without limitation, cellulose, methylcellulose, hydroxymethylcellulose, polypropylpyyrolidone, polyvinylpyrrolidone, polyvinylpyrrolidine, gelatin, gum Arabic, polyethylene glycol, starch, sugars such as, for example, sucrose kaoline, cellulose kaolin, and lactose. Nonlimiting examples of surface modifying agents include, but are not limited to, poloxamer 188, benzalkonium chloride, calcium stearate, cetostearl alcohol, sorbitan esters, colloidal, silicon dioxide, phosphates, sodium dodecylsulfate, magnesium aluminum silicate, lauryl sulfates, and triethanolamine. Examples of lubricants include, without limitation, magnesium stearate, light anhydrous silicic acid, talc and sodium lauryl sulfate. Examples of granulating agents include, without limitation, silicon dioxide, microcrystalline cellulose, starch, calcium carbonate, pectin, crospovidone, and polyplasdone. Examples of disintegrating agents include, without limitation, pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), carboxymethylcellulose, hydroxypropylstarch, substituted hydroxypropylcellulose, sodium bicarbonate, calcium phosphate, and calcium citrate. Examples of emollients include, without limitation, stearyl alcohol, mink oil, cetyl alcohol, oleyl alcohol, isopropyl laurate, polyethylene glycol, olive oil, petroleum jelly, palmitic acid, oleic acid, and myristyl myristate.

Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surface modifying agents (including surfactants), suspending or stabilizing agents as described above.

Oral formulations herein may utilize standard delay or time-release formulations to alter the absorption of the active compound(s). The oral formulation may also consist of administering the active ingredient in water or a fruit juice, containing appropriate solubilizers or emulsifiers as needed.

In some cases it may be desirable to administer the compounds (including the salts) and the compositions of the present invention directly to the airways in the form of an aerosol.

The compounds (including salts, hydrates and solvates) and the compositions of the present invention may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds (including the salts) and the compositions of the present invention can be prepared in water optionally mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to inhibit the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

For the purposes of this disclosure, transdermal administrations are understood to include all administrations across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such administrations may be carried out using the present compounds, or pharmaceutically acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

Transdermal administration may be accomplished through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non-toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semi-permeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

In some embodiments, sustained delivery devices can be used, in order to avoid the necessity to take medications on a daily basis. The term “sustained delivery” is used herein to refer to delaying the release of an active agent, i.e., a compound of Formula I, until after placement in a delivery environment, followed by a sustained release of the agent at a later time. A number of sustained delivery devices are known in the art and include, for example, hydrogels (U.S. Pat. Nos. 5,266,325; 4,959,217; 5,292,515), osmotic pumps (U.S. Pat. Nos. 4,295,987 and 5,273,752 and European Pat. No. 314,206, among others; hydrophobic membrane materials, such as ethylenemethacrylate (EMA) and ethylenevinylacetate (EVA); bioresorbable polymer systems (International Patent Publication No. WO 98/44964 and U.S. Pat. Nos. 5,756,127 and 5,854,388); and other bioresorbable implant devises composed of, for example, polyesters, polyanhydrides, or lactic acid/glycolic acid copolymers (U.S. Pat. No. 5,817,343). For use in such sustained delivery devices, the compounds of the invention can be formulated as described herein.

Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water-soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

Additional numerous various excipients, dosage forms, dispersing agents and the like that are suitable for use in connection with the salt forms of the invention are known in the art and described in, for example, *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, which is incorporated herein by reference in its entirety.

The compounds of Formula I have utility for the repression and/or treatment of disorders involving the mGluR5 receptor, such as anxiety and depression disorders. Examples of disorders or conditions which can be treated by the compounds, compositions and methods of this invention include anxiety and depression disorders. Anxiety disorders can include, for example, generalized anxiety disorder, panic disorder, PTSD, and social anxiety disorder. Depression disorders can include, for example, depression in cancer patients, depression in Parkinson’s patients, post-mycardial infarction depression, depression in patients with human immunodeficiency virus (HIV), Subsyndromal Symptomatic depression, depression in infertile women, pediatric depression, major depression, single episode depression, recurrent depression, child abuse induced depression, post partum depression, DSM-IV major depression, treatment-refractory major depression, severe depression, psychotic depression, post-stroke depression,

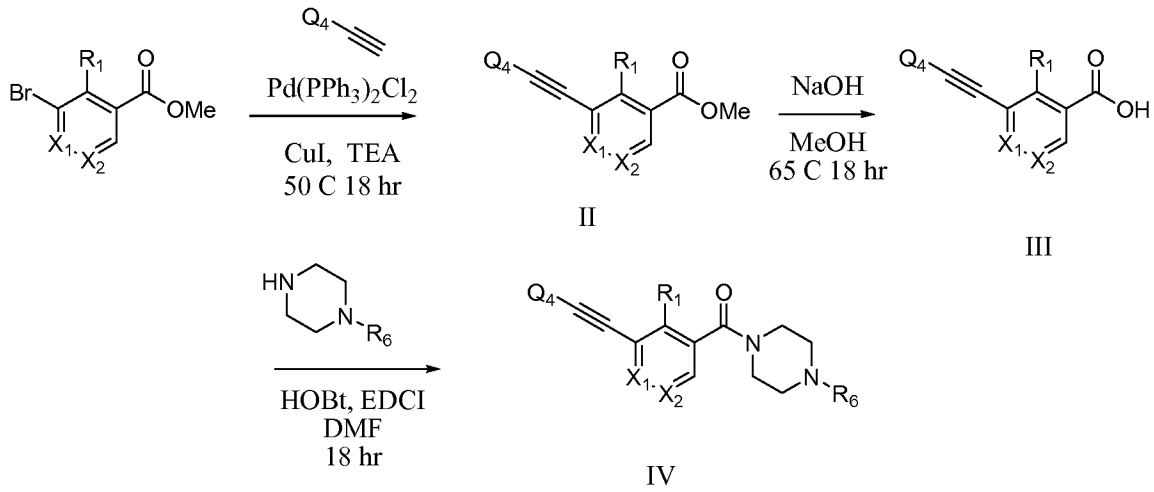
neuropathic pain, manic depressive illness, including manic depressive illness with mixed episodes and manic depressive illness with depressive episodes, seasonal affective disorder, bipolar depression BP 1, bipolar depression BP II, or major depression with dysthymia.

Preparation of Compounds of the Invention

General Preparative Schemes

Compounds of the invention can be prepared using the six general schemes outlined below, together with synthetic methods known in the synthetic organic arts or variations of these methods by one skilled in the art. See, Comprehensive Organic Synthesis, "Selectivity, Strategy & Efficiency in Modern Organic Chemistry", ed., I. Fleming, Pergamon Press, New York (1991); Comprehensive Organic Chemistry, "The Synthesis and Reactions of Organic Compounds", ed. J.F. Stoddard, Pergamon Press, New York (1979).

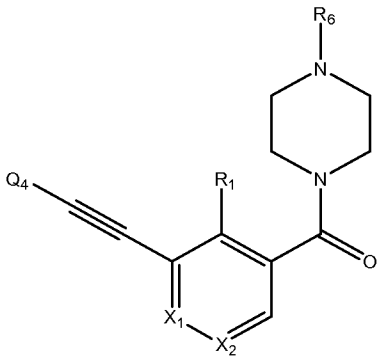
In some embodiments, compounds of the invention are produced in accordance with Scheme 1 below. Unless otherwise indicated, the constituent variables of the following Schemes are as defined above.



Scheme I

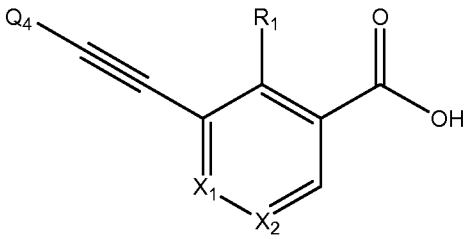
In accordance with Scheme 1, Sonagashira coupling of bromoaromatics with alkenes using Pd and catalytic CuI in TEA is used to produce the desired acetylenes (II) (Matsunaga, N. *et al. Bioorg. Med. Chem.* **2004**, *12*, 2251). Basic hydrolysis using NaOH in aqueous methanol produces acid (III). Reaction of the acid (III) with N-substituted piperazines using EDCI peptide coupling conditions (Rich, D. H. *et al.*, *Peptides (New York, 1979-1987)* **1979**, *1*, 241-261) produced the target compounds (IV).

Accordingly, in some embodiments, the invention provides a method for preparing compound a compound of Formula IV:



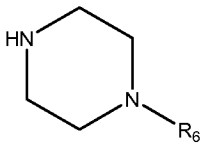
IV

comprising reacting a compound of Formula III:



III

with an N-substituted piperazine of Formula IIIa:

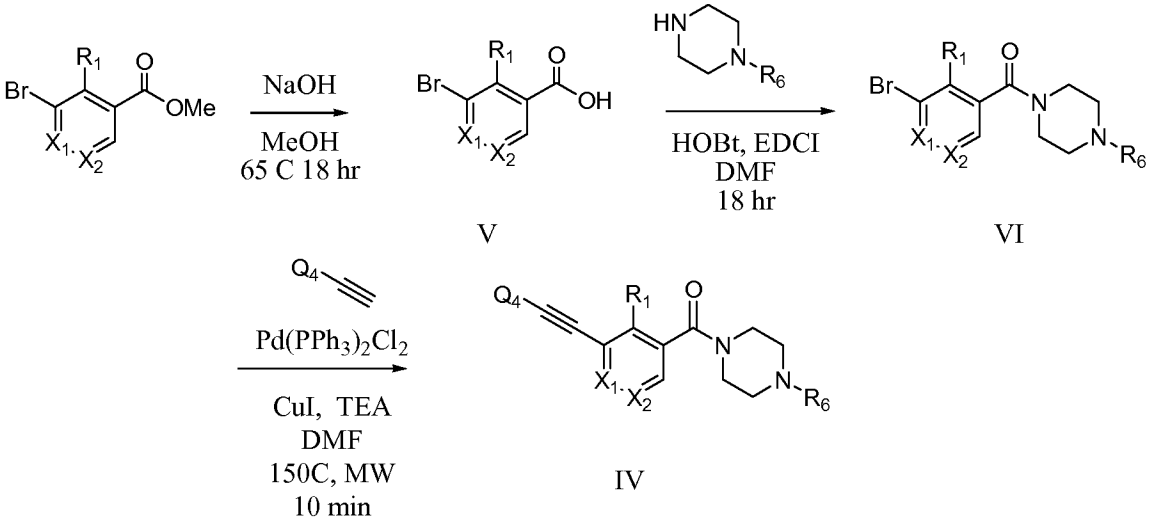


IIIa

for a time and under conditions effective to form the compound of Formula IV;

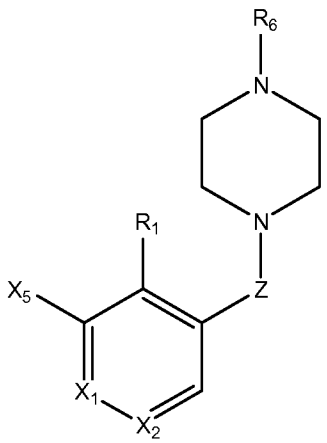
wherein X_1, X_2, R_6 , R_1 and Q_4 are as defined above.

In some embodiments, compounds of the invention are produced in accordance with Scheme 2 below.



Scheme 2

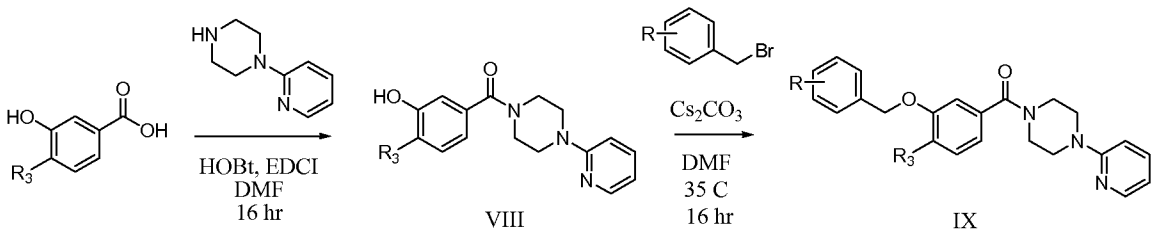
In this procedure, basic hydrolysis using NaOH in aqueous methanol produces an acid (V). The acid (V) is reacted with N-substituted piperazines using EDCI peptide coupling conditions (Rich, D. H. *et al.*, *Peptides (New York, 1979-1987)* **1979**, *1*, 241-261) producing amides (VI). Sonagashira coupling of Bromoaromatics (VI) with Acetylenes using $Pd(PPh_3)_2Cl_2$ in the presence of CuI and TEA under microwave conditions produced the desired target compounds (IV) (see WO 2005/123713). Accordingly, in some embodiments, processes are provided for preparing a compound of Formula IV comprising reacting a compound of Formula VI:



VI

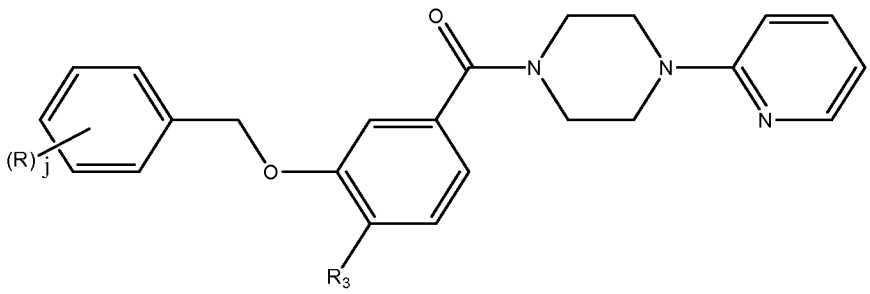
where the R_r, R_6, X_1, X_2 and Z variables are as described above and X_5 is halogen or bromine, with an acetylene of Formula Q_4-CCH, in the presence of a palladium triphenyphosphine-containing catalyst for a time and under conditions effective to form a compound of Formula IV. In some embodiments, the palladium triphenyphosphine-containing catalyst is $Pd(PPh_3)_2Cl_2$.

In further embodiments, compounds of the invention having the general Formula IX are produced in accordance with Scheme 3 below.



Scheme 3

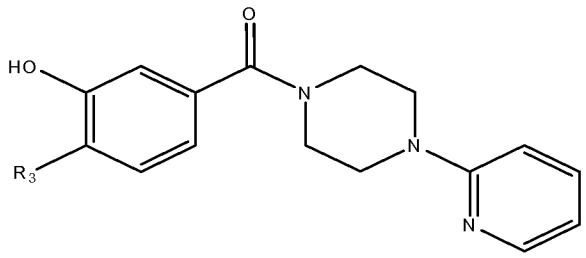
In accordance with Scheme 3, reaction of benzoic acids with N-substituted piperazines using EDCI peptide coupling conditions (Rich, D. H. *et al.*, *Peptides (New York, 1979-1987)* **1979**, *1*, 241-261) produced amides (VIII). Subsequent alkylation of the phenol (VIII) with Cs_2CO_3 and the benzyl bromide derivatives produced the desired target compounds (IX). Accordingly, in some embodiments, processes are provided for preparing compounds of Formula IX:



IX

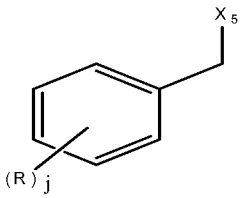
wherein R_3 is as defined above, R is C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl $-NH_2$, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl) or CN; and j is 0, 1, 2, or 3;

comprising reacting a compound of Formula VIII:



VIII

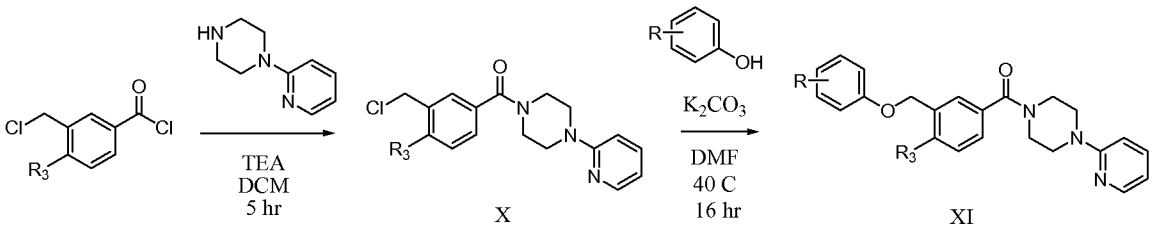
with a benzyl halide derivative of Formula VIIIa:



VIIIa

where X_5 is halogen, for a time and under conditions effective to form the compound of Formula IX. In some embodiments, X_5 is bromine.

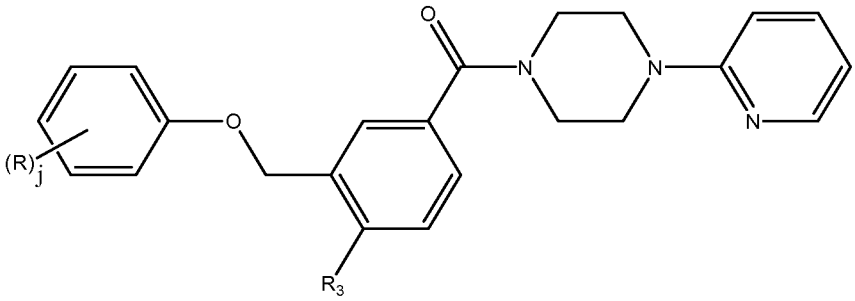
In further embodiments, compounds of the invention having the general Formula XI are produced in accordance with Scheme 4 below.



Scheme 4

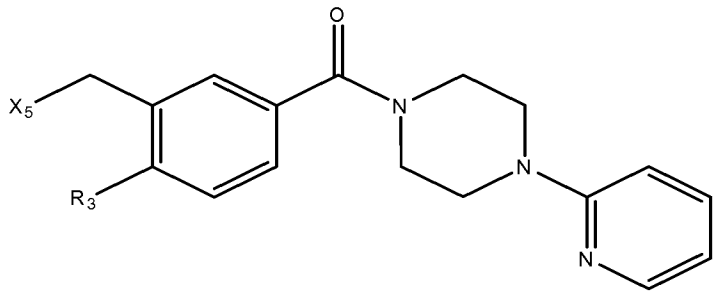
In accordance with Scheme 4, acid chlorides are reacted with N-substituted piperazines using TEA in DCM producing an amide (X). Alkylation of the resulting benzyl chloride (X) with phenol derivatives and K_2CO_3 produced the desired target compounds (XI).

Accordingly, in some embodiments, processes are provided for preparing compounds of Formula XI:



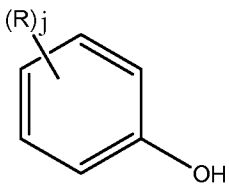
XI

comprising reacting a compound of Formula X:



X

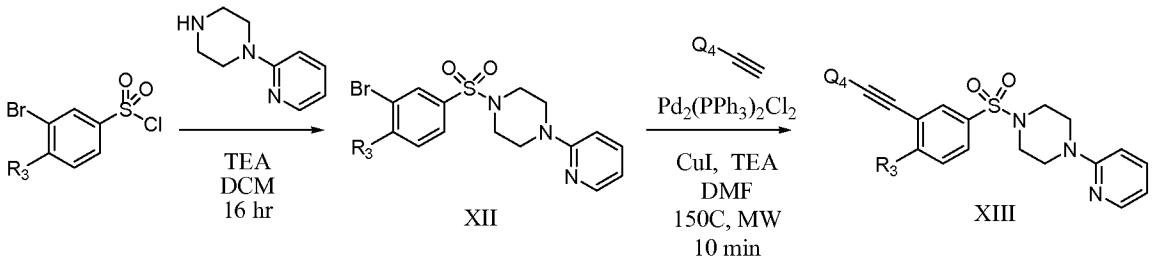
with a phenol derivative of Formula Xa:



Xa

for a time and under conditions effective to form the compound of Formula XI; wherein the constituent variables are as defined above.

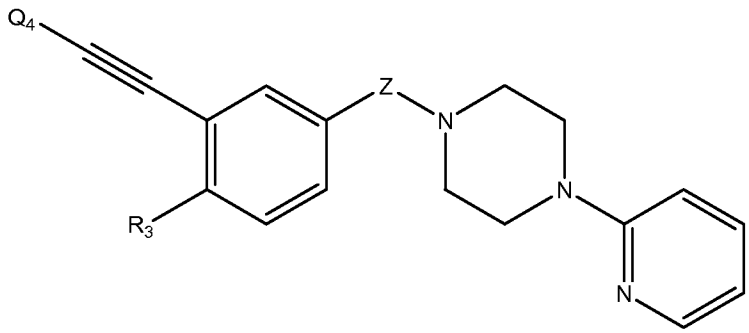
In further embodiments, compounds of the invention having the general Formula XII are produced in accordance with Scheme 5 below.



Scheme 5

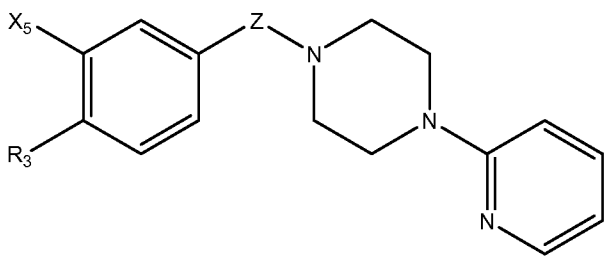
In accordance with Scheme 5, reaction of sulfonyl chlorides with N-substituted piperazines using TEA in DCM produced sulfonamides (XII). Sonagashira coupling of bromoaromatics (XII) with acetylenes using $Pd(PPh_3)_2Cl_2$ in the presence of CuI and TEA under microwave conditions produced the desired target compounds (XIII) (see WO 2005/123713).

Accordingly, in some embodiments, processes are provided for preparing a compound of Formula XIII:



XIII

comprising reacting a compound of Formula XII:

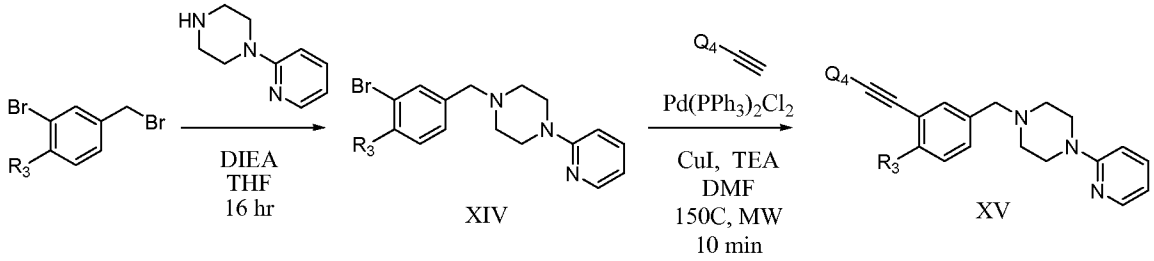


XII

wherein the constituent variables are as defined above, and X_5 is halogen, with an acetylene of Formula Q_4-CCH; in the presence of a palladium triphenyphosphine-containing catalyst for a time

and under conditions effective to form the compounds of Formula XII. In some embodiments, the palladium triphenyphosphine-containing catalyst is $Pd(PPh_3)_2Cl_2$.

In further embodiments, compounds of the invention having the general Formula XV are produced in accordance with Scheme 6 below.



Scheme 6

In accordance with Scheme 6, reaction of benzyl bromides with N-substituted piperazines using DIEA in THF produced benzyl piperazines (XIV). Sonagashira coupling of bromoaromatics (XIV) with acetylenes using Pd $(PPh_3)_2Cl_2$ in the presence of CuI and TEA under microwave conditions produced the desired product (XV) (see WO 2005/123713). Accordingly, in some embodiments, processes are provided for preparing compounds of Formula XV, wherein the constituent variables are as defined above, comprising reacting a compound of Formula XIV with an acetylene as shown in Scheme 6, in the presence of a palladium triphenyphosphine-containing catalyst, for example $Pd(PPh_3)_2Cl_2$, for a time and under conditions effective to form the compound of Formula XV.

Analytical Methods

The following methods were used for the characterization of compounds appearing in the Examples below.

Standard LCMS Conditions for Compound Characterization:

HPLC Conditions: Instrument - Agilent 1100

Column: Thermo Aquasil C18, 50 x 2.1 mm, 5 µm

Mobile Phase A: 0.1% Formic Acid in water

B: 0.1% Formic Acid in ACN

Flow Rate: 0.800 mL/min

Column Temperature: 40°C

Injection Volume: 5 mL

UV: monitor 215, 230, 254, 280, and 300 nm

Purity is reported at 254 nm unless otherwise noted.

Gradient Table:

Time (min)	%B
0	0
2.5	100
4.0	100
4.1	0
5.5	0

MS Conditions: Instrument: Agilent MSD; Ionization Mode: API-ES; Gas Temperature: 350°C; Drying Gas: 11.0 L/min.; Nebulizer Pressure: 55 psig; Polarity: 50% positive, 50% negative; VCap: 3000 V (positive), 2500 V (negative); Fragmentor: 80 (positive), 120 (negative); Mass Range: 100 – 1000 m/z; Threshold: 150; Step size: 0.15; Gain: 1; Peak width: 0.15 minutes.

Preparative reverse-phase HPLC (RP-HPLC): Compounds were in dissolved in 2 mL of 1:1 DMSO:MeCN, filtered through a 0.45 µm GMF, and purified on a Gilson HPLC, using a Phenomenex LUNA C_{18} column: 60 mm x 21.2 mm I.D., 5 um particle size: with ACN/H_2O (containing 0.2% TFA) gradient elution (95:5 H_2O:MeCN to 10:90 H_2O:MeCN; 8 minute run.

Determination of Activity Of Compounds

Compounds of the invention were prepared and analyzed to identify affinity at the rat mGluR5 receptor, based on their ability to displace [^{3}H] labeled 2-methyl-6-(phenylethyl)-pyridine ("MPEP"; a mGluR5 selective negative allosteric modulator) from Hek-293 cell membranes expressing a rat mGluR5 receptor.

MGluR5 expressing HEK-293 cells were scraped off a plate, transferred to centrifuge tubes and washed twice by centrifugation (2000 rpm for 10 minutes, at 4°C) in buffer (50 mM Tris pH 7.5). The resulting pellets were aliquoted and stored at minus 80°C. On the day of assay, the cells were thawed on ice and re-suspended in buffer. The binding assay was performed in a 96 well microtiter plate in a total volume of 250 µm. Non-specific binding was determined in the presence of 10 µM MPEP. The binding reaction included a final radioligand [^{3}H]-MPEP

concentration of 4 nM and 12-25 μg membrane protein per well. Following a 60 minute incubation at room temperature, the reaction was terminated by the addition of ice cold buffer and rapid filtration through a GF/B filter that had been presoaked for 30 minutes in 0.5% PEI. Compounds were initially tested in a single point assay to determine percent inhibition at 10 μM. Subsequently, K_i values were determined for compounds considered to be active.

Percent inhibition and K_i values were generated by GraphPad Prism and Excel Fit. IC_{50} values were calculated using GraphPad by fitting to a 1 or 2 site-binding model. K_i values were calculated from the apparent IC_{50} values using the Cheng-Prussof Equation (Biochem. Pharmacol. 22:3099-3108, 1973):

$$K_i = IC_{50} / 1+([L]/K_d)$$

where [L] is the concentration of free radioligand and K_d is the dissociation constant of radioligand for the receptor.

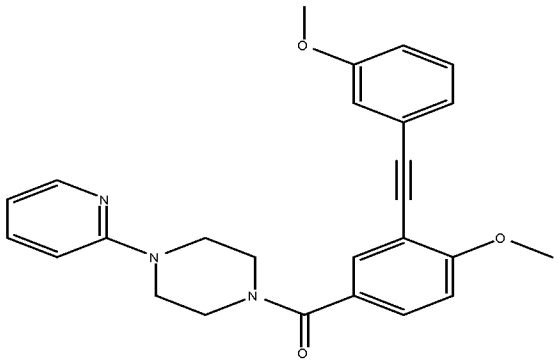
Preparation of Exemplary Compounds

The following examples are provided to illustrate the production and activity of representative compounds of the present teachings and to illustrate their performance in a screening assay. One skilled in the art will appreciate that although specific reagents and conditions are outlined in the following examples, these reagents and conditions are not a limitation on the present teachings. In the following examples, chemical structures and names were produced using Chemdraw v 7.0.3. In any conflict between chemical nomenclature and structure, the structure should prevail.

EXAMPLES

Example 1

1-{4-methoxy-3-[(3-methoxyphenyl)ethynyl]benzoyl}-4-pyridin-2-ylpiperazine (Compound 17)



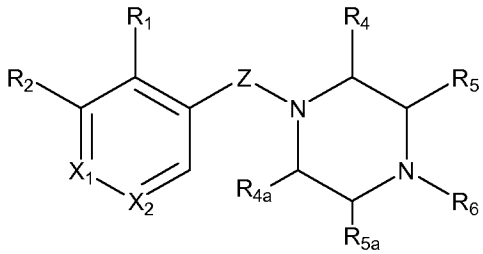
Step 1: (3-bromo-4-methoxyphenyl)(4-(pyridine-2-yl)piperazin-1-yl)methanone

1-(pyridin-2-yl)piperazine (13 mmol) was added to a solution of 3-bromo-4-methoxybenzoic acid (8.7 mmol) in DMF (100 mL) and DIEA (17.4 mmol). The solution was allowed to stir at room temperature for 10 minutes, and then HOBt (13 mmol) and 1-(3-(dimethylamino)propyl)-3-ethyl-carbodiimide hydrochloride (WSCDI) (13 mmol) were added. The reaction was allowed to stir at room temperature for 16 hours, at which time Liquid Chromatography – Mass Spectrophotometry (LCMS) analysis indicated the reaction was complete. The solution was diluted with 100 mL ethyl acetate (EtOAc) and washed with 100 mL water. The organic layer was dried over $MgSO_4$, and concentrated in vacuo. Purification via silica column chromatography (Hex:EtOAc as eluent) produced the intermediate compound (3-bromo-4-methoxyphenyl)(4-(pyridin-2-yl)piperazin-1-yl)methanone.

Step 2: 1-{4-methoxy-3-[(3-methoxyphenyl)ethynyl]benzoyl}-4-pyridin-2-ylpiperazine (Compound 17)

To a solution of (3-bromo-4-methoxyphenyl)(4-(pyridin-2-yl)piperazin-1-yl)methanone (0.15 mmol) and 3-ethynylanisole (0.23 mmol) in DMF (2 mL) in a microwave vial was added copper iodide (0.03 mmol) and TEA (0.45 mmol). $Pd(PPh_3)_2Cl_2$ (0.03 mmol) was added to the resulting suspension, and the vial was purged with N_2, capped, and microwaved for 10 minutes at 150°C. The solution was concentrated on a speedvac and purified via preparative HPLC (Gilson with NH_4OH additive) to produce the title compound. LCMS Rt = 1.84 min (MS = 370).

Compounds 1-68, shown in Tables 1 and 1A below, were prepared using the procedure of Example 1 described above.

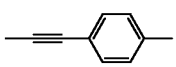
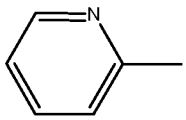
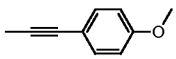
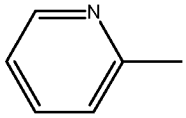
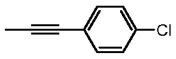
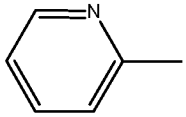
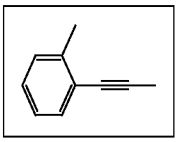
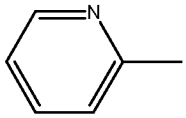
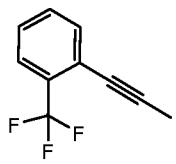
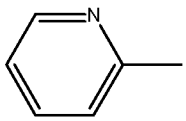
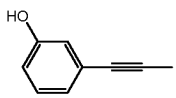
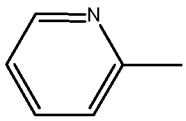


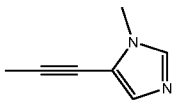
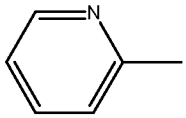
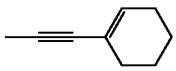
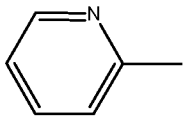
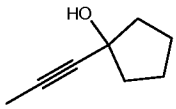
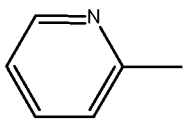
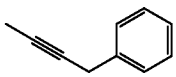
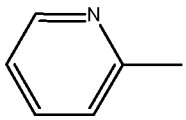
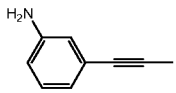
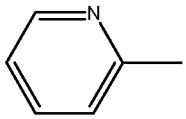
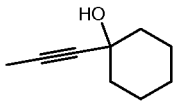
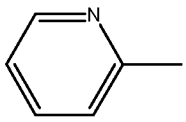
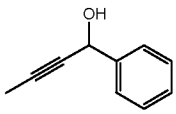
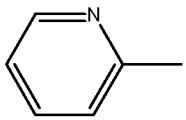
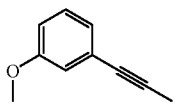
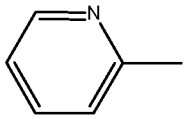
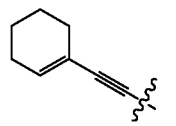
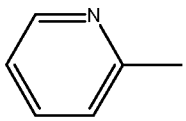
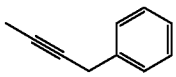
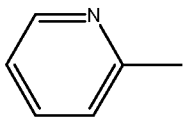
I

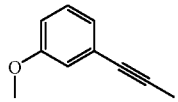
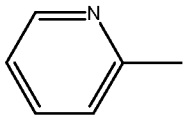
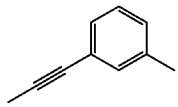
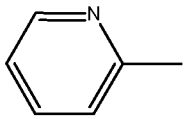
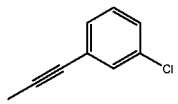
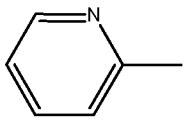
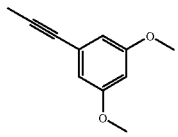
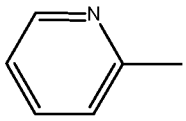
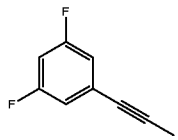
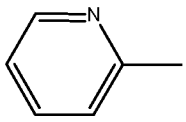
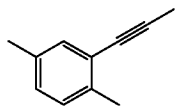
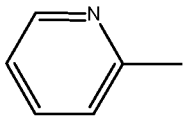
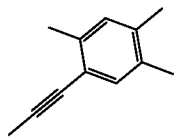
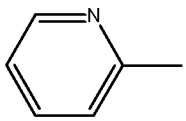
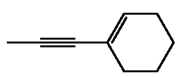
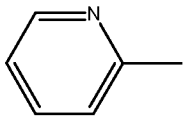
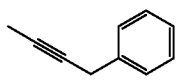
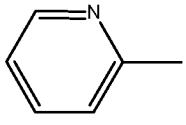
THE FOLLOWING VALUES REFER TO FORMULA I

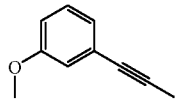
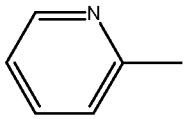
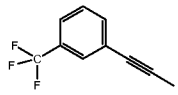
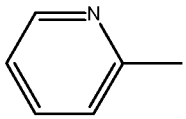
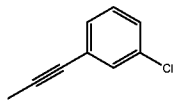
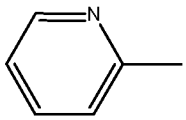
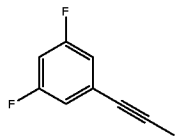
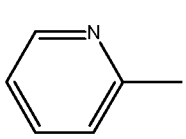
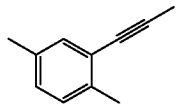
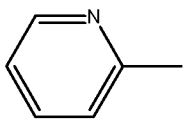
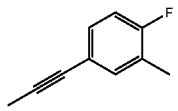
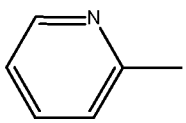
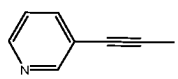
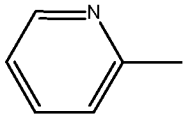
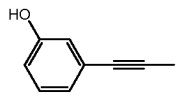
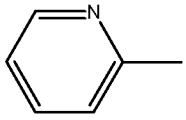
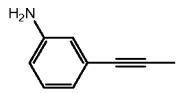
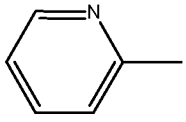
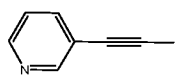
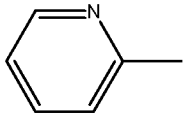
WHEREIN R_1, R_4, R_{4a}, R_5, R_{5a} = H; X_2 = CH; Z = CO

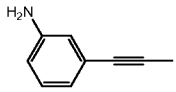
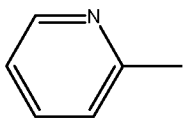
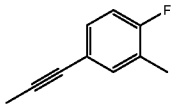
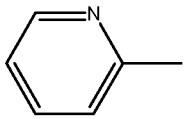
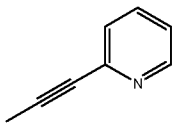
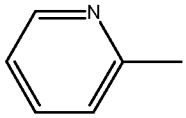
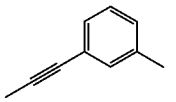
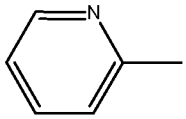
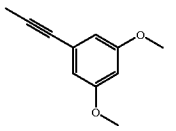
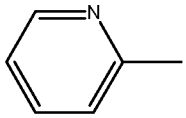
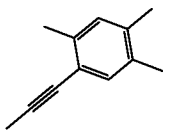
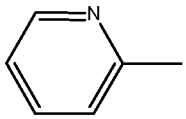
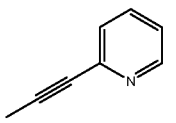
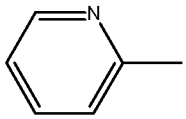
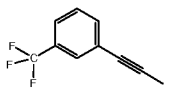
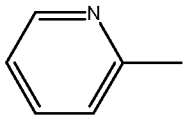
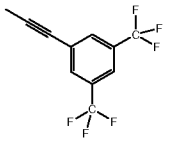
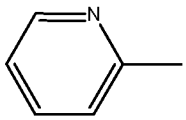
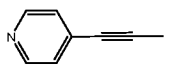
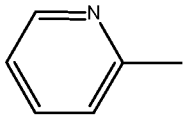
TABLE 1

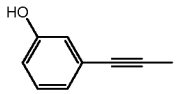
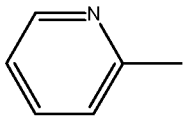
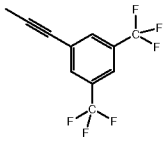
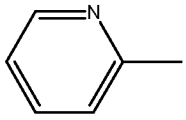
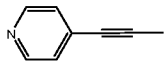
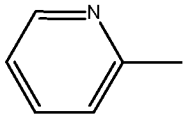
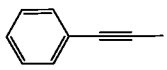
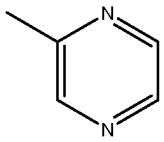
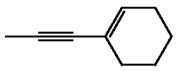
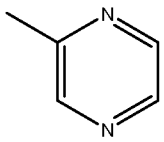
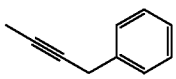
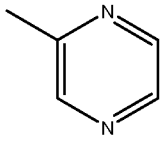
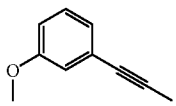
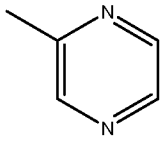
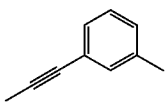
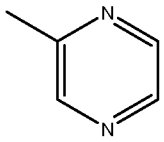
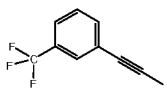
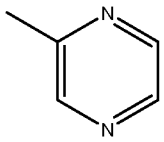
Compound	Name	R_2	X_1	R_6
1	1-{3-[(4-methylphenyl) ethynyl]benzoyl}-4-pyridin-2-yl piperazine		CH	
2	1-{3-[(4-methoxyphenyl) ethynyl]benzoyl}-4-pyridin-2-yl piperazine		CH	
3	1-{3-[(4-chlorophenyl) ethynyl]benzoyl}-4-pyridin-2-ylpiperazine		CH	
4	1-{3-[(2-methylphenyl) ethynyl]benzoyl}-4-pyridin-2-ylpiperazine		CH	
5	1-pyridin-2-yl-4-(3-{[2-(trifluoro methyl)phenyl]ethynyl}benzoyl)piperazine		CH	
6	3-({3-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]phenyl}ethynyl) phenol		CH	

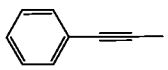
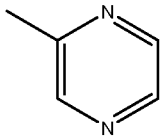
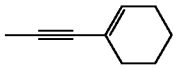
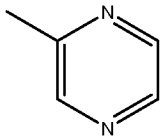
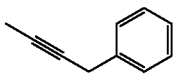
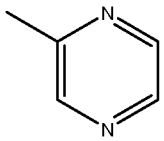
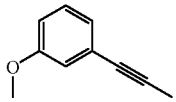
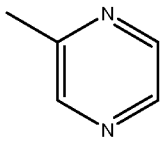
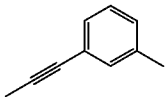
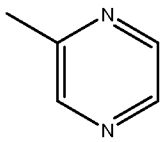
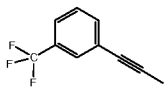
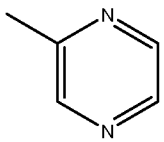
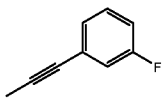
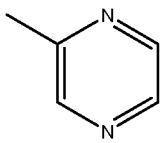
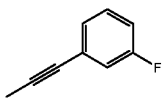
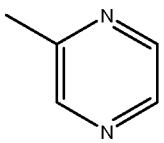
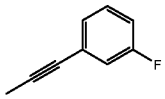
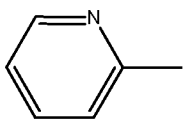
7	1-{3-[(1-methyl-1*H*-imidazol-5-yl)ethynyl]benzoyl}-4-pyridin-2-ylpiperazine		CH	
8	1-[3-(cyclohex-1-en-1-yl ethynyl)benzoyl]-4-pyridin-2-yl piperazine		CH	
9	1-({3-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]phenyl}ethynyl) cyclopentanol		CH	
10	1-[3-(3-phenylprop-1-yn-1-yl)benzoyl]-4-pyridin-2-yl piperazine		CH	
11	3-({3-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]phenyl}ethynyl) aniline		CH	
12	1-({3-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]phenyl}ethynyl) cyclohexanol		CH	
13	1-phenyl-3-{3-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl] phenyl}prop-2-yn-1-ol		CH	
14	1-{3-[(3-methoxyphenyl) ethynyl]benzoyl}-4-pyridin-2-ylpiperazine		CH	
15	1-[3-(cyclohex-1-en-1-yl ethynyl)-4-methoxybenzoyl]-4-pyridin-2-ylpiperazine		COMe	
16	1-[4-methoxy-3-(3-phenylprop-1-yn-1-yl)benzoyl]-4-pyridin-2-ylpiperazine		COMe	

17	1-{4-methoxy-3-[(3-methoxy phenyl)ethynyl]benzoyl}-4-pyridin-2-ylpiperazine		COMe	
18	1-{4-methoxy-3-[(3-methyl phenyl)ethynyl]benzoyl}-4-pyridin-2-ylpiperazine		COMe	
19	1-{3-[(3-chlorophenyl)ethynyl]-4-methoxybenzoyl}-4-pyridin-2-ylpiperazine		COMe	
20	1-{3-[(3,5-dimethoxyphenyl) ethynyl]-4-methoxybenzoyl}-4-pyridin-2-ylpiperazine		COMe	
21	1-{3-[(3,5-difluorophenyl) ethynyl]-4-methoxybenzoyl}-4-pyridin-2-ylpiperazine		COMe	
22	1-{3-[(2,5-dimethylphenyl) ethynyl]-4-methoxybenzoyl}-4-pyridin-2-ylpiperazine		COMe	
23	1-{4-methoxy-3-[(2,4,5-trimethylphenyl)ethynyl]benzoyl}-4-pyridin-2-ylpiperazine		COMe	
24	1-[3-(cyclohex-1-en-1-ylethynyl)-4-methylbenzoyl]-4-pyridin-2-ylpiperazine		CCH_3	
25	1-[4-methyl-3-(3-phenylprop-1-yn-1-yl)benzoyl]-4-pyridin-2-ylpiperazine		CCH_3	

26	1-{3-[(3-methoxyphenyl) ethynyl]-4-methylbenzoyl}-4-pyridin-2-ylpiperazine		CCH_3	
27	1-(4-methyl-3-{[3-(trifluoromethyl) phenyl]ethynyl}benzoyl)-4-pyridin-2-ylpiperazine		CCH_3	
28	1-{3-[(3-chlorophenyl)ethynyl]-4-methylbenzoyl}-4-pyridin-2-ylpiperazine		CCH_3	
29	1-{3-[(3,5-difluorophenyl) ethynyl]-4-methylbenzoyl}-4-pyridin-2-ylpiperazine		CCH_3	
30	1-{3-[(2,5-dimethylphenyl) ethynyl]-4-methylbenzoyl}-4-pyridin-2-ylpiperazine		CCH_3	
31	1-{3-[(4-fluoro-3-methylphenyl) ethynyl]-4-methylbenzoyl}-4-pyridin-2-ylpiperazine		CCH_3	
32	1-[4-methyl-3-(pyridin-3-ylethynyl)benzoyl]-4-pyridin-2-ylpiperazine		CCH_3	
33	3-({2-methoxy-5-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl] phenyl}ethynyl)phenol		COMe	
34	3-({2-methoxy-5-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl] phenyl}ethynyl)aniline		COMe	
35	1-[4-methoxy-3-(pyridin-3-ylethynyl)benzoyl]-4-pyridin-2-ylpiperazine		COMe	

36	3-({2-methyl-5-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl] phenyl}ethynyl)aniline		CCH_3	
37	1-{3-[(4-fluoro-3-methylphenyl) ethynyl]-4-methoxybenzoyl}-4-pyridin-2-ylpiperazine		COMe	
38	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-pyridin-2-ylpiperazine		COMe	
39	1-{4-methyl-3-[(3-methyl phenyl)ethynyl]benzoyl}-4-pyridin-2-ylpiperazine		CCH_3	
40	1-{3-[(3,5-dimethoxyphenyl) ethynyl]-4-methylbenzoyl}-4-pyridin-2-ylpiperazine		CCH_3	
41	1-{4-methyl-3-[(2,4,5-trimethyl phenyl)ethynyl]benzoyl}-4-pyridin-2-ylpiperazine		CCH_3	
42	1-[4-methyl-3-(pyridin-2-ylethynyl)benzoyl]-4-pyridin-2-ylpiperazine		CCH_3	
43	1-(4-methoxy-3-{[3-(trifluoro methyl)phenyl]ethynyl}benzoyl)-4-pyridin-2-ylpiperazine		COMe	
44	1-(3-{[3,5-bis(trifluoromethyl) phenyl]ethynyl}-4-methoxy benzoyl)-4-pyridin-2-yl piperazine		COMe	
45	1-[4-methoxy-3-(pyridin-4-ylethynyl)benzoyl]-4-pyridin-2-ylpiperazine		COMe	

46	3-({2-methyl-5-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl] phenyl}ethynyl)phenol		CCH_3	
47	1-(3-{[3,5-bis(trifluoromethyl) phenyl]ethynyl}-4-methyl benzoyl)-4-pyridin-2-yl piperazine		CCH_3	
48	1-[4-methyl-3-(pyridin-4-ylethynyl)benzoyl]-4-pyridin-2-ylpiperazine		CCH_3	
49	2-{4-[4-methoxy-3-(phenyl ethynyl)benzoyl]piperazin-1-yl}pyrazine		COMe	
50	2-{4-[3-(cyclohex-1-en-1-ylethynyl)-4-methoxy benzoyl]piperazin-1-yl}pyrazine		COMe	
51	2-{4-[4-methoxy-3-(3-phenylprop-1-yn-1-yl) benzoyl]piperazin-1-yl} pyrazine		COMe	
52	2-(4-{4-methoxy-3-[(3-methoxy phenyl)ethynyl]benzoyl}piperazin-1-yl)pyrazine		COMe	
53	2-(4-{4-methoxy-3-[(3-methylphenyl)ethynyl]benzoyl} piperazin-1-yl)pyrazine		COMe	
54	2-[4-(4-methoxy-3-{[3-(trifluoro methyl)phenyl]ethynyl}benzoyl)piperazin-1-yl]pyrazine		COMe	

55	2-{4-[4-methyl-3-(phenyl ethynyl)benzoyl]piperazin-1-yl}pyrazine		CCH_3	
56	2-{4-[3-(cyclohex-1-en-1-ylethynyl)-4-methylbenzoyl] piperazin-1-yl}pyrazine		CCH_3	
57	2-{4-[4-methyl-3-(3-phenylprop-1-yn-1-yl) benzoyl]piperazin-1-yl} pyrazine		CCH_3	
58	2-(4-{3-[(3-methoxyphenyl) ethynyl]-4-methylbenzoyl} piperazin-1-yl)pyrazine		CCH_3	
59	2-(4-{4-methyl-3-[(3-methyl phenyl)ethynyl]benzoyl}piperazin-1-yl)pyrazine		CCH_3	
60	2-[4-(4-methyl-3-{[3-(trifluoro methyl)phenyl]ethynyl}benzoyl)piperazin-1-yl]pyrazine		CCH_3	
61	2-(4-{3-[(3-fluorophenyl)e thynyl]-4-methoxybenzoyl} piperazin-1-yl)pyrazine		COMe	
62	2-(4-{3-[(3-fluorophenyl) ethynyl]-4-methylbenzoyl} piperazin-1-yl)pyrazine		CCH_3	
63	1-{3-[(3-fluorophenyl)ethynyl]-4-methoxybenzoyl}-4-pyridin-2-ylpiperazine		COMe	

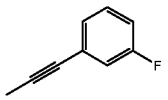
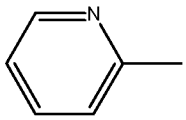
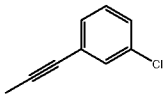
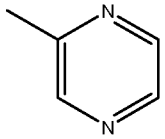
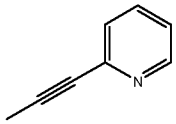
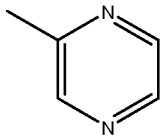
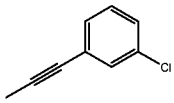
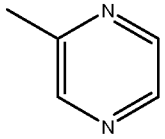
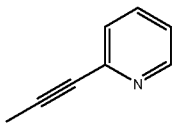
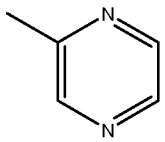
64	1-{3-[(3-fluorophenyl)ethynyl]-4-methylbenzoyl}-4-pyridin-2-ylpiperazine		CCH_3	
65	2-(4-{3-[(3-chlorophenyl) ethynyl]-4-methoxybenzoyl} piperazin-1-yl)pyrazine		COMe	
66	2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrazine		COMe	
67	2-(4-{3-[(3-chlorophenyl) ethynyl]-4-methylbenzoyl} piperazin-1-yl)pyrazine		CCH_3	
68	2-{4-[4-methyl-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrazine		CCH_3	

TABLE 1A

Cmpd	Name	LCMS data			Biological Activity	
		Time (min.)	Mass	Ion	Median Ki (μM)	PCT INHIB (%) @ 10 μM
1	1-{3-[(4-methylphenyl) ethynyl]benzoyl}-4-pyridin-2-ylpiperazine	2.24	382.2	M+H	1.906	55
2	1-{3-[(4-methoxyphenyl) ethynyl]benzoyl}-4-pyridin-2-ylpiperazine	2.14	398.2	M+H	2.356	58

3	1-{3-[(4-chlorophenyl) ethynyl]benzoyl}-4-pyridin-2-ylpiperazine	2.3	402.1	M+H		45
4	1-{3-[(2-methylphenyl) ethynyl]benzoyl}-4-pyridin-2-ylpiperazine	2.23	382.2	M+H		0
5	1-pyridin-2-yl-4-(3-{[2-(trifluoromethyl)phenyl]ethynyl}benzoyl)piperazine	2.25	436.2	M+H		0
6	3-({3-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl] phenyl}ethynyl)phenol	1.87	384.2	M+H	1.11554	75
7	1-{3-[(1-methyl-1*H*-imidazol-5-yl)ethynyl]benzoyl}-4-pyridin-2-ylpiperazine	1.44	372.2	M+H		0
8	1-[3-(cyclohex-1-en-1-yl ethynyl)benzoyl]-4-pyridin-2-yl piperazine	2.18	372.2	M+H	1.21615	78
9	1-({3-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]phenyl}ethynyl) cyclopentanol	1.76	376.2	M+H		0
10	1-[3-(3-phenylprop-1-yn-1-yl)benzoyl]-4-pyridin-2-yl piperazine	2.08	382.2	M+H	0.13881	89
11	3-({3-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl] phenyl}ethynyl)aniline	1.75	383.2	M+H	0.42992	85
12	1-({3-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]phenyl}ethynyl) cyclohexanol	1.83	390.2	M+H		0
13	1-phenyl-3-{3-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl] phenyl}prop-2-yn-1-ol	1.8	398.2	M+H		15
14	1-{3-[(3-methoxyphenyl) ethynyl]benzoyl}-4-pyridin-2-ylpiperazine	2.08	398.2	M+H	0.21238	87

15	1-[3-(cyclohex-1-en-1-ylethynyl)-4-methoxybenzoyl]-4-pyridin-2-ylpiperazine	2.18	402.2	M+H	0.236	76
16	1-[4-methoxy-3-(3-phenylprop-1-yn-1-yl) benzoyl]-4-pyridin-2-yl piperazine	1.95	412.2	M+H	0.043	84
17	1-{4-methoxy-3-[(3-methoxy phenyl)ethynyl]benzoyl}-4-pyridin-2-ylpiperazine	2.07	428.2	M+H	0.051	91
18	1-{4-methoxy-3-[(3-methyl phenyl)ethynyl]benzoyl}-4-pyridin-2-ylpiperazine	2.02	412.2	M+H	0.006	99
19	1-{3-[(3-chlorophenyl) ethynyl]-4-methoxybenzoyl}-4-pyridin-2-ylpiperazine	2.22	432.1	M+H	0.006	97
20	1-{3-[(3,5-dimethoxyphenyl) ethynyl]-4-methoxybenzoyl}-4-pyridin-2-ylpiperazine	2.11	458.2	M+H		0
21	1-{3-[(3,5-difluorophenyl) ethynyl]-4-methoxybenzoyl}-4-pyridin-2-ylpiperazine	2.16	434.2	M+H	1.942	79
22	1-{3-[(2,5-dimethylphenyl) ethynyl]-4-methoxybenzoyl}-4-pyridin-2-ylpiperazine	2.28	426.2	M+H		43
23	1-{4-methoxy-3-[(2,4,5-trimethylphenyl)ethynyl]benzoyl}-4-pyridin-2-ylpiperazine	2.36	440.2	M+H		0
24	1-[3-(cyclohex-1-en-1-ylethynyl)-4-methylbenzoyl]-4-pyridin-2-ylpiperazine	2.34	386.2	M+H	1.287	71
25	1-[4-methyl-3-(3-phenylprop-1-yn-1-yl)benzoyl]-4-pyridin-2-ylpiperazine	2.06	396.2	M+H	0.452	63
26	1-{3-[(3-methoxyphenyl) ethynyl]-4-methylbenzoyl}-4-pyridin-2-ylpiperazine	2.21	412.2	M+H	0.322	86

27	1-(4-methyl-3-{[3-(trifluoro methyl)phenyl]ethynyl}benzo yl)-4-pyridin-2-ylpiperazine	2.38	450.2	M+H	0.469	81
28	1-{3-[(3-chlorophenyl)ethynyl] -4-methylbenzoyl}-4-pyridin-2-ylpiperazine	2.36	416.1	M+H	0.076	79
29	1-{3-[(3,5-difluorophenyl) ethynyl]-4-methylbenzoyl}-4-pyridin-2-ylpiperazine	2.29	418.2	M+H		41
30	1-{3-[(2,5-dimethylphenyl) ethynyl]-4-methylbenzoyl}-4-pyridin-2-ylpiperazine	2.414	410.2	M+H	3.81	55
31	1-{3-[(4-fluoro-3-methyl phenyl)ethynyl]-4-methyl benzoyl}-4-pyridin-2-ylpiperazine	2.35	414.2	M+H	0.472	68
32	1-[4-methyl-3-(pyridin-3-ylethynyl)benzoyl]-4-pyridin-2-ylpiperazine	1.88	383.2	M+H	3.107	68
33	3-({2-methoxy-5-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl] phenyl}ethynyl)phenol	1.88	414.2	M+H	0.54077	82
34	3-({2-methoxy-5-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl] phenyl}ethynyl)aniline	1.76	413.2	M+H	0.29887	62
35	1-[4-methoxy-3-(pyridin-3-ylethynyl)benzoyl]-4-pyridin-2-ylpiperazine	1.75	399.2	M+H	0.89806	67
36	3-({2-methyl-5-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl] phenyl}ethynyl)aniline	1.89	397.2	M+H	0.47427	79
37	1-{3-[(4-fluoro-3-methyl phenyl)ethynyl]-4-methoxy benzoyl}-4-pyridin-2-yl piperazine	2.19	430.2	M+H	0.05471	74

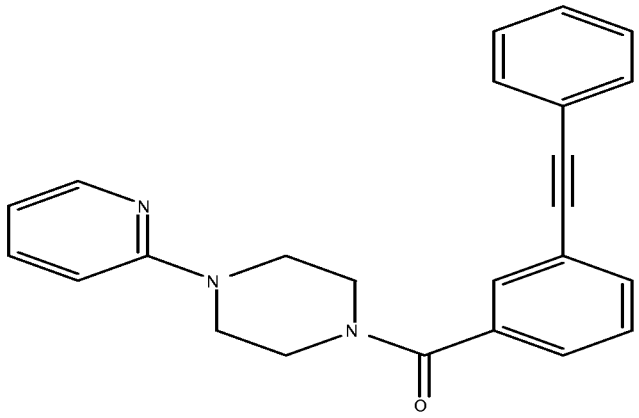
38	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-pyridin-2-ylpiperazine	1.77	399.2	M+H	0.02236	81
39	1-{4-methyl-3-[(3-methyl phenyl)ethynyl]benzoyl}-4-pyridin-2-ylpiperazine	2.29	396.2	M+H	0.05706	83
40	1-{3-[(3,5-dimethoxy phenyl)ethynyl]-4-methylbenzoyl}-4-pyridin-2-ylpiperazine	2.22	442.2	M+H		0
41	1-{4-methyl-3-[(2,4,5-trimethylphenyl)ethynyl]benzoyl}-4-pyridin-2-ylpiperazine	2.51	424.2	M+H		0
42	1-[4-methyl-3-(pyridin-2-ylethynyl)benzoyl]-4-pyridin-2-ylpiperazine	1.89	383.2	M+H	0.0059	96
43	1-(4-methoxy-3-{[3-(trifluoro methyl)phenyl]ethynyl}benzoyl)-4-pyridin-2-ylpiperazine	2.26	466.2	M+H	0.27753	82
44	1-(3-{[3,5-bis(trifluoro methyl)phenyl]ethynyl}-4-methoxybenzoyl)-4-pyridin-2-ylpiperazine	2.44	534.2	M+H		0
45	1-[4-methoxy-3-(pyridin-4-ylethynyl)benzoyl]-4-pyridin-2-ylpiperazine	1.61	399.2	M+H	0.99013	68
46	3-({2-methyl-5-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl] phenyl}ethynyl)phenol	1.97	398.2	M+H	1.306	71
47	1-(3-{[3,5-bis(trifluoromethyl) phenyl]ethynyl}-4-methyl benzoyl)-4-pyridin-2-yl piperazine	2.52	518.2	M+H		0
48	1-[4-methyl-3-(pyridin-4-ylethynyl)benzoyl]-4-pyridin-2-ylpiperazine	1.71	383.2	M+H		49

49	2-{4-[4-methoxy-3-(phenyl ethynyl)benzoyl]piperazin-1-yl}pyrazine	2.45	399.2	M+H	0.02343	95
50	2-{4-[3-(cyclohex-1-en-1-ylethynyl)-4-methoxy benzoyl]piperazin-1-yl} pyrazine	2.57	403.2	M+H	0.17084	90
51	2-{4-[4-methoxy-3-(3-phenylprop-1-yn-1-yl) benzoyl]piperazin-1-yl} pyrazine	2.45	413.2	M+H	0.0339	92
52	2-(4-{4-methoxy-3-[(3-methoxyphenyl)ethynyl]benzoyl}piperazin-1-yl)pyrazine	2.49	429.2	M+H	0.06008	81
53	2-(4-{4-methoxy-3-[(3-methyl phenyl)ethynyl]benzoyl} piperazin-1-yl)pyrazine	2.56	413.2	M+H	0.00863	95
54	2-[4-(4-methoxy-3-{[3-(trifluoromethyl)phenyl]ethynyl}benzoyl)piperazin-1-yl] pyrazine	2.65	467.2	M+H	0.10893	96
55	2-{4-[4-methyl-3-(phenyl ethynyl)benzoyl]piperazin-1-yl}pyrazine	2.63	383.2	M+H	0.14539	88
56	2-{4-[3-(cyclohex-1-en-1-ylethynyl)-4-methylbenzoyl] piperazin-1-yl}pyrazine	2.79	387.2	M+H	1.88662	70
57	2-{4-[4-methyl-3-(3-phenyl prop-1-yn-1-yl)benzoyl] piperazin-1-yl}pyrazine	2.61	397.2	M+H	0.36268	87
58	2-(4-{3-[(3-methoxyphenyl) ethynyl]-4-methylbenzoyl} piperazin-1-yl)pyrazine	2.61	413.2	M+H	0.3222	93
59	2-(4-{4-methyl-3-[(3-methyl phenyl)ethynyl]benzoyl}piperazin-1-yl)pyrazine	2.74	397.2	M+H	0.06254	100

60	2-[4-(4-methyl-3-{[3-(trifluoromethyl)phenyl]ethynyl}benzoyl)piperazin-1-yl]pyrazine	2.75	451.2	M+H	0.74903	85
61	2-(4-{3-[(3-fluorophenyl)ethynyl]-4-methoxybenzoyl}piperazin-1-yl)pyrazine	2.52	417.2	M+H	0.02172	
62	2-(4-{3-[(3-fluorophenyl)ethynyl]-4-methylbenzoyl}piperazin-1-yl)pyrazine	2.7	401.2	M+H	0.12052	
63	1-{3-[(3-fluorophenyl)ethynyl]-4-methoxybenzoyl}-4-pyridin-2-ylpiperazine	2.02	416.2	M+H	0.00734	
64	1-{3-[(3-fluorophenyl)ethynyl]-4-methylbenzoyl}-4-pyridin-2-ylpiperazine	2.17	400.2	M+H	0.13084	
65	2-(4-{3-[(3-chlorophenyl)ethynyl]-4-methoxybenzoyl}piperazin-1-yl)pyrazine	2.67	433.1	M+H	0.00211	
66	2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrazine	2.15	400.2	M+H	0.02116	
67	2-(4-{3-[(3-chlorophenyl)ethynyl]-4-methylbenzoyl}piperazin-1-yl)pyrazine	2.86	417.1	M+H	0.04907	
68	2-{4-[4-methyl-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrazine	2.32	384.2	M+H	0.00884	

Example 2

1-[3-(phenylethynyl)benzoyl]-4-pyridin-2-ylpiperazine (Compound 69)



Step 1: Ethyl 3-(phenylethynyl)benzoate

To ethyl 3-bromobenzoate (12.49 mmol), phenylacetylene (13.74 mmol), and bis(triphenylphosphine)palladium(II) dichloride (0.350 mmol) in TEA (40 ml) was added to copper(I) iodide (0.300 mmol). The reaction was flushed with N_2, capped and stirred at 50°C overnight. The reaction was cooled to room temperature, filtered through Celite, and the filtrate evaporated. The resultant residue was passed through short silica gel filtration in a fritted funnel (3:1 Hexanes: EtOAc) affording crude ethyl 3-(phenylethynyl)benzoate.

Step 2: 3-(phenylethynyl)benzoic acid

To the crude ethyl 3-(phenylethynyl)benzoate was added 10% aqueous NaOH (60 ml) and MeOH (30 ml). This reaction mixture was heated to 65 °C and stirred overnight. After the reaction was determined to be complete via Liquid Chromatography/Mass Spectrophotometer (LCMS), the organic solvent was evaporated. To the remaining solution was added water and EtOAC and then the phases were separated. The aqueous layer was acidified to pH 2 and extracted with EtOAc. The organic layer was dried, filtered and evaporated to afford 1.16 grams of 3-(phenylethynyl)benzoic acid, 42% over two steps.

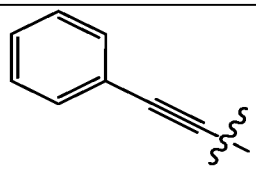
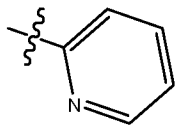
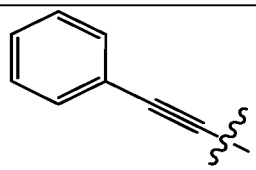
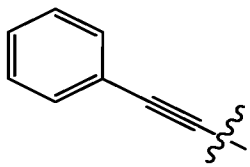
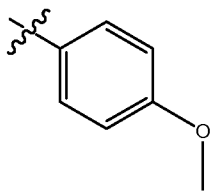
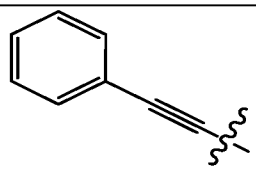
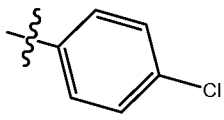
Step 3: 2-Chloro-N-[3-(morpholin-4-ylcarbonyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thien- 2-yl]benzamide

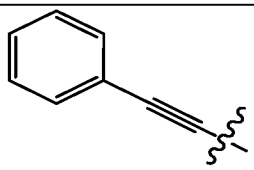
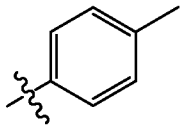
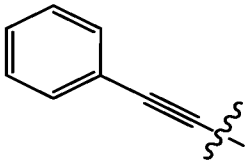
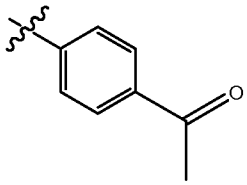
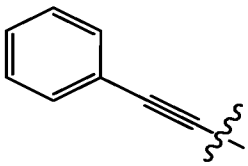
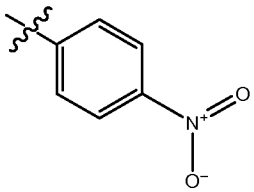
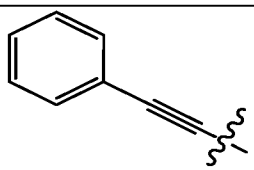
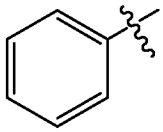
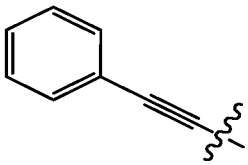
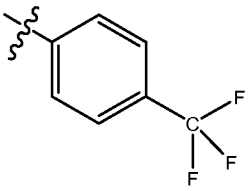
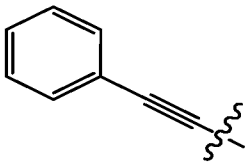
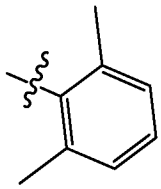
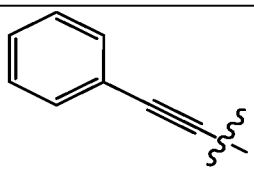
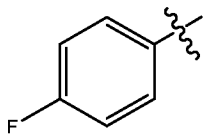
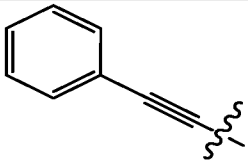
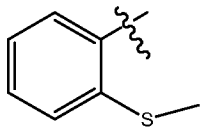
1-(pyridin-2-yl)piperazine (0.051 ml, 0.337 mmol) was added to 3-(phenylethynyl)benzoic acid (50 mg, 0.225 mmol) in DMF (1 ml). This solution was stirred for 15 minutes at which time HOBt (51.7 mg, 0.337 mmol) and EDCI (64.7 mg, 0.337 mmol) were added, and the reaction was allowed to stir overnight. The reaction was then concentrated on a speedvac and purified via prep HPLC (Gilson with TFA additive) to afford 53.4 mg of 2-chloro-N-[3-(morpholin-4-ylcarbonyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thien- 2-yl]benzamide as a white TFA salt. LCMS Rt =1.99 min (MS = 368.2)

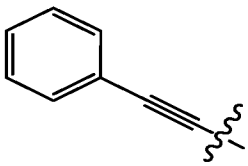
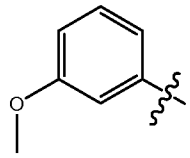
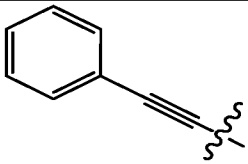
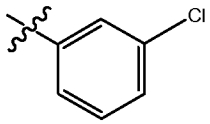
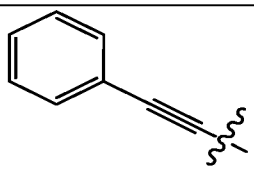
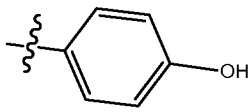
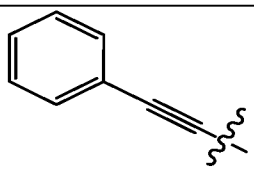
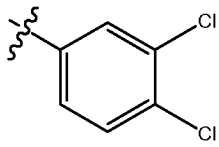
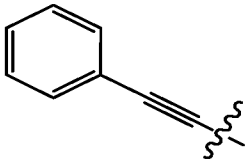
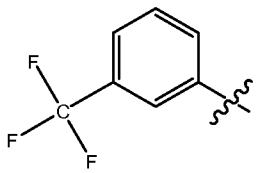
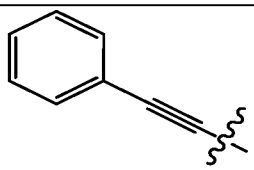
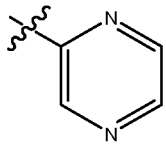
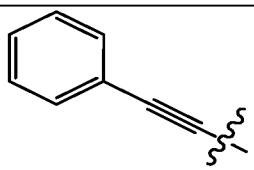
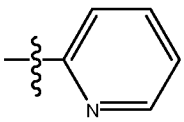
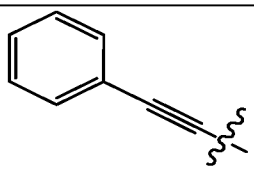
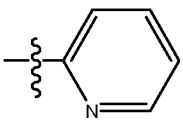
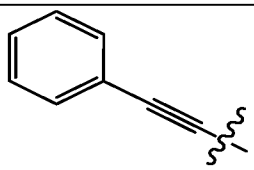
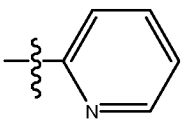
Compounds 69-149, shown in Tables 2 and 2A below, were prepared using the procedure of Example 2 described above.

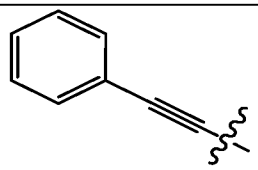
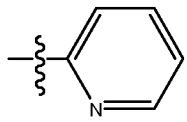
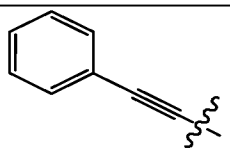
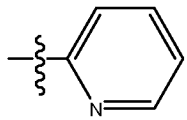
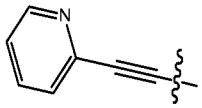
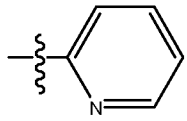
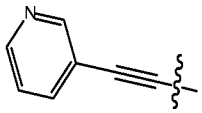
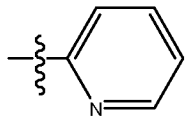
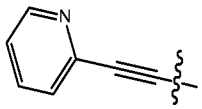
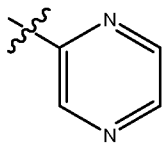
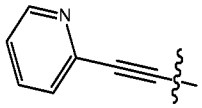
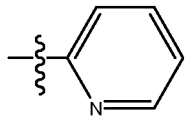
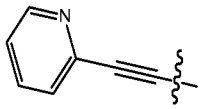
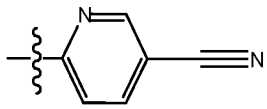
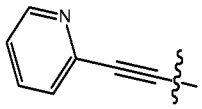
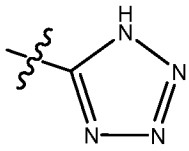
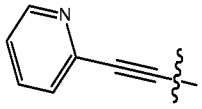
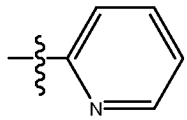
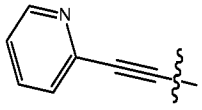
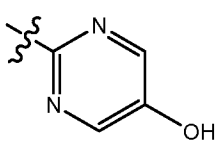
UNLESS NOTED OTHERWISE THE FOLLOWING VALUES
IN TABLE 2 REFER TO FORMULA I
WHEREIN R_1, R_4, R_{4a}, R_5, R_{5a} = H; X_1 AND X_2 = CH; AND Z = CO

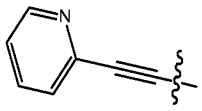
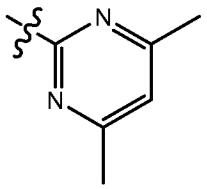
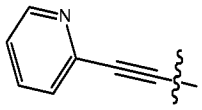
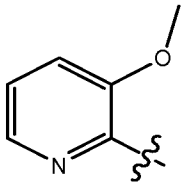
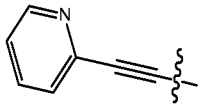
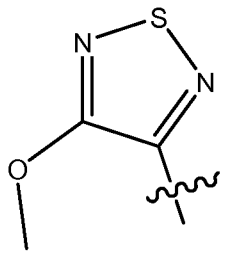
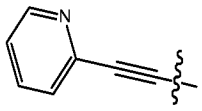
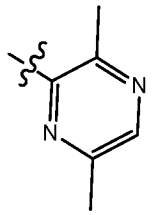
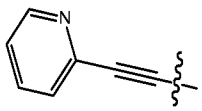
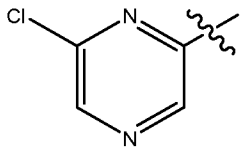
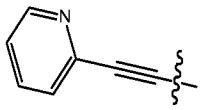
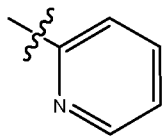
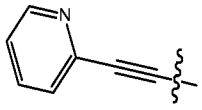
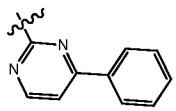
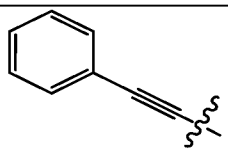
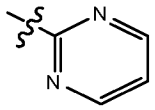
TABLE 2

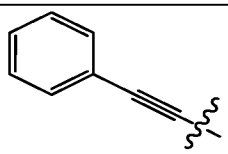
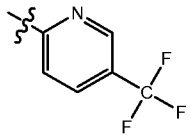
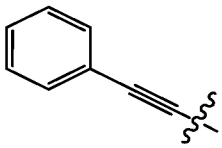
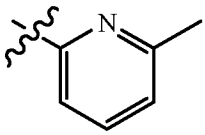
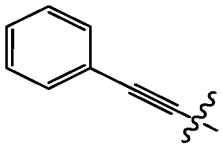
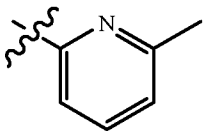
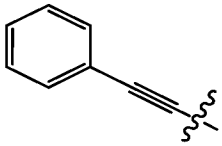
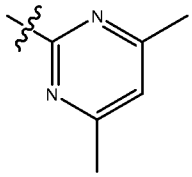
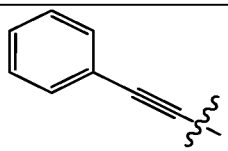
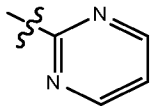
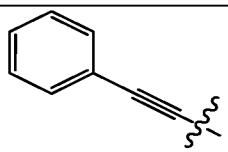
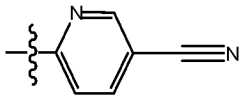
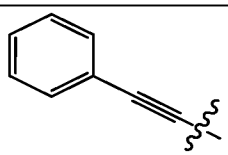
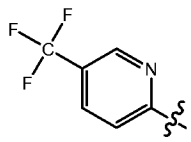
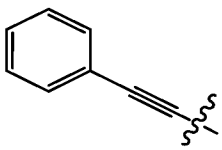
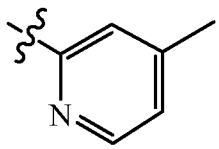
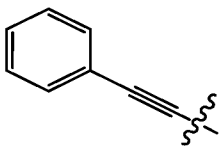
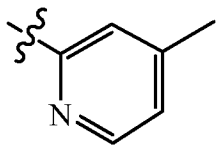
Cmpd	Name	R_2	Noted Values	R_6
69	1-[3-(phenylethynyl) benzoyl]-4-pyridin-2-yl piperazine			
70	1-methyl-4-[3-(phenylethynyl)benzoyl]piperazine			CH_3
71	1-(4-methoxyphenyl)-4-[3-(phenylethynyl)benzoyl]piperazine			
72	1-(4-chlorophenyl)-4-[3-(phenylethynyl)benzoyl]piperazine			

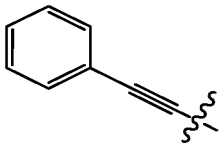
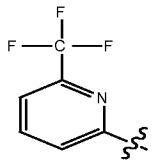
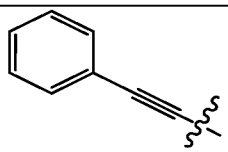
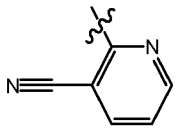
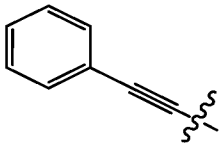
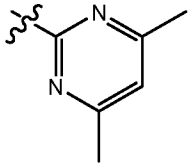
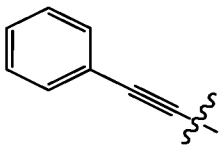
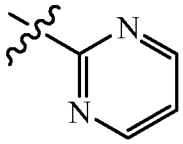
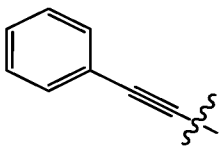
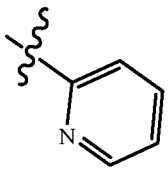
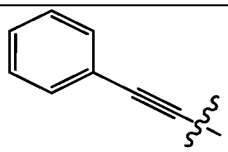
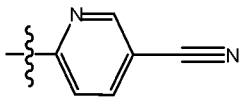
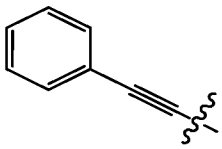
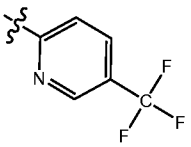
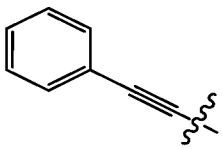
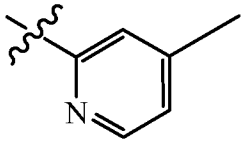
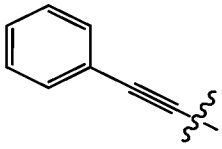
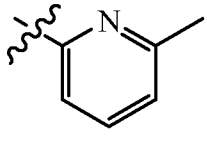
73	1-(4-methylphenyl)-4-[3-(phenylethynyl)benzoyl]piperazine			
74	1-(4-{4-[3-(phenylethynyl)benzoyl]piperazin-1-yl}phenyl)ethanone			
75	1-(4-nitrophenyl)-4-[3-(phenylethynyl)benzoyl]piperazine			
76	1-phenyl-4-[3-(phenylethynyl)benzoyl]piperazine			
77	1-[3-(phenylethynyl)benzoyl]-4-[4-(trifluoromethyl)phenyl]piperazine			
78	1-(2,6-dimethylphenyl)-4-[3-(phenylethynyl)benzoyl]piperazine			
79	1-(4-fluorophenyl)-4-[3-(phenylethynyl)benzoyl]piperazine			
80	1-[2-(methylthio)phenyl]-4-[3-(phenylethynyl)benzoyl]piperazine			

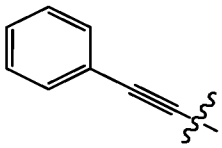
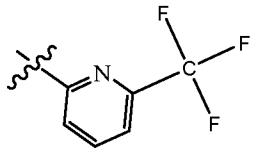
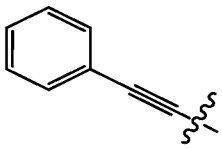
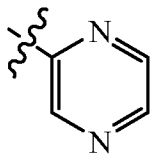
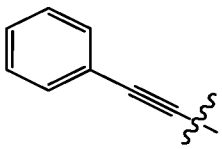
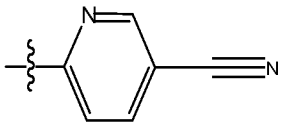
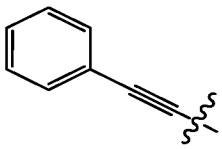
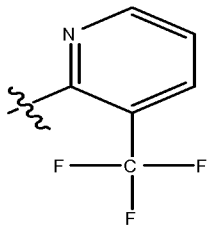
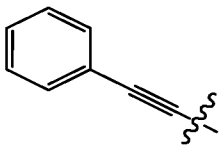
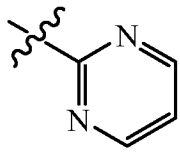
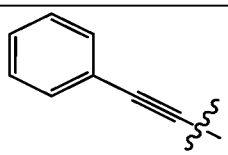
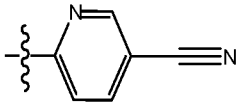
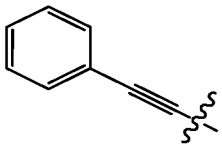
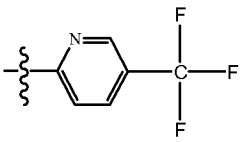
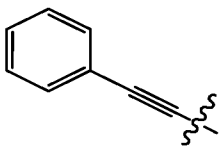
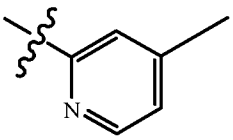
81	1-(3-methoxyphenyl)-4-[3-(phenylethynyl)benzoyl]piperazine			
82	1-(3-chlorophenyl)-4-[3-(phenylethynyl)benzoyl]piperazine			
83	4-{4-[3-(phenylethynyl)benzoyl]piperazin-1-yl}phenol			
84	1-(3,4-dichlorophenyl)-4-[3-(phenylethynyl)benzoyl]piperazine			
85	1-[3-(phenylethynyl)benzoyl]-4-[3-(trifluoromethyl)phenyl]piperazine			
86	2-{4-[3-(phenylethynyl)benzoyl]piperazin-1-yl}pyrazine			
87	1-{[5-(phenylethynyl)pyridin-3-yl]carbonyl}-4-pyridin-2-ylpiperazine		X_2 = N	
88	1-[4-methyl-3-(phenylethynyl)benzoyl]-4-pyridin-2-ylpiperazine		R_1 = F	
89	1-[4-fluoro-3-(phenylethynyl)benzoyl]-4-pyridin-2-ylpiperazine		R_1 = OCH_3	

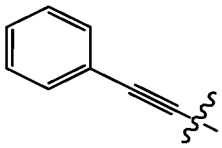
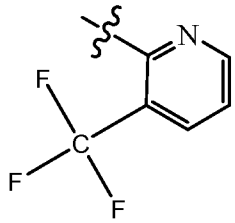
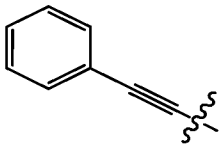
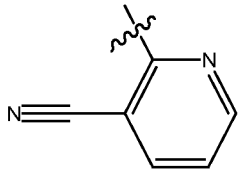
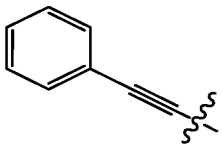
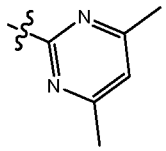
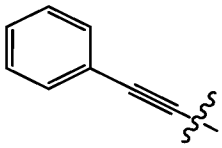
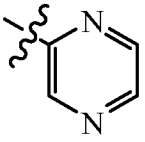
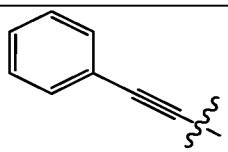
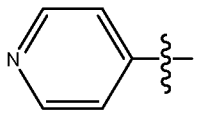
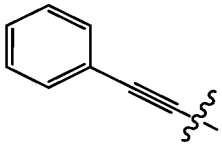
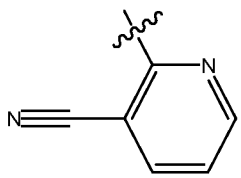
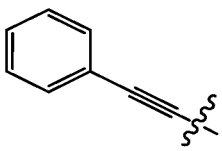
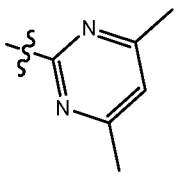
90	1-[4-methoxy-3-(phenylethynyl)benzoyl]-4-pyridin-2-ylpiperazine		$R_1 = OCH_3$	
91	1-[2-methyl-3-(phenylethynyl)benzoyl]-4-pyridin-2-ylpiperazine		$R_1 = CH_3$	
92	1-pyridin-2-yl-4-[3-(pyridin-2-ylethynyl)benzoyl]piperazine			
93	1-pyridin-2-yl-4-[3-(pyridin-3-ylethynyl)benzoyl]piperazine			
94	2-{4-[3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrazine			
95	1-pyridin-4-yl-4-[3-(pyridin-2-ylethynyl)benzoyl]piperazine			
96	6-{4-[3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}nicotinonitrile			
97	1-[3-(pyridin-2-ylethynyl)benzoyl]-4-(1*H*-tetrazol-5-yl)piperazine			
98	2-methyl-4-pyridin-2-yl-1-[3-(pyridin-2-ylethynyl)benzoyl]piperazine		$R_4 = CH_3$	
99	2-{4-[3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidin-5-ol			

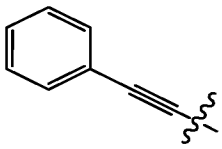
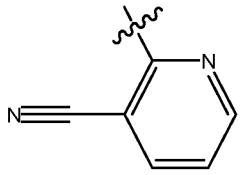
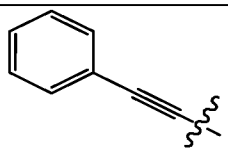
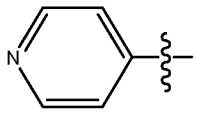
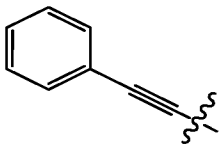
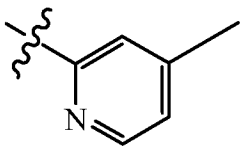
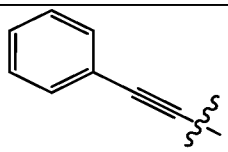
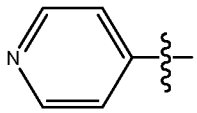
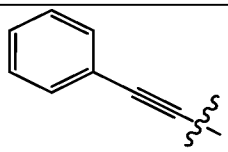
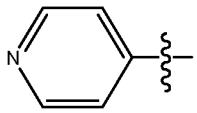
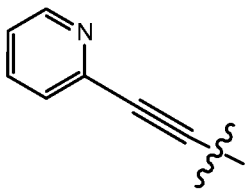
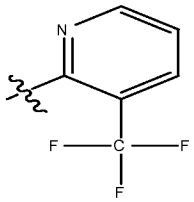
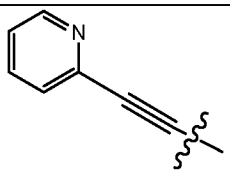
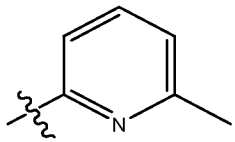
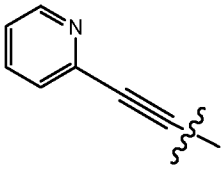
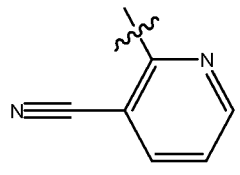
100	4,6-dimethyl-2-{4-[3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine			
101	1-(3-methoxypyridin-2-yl)-4-[3-(pyridin-2-ylethynyl)benzoyl]piperazine			
102	1-(4-methoxy-1,2,5-thiadiazol-3-yl)-4-[3-(pyridin-2-ylethynyl)benzoyl]piperazine			
103	2,5-dimethyl-3-{4-[3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrazine			
104	2-chloro-6-{4-[3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrazine			
105	2-methyl-1-pyridin-2-yl-4-[3-(pyridin-2-ylethynyl)benzoyl] piperazine (R_5 = CH_3)			
106	4-phenyl-2-{4-[3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine			
107	2-{4-[3-(phenylethynyl) benzoyl]piperazin-1-yl} pyrimidine			

108	1-[3-(phenylethynyl) benzoyl]-4-[5-(trifluoro methyl)pyridin-2-yl] piperazine			
109	1-(4-methylpyridin-2-yl)-4-[3-(phenylethynyl)benzoyl]pipe razine			
110	1-(6-methylpyridin-2-yl)-4-[3-(phenylethynyl)benzoyl]pipe razine			
111	4,6-dimethyl-2-{4-[3-(phenylethynyl)benzoyl]pipe razin-1-yl}pyrimidine			
112	2-{4-[4-methoxy-3-(phenylethynyl)benzoyl]pipe razin-1-yl}pyrimidine		X_1= COMe	
113	6-{4-[4-methoxy-3-(phenylethynyl)benzoyl]pipe razin-1-yl}nicotinonitrile		X_1= COMe	
114	1-[4-methoxy-3-(phenylethynyl)benzoyl]-4-[5-(trifluoromethyl)pyridin-2-yl]piperazine		X_1= COMe	
115	1-[4-methoxy-3-(phenyl ethynyl)benzoyl]-4-(4-methylpyridin-2-yl)piperazine		X_1= COMe	
116	1-[4-methoxy-3-(phenyl ethynyl)benzoyl]-4-(6-methylpyridin-2-yl)piperazine		X_1= COMe	

117	1-[4-methoxy-3-(phenyl ethynyl)benzoyl]-4-[6-(trifluoromethyl)pyridin-2-yl]piperazine		X_1= COMe	
118	2-{4-[4-methoxy-3-(phenyl ethynyl)benzoyl]piperazin-1-yl}nicotinonitrile		X_1= COMe	
119	2-{4-[4-methoxy-3-(phenyl ethynyl)benzoyl]piperazin-1-yl}-4,6-dimethylpyrimidine		X_1= COMe	
120	2-{4-[2-(phenylethynyl) isonicotinoyl]piperazin-1-yl}pyrimidine		X_2 = N	
121	1-[2-(phenylethynyl) isonicotinoyl]-4-pyridin-2-ylpiperazine		X_2 = N	
122	6-{4-[2-(phenylethynyl) isonicotinoyl]piperazin-1-yl}nicotinonitrile		X_2 = N	
123	1-[2-(phenylethynyl) isonicotinoyl]-4-[5-(trifluoromethyl)pyridin-2-yl]piperazine		X_2 = N	
124	1-(4-methylpyridin-2-yl)-4-[2-(phenylethynyl)isonicotinoyl] piperazine		X_2 = N	
125	1-(6-methylpyridin-2-yl)-4-[2-(phenylethynyl)isonicotinoyl] piperazine		X_2 = N	

126	1-[2-(phenylethynyl) isonicotinoyl]-4-[6-(trifluoromethyl)pyridin-2-yl]piperazine		X_2 = N	
127	2-{4-[2-(phenylethynyl) isonicotinoyl]piperazin-1-yl}pyrazine		X_2 = N	
128	6-{4-[3-(phenylethynyl) benzoyl]piperazin-1-yl}nicotinonitrile			
129	1-[3-(phenylethynyl)benzoyl]-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine			
130	2-(4-{[5-(phenylethynyl)pyridin-3-yl]carbonyl}piperazin-1-yl)pyrimidine			
131	6-(4-{[5-(phenylethynyl)pyridin-3-yl]carbonyl}piperazin-1-yl)nicotinonitrile			
132	1-{[5-(phenylethynyl)pyridin-3-yl]carbonyl}-4-[5-(trifluoromethyl)pyridin-2-yl]piperazine			
133	1-(4-methylpyridin-2-yl)-4-{[5-(phenylethynyl)pyridin-3-yl]carbonyl}piperazine			

134	1-{[5-(phenylethynyl)pyridin-3-yl]carbonyl}-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine			
135	2-(4-{[5-(phenyl ethynyl)pyridin-3-yl]carbonyl}piperazin-1-yl)nicotinonitrile			
136	4,6-dimethyl-2-(4-{[5-(phenylethynyl)pyridin-3-yl]carbonyl}piperazin-1-yl)pyrimidine			
137	2-(4-{[5-(phenylethynyl)pyridin-3-yl]carbonyl}piperazin-1-yl)pyrazine			
138	1-{[5-(phenylethynyl)pyridin-3-yl]carbonyl}-4-pyridin-4-ylpiperazine			
139	2-{4-[2-(phenylethynyl)isonicotinoyl]piperazin-1-yl}nicotinonitrile			
140	4,6-dimethyl-2-{4-[2-(phenylethynyl)isonicotinoyl]piperazin-1-yl}pyrimidine		X_1 = N	

141	2-{4-[3-(phenylethynyl)benzoyl]piperazin-1-yl}nicotinonitrile			
142	1-[3-(phenylethynyl)benzoyl]-4-pyridin-4-ylpiperazine			
143	1-(6-methylpyridin-2-yl)-4-{[5-(phenylethynyl)pyridin-3-yl]carbonyl}piperazine		X_2 = N	
144	1-[2-(phenylethynyl)isonicotinoyl]-4-pyridin-4-ylpiperazine		X_1 = N	
145	1-[4-methoxy-3-(phenylethynyl)benzoyl]-4-pyridin-4-ylpiperazine			
146	1-[3-(pyridin-2-ylethynyl)benzoyl]-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine			
147	1-(6-methylpyridin-2-yl)-4-[3-(pyridin-2-ylethynyl)benzoyl]piperazine			
148	2-{4-[3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}nicotinonitrile			

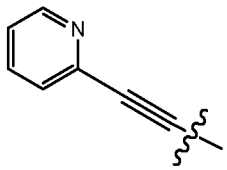
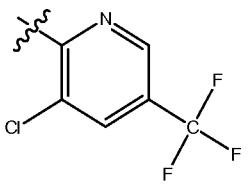
149	1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-4-[3-(pyridin-2-ylethynyl)benzoyl]piperazine			

TABLE 2A

Cmpd	Name	LCMS Data			Biological Activity	
		Time (min.)	Mass	Ion	Median Ki (μM)	PCT INHIB (%) @ 10 μM
69	1-[3-(phenylethynyl) benzoyl]-4-pyridin-2-yl piperazine	1.99	368.2	M+H	0.15473	95
70	1-methyl-4-[3-(phenyl ethynyl)benzoyl]piperazine	1.82	305.2	M+H		0
71	1-(4-methoxyphenyl)-4-[3-(phenylethynyl)benzoyl]piperazine	2.43	397.2	M+H		40
72	1-(4-chlorophenyl)-4-[3-(phenylethynyl)benzoyl]piperazine	2.59	401.1	M+H		30
73	1-(4-methylphenyl)-4-[3-(phenylethynyl)benzoyl]piperazine	2.56	381.2	M+H		0
74	1-(4-{4-[3-(phenylethynyl) benzoyl]piperazin-1-yl} phenyl)ethanone	2.4	409.2	M+H		20
75	1-(4-nitrophenyl)-4-[3-(phenylethynyl)benzoyl]piperazine	2.45	412.2	M+H		20
76	1-phenyl-4-[3-(phenyl ethynyl)benzoyl]piperazine	2.5	367.2	M+H	1.287	86
77	1-[3-(phenylethynyl) benzoyl]-4-[4-(trifluoro methyl)phenyl]piperazine	2.6	435.2	M+H		0

78	1-(2,6-dimethylphenyl)-4-[3-(phenylethynyl)benzoyl] piperazine	2.7	395.2	M+H	>10.000	53
79	1-(4-fluorophenyl)-4-[3-(phenylethynyl)benzoyl] piperazine	2.5	385.2	M+H		28
80	1-[2-(methylthio)phenyl]-4-[3-(phenylethynyl) benzoyl]piperazine	2.61	413.2	M+H		24
81	1-(3-methoxyphenyl)-4-[3-(phenylethynyl)benzoyl]piperazine	2.48	397.2	M+H	3.389	78
82	1-(3-chlorophenyl)-4-[3-(phenylethynyl)benzoyl] piperazine	2.59	401.1	M+H	2.774	58
83	4-{4-[3-(phenylethynyl) benzoyl]piperazin-1-yl} phenol	2.18	383.2	M+H	>10.000	74
84	1-(3,4-dichlorophenyl)-4-[3-(phenylethynyl) benzoyl]piperazine	2.67	435.1	M+H		0
85	1-[3-(phenylethynyl) benzoyl]-4-[3-(trifluoro methyl)phenyl]piperazine	2.6	435.2	M+H		32
86	2-{4-[3-(phenylethynyl) benzoyl]piperazin-1-yl} pyrazine	2.37	369.2	M+H	0.444	85
87	1-{[5-(phenylethynyl) pyridin-3-yl]carbonyl}-4-pyridin-2-ylpiperazine	1.95	369.2	M+H	3.312	56
88	1-[4-methyl-3-(phenyl ethynyl)benzoyl]-4-pyridin-2-ylpiperazine	2.22	382.2	M+H	0.059	84
89	1-[4-fluoro-3-(phenyl ethynyl)benzoyl]-4-pyridin-2-ylpiperazine	2.15	386.2	M+H	0.05	51

90	1-[4-methoxy-3-(phenyl ethynyl)benzoyl]-4-pyridin-2-ylpiperazine	2.06	398.2	M+H	0.025	83
91	1-[2-methyl-3-(phenyl ethynyl)benzoyl]-4-pyridin-2-ylpiperazine	2.2	382.2	M+H		18
92	1-pyridin-2-yl-4-[3-(pyridin-2-ylethynyl)benzoyl] piperazine	1.8	369.2	M+H	0.04852	98
93	1-pyridin-2-yl-4-[3-(pyridin-3-ylethynyl)benzoyl] piperazine	1.83	369.2	M+H		26
94	2-{4-[3-(pyridin-2-yl ethynyl)benzoyl]piperazin-1-yl}pyrazine	2.23	370.2	M+H	0.39535	79
95	1-pyridin-4-yl-4-[3-(pyridin-2-ylethynyl)benzoyl] piperazine	1.74	369.2	M+H		30
96	6-{4-[3-(pyridin-2-yl ethynyl)benzoyl]piperazin-1-yl}nicotinonitrile	2.29	394.2	M+H	3.23792	50
97	1-[3-(pyridin-2-ylethynyl) benzoyl]-4-(1*H*-tetrazol-5-yl)piperazine	1.84	360.1	M+H		0
98	2-methyl-4-pyridin-2-yl-1-[3-(pyridin-2-ylethynyl) benzoyl]piperazine	1.84	383.2	M+H	0.67926	72
99	2-{4-[3-(pyridin-2-yl ethynyl)benzoyl]piperazin-1-yl}pyrimidin-5-ol	1.89	386.2	M+H	1.45242	64
100	4,6-dimethyl-2-{4-[3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl} pyrimidine	2.31	398.2	M+H	2.16349	55
101	1-(3-methoxypyridin-2-yl)-4-[3-(pyridin-2-ylethynyl) benzoyl]piperazine	2.08	399.2	M+H	2.34784	52

102	1-(4-methoxy-1,2,5-thiadiazol-3-yl)-4-[3-(pyridin-2-ylethynyl) benzoyl]piperazine	2.41	406.1	M+H	0.08	92
103	2,5-dimethyl-3-{4-[3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}pyrazine	2.41	398.2	M+H		16
104	2-chloro-6-{4-[3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrazine	2.26	404.1	M+H	1.46122	71
105	2-methyl-1-pyridin-2-yl-4-[3-(pyridin-2-ylethynyl) benzoyl]piperazine	1.83	383.2	M+H	0.8261	58
106	4-phenyl-2-{4-[3-(pyridin-2-ylethynyl)benzoyl] piperazin-1-yl}pyrimidine	2.64	446.2	M+H	0.00219	86
107	2-{4-[3-(phenylethynyl) benzoyl]piperazin-1-yl} pyrimidine	369.3	2.8	M+H	0.45101	90
108	1-[3-(phenylethynyl) benzoyl]-4-[5-(trifluoro methyl)pyridin-2-yl] iperazine	436.4	3	M+H		0
109	1-(4-methylpyridin-2-yl)-4-[3-(phenylethynyl)benzoyl] piperazine	382.3	3	M+H	0.06506	91
110	1-(6-methylpyridin-2-yl)-4-[3-(phenylethynyl)benzoyl] piperazine	382.3	3	M+H	3.41435	68
111	4,6-dimethyl-2-{4-[3-(phenylethynyl)benzoyl]piperazin-1-yl}pyrimidine	397.4	3.1	M+H		0
112	2-{4-[4-methoxy-3-(phenylethynyl)benzoyl]piperazin-1-yl}pyrimidine	399.3	2.8	M+H	0.06247	90

113	6-{4-[4-methoxy-3-(phenylethynyl)benzoyl]piperazin-1-yl}nicotinonitrile	423.4	2.7	M+H	0.35656	81
114	1-[4-methoxy-3-(phenylethynyl)benzoyl]-4-[5-(trifluoromethyl)pyridin-2-yl]piperazine	466.4	3	M+H		26
115	1-[4-methoxy-3-(phenyl ethynyl)benzoyl]-4-(4-methylpyridin-2-yl) piperazine	412.4	2.9	M+H	0.00315	93
116	1-[4-methoxy-3-(phenyl ethynyl)benzoyl]-4-(6-methylpyridin-2-yl) piperazine	412.4	2.9	M+H	0.85296	77
117	1-[4-methoxy-3-(phenyle thynyl)benzoyl]-4-[6-(trifluoromethyl)pyridin-2-yl]piperazine	466.4	3	M+H		35
118	2-{4-[4-methoxy-3-(phenylethynyl)benzoyl]piperazin-1-yl}nicotinonitrile	423.4	2.8	M+H	1.75877	78
119	2-{4-[4-methoxy-3-(phenyl ethynyl)benzoyl]piperazin-1-yl}-4,6-dimethyl pyrimidine	427.4	3	M+H		35
120	2-{4-[2-(phenylethynyl) isonicotinoyl]piperazin-1-yl}pyrimidine	370.4	2.6	M+H	2.88919	49
121	1-[2-(phenylethynyl) isonicotinoyl]-4-pyridin-2-ylpiperazine	369.4	2.7	M+H	1.12941	72
122	6-{4-[2-(phenylethynyl) isonicotinoyl]piperazin-1-yl}nicotinonitrile	394.4	2.6	M+H		0

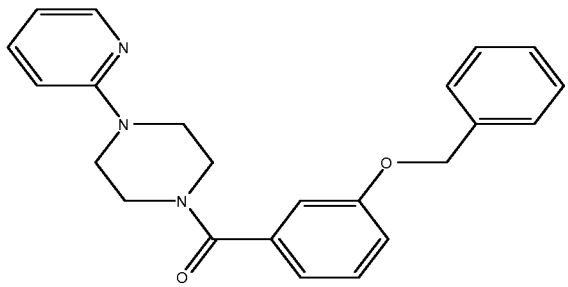
123	1-[2-(phenylethynyl) isonicotinoyl]-4-[5-(trifluoromethyl)pyridin-2-yl]piperazine	437.4	2.8	M+H		0
124	1-(4-methylpyridin-2-yl)-4-[2-(phenylethynyl) isonicotinoyl]piperazine	383.4	2.8	M+H	0.33843	84
125	1-(6-methylpyridin-2-yl)-4-[2-(phenylethynyl) isonicotinoyl]piperazine	383.4	2.8	M+H		30
126	1-[2-(phenylethynyl) isonicotinoyl]-4-[6-(trifluoromethyl)pyridin-2-yl]piperazine	437.4	2.9	M+H		54
127	2-{4-[2-(phenylethynyl) isonicotinoyl]piperazin-1-yl} pyrazine	370.4	2.5	M+H		36
128	6-{4-[3-(phenylethynyl) benzoyl]piperazin-1-yl} nicotinonitrile	393.3	2.8	M+H		48
129	1-[3-(phenylethynyl) benzoyl]-4-[3-(trifluoro methyl)pyridin-2-yl] piperazine	436.4	3.1	M+H		45
130	2-(4-{[5-(phenylethynyl) pyridin-3-yl]carbonyl}piperazin-1-yl)pyrimidine	370.4	2.7	M+H		47
131	6-(4-{[5-(phenylethynyl) pyridin-3-yl]carbonyl}piperazin-1-yl)nicotinonitrile	394.4	2.6	M+H		0
132	1-{[5-(phenylethynyl) pyridin-3-yl]carbonyl}-4-[5-(trifluoromethyl)pyridin-2-yl]piperazine					0

133	1-(4-methylpyridin-2-yl)-4-{[5-(phenylethynyl)pyridin-3-yl]carbonyl}piperazine	383.4	2.8	M+H	0.65119	52
134	1-{[5-(phenylethynyl) pyridin-3-yl]carbonyl}-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine	437.4	2.9	M+H		0
135	2-(4-{[5-(phenylethynyl) pyridin-3-yl]carbonyl} piperazin-1-yl) nicotinonitrile	394.4	2.7	M+H		28
136	4,6-dimethyl-2-(4-{[5-(phenylethynyl)pyridin-3-yl]carbonyl}piperazin-1-yl)pyrimidine	398.4	2.9	M+H		0
137	2-(4-{[5-(phenylethynyl) pyridin-3-yl]carbonyl} piperazin-1-yl)pyrazine	370.3	2.6	M+H		32
138	1-{[5-(phenylethynyl) pyridin-3-yl]carbonyl}-4-pyridin-4-ylpiperazine	369.4	3.4	M+H		0
139	2-{4-[2-(phenylethynyl) isonicotinoyl]piperazin-1-yl}nicotinonitrile	394.4	2.6	M+H		40
140	4,6-dimethyl-2-{4-[2-(phenylethynyl)isonicotinoyl]piperazin-1-yl}pyrimidine	398.4	2.9	M+H		37
141	2-{4-[3-(phenylethynyl) benzoyl]piperazin-1-yl} nicotinonitrile	393.3	2.8	M+H	1.08866	78
142	1-[3-(phenylethynyl) benzoyl]-4-pyridin-4-yl piperazine	368.4	3.5	M+H		53
143	1-(6-methylpyridin-2-yl)-4-{[5-(phenylethynyl)pyridin-3-yl]carbonyl}piperazine	383.4	2.9	M+H		49

144	1-[2-(phenylethynyl) isonicotinoyl]-4-pyridin-4-ylpiperazine	369.4	3.1	M+H		10
145	1-[4-methoxy-3-(phenyl ethynyl)benzoyl]-4-pyridin-4-ylpiperazine	398.4	3.4	M+H	1.29949	91
146	1-[3-(pyridin-2-ylethynyl) benzoyl]-4-[3-(trifluoro methyl)pyridin-2-yl] piperazine	2.5	437.2	M+H		48
147	1-(6-methylpyridin-2-yl)-4-[3-(pyridin-2-ylethynyl) benzoyl]piperazine	1.83	383.2	M+H	3.01907	80
148	2-{4-[3-(pyridin-2-yl ethynyl)benzoyl]piperazin-1-yl}nicotinonitrile	2.27	394.2	M+H	1.62992	74
149	1-[3-chloro-5-(trifluoro methyl)pyridin-2-yl]-4-[3-(pyridin-2-ylethynyl) benzoyl]piperazine	2.64	471.1	M+H	2.76451	72

Example 3

1-[3-(benzyloxy)benzoyl]-4-pyridin-2-ylpiperazine (Compound153)



5

Step 1: (3-hydroxyphenyl)(4-(pyridin-2-yl)piperazin-1-yl)methanone

To 1-(pyridin-2-yl)piperazine (5.18 mmol) and 3-hydroxybenzoic acid (5.18 mmol) was added 50 ml DMF. To this mixture was added HOBT (6.48 mmol), 1-(3-(dimethylamino)propyl)-3-ethyl-carbodiimide hydrochloride (WSCDI) (6.48 mmol), followed by DIEA (10.37 mmol). The

solution was stirred for 16 hours at which time LCMS indicated the reaction was complete. 200 mL Water and 150 mL EtOAc were added to the solution. The organic layer was collected, dried with Na_2SO_4, and concentrated in vacuo giving 0.83 g of (3-hydroxyphenyl)(4-(pyridin-2-yl)piperazin-1-yl)methanone compound as an off white solid that was triturated with Et_2O. LCMS Rt = 0.29 min (MS = 284)

Step 2: 1-[3-(benzyloxy)benzoyl]-4-pyridin-2-ylpiperazine

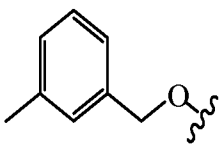
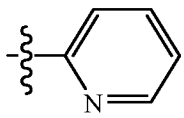
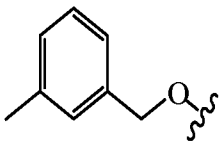
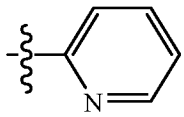
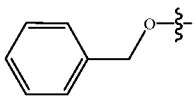
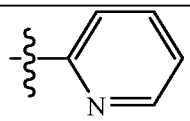
2 ml DMF was added to cesium carbonate (0.265 mmol) and (3-hydroxyphenyl)(4-(pyridin-2-yl)piperazin-1-yl)methanone (0.176 mmol). This mixture was heated to 35°C for 30 minutes and (bromomethyl)benzene (0.194 mmol) was added to the mixture. The mixture was stirred for 16 hours at 35°C. The mixture was concentrated on a speedvac and purified via prep HPLC (Gilson with NH_4OH additive) giving 30 mg of 1-[3-(benzyloxy)benzoyl]-4-pyridin-2-ylpiperazine. LCMS Rt = 1.95 min (MS = 374).

Compounds 150-163, shown in Tables 3 and 3A below, were prepared using the procedure of Example 3 described above.

THE FOLLOWING VALUES REFER TO FORMULA I

WHEREIN R_1, R_4, R_{4a}, R_5, R_{5a} = H; X_2 = CH; Z = CO

TABLE 3

Cmpd	Name	R_2	X_1	R_6
150	1-{3-[(3-methylbenzyl)oxy]benzoyl}-4-pyridin-2-ylpiperazine		CH	
151	1-{4-methoxy-3-[(3-methylbenzyl)oxy]benzoyl}-4-pyridin-2-ylpiperazine		COMe	
152	1-[3-(benzyloxy)benzoyl]-4-pyridin-2-ylpiperazine		CH	

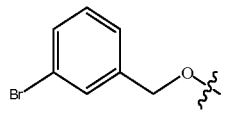
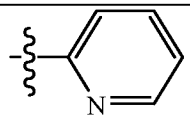
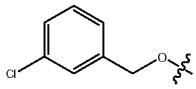
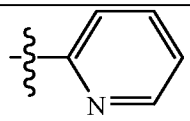
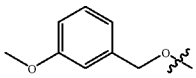
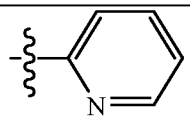
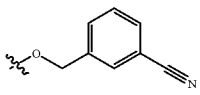
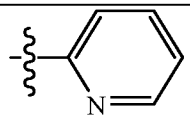
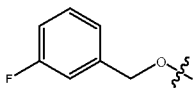
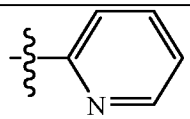
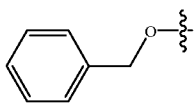
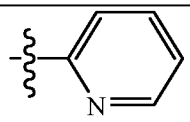
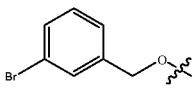
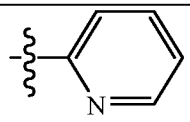
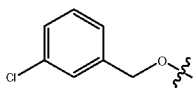
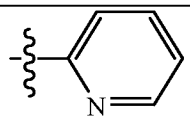
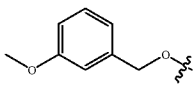
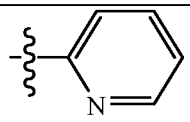
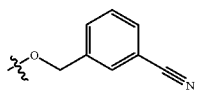
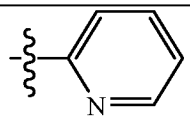
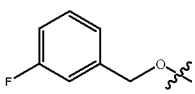
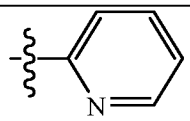
153	1-{3-[(3-bromobenzyl)oxy]benzoyl}-4-pyridin-2-ylpiperazine		CH	
154	1-{3-[(3-chlorobenzyl)oxy]benzoyl}-4-pyridin-2-ylpiperazine		CH	
155	1-{3-[(3-methoxybenzyl)oxy]benzoyl}-4-pyridin-2-ylpiperazine		CH	
156	3-({3-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]phenoxy}methyl)benzonitrile		CH	
157	1-{3-[(3-fluorobenzyl)oxy]benzoyl}-4-pyridin-2-ylpiperazine		CH	
158	1-[3-(benzyloxy)-4-methoxybenzoyl]-4-pyridin-2-ylpiperazine		COMe	
159	1-{3-[(3-bromobenzyl)oxy]-4-methoxybenzoyl}-4-pyridin-2-ylpiperazine		COMe	
160	1-{3-[(3-chlorobenzyl)oxy]-4-methoxybenzoyl}-4-pyridin-2-ylpiperazine		COMe	
161	1-{4-methoxy-3-[(3-methoxybenzyl)oxy]benzoyl}-4-pyridin-2-ylpiperazine		COMe	
162	3-({2-methoxy-5-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]phenoxy}methyl)benzonitrile		COMe	
163	1-{3-[(3-fluorobenzyl)oxy]-4-methoxybenzoyl}-4-pyridin-2-ylpiperazine		COMe	

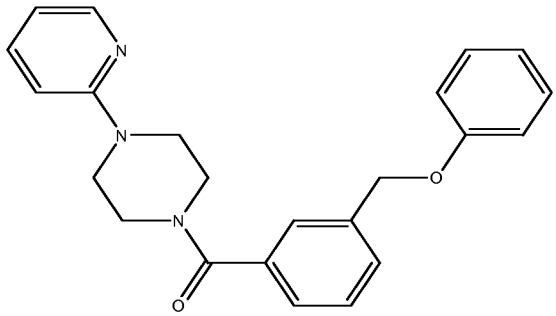
TABLE 3A

Cmpd	Name	LCMS Data			Biological Activity
		Time (min.)	Mass	Ion	PCT INHIB (%) @ 10 μM
150	1-{3-[(3-methylbenzyl)oxy]benzoyl}-4-pyridin-2-ylpiperazine	2.04	388.2	M+H	0
151	1-{4-methoxy-3-[(3-methylbenzyl)oxy]benzoyl}-4-pyridin-2-ylpiperazine	1.99	418.2	M+H	0
152	1-[3-(benzyloxy)benzoyl]-4-pyridin-2-ylpiperazine	1.95	374.2	M+H	0
153	1-{3-[(3-bromobenzyl)oxy]benzoyl}-4-pyridin-2-ylpiperazine	2.11	452.1	M+H	23
154	1-{3-[(3-chlorobenzyl)oxy]benzoyl}-4-pyridin-2-ylpiperazine	2.07	408.1	M+H	36
155	1-{3-[(3-methoxybenzyl)oxy]benzoyl}-4-pyridin-2-ylpiperazine	1.96	404.2	M+H	0
156	3-({3-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]phenoxy}methyl)benzonitrile	1.9	399.2	M+H	0
157	1-{3-[(3-fluorobenzyl)oxy]benzoyl}-4-pyridin-2-ylpiperazine	1.98	392.2	M+H	18
158	1-[3-(benzyloxy)-4-methoxybenzoyl]-4-pyridin-2-ylpiperazine	1.89	404.2	M+H	0
159	1-{3-[(3-bromobenzyl)oxy]-4-methoxybenzoyl}-4-pyridin-2-ylpiperazine	2.05	482.1	M+H	26
160	1-{3-[(3-chlorobenzyl)oxy]-4-methoxybenzoyl}-4-pyridin-2-ylpiperazine	2.02	438.2	M+H	11
161	1-{4-methoxy-3-[(3-methoxybenzyl)oxy]benzoyl}-4-pyridin-2-ylpiperazine	1.91	434.2	M+H	0

162	3-({2-methoxy-5-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]phenoxy}methyl)benzonitrile	1.86	429.2	M+H	0
163	1-{3-[(3-fluorobenzyl)oxy]-4-methoxybenzoyl}-4-pyridin-2-ylpiperazine	1.94	422.2	M+H	11

Example 4

1-[3-(phenoxymethyl)benzoyl]-4-pyridin-2-ylpiperazine (Compound 171)



Step 1: 3-(chloromethyl)phenyl)(4-(pyridin-2-yl)piperazin-1-yl)methanone

3-(chloromethyl)benzoyl chloride (5.29 mmol) was added to a solution of 1-(pyridin-2-yl)piperazine (5.29 mmol) and TEA (5.29 mmol) in 50 mL DCM cooled to 0 °C. The reaction was stirred at room temperature for 5 hours at which time LCMS indicated the reaction was complete. The reaction was washed with 100 mL water, 100 mL saturated $NaHCO_3$, and 100 mL dilute HCl. The organic layer was dried with Na_2SO_4 and concentrated in vacuo producing 0.98 g (3-(chloromethyl)phenyl)(4-(pyridin-2-yl)piperazin-1-yl)methanone as a slightly yellow oily solid. LCMS Rt = 0.61 min (MS = 316).

Step 2: 1-[3-(phenoxymethyl)benzoyl]-4-pyridin-2-ylpiperazine

A solution of potassium carbonate (0.277 mmol) and phenol (0.277 mmol) in DMF (1.5 ml) was prepared and stirred for 25 minutes. To this was added a solution of (3-(chloromethyl)phenyl)(4-(pyridin-2-yl)piperazin-1-yl)methanone (0.222 mmol) in DMF (1.5 ml). After stirring for 30 minutes at room temperature, the reaction was heated to 40°C and stirred for 16 hours. The reaction was concentrated on a speedvac and purified via prep HPLC (Gilson with

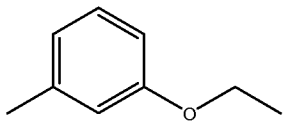
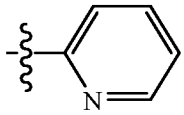
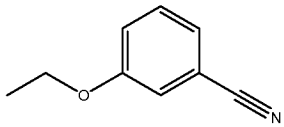
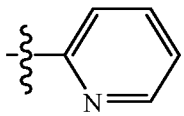
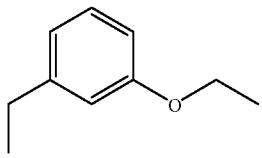
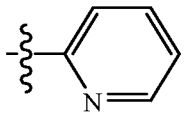
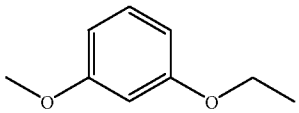
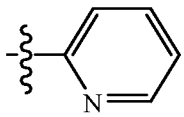
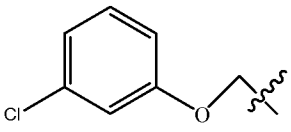
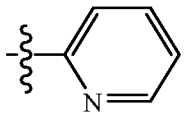
TFA additive) producing 37 mg of 1-[3-(phenoxymethyl)benzoyl]-4-pyridin-2-ylpiperazine. LCMS Rt = 1.86 min (MS = 374)

Compounds 164-171, shown in Tables 4 and 4A below, were prepared using the procedure of Example 4 described above.

THE FOLLOWING VALUES REFER TO FORMULA I

WHEREIN R_1, R_4, R_{4a}, R_5, R_{5a} = H; X_1 AND X_2 = CH; Z = CO

TABLE 4

Cmpd	Name	R_2	R_6
164	1-{3-[(3-methylphenoxy)methyl] benzoyl}-4-pyridin-2-yl piperazine		
165	3-({3-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]benzyl}oxy) benzonitrile		
166	1-{3-[(3-ethylphenoxy)methyl]benzoyl}-4-pyridin-2-ylpiperazine		
167	1-{3-[(3-methoxyphenoxy)methyl]benzoyl}-4-pyridin-2-ylpiperazine		
168	1-{3-[(3-chlorophenoxy)methyl]benzoyl}-4-pyridin-2-ylpiperazine		

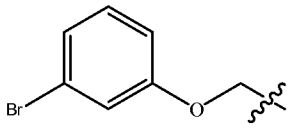
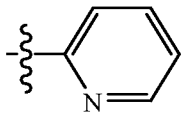
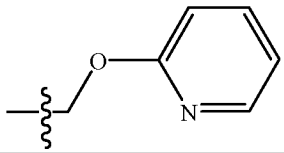
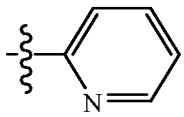
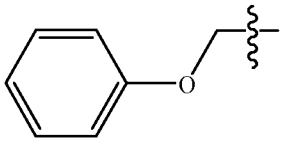
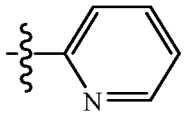
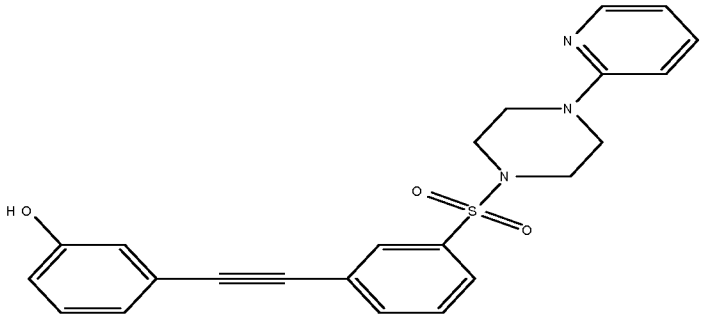
169	1-{3-[(3-bromophenoxy)methyl]benzoyl}-4-pyridin-2-ylpiperazine		
170	1-pyridin-2-yl-4-{3-[(pyridin-2-yloxy)methyl]benzoyl}piperazine		
171	1-[3-(phenoxymethyl)benzoyl]-4-pyridin-2-ylpiperazine		

TABLE 4A

Cmpd	Name	LCMS Data			Biological Activity
		Time (min.)	Mass	Ion	Median Ki (μM)
164	1-{3-[(3-methylphenoxy)methyl]benzoyl}-4-pyridin-2-ylpiperazine	1.98	388.2	M+H	1.747
165	3-({3-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]benzyl}oxy)benzonitrile	1.83	399.2	M+H	2.966
166	1-{3-[(3-ethylphenoxy)methyl]benzoyl}-4-pyridin-2-ylpiperazine	2.07	402.2	M+H	>10.00
167	1-{3-[(3-methoxyphenoxy)methyl]benzoyl}-4-pyridin-2-ylpiperazine	1.88	404.2	M+H	>10.00
168	1-{3-[(3-chlorophenoxy)methyl]benzoyl}-4-pyridin-2-ylpiperazine	2.02	408.1	M+H	0.813
169	1-{3-[(3-bromophenoxy)methyl]benzoyl}-4-pyridin-2-ylpiperazine	2.05	452.1	M+H	0.862
170	1-pyridin-2-yl-4-{3-[(pyridin-2-yloxy)methyl]benzoyl}piperazine	1.46	375.2	M+H	>10.00
171	1-[3-(phenoxymethyl)benzoyl]-4-pyridin-2-ylpiperazine	1.86	374.2	M+H	>10.00

Example 5

3-({3-[(4-pyridin-2-ylpiperazin-1-yl)sulfonyl]phenyl}ethynyl)phenol (Compound 172)



Step 1: 3-bromo-N-(2-(ethyl(pyridin-2-yl)amino)ethyl)-N-methylbenzenesulfonamide

To a solution of 1-(pyridin-2-yl)piperazine (6.21 mmol) and TEA (6.71 mmol) in 30 mL DCM was added dropwise a solution of 3-bromobenzene-1-sulfonyl chloride (6.21 mmol) in 10 mL DCM. The reaction was stirred at room temperature for 16 hours. The reaction was diluted with 20 mL DCM, washed with 30 mL water, 20 mL 5 percent (%) aq. K_2CO_3 solution, and brine. The organic layer was dried with MgSO4 and concentrated in vacuo producing 3-bromo-N-(2-(ethyl(pyridin-2-yl)amino)ethyl)-N-methylbenzenesulfonamide as a white solid used without further purification.

Step 2: 3-({3-[(4-pyridin-2-ylpiperazin-1-yl)sulfonyl] phenyl} ethynyl)phenol

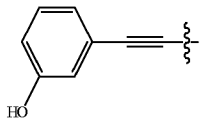
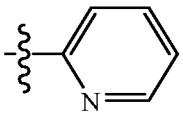
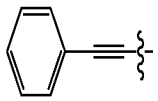
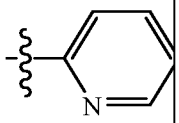
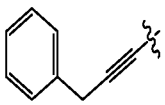
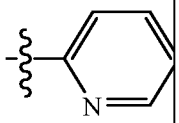
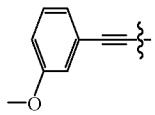
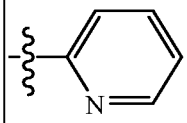
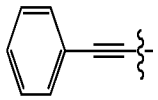
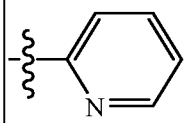
To a solution of 3-bromo-N-(2-(ethyl(pyridin-2-yl)amino)ethyl)-N-methylbenzenesulfonamide (0.13 mmol) and 3-hydroxyphenylacetylene (0.19 mmol) in DMF (2 mL) in a microwave vial was added copper iodide (0.026 mmol) and TEA (0.39 mmol). To the suspension was added $Pd(PPh_3)_2Cl_2$ (0.026 mmol). The vial was purged with N_2, capped, and microwaved for 10 minutes at 150°C. The product was concentrated on a speedvac and purified via prep HPLC (Gilson with TFA additive) to produce 3-({3-[(4-pyridin-2-ylpiperazin-1-yl)sulfonyl]phenyl}ethynyl)phenol. LCMS Rt = 2.07 min (MS = 420).

Compounds 172-176, shown in Table 5 below, were prepared using the procedure of Example 5 described above.

THE FOLLOWING VALUES REFER TO FORMULA I

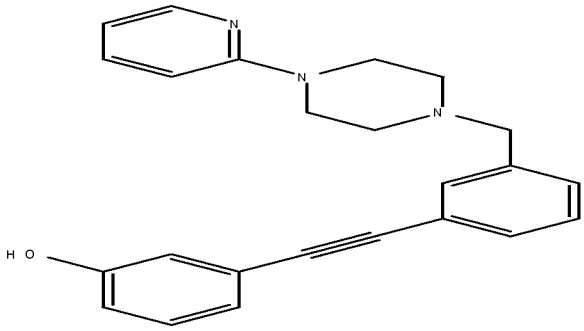
WHEREIN R_1, R_4, R_{4a}, R_5, R_{5a} = H; X_1 AND X_2 = CH; Z = SO_2

TABLE 5

Cmpd	Name	R_2	R_6	LCMS Data			Biological Activity
				Time (min.)	Mass	Ion	PCT INHIB (%) @ 10 μM
172	3-({3-[(4-pyridin-2-ylpiperazin-1-yl)sulfonyl] phenyl}ethynyl)phenol			2.07	420.1	M+H	0
173	1-{[3-(cyclohex-1-en-1-ylethynyl)phenyl]sulfonyl} -4-pyridin-2-ylpiperazine			2.46	408.2	M+H	0
174	1-{[3-(3-phenylprop-1-yn-1-yl)phenyl]sulfonyl}-4-pyridin-2-ylpiperazine			2.02	418.2	M+H	0
175	1-({3-[(3-methoxyphenyl) ethynyl]phenyl}sulfonyl)-4-pyridin-2-ylpiperazine			2.34	434.1	M+H	0
176	1-{[3-(phenylethynyl) phenyl]sulfonyl}-4-pyridin-2-ylpiperazine			2.32	404.1	M+H	0

Example 6

3-({3-[(4-pyridin-2-ylpiperazin-1-yl)methyl]phenyl}ethynyl)phenol (Compound 177)



Step 1: 1-(3-bromobenzyl)-4-(pyridin-2-yl)piperazine

To a solution of 1-(pyridin-2-yl)piperazine (6.1 mmol) and DIEA (18.4 mmol) in 20 mL THF was added 1-bromo-3-(bromomethyl)benzene (7.4 mmol). The reaction was stirred at room temperature for 16 hours at which time LCMS indicated the reaction was complete. The reaction was diluted with 50 mL EtOAc and washed with 10 mL saturated NH_4Cl, 10 mL water, and 50 mL brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification via silica column chromatography (Hex:EtOac as eluent) produced 1-(3-bromobenzyl)-4-(pyridin-2-yl)piperazine.

Step 2: 3-({3-[(4-pyridin-2-ylpiperazin-1-yl)methyl]phenyl} ethynyl)phenol

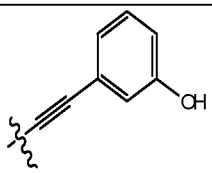
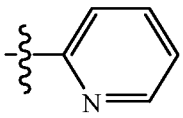
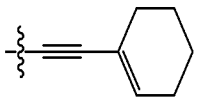
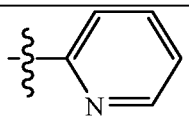
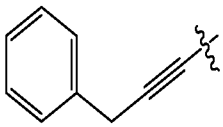
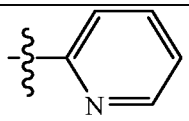
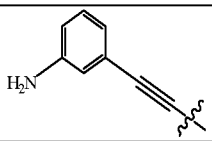
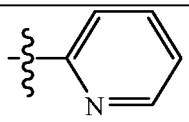
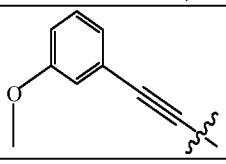
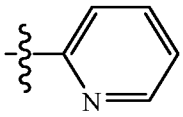
To a solution of 1-(3-bromobenzyl)-4-(pyridin-2-yl)piperazine (0.15 mmol) and 3-hydroxyphenylacetylene (0.23 mmol) in DMF (2 mL) was added copper iodide (0.03 mmol) and TEA (0.45 mmol). To the suspension was added $Pd(PPh_3)_2Cl_2$ (0.03 mmol). The vial was purged with N_2, capped, and microwaved for 10 minutes at 150°C. The reaction was concentrated on a speedvac and purified via prep HPLC (Gilson with TFA additive) producing 3-({3-[(4-pyridin-2-ylpiperazin-1-yl)methyl]phenyl}ethynyl)phenol. LCMS Rt = 1.84 min (MS = 370).

Compounds 177-181, shown in Table 6 below, were prepared using the procedure of Example 6 described above.

THE FOLLOWING VALUES REFER TO FORMULA I

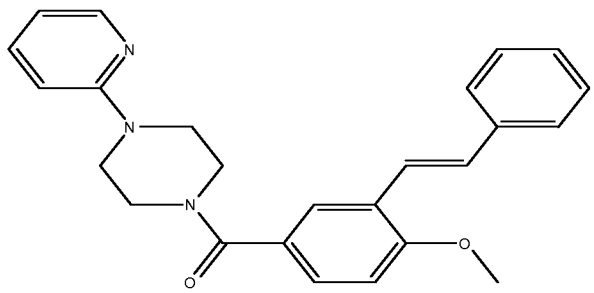
WHEREIN R_1, R_4, R_{4a}, R_5, R_{5a} = H; X_1 AND X_2 = CH; Z = CH_2

TABLE 6

Cmpd	Name	R_2	R_6	LCMS Data			Biological Activity
				Time (min.)	Mass	Ion	PCT INHIB (%) @ 10 μM
177	3-({3-[(4-pyridin-2-ylpiperazin-1-yl)methyl] phenyl}ethynyl)phenol			1.84	370.2	M+H	13
178	1-[3-(cyclohex-1-en-1-ylethynyl)benzyl]-4-pyridin-2-ylpiperazine			2.15	358.2	M+H	0
179	1-[3-(3-phenylprop-1-yn-1-yl)benzyl]-4-pyridin-2-ylpiperazine			2.14	368.2	M+H	0
180	3-({3-[(4-pyridin-2-ylpiperazin-1-yl)methyl]phenyl}ethynyl)aniline			1.74	369.2	M+H	0
181	1-{3-[(3-methoxy phenyl)ethynyl]benzyl}-4-pyridin-2-ylpiperazine			1.98	384.2	M+H	0

Example 7

1-{4-methoxy-3-[(E)-2-phenylvinyl]benzoyl}-4-pyridin-2-ylpiperazine (Compound 182)



To a solution of (3-bromo-4-methoxyphenyl)(4-(pyridin-2-yl)piperazin-1-yl)methanone (0.2 mmol; as synthesized in Example 1) in NMP (1 mL) was added N,N dimethyl glycine (0.02 mmol), K_2CO_3 (0.4 mmol), styrene (0.3 mmol), and $Pd(OAc)_2$ (0.02 mmol). The vial was purged with N_2, capped, and heated to 130 °C for 18 hours. The reaction was concentrated on a speedvac and purified via prep HPLC (Gilson with TFA additive) to produce 1-{4-methoxy-3-[(E)-2-phenylvinyl]benzoyl}-4-pyridin-2-ylpiperazine. LCMS Rt = 2.15min (MS = 400.2).

The properties of Compound 182 are shown in Tables 7 and 7A below.

THE FOLLOWING VALUES REFER TO FORMULA I

R_1, R_4, R_{4a}, R_5, R_{5a} = H; X_2 = CH; Z = CO

TABLE 7

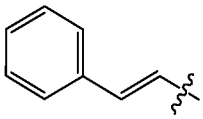
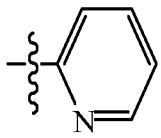
Cmpd	Name	R_2	X_1	R_6
182	1-{4-methoxy-3-[(E)-2-phenylvinyl]benzoyl}-4-pyridin-2-ylpiperazine		COMe	

TABLE 7A

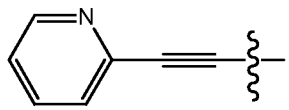
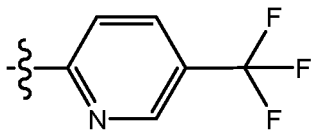
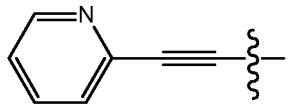
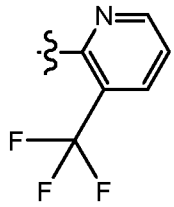
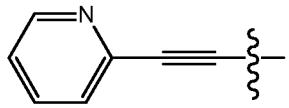
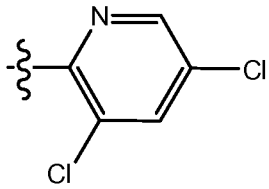
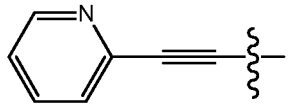
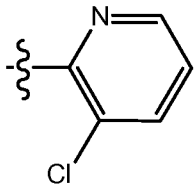
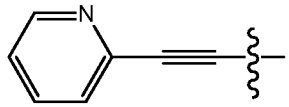
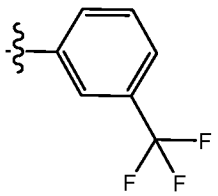
Cmpd	Name	LCMS Data			Biological Activity	
		Time (min.)	Mass	Ion	Median K_i (μM)	PCT INHIB (%) @ 10 μM
182	1-{4-methoxy-3-[(E)-2-phenylvinyl]benzoyl}-4-pyridin-2-ylpiperazine	2.15	400.2	M+H	0.82716	86

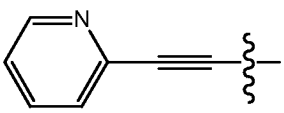
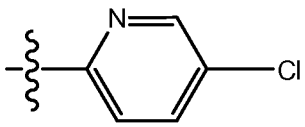
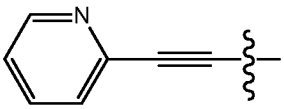
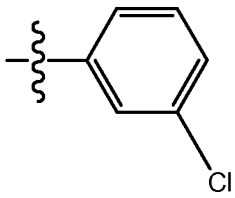
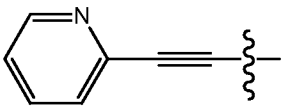
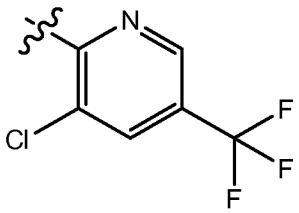
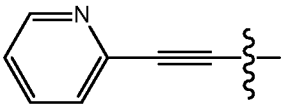
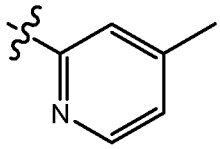
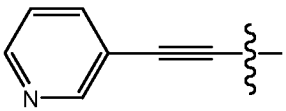
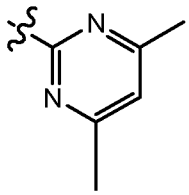
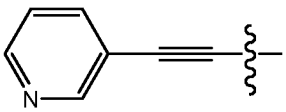
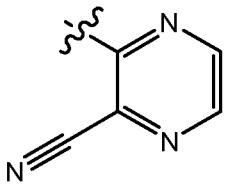
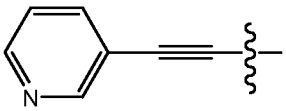
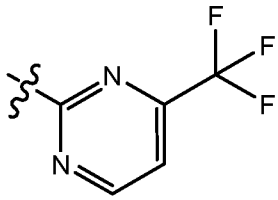
Compounds 183-291, shown in Table 8 and 8A below, were prepared using the procedure of Example 2 described above.

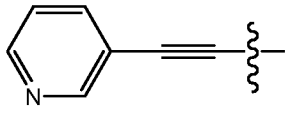
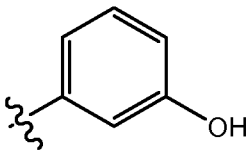
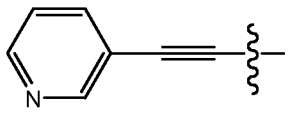
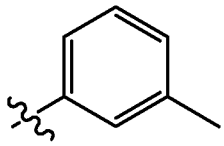
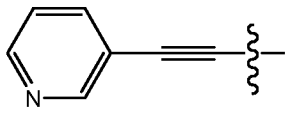
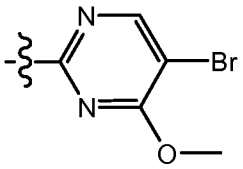
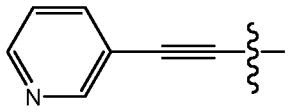
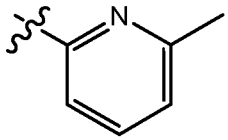
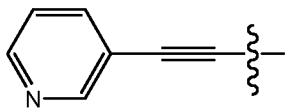
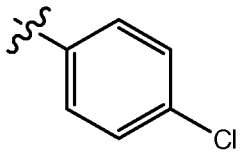
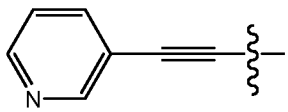
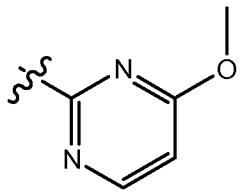
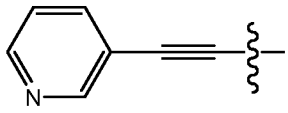
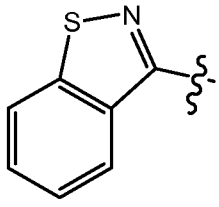
UNLESS NOTED OTHERWISE THE FOLLOWING VALUES REFER TO FORMULA I

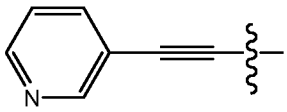
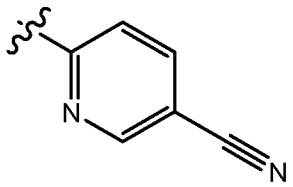
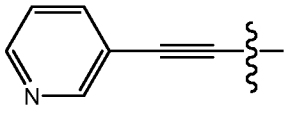
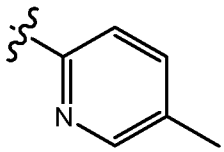
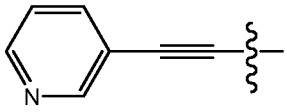
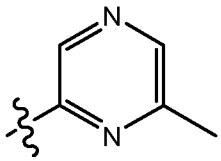
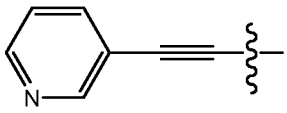
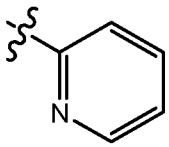
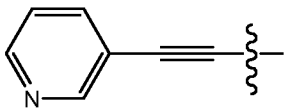
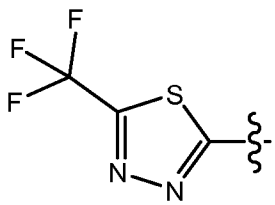
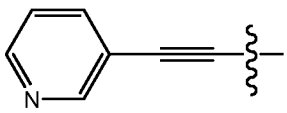
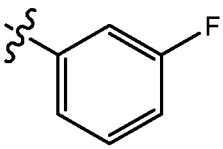
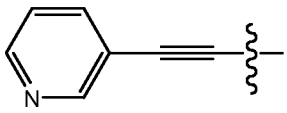
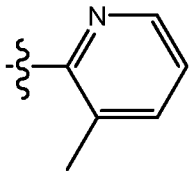
WHEREIN R_1, R_4, R_{4a}, R_5, R_{5a} = H; X_1 = COMe, X_2 = CH; Z = CO

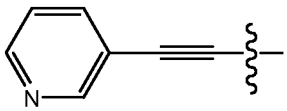
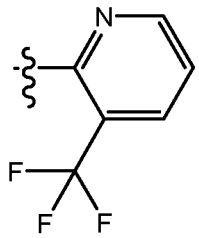
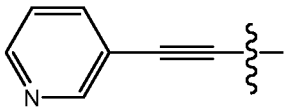
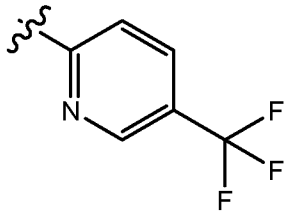
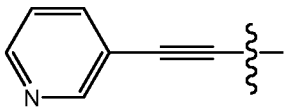
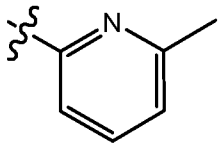
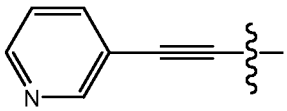
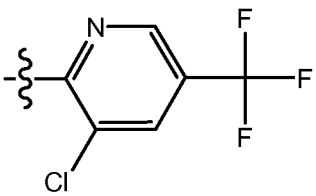
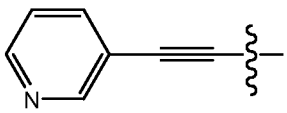
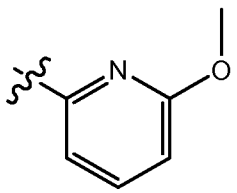
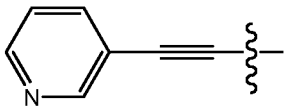
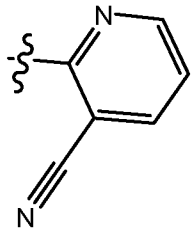
TABLE 8

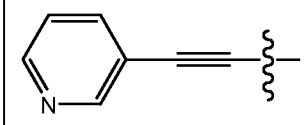
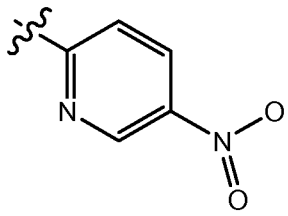
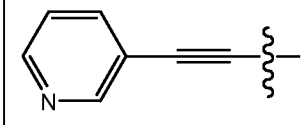
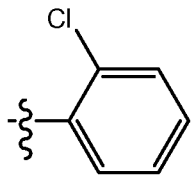
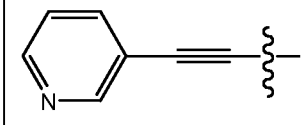
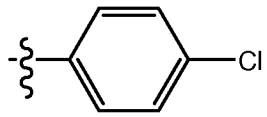
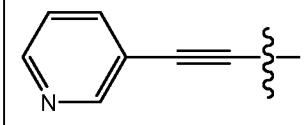
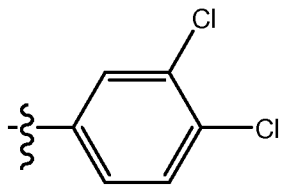
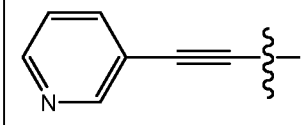
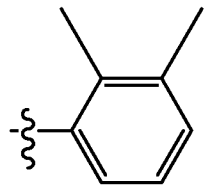
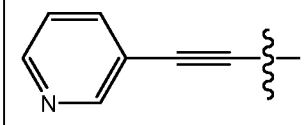
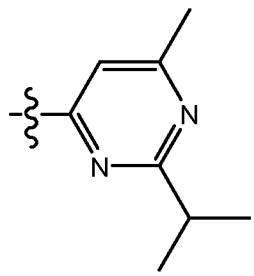
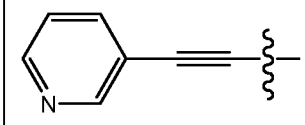
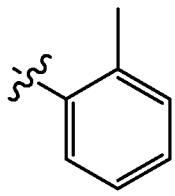
Cmpd	Name	R_2	Noted Values	R_6
183	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-[5-(trifluoromethyl)pyridin-2- yl]piperazine			
184	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-[3-(trifluoromethyl)pyridin-2- yl]piperazine			
185	1-(3,5-dichloro pyridin-2-yl)-4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazine			
186	1-(3-chloropyridin-2-yl)-4-[4-methoxy-3-(pyridin-2-yl ethynyl)benzoyl]piperazine			
187	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-[3-(trifluoromethyl)phenyl]piperazine			

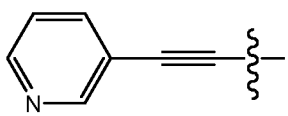
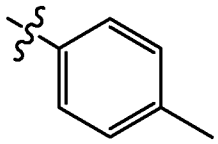
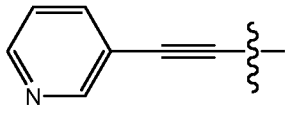
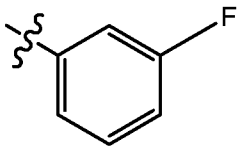
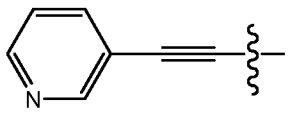
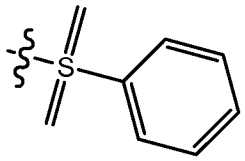
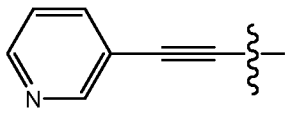
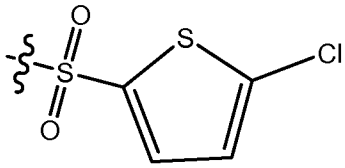
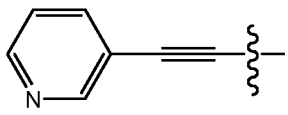
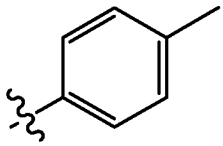
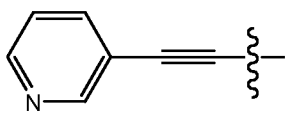
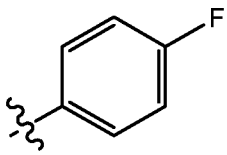
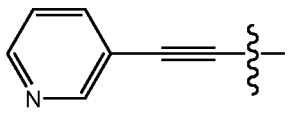
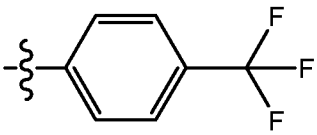
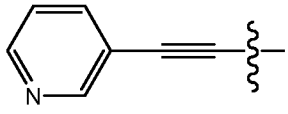
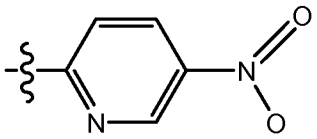
188	1-(5-chloropyridin-2-yl)-4-[4-methoxy-3-(pyridin-2-yl ethynyl) benzoyl]piperazine			
189	1-(3-chlorophenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazine			
190	1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazine			
191	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-(4-methyl pyridin-2-yl)piperazine			
192	2-{4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}-4,6- dimethyl pyrimidine			
193	3-{4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}pyrazine-2-carbonitrile			
194	2-{4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}-4- (trifluoro methyl)pyrimidine			

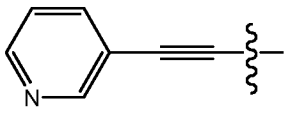
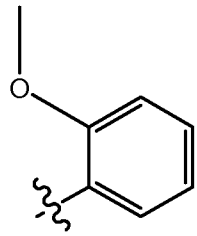
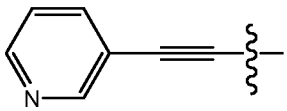
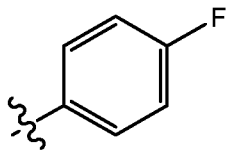
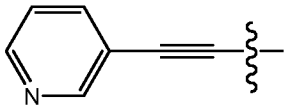
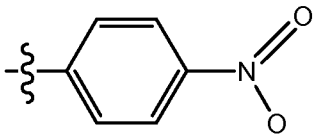
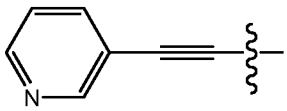
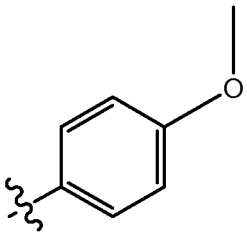
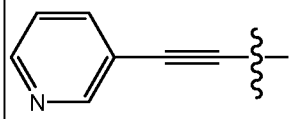
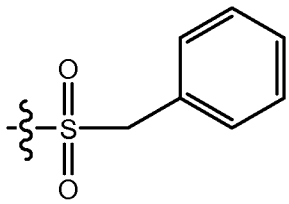
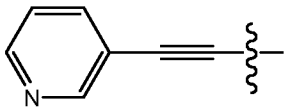
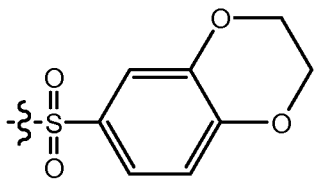
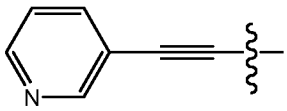
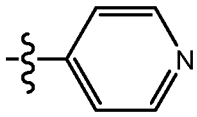
195	3-{4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}phenol			
196	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-(3-methylphenyl)piperazine			
197	5-bromo-4-methoxy-2-{4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}pyrimidine			
198	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-(6-methylpyridin-2-yl)piperazine			
199	(1R,4S)-2-(4-chlorophenyl)-5-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-2,5- diazabicyclo [2.2.1] heptane		R_{4a}/R_5 = Bridging Methylene	
200	4-methoxy-2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1- yl} pyrimidine			
201	3-{4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}-1,2- benziso thiazole			

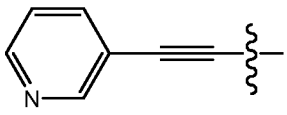
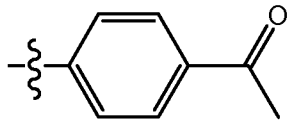
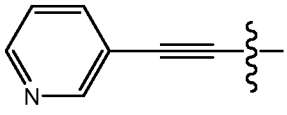
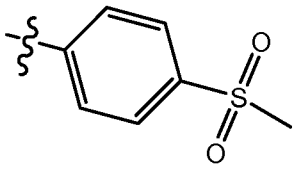
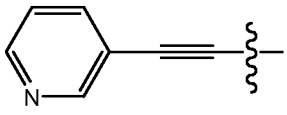
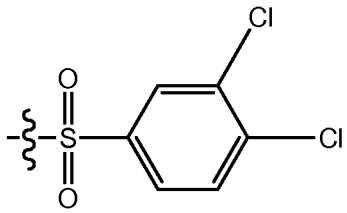
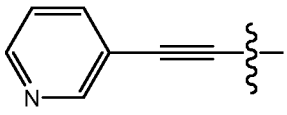
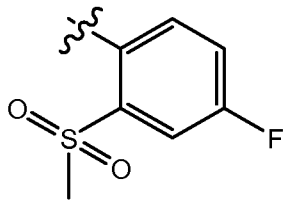
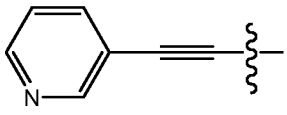
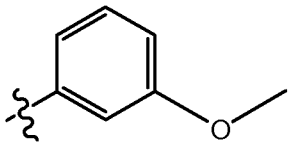
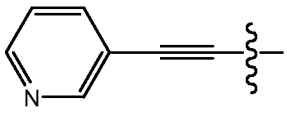
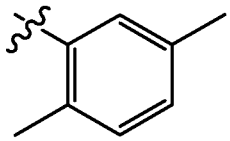
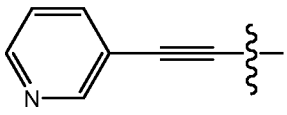
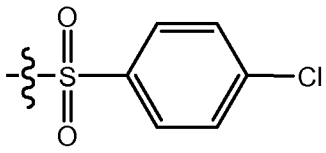
202	6-{4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-1,4-diazepan-1- yl} nicotinonitrile			
203	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-(5-methylpyridin-2-yl) piperazine			
204	2-{4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}-6-methyl pyrazine			
205	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-pyridin-2-yl-1,4-diazepane [n = 2]			
206	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-[5-(trifluoromethyl)-1,3,4- thiadiazol-2-yl]piperazine			
207	(1R,4S)-2-(3-fluorophenyl)-5-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-2,5- diazabicyclo [2.2.1]heptane		R_{4a}/R_5 = Bridging Methylene	
208	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-(3-methyl pyridin-2-yl) piperazine			

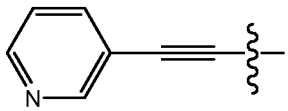
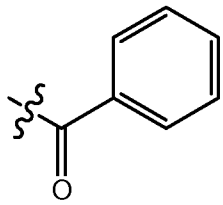
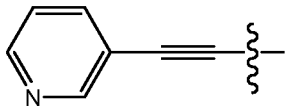
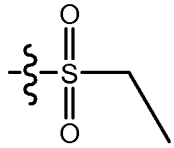
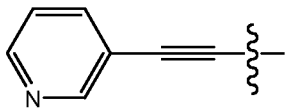
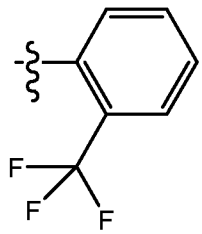
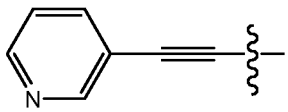
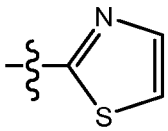
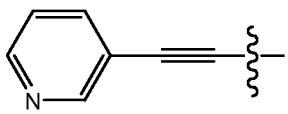
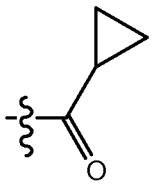
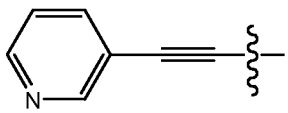
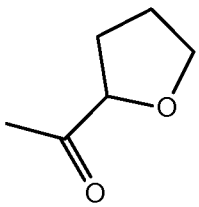
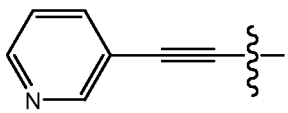
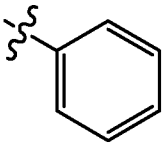
209	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-[3-(trifluoromethyl)pyridin-2- yl]-1,4-diazepane			
210	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-[5-(trifluoromethyl)pyridin-2- yl]-1,4-diazepane [n = 2]			
211	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-(6-methylpyridin-2-yl)-1,4- diazepane			
212	1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-1,4-diazepane [n = 2]			
213	1-(6-methoxy pyridin-2-yl)-4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl] piperazine			
214	2-{4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-1,4-diazepan-1- yl} nicotinonitrile [n = 2]			

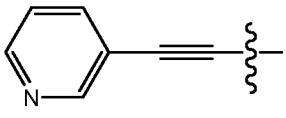
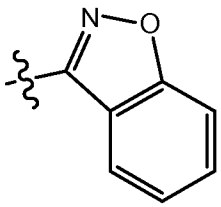
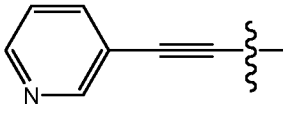
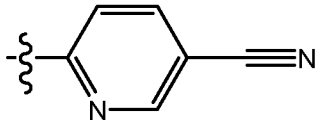
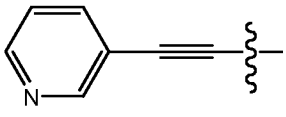
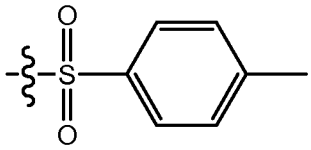
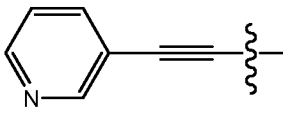
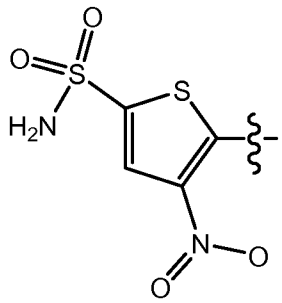
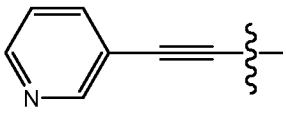
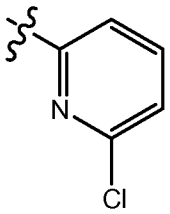
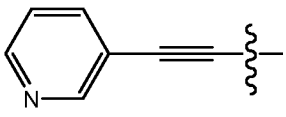
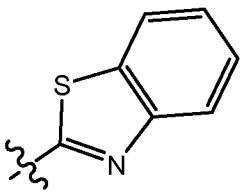
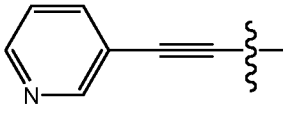
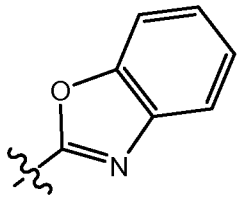
215	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-(5-nitropyridin-2-yl)-1,4-diazepane [n = 2]			
216	1-(2-chlorophenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazine			
217	1-(4-chlorophenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazine			
218	1-(3,4-dichloro phenyl)-4-[4-methoxy-3-(pyridin-2-yl ethynyl)benzoyl] piperazine			
219	1-(2,3-dimethyl phenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine			
220	2-isopropyl-4-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1-yl}-6-methylpyrimidine			
221	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-(2-methylphenyl) piperazine			

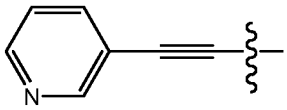
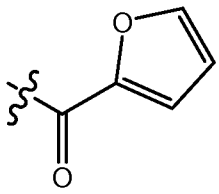
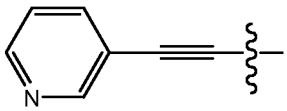
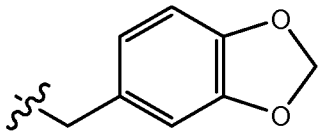
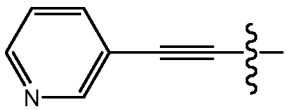
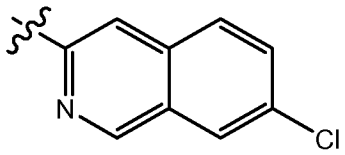
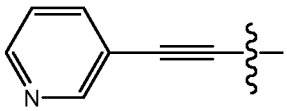
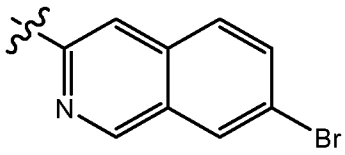
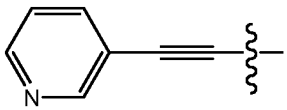
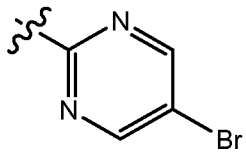
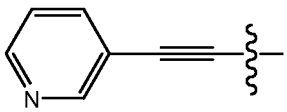
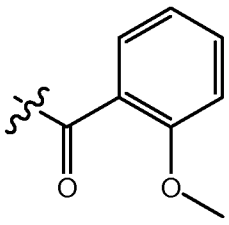
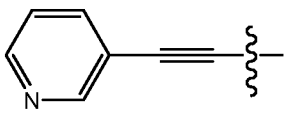
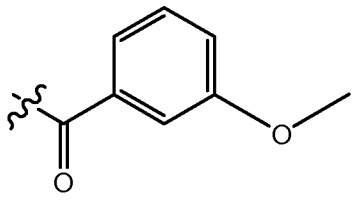
222	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-(4-methyl phenyl) piperazine			
223	1-(3-fluorophenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazine			
224	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-(phenyl sulfonyl)piperazine			
225	1-[(5-chloro-2-thienyl)sulfonyl]-4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl] piperazine			
226	(1R,4S)-2-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-5-(4-methylphenyl)-2,5-diazabicyclo [2.2.1] heptane		R_{4a}/R_5 = Bridging Methylene	
227	(1S,4R)-2-(4-fluorophenyl)-5-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-2,5- diazabicyclo [2.2.1]heptane		R_{4a}/R_5 = Bridging Methylene	
228	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-[4-(trifluoromethyl)phenyl]piperazine			
229	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-(5-nitropyridin-2-yl)piperazine			

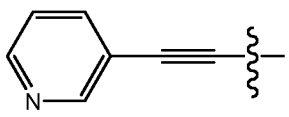
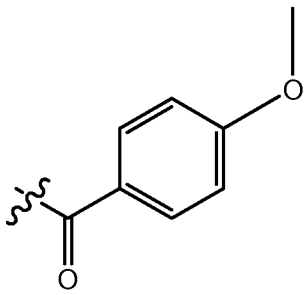
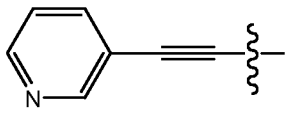
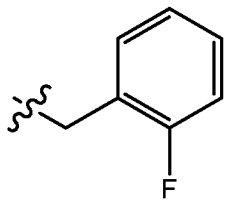
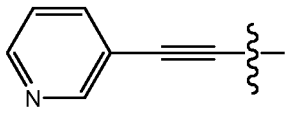
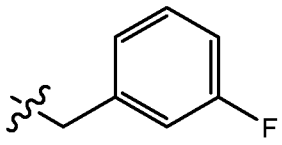
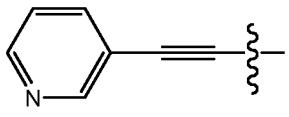
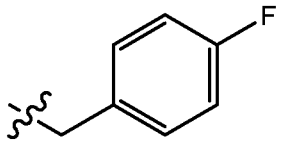
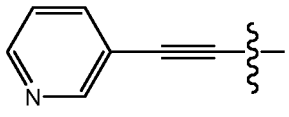
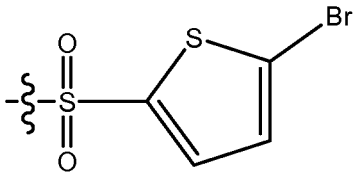
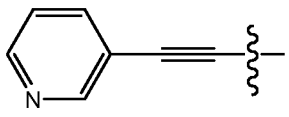
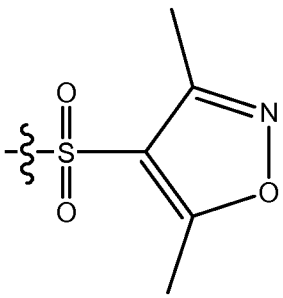
230	1-(2-methoxy phenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine			
231	1-(4-fluorophenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazine			
232	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-(4-nitro phenyl)piperazine			
233	1-(4-methoxy phenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine			
234	1-(benzylsulfonyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazine			
235	1-(2,3-dihydro-1,4-benzodioxin-6-ylsulfonyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine			
236	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-pyridin-4-ylpiperazine			

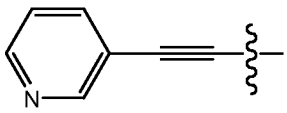
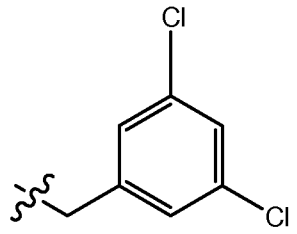
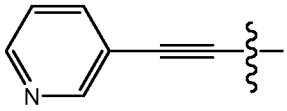
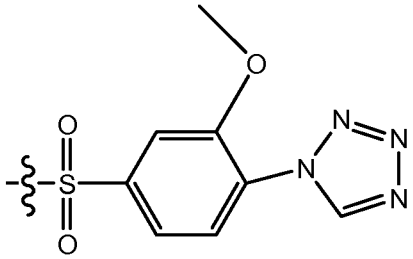
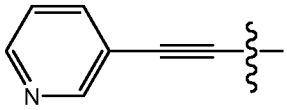
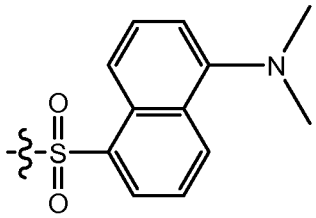
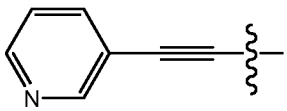
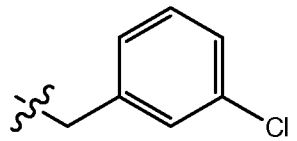
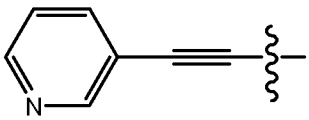
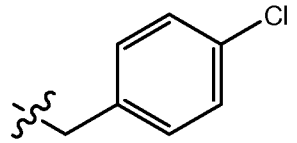
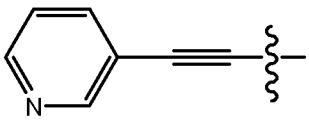
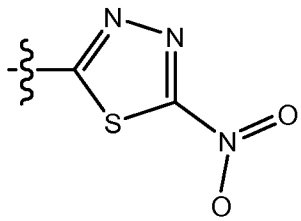
237	1-4-{4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}phenyl)ethanone			
238	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-[4- (methyl sulfonyl)phenyl] piperazine			
239	1-[(3,4-dichloro phenyl)sulfonyl]-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine			
240	1-[4-fluoro-2-(methylsulfonyl)phenyl]-4-[4-methoxy-3-(pyridin-2- ylethynyl) benzoyl]piperazine			
241	1-(3-methoxy phenyl)-4-[4-methoxy-3-(pyridin-2-yl ethynyl)benzoyl] piperazine			
242	1-(2,5-dimethyl phenyl)-4-[4-methoxy-3-(pyridin-2-yl ethynyl)benzoyl] piperazine			
243	1-[(4-chlorophenyl) sulfonyl]-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine			

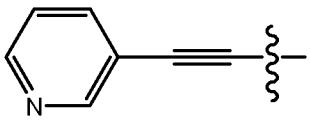
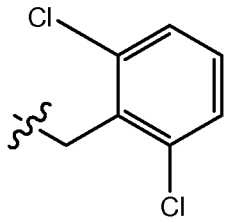
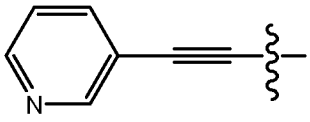
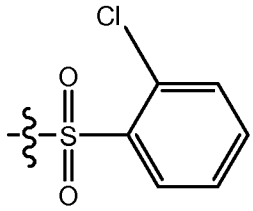
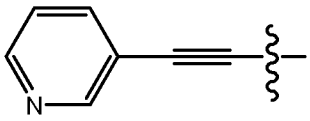
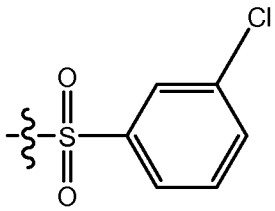
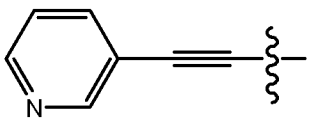
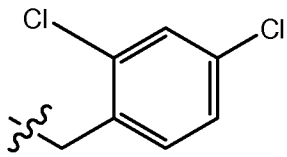
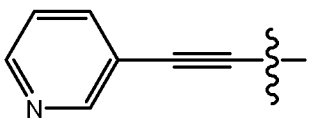
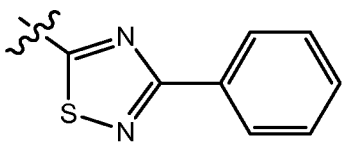
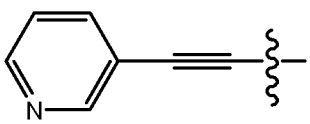
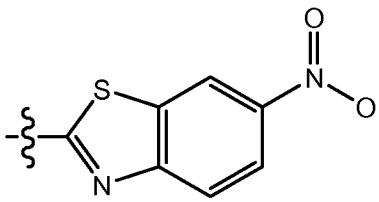
244	1-benzoyl-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine			
245	1-(ethylsulfonyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl] piperazine			
246	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-[2-(trifluoromethyl)phenyl]piperazine			
247	1-[4-methoxy-3-(pyridin-2-yl ethynyl)benzoyl]-4-(1,3-thiazol-2-yl) piperazine			
248	1-(cyclopropyl carbonyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine			
249	1-[4-methoxy-3-(pyridin-2-yl ethynyl)benzoyl]-4-(tetrahydrofuran-2-ylcarbonyl) piperazine			
250	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-2-methyl-4-phenylpiperazine [R_4 = CH_3]			

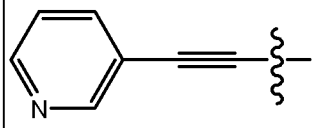
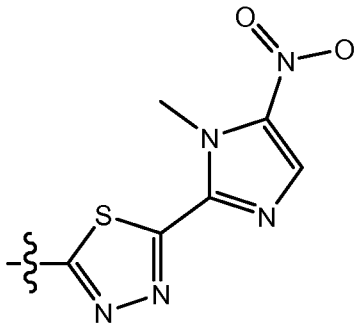
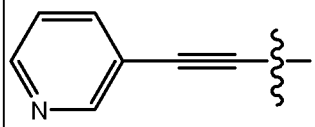
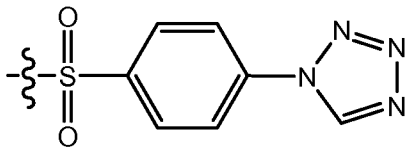
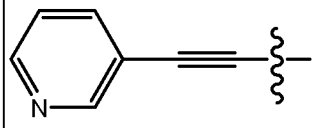
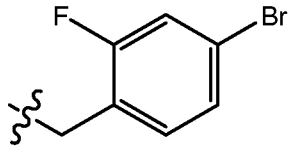
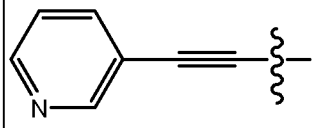
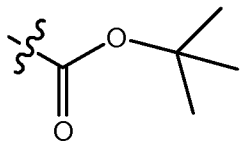
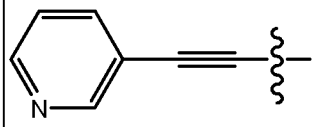
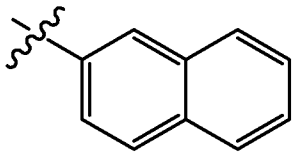
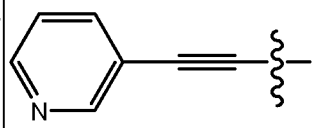
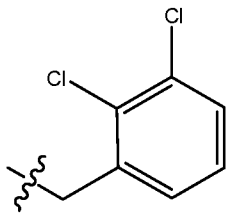
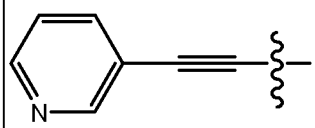
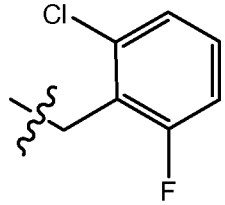
251	3-{4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}-1,2-benzisoxazole			
252	6-{4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}nicotinonitrile			
253	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-[(4-methylphenyl)sulfonyl]piperazine			
254	5-{4-[4-methoxy-3-(pyridin-2-yl ethynyl)benzoyl]piperazin-1-yl}-4-nitrothiophene- 2-sulfonamide			
255	1-(6-chloropyridin-2-yl)-4-[4-methoxy-3-(pyridin-2-yl ethynyl)benzoyl] piperazine			
256	2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-1,3-benzothiazole			
257	2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-1,3-benzoxazole			

258	1-(2-furoyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine			
259	1-(1,3-benzodioxol-5-ylmethyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine			
260	7-chloro-3-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1-yl}isoquinoline			
261	7-bromo-3-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1- yl} Isoquinoline			
262	5-bromo-2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1-yl}pyrimidine			
263	1-(2-methoxy benzoyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine			
264	1-(3-methoxy benzoyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine			

265	1-(4-methoxy benzoyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine			
266	1-(2-fluorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazine			
267	1-(3-fluorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine			
268	1-(4-fluorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine			
269	1-[(5-bromo-2-thienyl)sulfonyl]-4-[4-methoxy-3-(pyridin-2-yl ethynyl)benzoyl] piperazine			
270	1-[(3,5-dimethylisoxazol-4-yl)sulfonyl]-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine			

271	1-(3,5-dichlorophenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazine			
272	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-{[3-methoxy-4-(1H-tetrazol-1- yl)phenyl] sulfonyl}piperazine			
273	5-({4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}sulfonyl)-N,N-dimethylnaphthalen-1-amine			
274	1-(3-chlorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazine			
275	1-(4-chlorobenzyl)-4-[4-methoxy-3-(pyridin-2-yl ethynyl)benzoyl] piperazine			
276	1-[4-methoxy-3-(pyridin-2-yl ethynyl)benzoyl]-4-(5-nitro-1,3,4-thiadiazol-2- yl)piperazine			

277	1-(2,6-dichlorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazine			
278	1-[(2-chlorophenyl) sulfonyl]-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine			
279	1-[(3-chlorophenyl) sulfonyl]-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine			
280	1-(2,4-dichlorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazine			
281	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-(3-phenyl-1,2,4-thiadiazol-5- yl) piperazine			
282	2-{4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}-6-nitro-1,3-benzothiazole			

283	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-[5-(1-methyl-5-nitro-1H-imidazol- 2-yl)-1,3,4-thiadiazol-2-yl] piperazine			
284	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-{[4-(1H-tetrazol-1- yl)phenyl] sulfonyl}piperazine			
285	1-(4-bromo-2-fluorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine			
286	tert-butyl 4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine-1-carboxylate			
287	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-(2-naphthylsulfonyl) piperazine			
288	1-(3,4-dichloro benzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazine			
289	1-(2-chloro-6-fluorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine			

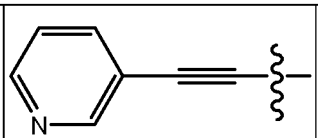
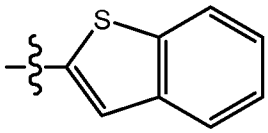
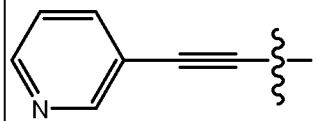
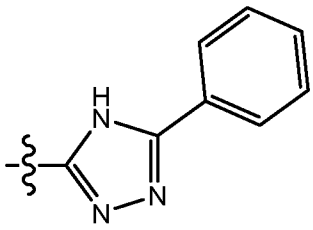
290	1-(1-benzothiophen-2-yl)-4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazine			
291	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-(5-phenyl-4H-1,2,4-triazol-3- yl) piperazine			

TABLE 8A

Cmpd	Name	LCMS data		Biological Activity	
		Mass	Ion	Median Ki (μM)	IC50 (uM)
183	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-[5-(trifluoromethyl)pyridin-2-yl]piperazine	467.2	M+H	0.041	0.066
184	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine	467.2	M+H	0.078	0.117
185	1-(3,5-dichloropyridin-2-yl)-4-[4-methoxy-3-(pyridin-2- ylethynyl) benzoyl]piperazine	467.1	M+H	0.047	0.043
186	1-(3-chloropyridin-2-yl)-4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazine	433.1	M+H	0.019	0.037
187	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-[3- (trifluoro methyl)phenyl]piperazine	466.2	M+H	0.005	0.834
188	1-(5-chloropyridin-2-yl)-4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazine	433.2	M+H	0.007	0.086
189	1-(3-chlorophenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine	432.2	M+H	0.004	0.148

190	1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	501.1	M+H	0.413	0.408
191	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(4-methylpyridin-2-yl)piperazine	413.2	M+H	0.019	0.031
192	2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-4,6-dimethylpyrimidine	428.3	M+H	0.045	0.109
193	3-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrazine-2- carbonitrile	425.2	M+H	0.034	0.046
194	2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-4-(trifluoromethyl)pyrimidine	468.2	M+H	0.004	0.078
195	3-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}phenol	414.2	M+H	0.026	0.702
196	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(3-methylphenyl)piperazine	412.2	M+H	0.016	0.065
197	5-bromo-4-methoxy-2-{4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1- yl}pyrimidine	508.1	M+H	0.012	0.056
198	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(6-methyl pyridin-2-yl)piperazine	413.2	M+H	0.030	0.034
199	(1R,4S)-2-(4-chlorophenyl)-5-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-2,5-diazabicyclo[2.2.1] heptane	444.2	M+H	0.076	>1.000
200	4-methoxy-2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1-yl}pyrimidine	430.2	M+H	0.021	0.024
201	3-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-1,2-benzisothiazole	455.2	M+H	0.003	0.024

202	6-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-1,4-diazepan-1-yl}nicotinonitrile	438.2	M+H	1.041	
203	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(5-methylpyridin-2-yl)piperazine	413.2	M+H	0.029	0.032
204	2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-6-methylpyrazine	414.2	M+H	0.029	0.132
205	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-pyridin-2-yl-1,4-diazepane	413.2	M+H	0.131	>1.000
206	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-[5-(trifluoromethyl)-1,3,4- thiadiazol-2-yl]piperazine	474.2	M+H	0.066	0.295
207	(1R,4S)-2-(3-fluorophenyl)-5-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-2,5- diazabicyclo[2.2.1]heptane	428.2	M+H	0.019	0.306
208	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(3-methylpyridin-2-yl)piperazine	413.2	M+H	0.021	0.141
209	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-[3-(trifluoromethyl)pyridin-2- yl]-1,4-diazepane	481.2	M+H	0.674	
210	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-[5-(trifluoromethyl)pyridin-2- yl]-1,4-diazepane	481.2	M+H	0.851	
211	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(6-methylpyridin-2-yl)-1,4- diazepane	427.2	M+H	0.619	
212	1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-1,4-diazepane	515.1	M+H	0.704	

213	1-(6-methoxypyridin-2-yl)-4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazine	429.2	M+H	0.011	0.086
214	2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-1,4-diazepan-1-yl}nicotinonitrile	438.2	M+H	0.458	
215	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(5-nitropyridin-2-yl)-1,4- diazepane	458.2	M+H	2.193	
216	1-(2-chlorophenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine	432.1	M+H	0.107	>1.000
217	1-(4-chlorophenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine	432.1	M+H	0.027	0.336
218	1-(3,4-dichlorophenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine	466	M+H	0.048	>1.000
219	1-(2,3-dimethylphenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine	426.1	M+H	0.168	>1.000
220	2-isopropyl-4-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-6-methylpyrimidine	456.2	M+H	0.089	>1.000
221	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(2-methylphenyl)piperazine	412.1	M+H	0.100	>1.000
222	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(4-methylphenyl)piperazine	412.1	M+H	0.074	>1.000
223	1-(3-fluorophenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	416.1	M+H	0.010	0.103
224	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(phenylsulfonyl)piperazine	462.1	M+H	0.115	
225	1-[(5-chloro-2-thienyl)sulfonyl]-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	502	M+H	0.051	>1.000

226	(1R,4S)-2-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-5-(4-methylphenyl)-2,5- diazabicyclo[2.2.1]heptane	424.1	M+H	0.277	>1.000
227	(1S,4R)-2-(4-fluorophenyl)-5-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-2,5- diazabicyclo[2.2.1]heptane	428.1	M+H	0.071	>1.000
228	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-[4-(trifluoromethyl)phenyl]piperazine	466.1	M+H	0.674	
229	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(5-nitropyridin-2-yl)piperazine	444.1	M+H	0.056	>1.000
230	1-(2-methoxyphenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	428.1	M+H	0.734	
231	1-(4-fluorophenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	416.1	M+H	0.023	0.244
232	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(4-nitrophenyl)piperazine	443.1	M+H	0.096	>1.000
233	1-(4-methoxyphenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	428.1	M+H	0.066	>1.000
234	1-(benzylsulfonyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	476.1	M+H	IC50 >10 uM	
235	1-(2,3-dihydro-1,4-benzodioxin-6-ylsulfonyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	520	M+H	0.075	>1.000
236	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-pyridin-4-ylpiperazine	399.1	M+H	0.078	>1.000
237	1-(4-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}phenyl)ethanone	440.12	M+H	0.021	0.119
238	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-[4-(methylsulfonyl)phenyl]piperazine	476.1	M+H	0.521	

239	1-[(3,4-dichlorophenyl)sulfonyl]-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	530	M+H	1.412	
240	1-[4-fluoro-2-(methylsulfonyl)phenyl]-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	494	M+H	IC50 >10 uM	
241	1-(3-methoxyphenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	428.1	M+H	0.015	0.081
242	1-(2,5-dimethylphenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	426.2	M+H	1.005	
243	1-[(4-chlorophenyl)sulfonyl]-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	496	M+H	0.014	0.154
244	1-benzoyl-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	426.1	M+H	0.054	0.237
245	1-(ethylsulfonyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	414.1	M+H	0.231	0.344
246	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-[2-(trifluoromethyl)phenyl]piperazine	466.1	M+H	2.842	
247	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(1,3-thiazol-2-yl)piperazine	405	M+H	0.017	0.085
248	1-(cyclopropylcarbonyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	390.1	M+H	0.083	>1.000
249	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(tetrahydrofuran-2-ylcarbonyl)piperazine	420.1	M+H	0.181	
250	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-2-methyl-4-phenylpiperazine	412.1	M+H	0.024	0.096
251	3-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-1,2-benzisoxazole	439.1	M+H	0.006	0.025

252	6-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}nicotinonitrile	424.1	M+H	0.033	0.192
253	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-[(4-methylphenyl)sulfonyl]piperazine	476.1	M+H	0.021	0.180
254	5-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-4-nitrothiophene- 2-sulfonamide	528	M+H	0.108	
255	1-(6-chloropyridin-2-yl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	433.1	M+H	0.009	0.129
256	2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-1,3-benzothiazole	445.1	M+H	0.043	0.100
257	2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-1,3-benzoxazole	439.1	M+H	0.038	0.110
258	1-(2-furoyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	416.1	M+H	0.041	0.095
259	1-(1,3-benzodioxol-5-ylmethyl)-4-[4-methoxy-3-(pyridin-2- ylethynyl) benzoyl]piperazine	456.1	M+H	0.038	0.157
260	7-chloro-3-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}isoquinoline	483.1	M+H	0.951	
261	7-bromo-3-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}isoquinoline	527	M+H	1.377	
262	5-bromo-2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine	478	M+H	0.017	0.148
263	1-(2-methoxybenzoyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine	456.1	M+H	0.169	
264	1-(3-methoxybenzoyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine	456.1	M+H	0.106	

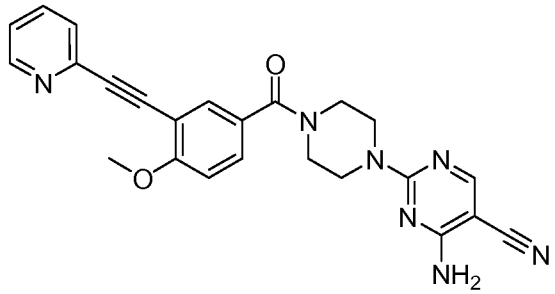
265	1-(4-methoxybenzoyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine	456.1	M+H	0.054	>1.000
266	1-(2-fluorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine	430.3	M+H	0.033	>1.000
267	1-(3-fluorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine	430.3	M+H	0.057	0.167
268	1-(4-fluorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine	430.3	M+H	0.057	0.219
269	1-[(5-bromo-2-thienyl)sulfonyl]-4-[4-methoxy-3-(pyridin-2- ylethynyl) benzoyl]piperazine	546	M+H	0.049	0.000
270	1-[(3,5-dimethylisoxazol-4-yl)sulfonyl]-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	481.2	M+H	1.539	
271	1-(3,5-dichlorophenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine	466.1	M+H	0.018	
272	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-{[3-methoxy-4-(1H-tetrazol-1- yl)phenyl]sulfonyl} piperazine	560.1	M+H	IC50 >10 uM	
273	5-({4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}sulfonyl)-N,N- dimethylnaphthalen-1-amine	555.1	M+H	1.740	
274	1-(3-chlorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	446.1	M+H	0.089	0.316
275	1-(4-chlorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	446.1	M+H	0.017	0.144
276	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(5-nitro-1,3,4-thiadiazol-2- yl)piperazine	451	M+H	0.139	
277	1-(2,6-dichlorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	480.1	M+H	0.272	
278	1-[(2-chlorophenyl)sulfonyl]-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	496.1	M+H	0.876	

279	1-[(3-chlorophenyl)sulfonyl]-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	496.1	M+H	0.832	
280	1-(2,4-dichlorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	480.1	M+H	0.043	0.317
281	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(3-phenyl-1,2,4-thiadiazol-5- yl)piperazine	482.1	M+H	0.197	
282	2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-6-nitro-1,3- benzothiazole	500	M+H	IC50 >10 uM	
283	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-[5-(1-methyl-5-nitro-1H-imidazol- 2-yl)-1,3,4-thiadiazol-2-yl]piperazine	531.1	M+H	2.308	
284	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-{[4-(1H-tetrazol-1-yl)phenyl]sulfonyl}piperazine	530.1	M+H	0.376	
285	1-(4-bromo-2-fluorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	508	M+H	0.007	0.326
286	tert-butyl 4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine-1-carboxylate	422.1	M+H		
287	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(2-naphthylsulfonyl)piperazine	512.1	M+H	0.070	>1000
288	1-(3,4-dichlorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	480	M+H	0.170	
289	1-(2-chloro-6-fluorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	464	M+H	0.269	
290	1-(1-benzothiophen-2-yl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	454.1	M+H	IC50 >10 uM	

291	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(5-phenyl-4H-1,2,4-triazol-3- yl)piperazine	465.2	M+H	0.199	

Example 9

4-Amino-2-(4-(4-methoxy-3-(pyridin-2-ylethynyl)benzoyl)piperazin-1-yl)pyrimidine-5-carbonitrile (Compound 293)



Step 1: Methyl 4-methoxy-3-(pyridin-2-ylethynyl)benzoate

To a solution of methyl 3-bromo-4-methoxybenzoate (5.0 g, 20.4 mmol) and 2-ethynylpyridine (3.14 mL, 31.1 mmol) in toluene (100 mL) was added CuI (0.78 g, 3.9 mmol) and TEA (6.2 mL, 44.7 mmol). $Pd(Ph_3P)_2Cl_2$ (2.9 g, 4.1 mmol) was then added to the resulting suspension. The vessel was purged with nitrogen and the reaction was stirred at 110°C for 10 hours. The contents of the flask were then washed through a plug of silica gel with EtOAc and the resulting solution was concentrated at reduced pressure and purified by flash chromatography on silica (5% MeOH in DCM) to yield 4.1 g (75%) of product as a brown solid.

Step 2: 4-Methoxy-3-(pyridin-2-ylethynyl)benzoic acid

To a solution of methyl 4-methoxy-3-(pyridin-2-ylethynyl)benzoate (4.1 g, 15.3 mmol) in THF (150 mL), MeOH (20 mL), and H_2O (40 mL) was added lithium hydroxide monohydrate (1.68

g, 40 mmol). The reaction was stirred at room temperature overnight and then concentrated at reduced pressure to an approximate volume of 40 mL. The remaining solution was diluted with an additional 50 mL of H_2O, washed with Et_2O (X2), and acidified to pH 4.0. The resulting precipitate was collected by suction filtration. The filtrate was saturated with solid NaCl and extracted with EtOAc (2 X 100 mL). The organic extracts were concentrated to yield a solid residue that was added to the collected precipitate and the combined solids were dried in a vacuum oven at 50°C for 3 hours to yield 3.44 g (84%) of the carboxylic acid as a tan solid. No additional purification of the carboxylic acid was required.

Step 3: *tert*-Butyl 4-(4-methoxy-3-(pyridin-2-ylethynyl)benzoyl)piperazine-1-carboxylate

To a stirred solution of 4-methoxy-3-(pyridin-2-ylethynyl)benzoic acid (1.50 g, 5.92 mmol) in DCM (45 mL) was added HOBT (1.45 g, 9.47 mmol) and EDC (1.70 g, 8.88 mmol). The resulting solution was stirred for 15 min, at which time tert-butyl piperazine-1-carboxylate (1.43 g, 7.70 mmol) and TEA (2.46 mL, 17.76 mmol) were added and the solution was stirred for 5 h. Upon completion, the solvent was removed under reduced pressure and the residue was purified via flash chromatography on silica gel (20:1 CH_2Cl_2/MeOH) to afford 2.02 g (81%) of the boc-piperazine as a light brown solid.

Step 4: (4-methoxy-3-(pyridin-2-ylethynyl)phenyl)(piperazin-1-yl)methanone hydrochloric acid salt

Acetyl chloride (186 mg, 2.38 mmol) was added in a dropwise fashion to a solution of *tert*-Butyl 4-(4-methoxy-3-(pyridin-2-ylethynyl)benzoyl)piperazine-1-carboxylate (1.00 g, 2.38 mmol) in MeOH (5 mL) cooled to 0 °C. After 45 min, additional acetyl chloride (186 mg, 2.38 mmol) was added to the solution. The reaction solution solidified with quantitative formation of the piperazine hydrochloric acid salt as shown by LCMS. The product was filtered, washed with hexanes and was used without further purification or modification.

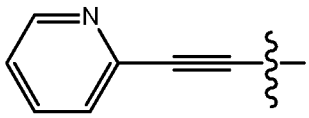
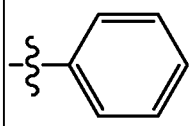
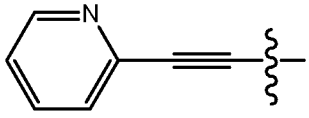
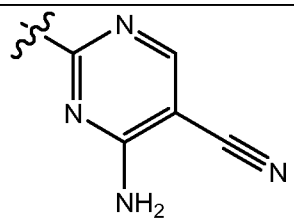
Step 5: 4-amino-2-(4-(4-methoxy-3-(pyridin-2-ylethynyl)benzoyl)piperazin-1-yl)pyrimidine-5-carbonitrile (Compound 293)

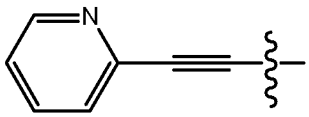
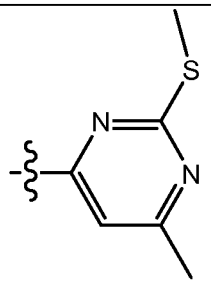
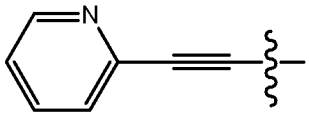
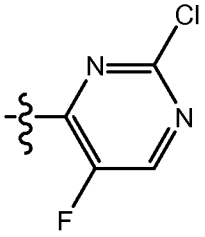
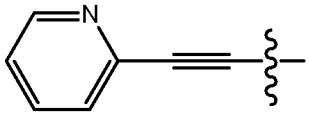
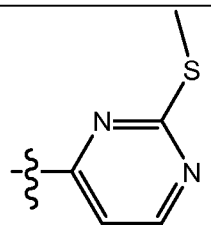
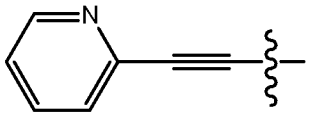
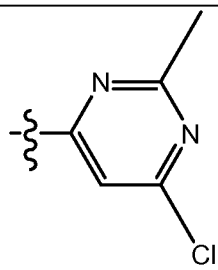
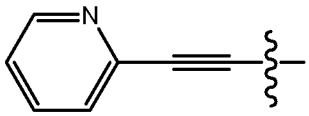
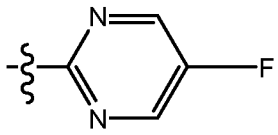
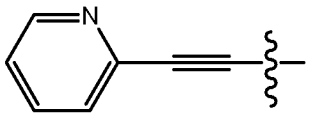
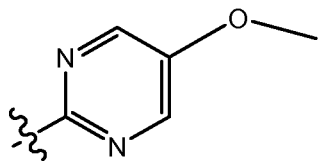
To a solution of (4-methoxy-3-(pyridin-2-ylethynyl)phenyl)(piperazin-1-yl)methanone hydrochloric acid salt (50 mg, 0.156 mmol) in isopropyl alcohol (0.40 mL) was added 4-amino-2-chloropyrimidine-5-carbonitrile (48 mg, 0.312 mmol) and TEA (0.065 mL). The vial was purged with nitrogen and the reaction solution was heated to 85 °C. The reaction was stirred for 24 h, at which point the solvent was removed under reduced pressure and the residue was purified via flash chromatography on silica gel (5% MeOH in DCM) to afford 51 mg (74%) of the title compound as an off-white solid.

Compounds 292-306, shown in Table 9 and 9A below, were prepared using the procedure of Example 9 described above.

UNLESS NOTED OTHERWISE THE FOLLOWING
VALUES REFER TO FORMULA I
WHEREIN R_1, R_4, R_{4a}, R_5, R_{5a} = H; X_1 = COMe, X_2 = CH; Z = CO

TABLE 9

Cmpd	Name	R_2	Noted Values	R_6
292	1-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-phenyl piperazine			
293	4-amino-2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine-5-carbonitrile			

294	4-chloro-6-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-2-(methylthio) pyrimidine			
295	2-chloro-5-fluoro-4-{4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}pyrimidine			
296	4-{4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}-2-(methylthio) pyrimidine			
297	4-chloro-6-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1-yl}-2-methylpyrimidine			
298	5-fluoro-2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1-yl} pyrimidine			
299	5-methoxy-2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1-yl} pyrimidine			

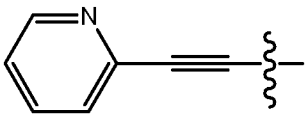
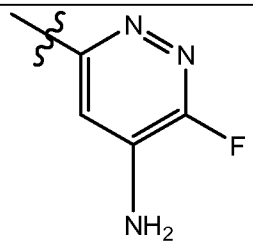
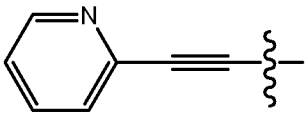
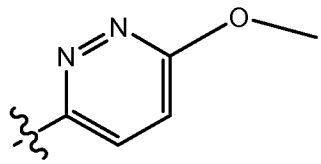
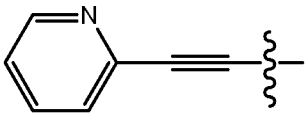
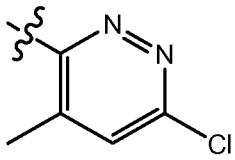
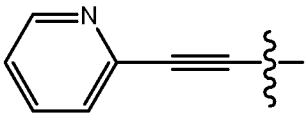
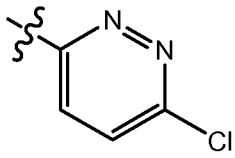
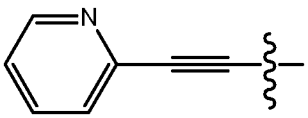
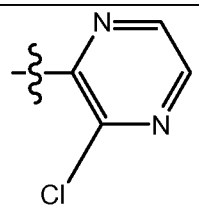
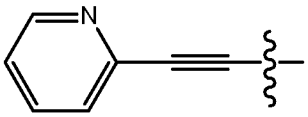
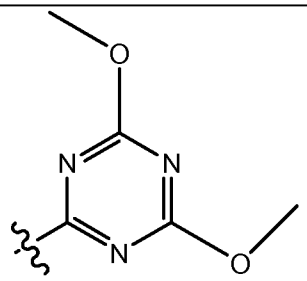
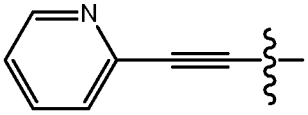
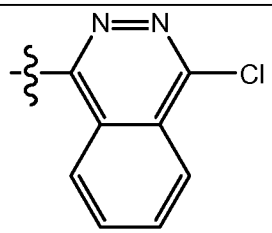
300	5-fluoro-2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1-yl} pyrimidin-4-amine			
301	3-methoxy-6-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1-yl} pyridizine			
302	6-chloro-3-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1-yl}-4-methylpyridazine			
303	3-chloro-6-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1-yl} pyridizine			
304	2-chloro-3-{4-[4-methoxy-3-(pyridin-2-yl ethynyl)benzoyl] piperazin-1-yl} pyrazine			
305	2,4-dimethoxy-6-{4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}-1,3,5-triazine			
306	1-chloro-4-{4-[4-methoxy-3-(pyridin-2-yl ethynyl)benzoyl] piperazin-1-yl} phthalazine			

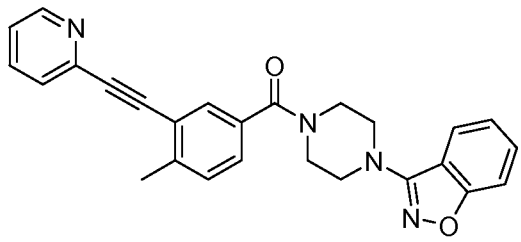
TABLE 9A

Cmpd	Name	LCMS data		Biological Activity	
		Mass	Ion	Median Ki (μM)	IC50 (uM)
292	1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-phenyl piperazine	398.2	M+H	0.014	0.208
293	4-amino-2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine-5-carbonitrile	440.2	M+H	0.058	>1.000
294	4-chloro-6-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-2-(methylthio)pyrimidine	480.1	M+H	0.099	
295	2-chloro-5-fluoro-4-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine	452.1	M+H	0.102	
296	4-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-2-(methylthio)pyrimidine	446.2	M+H	0.022	>1.000
297	4-chloro-6-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-2-methylpyrimidine	448	M+H	0.159	
298	5-fluoro-2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1-yl}pyrimidine	418	M+H	0.033	0.102
299	5-methoxy-2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1-yl}pyrimidine	430.2	M+H	0.025	0.119
300	5-fluoro-2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1-yl}pyrimidin-4-amine	433.2	M+H	0.030	0.198
301	3-methoxy-6-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1-yl}pyridazine	430.2	M+H	0.083	0.204

302	6-chloro-3-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1-yl}-4-methyl pyridazine	448.2	M+H	0.039	>1.000
303	3-chloro-6-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1-yl}pyridazine	434.1	M+H	0.031	>1.000
304	2-chloro-3-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1-yl}pyrazine	434.1	M+H	0.052	0.408
305	2,4-dimethoxy-6-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-1,3,5-triazine	461.1	M+H	0.229	
306	1-chloro-4-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1-yl}phthalazine	484.1	M+H	0.072	0.356

Example 10

3-{4-[4-Methyl-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-1,2-benzisoxazole (Compound 307)



Step 1: Methyl 4-methyl-3-(pyridin-2-ylethynyl)benzoate

Methyl 3-iodo-4-methylbenzoate (5.52 g, 20 mmol), 2-ethynylpyridine (3.2 mL, 31 mmol), and triethylamine (6.2 mL, 44.7 mmol) were dissolved in 100 mL of toluene and purged with nitrogen. Then CuI (0.78 g, 3.9 mmol) and $Pd(Ph_3P)_2Cl_2$ (2.9 g, 4.1 mmol) were added and the

resulting suspension was stirred at 100 °C for 6 hours. The reaction was concentrated at reduced pressure and purified by flash chromatography on silica (40:1 CH_2Cl_2/EtOAc) to yield 2.63 g (52%) of the product as a greenish solid.

Step 2: 4-Methyl-3-(pyridin-2-ylethynyl)benzoic acid

Methyl 4-methyl-3-(pyridin-2-ylethynyl)benzoate (2.2 g, 8.7 mmol) was dissolved in a mixture of THF (75 mL), MeOH (25 mL), and H_2O (25 mL) and treated with lithium hydroxide monohydrate (420 mg, 10 mmol). The reaction was stirred at room temperature overnight and then concentrated at reduced pressure. The remaining residue was diluted with 50 mL of H_2O and acidified to pH 4.0 with 1N HCl. The resulting precipitate was collected by suction filtration. The collected precipitate was dried in a vacuum oven at 50 °C for 3 hours to yield 1.57 g (76%) of the carboxylic acid as a gray solid. No additional purification of the carboxylic acid was required.

Step 3: (4-(Benzo[d]isoxazol-3-yl)piperazin-1-yl)(4-methyl-3-(pyridin-2-ylethynyl)phenyl) methanone (Compound 307)

4-Methyl-3-(pyridin-2-ylethynyl)benzoic acid (593 mg, 2.5 mmol), 3-(piperazin-1-yl)benzo[d]isoxazole (570 mg, 2.8 mmol), and triethylamine (1.05 mL, 7.5 mmol) are dissolved in 25 mL of CH_2Cl_2 and treated with EDCI (528 mg, 2.75 mmol) and HOBT (371 mg, 2.75 mmol). The reaction is stirred at room temperature overnight. The crude mixture is diluted EtOAc and washed with water and brine. The organic layer is dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc) to yield 887 mg (84%) of the product as an off white solid.

UNLESS NOTED OTHERWISE THE FOLLOWING
VALUES REFER TO FORMULA I
WHEREIN R_1, R_4, R_{4a}, R_5, R_{5a} = H; X_2 = CH; Z = CO

TABLE 10

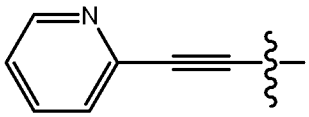
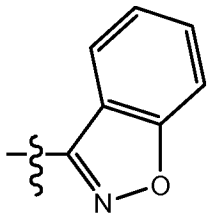
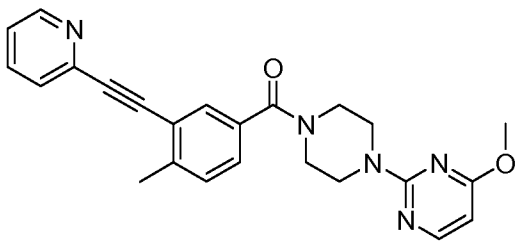
Cmpd	Name	R_2	X_1	R_6
307	3-{4-[4-methyl-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}-1,2-benzisoxazole		CCH_3	

TABLE 10A

Cmpd	Name	LCMS Data			Biological Activity	
		Time (min.)	Mass	Ion	Median K_i (μM)	IC50 (uM)
307	3-{4-[4-methyl-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-1,2-benzisoxazole		423.2	M+H	0.001	0.050

Example 11

4-Methoxy-2-{4-[4-methyl-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1-yl}pyrimidine (Compound 308)



4-Methyl-3-(pyridin-2-ylethynyl)benzoic acid (47 mg, 0.2 mmol), 4-methoxy-2-(piperazin-1-yl)pyrimidine (49 mg, 0.25 mmol), and triethylamine (139 uL, 1.0 mmol) were dissolved in 3 mL of

CH_2Cl_2 and treated with PyBOP (130 mg, 0.25 mmol). The reaction was stirred at room temperature overnight and directly purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc) to yield 47 mg (57%) of the product as a white solid.

Compounds 308 - 311, shown in Table 11 and Table 11A below, were prepared using the procedure of Example 11 described above.

UNLESS NOTED OTHERWISE THE FOLLOWING
VALUES REFER TO FORMULA I
WHEREIN R_1, R_4, R_{4a}, R_5, R_{5a} = H; X_2 = CH; Z = CO

TABLE 11

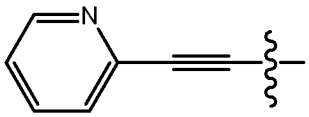
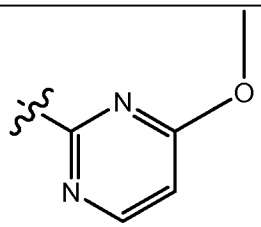
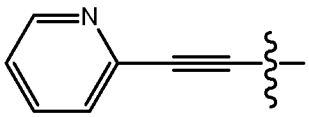
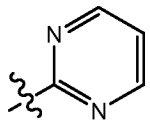
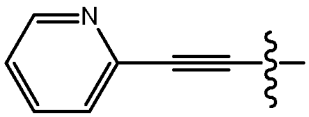
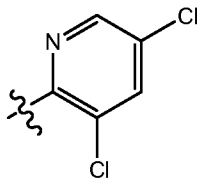
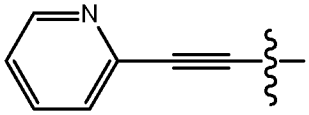
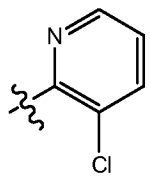
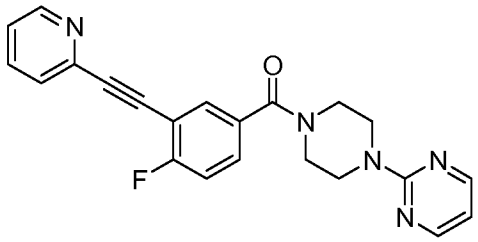
Cmpd	Name	R_2	X_1	R_6
308	4-methoxy-2-{4-[4-methyl-3-(pyridin-2-yl ethynyl)benzoyl]piperazin-1-yl} pyrimidine		CCH_3	
309	2-{4-[4-methyl-3-(pyridin-2-yl ethynyl)benzoyl]-1-yl}pyrimidine		CCH_3	
310	1-(3,5-dichloro pyridin-2-yl)-4-[4-methyl-3-(pyridin-2-ylethynyl) benzoyl] piperazine		CCH_3	
311	1-(3-chloropyridin-2-yl)-4-[4-methyl-3-(pyridin-2-yl ethynyl)benzoyl]piperazine		CCH_3	

TABLE 11A

Cmpd	Name	LCMS data			Biological Activity	
		Time (min.)	Mass	Ion	Median Ki (μM)	IC50 (uM)
308	4-methoxy-2-{4-[4-methyl-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1-yl}pyrimidine		414.2	M+H	0.008	0.107
309	2-{4-[4-methyl-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine		384.2	M+H	0.034	0.193
310	1-(3,5-dichloropyridin-2-yl)-4-[4-methyl-3-(pyridin-2-yl ethynyl)benzoyl]piperazine		451.1	M+H	0.745	
311	1-(3-chloropyridin-2-yl)-4-[4-methyl-3-(pyridin-2-yl ethynyl)benzoyl]piperazine		417.2	M+H	0.140	

EXAMPLE 12

2-{4-[4-Fluoro-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine (Compound 312)



Step 1: Methyl 4-fluoro-3-(pyridin-2-ylethynyl)benzoate

Methyl 3-bromo-4-fluorobenzoate (4.66 g, 20 mmol), 2-ethynylpyridine (3.2 mL, 31 mmol), and triethylamine (6.2 mL, 44.7 mmol) were dissolved in 100 mL of toluene and purged with nitrogen. Then CuI (0.78 g, 3.9 mmol) and $Pd(Ph_3P)_2Cl_2$ (2.9 g, 4.1 mmol) were added and the

resulting suspension was stirred at 100 °C for 6 hours. The reaction was concentrated at reduced pressure and purified by flash chromatography on silica (40:1 CH_2Cl_2/EtOAc) to yield 2.0 g (39%) of the product as a brown solid.

Step 2: 4-fluoro-3-(pyridin-2-ylethynyl)benzoic acid

Methyl 4-fluoro-3-(pyridin-2-ylethynyl)benzoate (1.7 g, 6.6 mmol) was dissolved in a mixture of THF (75 mL), MeOH (25 mL), and H_2O (25 mL) and treated with lithium hydroxide monohydrate (420 mg, 10 mmol). The reaction was stirred at room temperature overnight and then concentrated at reduced pressure. The remaining residue was diluted with 50 mL of H_2O and acidified to pH 4.0 with 1N HCl. The resulting precipitate was collected by suction filtration. The collected precipitate was dried in a vacuum oven at 50 °C for 3 hours to yield 1.24 g (78%) of the carboxylic acid as a tan solid. No additional purification of the carboxylic acid was required.

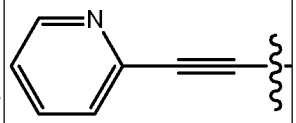
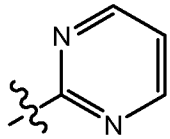
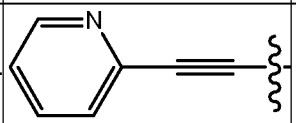
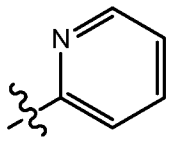
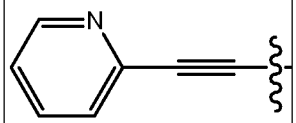
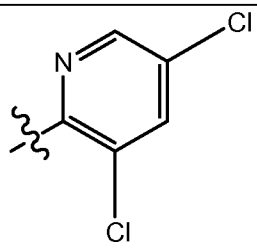
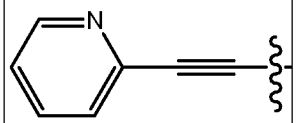
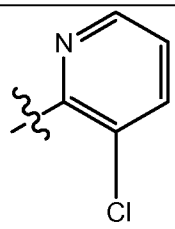
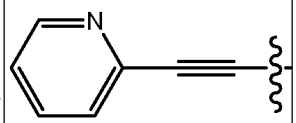
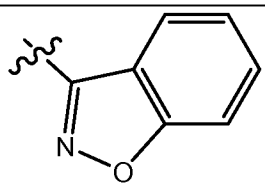
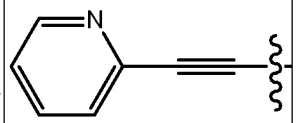
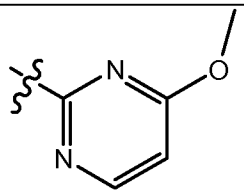
Step 3: 2-{4-[4-Fluoro-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine (Compound 312)

4-Fluoro-3-(pyridin-2-ylethynyl)benzoic acid (48 mg, 0.2 mmol), 2-(piperazin-1-yl)pyrimidine (38 uL, 0.25 mmol), and triethylamine (139 uL, 1.0 mmol) were dissolved in 3 mL of CH_2Cl_2 and treated with PyBOP (130 mg, 0.25 mmol). The reaction was stirred at room temperature overnight and directly purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc) to yield 54 mg (70%) of the product as a pink solid.

Compounds 312 - 317, shown in Table 12 below, were prepared using the procedure of Example 12 described above.

UNLESS NOTED OTHERWISE THE FOLLOWING
VALUES REFER TO FORMULA I
WHEREIN R_1, R_4, R_{4a}, R_5, R_{5a} = H; X_2 = CH; Z = CO

TABLE 12

Cmpd	Name	R_2	X_1	R_6
312	2-{4-[4-fluoro-3-(pyridin-2-yl ethynyl)benzoyl]piperazin-1-yl} pyrimidine		CF	
313	1-[4-fluoro-3-(pyridin-2-yl ethynyl)benzoyl]-4-pyridin-2-yl piperazine		CF	
314	1-(3,5-dichloro pyridin-2-yl)-4-[4-fluoro-3-(pyridin-2 ylethynyl)benzoyl]piperazine		CF	
315	1-(3-chloropyridin-2-yl)-4-[4-fluoro-3-(pyridin-2-yl ethynyl)benzoyl] piperazine		CF	
316	3-{4-[4-fluoro-3-(pyridin-2-yl ethynyl)benzoyl]piperazin-1-yl}-1,2-benzisoxazole		CF	
317	2-{4-[4-fluoro-3-(pyridin-2-yl ethynyl)benzoyl]piperazin-1-yl}-4-methoxy pyrimidine		CF	

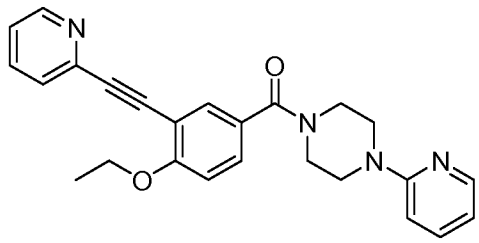
5

TABLE 12A

Cmpd	Name	LCMS data		Biological Activity	
		Mass	Ion	Median Ki (μM)	IC50 (uM)
312	2-{4-[4-fluoro-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine	388.2	M+H	0.084	
313	1-[4-fluoro-3-(pyridin-2-yl ethynyl)benzoyl]-4-pyridin-2-ylpiperazine	387.1	M+H	0.023	0.062
314	1-(3,5-dichloropyridin-2-yl)-4-[4-fluoro-3-(pyridin-2-ylethynyl)benzoyl]piperazine	455.0	M+H	1.843	
315	1-(3-chloropyridin-2-yl)-4-[4-fluoro-3-(pyridin-2-ylethynyl) benzoyl] piperazine	421.1	M+H	0.270	
316	3-{4-[4-fluoro-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}-1,2-benzisoxazole	427.1	M+H	0.002	0.024
317	2-{4-[4-fluoro-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}-4-methoxy pyrimidine	418.1	M+H	0.020	0.030

EXAMPLE 13

1-[4-Ethoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-pyridin-2-ylpiperazine (Compound 318)



Step 1: Methyl 4-ethoxy-3-iodobenzoate

Methyl 4-hydroxy-3-iodobenzoate (2.78 g, 10 mmol) was dissolved in 20 mL of DMF and treated with Cs_2CO_3 (6.5 g, 20 mmol) and ethyliodide (1.0 mL, 12 mmol). The resulting suspension was stirred at room temperature overnight. The reaction mixture was subsequently diluted with EtOAc and washed with water (X2) and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated at reduced pressure to yield 3.0 g of a white solid. The crude material was used in the next step without additional purification.

Step 2: Methyl 4-ethoxy-3-(pyridin-2-ylethynyl)benzoate

Crude methyl 4-ethoxy-3-iodobenzoate (10 mmol), 2-ethynylpyridine (1.6 mL, 15 mmol), and triethylamine (3.1 mL, 22 mmol) are dissolved in 50 mL of toluene and purged with nitrogen. Then CuI (390 mg, 2 mmol) and $Pd(Ph_3P)_2Cl_2$ (1.45 g, 2 mmol) are added and the resulting suspension is stirred at 100 °C for 6 hours. The reaction is concentrated at reduced pressure and purified by flash chromatography on silica (40:1 CH_2Cl_2/EtOAc) to yield 1.25 g (44% for 2 steps) of the product as a white solid.

Step 3: 4-Ethoxy-3-(pyridin-2-ylethynyl)benzoic acid

Methyl 4-ethoxy-3-(pyridin-2-ylethynyl)benzoate (1.1 g, 3.9 mmol) was dissolved in a mixture of THF (75 mL), MeOH (25 mL), and H_2O (25 mL) and treated with lithium hydroxide

monohydrate (420 mg, 10 mmol). The reaction was stirred at room temperature overnight and then concentrated at reduced pressure. The remaining residue was diluted with 50 mL of H_2O and acidified to pH 4.0 with 1N HCl. The resulting precipitate was collected by suction filtration. The collected precipitate was dried in a vacuum oven at 50 °C for 3 hours to yield 857 mg (82%) of the carboxylic acid as an off-white solid. No additional purification of the carboxylic acid was required.

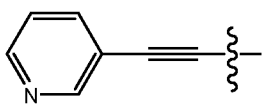
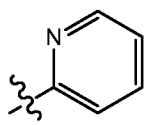
Step 4: 1-[4-Ethoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-pyridin-2-ylpiperazine (Compound 318)

4-Ethoxy-3-(pyridin-2-ylethynyl)benzoic acid (53 mg, 0.2 mmol), 1-(pyridin-2-yl)piperazine (38 uL, 0.25 mmol), and triethylamine (139 uL, 1.0 mmol) were dissolved in 3 mL of CH_2Cl_2 and treated with PyBOP (130 mg, 0.25 mmol). The reaction was stirred at room temperature overnight and directly purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc) to yield 59 mg (92%) of the product as a tan solid.

Compounds 318 - 322, shown in Table 13 below, were prepared using the procedure of Example 13 described above.

UNLESS NOTED OTHERWISE THE FOLLOWING
VALUES REFER TO FORMULA I
WHEREIN R_1, R_4, R_{4a}, R_5, R_{5a} = H; X_2 = CH; Z = CO

TABLE 13

Cmpd	Name	R_2	X_1	R_6
318	1-[4-ethoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-pyridin-2-ylpiperazine		COC_2H_5	

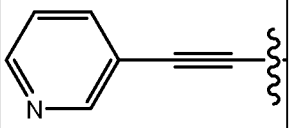
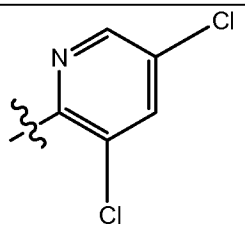
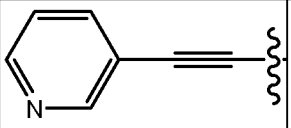
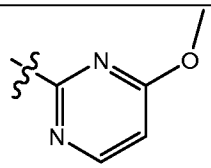
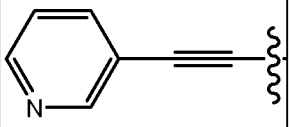
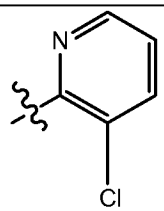
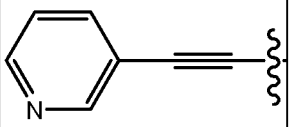
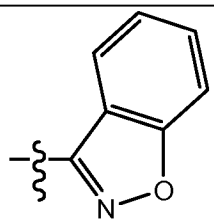
319	1-(3,5-dichloro pyridin-2-yl)-4-[4-ethoxy-3-(pyridin-2-ylethynyl) benzoyl] piperazine		COC_2H_5	
320	2-{4-[4-ethoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}-4-methoxy pyrimidine		COC_2H_5	
321	1-(3-chloropyridin-2-yl)-4-[4-ethoxy-3-(pyridin-2-ylethynyl) benzoyl] piperazine		COC_2H_5	
322	3-{4-[4-ethoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}-1,2-benzisoxazole		COC_2H_5	

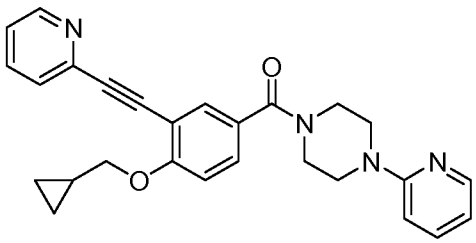
TABLE 13A

Cmpd	Name	LCMS data		Biological Activity	
		Mass	Ion	Median Ki (μM)	IC50 (uM)
318	1-[4-ethoxy-3-(pyridin-2-ylethynyl) benzoyl]-4-pyridin-2-ylpiperazine	413.1	M+H	0.018	0.019
319	1-(3,5-dichloropyridin-2-yl)-4-[4-ethoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazine	481.1	M+H	0.652	

320	2-{4-[4-ethoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}-4-methoxypyrimidine	444.2	M+H	0.020	0.031
321	1-(3-chloropyridin-2-yl)-4-[4-ethoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine	447.1	M+H	0.149	
322	3-{4-[4-ethoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}-1,2-benzisoxazole	453.1	M+H	0.006	0.035

Example 14

1-{[4-(Cyclopropylmethoxy)-3-(pyridin-2-ylethynyl)phenyl] carbonyl}-4-pyridin-2-ylpiperazine (Compound 323)



Step 1: Methyl 4-(cyclopropylmethoxy)-3-iodobenzoate

Methyl 4-hydroxy-3-iodobenzoate (2.78 g, 10 mmol) was dissolved in 20 mL of DMF and treated with Cs_2CO_3 (6.5 g, 20 mmol) and cyclopropylmethyl bromide (1.25 mL, 12 mmol). The resulting suspension was stirred at room temperature overnight. The reaction mixture was subsequently diluted with EtOAc and washed with water (X2) and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated at reduced pressure to yield 3.3 g of a pale yellow oil. The crude material was used in the next step without additional purification.

Step 2: Methyl 4-(cyclopropylmethoxy)-3-(pyridin-2-ylethynyl) benzoate

Crude methyl 4-(cyclopropylmethoxy)-3-iodobenzoate (10 mmol), 2-ethynylpyridine (1.6 mL, 15 mmol), and triethylamine (3.1 mL, 22 mmol) were dissolved in 50 mL of toluene and purged with nitrogen. Then CuI (390 mg, 2 mmol) and $Pd(Ph_3P)_2Cl_2$ (1.45 g, 2 mmol) were added and the resulting suspension was stirred at 100 °C for 6 hours. The reaction was concentrated at reduced pressure and purified by flash chromatography on silica (CH_2Cl_2/EtOAc) to yield 1.52 g (50% for 2 steps) of the product as an oil.

Step 3: 4-(Cyclopropylmethoxy)-3-(pyridin-2-ylethynyl)benzoic acid

Methyl 4-(cyclopropylmethoxy)-3-(pyridin-2-ylethynyl)benzoate (1.5 g, 4.9 mmol) was dissolved in a mixture of THF (75 mL), MeOH (25 mL), and H_2O (25 mL) and treated with lithium hydroxide monohydrate (420 mg, 10 mmol). The reaction was stirred at room temperature overnight and then concentrated at reduced pressure. The remaining residue was diluted with 50 mL of H_2O and acidified to pH 4.0 with 1N HCl. The resulting precipitate was collected by suction filtration. The collected precipitate was dried in a vacuum oven at 50 °C for 3 hours to yield 1.31 g (91%) of the carboxylic acid as a pale yellow solid. No additional purification of the carboxylic acid was required.

Step 4: 1-{[4-(Cyclopropylmethoxy)-3-(pyridin-2-ylethynyl)phenyl] carbonyl}-4-pyridin-2-ylpiperazine (Compound 323)

4-(Cyclopropylmethoxy)-3-(pyridin-2-ylethynyl)benzoic acid (59 mg, 0.2 mmol), 1-(pyridin-2-yl)piperazine (61 uL, 0.4 mmol), and triethylamine (84 uL, 0.6 mmol) were dissolved in 4 mL of CH_2Cl_2 and treated with HOBt (40 mg, 0.3 mmol) and EDC (58 mg, 0.3 mmol). The reaction was stirred at room temperature overnight and directly purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc) to yield 79 mg (90%) of the product as a white solid.

Compounds 323 - 325, shown in Table 14, were prepared using the procedure of Example 13 described above.

UNLESS NOTED OTHERWISE THE FOLLOWING
VALUES REFER TO FORMULA I
WHEREIN R_1, R_4, R_{4a}, R_5, R_{5a} = H; X_2 = CH; Z = CO

TABLE 14

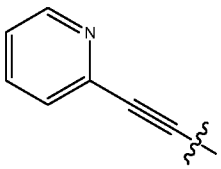
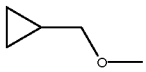
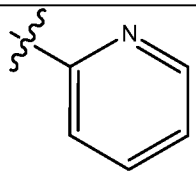
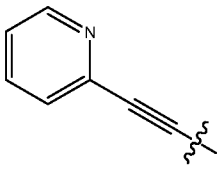
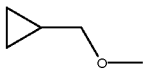
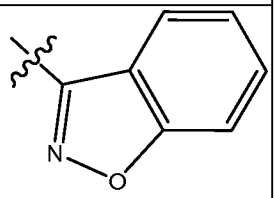
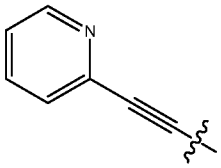
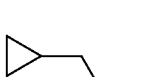
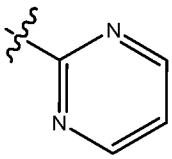
Cmpd	Name	R_2	X_1	R_6
323	1-{[4-(cyclopropyl methoxy)-3-(pyridin-2-ylethynyl)phenyl] carbonyl}-4-pyridin-2-ylpiperazine			
324	3-(4-{[4-(cyclopropyl methoxy)-3-(pyridin-2-ylethynyl)phenyl] carbonyl}piperazin-1-yl)-1,2-benzisoxazole			
325	2-(4-{[4-(cyclopropyl methoxy)-3-(pyridin-2-ylethynyl)phenyl] carbonyl}piperazin-1-yl)pyrimidine			

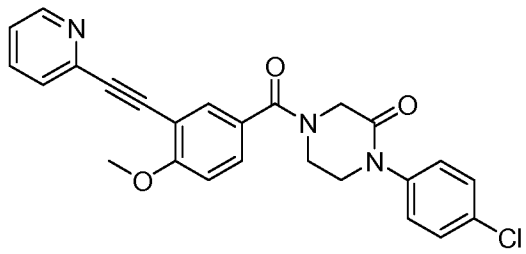
TABLE 14A

Cmpd	Name	LCMS data		Biological Activity	
		Mass	Ion	Median Ki (μM)	IC50 (uM)
323	1-{[4-(cyclopropylmethoxy)-3-(pyridin-2-ylethynyl)phenyl]carbonyl}-4-pyridin-2-ylpiperazine	439.2	M+H	0.198	

324	3-(4-{[4-(cyclopropylmethoxy)-3-(pyridin-2-ylethynyl)phenyl]carbonyl}piperazin-1-yl)-1,2-benzisoxazole	479.1	M+H	0.005	0.078
325	2-(4-{[4-(cyclopropylmethoxy)-3-(pyridin-2-ylethynyl)phenyl]carbonyl}piperazin-1-yl)pyrimidine	440.1	M+H	1.343	

Example 15

1-(4-Chlorophenyl)-4-{[4-methoxy-3-(pyridin-2-ylethynyl)phenyl]carbonyl}piperazin-2-one (Compound 326)



Step 1: Methyl 4-methoxy-3-(pyridin-2-ylethynyl)benzoate

Methyl 3-iodo-4-methoxybenzoate (6.0 g, 20.4 mmol), 2-ethynylpyridine (3.14 mL, 31.1 mmol), and triethylamine (6.2 mL, 44.7 mmol) were dissolved in 100 mL of toluene and purged with nitrogen. Then CuI (0.78 g, 3.9 mmol) and $Pd(Ph_3P)_2Cl_2$ (2.9 g, 4.1 mmol) were added and the resulting suspension was stirred at 100 °C for 6 hours. The reaction was concentrated at reduced pressure and purified by flash chromatography on silica (20:1 CH_2Cl_2/EtOAc) to yield 5.3 g (96%) of product as a brown solid.

Step 2: 4-Methoxy-3-(pyridin-2-ylethynyl)benzoic acid

Methyl 4-methoxy-3-(pyridin-2-ylethynyl)benzoate (5.3 g, 20 mmol) was dissolved in a mixture of THF (150 mL), MeOH (20 mL), and H_2O (40 mL) and treated

with lithium hydroxide monohydrate (1.68 g, 40 mmol). The reaction was stirred at room temperature overnight and then concentrated at reduced pressure to an approximate volume of 40 mL. The remaining solution was diluted with an additional 50 mL of H_2O, washed with Et_2O (X2), and acidified to pH 4.0. The resulting precipitate was collected by suction filtration. The filtrate was saturated with solid NaCl and extracted with EtOAc (2 X 100 mL). The organic extracts were concentrated to yield a solid residue that was added to the collected precipitate and the combined solids were dried in a vacuum oven at 50 °C for 3 hours to yield 4.65 g (93%) of the carboxylic acid as a tan solid. No additional purification of the carboxylic acid was required.

Step 3 1-(4-Chlorophenyl)-4-{[4-methoxy-3-(pyridin-2-ylethynyl) phenyl]carbonyl} piperazin-2-one (Compound 326)

4-Methoxy-3-(pyridin-2-ylethynyl)benzoic acid (51 mg, 0.2 mmol), 1-(4-chlorophenyl)piperazin-2-one (74 mg, 0.3 mmol), and triethylamine (105 uL, 0.75 mmol) were dissolved in 3 mL of CH_2Cl_2 and treated with HOBt (34 mg, 0.25 mmol) and EDC (48 mg, 0.25 mmol). The reaction was stirred at room temperature overnight and directly purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc) to yield 85 mg (95%) of the product as a white solid.

Compounds 326 - 330, shown in Table 15 below, were prepared using the procedure of Example 15 described above.

UNLESS NOTED OTHERWISE THE FOLLOWING
VALUES REFER TO FORMULA I
WHEREIN R_1, R_4, R_{4a}, R_5, R_{5a} = H; X_2 = CH; Z = CO

TABLE 15

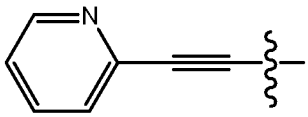
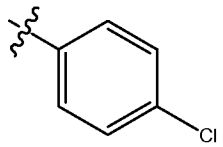
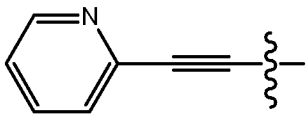
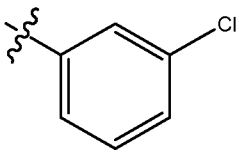
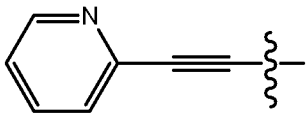
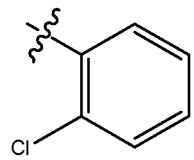
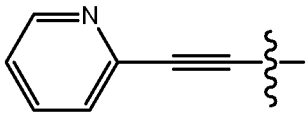
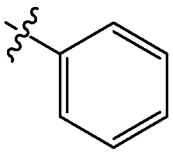
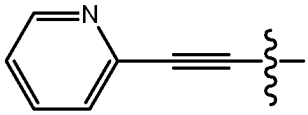
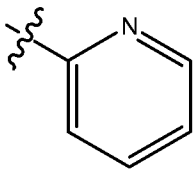
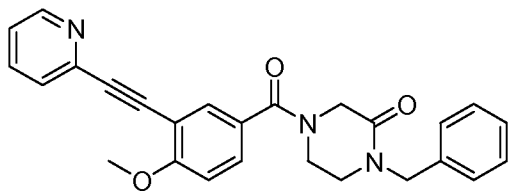
Cmpd	Name	R_2	X_1	R_5	R_6
326	1-(4-chlorophenyl)-4-{[4-methoxy-3-(pyridin-2-yl ethynyl)phenyl]carbonyl}piperazin-2-one		COMe		
327	1-(3-chlorophenyl)-4-{[4-methoxy-3-(pyridin-2-yl ethynyl)phenyl]carbonyl}piperazin-2-one		COMe		
328	1-(2-chlorophenyl)-4-{[4-methoxy-3-(pyridin-2-yl ethynyl)phenyl]carbonyl}piperazin-2-one		COMe		
329	4-{[4-methoxy-3-(pyridin-2-yl ethynyl)phenyl]carbonyl}-1-phenyl piperazin-2-one		COMe		
330	4-{[4-methoxy-3-(pyridin-2-ylethynyl)phenyl]carbonyl}-1-pyridin-2-ylpiperazin-2-one		COMe		

TABLE 15A

Cmpd	Name	LCMS data		Biological Activity	
		Mass	Ion	Median Ki (μM)	IC50 (uM)
326	1-(4-chlorophenyl)-4-{[4-methoxy-3-(pyridin-2-ylethynyl)phenyl]carbonyl} piperazin-2-one	446.1	M+H	0.072	0.029
327	1-(3-chlorophenyl)-4-{[4-methoxy-3-(pyridin-2-ylethynyl)phenyl]carbonyl} piperazin-2-one	446.1	M+H	0.040	0.049
328	1-(2-chlorophenyl)-4-{[4-methoxy-3-(pyridin-2-ylethynyl)phenyl]carbonyl} piperazin-2-one	446.1	M+H	0.096	0.050
329	4-{[4-methoxy-3-(pyridin-2-ylethynyl) phenyl]carbonyl}-1-phenylpiperazin-2-one	412.1	M+H	0.084	0.118
330	4-{[4-methoxy-3-(pyridin-2-ylethynyl) phenyl]carbonyl}-1-pyridin-2-ylpiperazin-2-one	413.1	M+H	0.122	

Example 16

1-Benzyl-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-2-one (Compound 331)



Step 1: 4-(4-Methoxy-3-(pyridin-2-ylethynyl)benzoyl)piperazin-2-one

4-Methoxy-3-(pyridin-2-ylethynyl)benzoic acid (760 mg, 3.0 mmol), piperazin-2-one (455 mg, 4.5 mmol), and triethylamine (0.7 mL, 5 mmol) were

dissolved in 30 mL of CH_2Cl_2 and treated with HOBt (608 mg, 4.5 mmol) and EDC (864 mg, 4.5 mmol). The reaction was stirred at room temperature overnight. The reaction was diluted with EtOAc and washed with water and brine. The organic layer was dried (Na_2SO_4), filtered, and purified by flash chromatography on silica gel (CH_2Cl_2/MeOH) to yield 469 mg (47%) of the product as a tan solid.

Step 2: 1-Benzyl-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazin-2-one (Compound 331)

4-(4-Methoxy-3-(pyridin-2-ylethynyl)benzoyl)piperazin-2-one (50 mg, 0.15 mmol) was dissolved in 3 mL of DMF, cooled to -50 °C, and treated with 400 uL of 0.5 M KHMDS in toluene (0.2 mmol). The reaction was stirred at -50 °C for 2 min. and treated with BnBr (42 uL, 0.35 mmol). The cold bath was removed and the reaction was warmed to room temperature. Upon reaching room temperature, the reaction was quenched with water, diluted with EtOAc, and washed with water and brine. The organic layer was dried (Na_2SO_4), filtered, and purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc) to yield 30 mg (47%) of the product as an off white solid.

Compounds 331 - 334, shown in Table 16 below, were prepared using the procedure of Example 16 described above.

UNLESS NOTED OTHERWISE THE FOLLOWING
VALUES REFER TO FORMULA I
WHEREIN R_1, R_4, R_{4a}, R_5, R_{5a} = H; X_2 = CH; Z = CO

TABLE 16

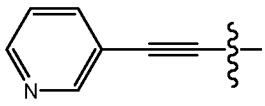
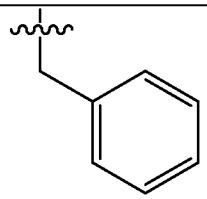
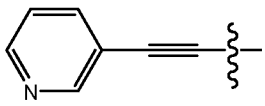
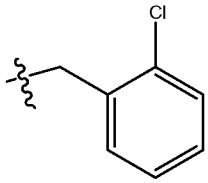
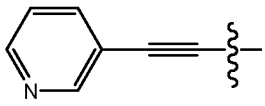
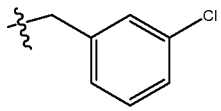
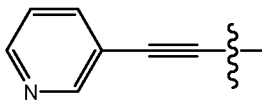
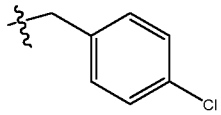
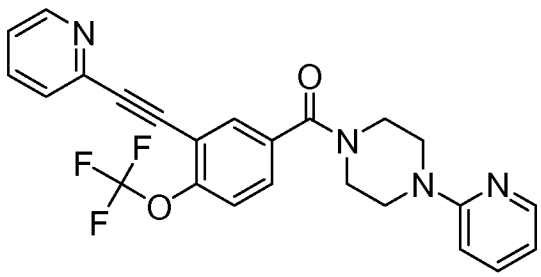
Cmpd	Name	R_2	X_1	R_5	R_6
331	1-benzyl-4-[4-methoxy-3-(pyridin-2-yl ethynyl)benzoyl] piperazin-2-one		COMe		
332	1-(2-chlorobenzyl) -4-[4-methoxy-3-(pyridin-2-yl ethynyl)benzoyl] piperazin-2-one		COMe		
333	1-(3-chlorobenzyl) -4-[4-methoxy-3-(pyridin-2-yl ethynyl)benzoyl] piperazin-2-one		COMe		
334	1-(4-chlorobenzyl) -4-[4-methoxy-3-(pyridin-2-yl ethynyl)benzoyl] piperazin-2-one		COMe		

TABLE 16A

Cmpd	Name	LCMS data		Biological Activity	
		Mass	Ion	Median Ki (μM)	IC50 (uM)
331	1-benzyl-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazin-2-one	426.5	M+H	0.061	0.051
332	1-(2-chlorobenzyl)-4-[4-methoxy-3-(pyridin-2-yl ethynyl)benzoyl]piperazin-2-one	460.9	M+H	0.032	0.051
333	1-(3-chlorobenzyl)-4-[4-methoxy-3-(pyridin-2-yle thynyl)benzoyl]piperazin-2-one	460.9	M+H	0.034	0.053
334	1-(4-chlorobenzyl)-4-[4-methoxy-3-(pyridin-2-yl ethynyl)benzoyl]piperazin-2-one	460.9	M+H	0.054	0.096

EXAMPLE 17

1-Pyridin-2-yl-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethoxy)phenyl]carbonyl}piperazine (Compound 340)



Step 1: 3-Bromo-4-(trifluoromethoxy)benzoic acid

A solution of hydrogen peroxide (30% in water, 115 mL) in 15% aqueous NaOH was added slowly to a solution of 3-bromo-4-(trifluoromethoxy)benzaldehyde (25 g, 93 mmol) in methanol (115 mL) at 0 °C. After the addition the reaction mixture

was warmed up to room temperature and stirred for 4 hours. The reaction was monitored by TLC (10% MeOH in CH_2Cl_2). After the reaction was complete the reaction mixture was acidified with 5 N HCl to pH = 1. The white solid formed was isolated by filtration, washed with water (2X), and then dried at 50 °C overnight to yield the title compound as a white solid (24.1 g, 91% yield).

Step 2: Methyl 3-bromo-4-(trifluoromethoxy)benzoate

HCl (concentrated, 20 mL) was added to a solution of 3-bromo-4-(trifluoromethoxy)benzoic acid (30 g, 105 mmol) in methanol (160 mL). The mixture was heated at 70 °C for 20 h. After the reaction is complete the reaction mixture was concentrated to give a semi-solid. This solid was stirred in hexane (250 mL) for 2 h. Unreacted solid was removed by filtration. The filtrate was evaporated to yield the title compound as an oil (28.1 g, 89% yield).

Step 3: Methyl 4-(trifluoromethoxy)-3-(pyridin-2-ylethynyl) benzoate

The title compound was prepared from methyl 3-bromo-4-(trifluoromethoxy)benzoate (step 2) in substantially the same manner as described in Example 3, step 3.

Step 4: 3-(Pyridin-2-ylethynyl)-4-(trifluoromethoxy)benzoic acid

The title compound was prepared from methyl 4-(trifluoromethoxy)-3-(pyridin-2-ylethynyl)benzoate (step 3) in substantially the same manner as described in Example 3, step 4.

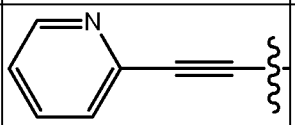
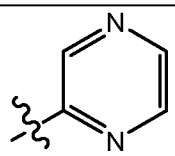
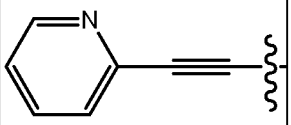
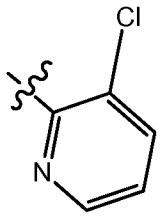
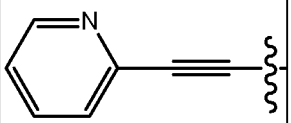
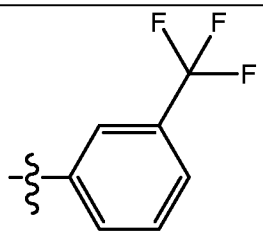
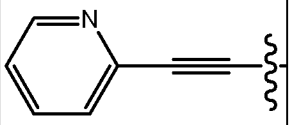
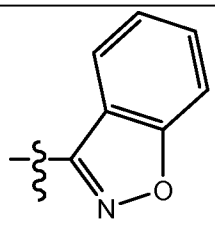
Step 5: 1-Pyridin-2-yl-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoro methoxy)phenyl] carbonyl}piperazine

The title compound was prepared from 3-(pyridin-2-ylethynyl)-4-(trifluoro methoxy)benzoic acid (step 4) and 1-(pyridin-2-yl)piperazine in substantially the same manner as described in Example 3, step 5.

Compounds 335-340 were synthesized according to Example 17.

UNLESS NOTED OTHERWISE THE FOLLOWING VALUES REFER TO FORMULA I WHEREIN R_1, R_4, R_{4a}, R_5, R_{5a} = H; X_2 = CH; Z = CO

TABLE 17

Cmpd	Name	R_2	X_1	R_6
335	2-{4-[3-(pyridin-2-yl ethynyl)-4-(trifluoro methoxy)benzoyl]pipe razin-1-yl}pyrazine		$COCF_3$	
336	1-(3-chloropyridin-2-yl)-4-[3-(pyridin-2-yl ethynyl)-4-(trifluoro methoxy)benzoyl]pipe razine		$COCF_3$	
337	1-[3-(pyridin-2-ylethynyl)-4-(trifluoro methoxy)benzoyl]-4-[3-(trifluoromethyl) phenyl]piperazine		$COCF_3$	
338	3-{4-[3-(pyridin-2-ylethynyl)-4-(trifluoro methoxy)benzoyl] piperazin-1-yl}-1,2-benzisoxazole		$COCF_3$	

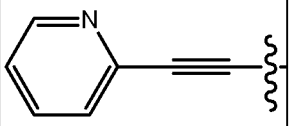
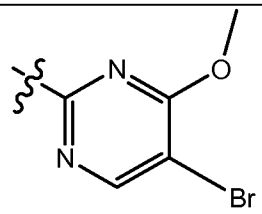
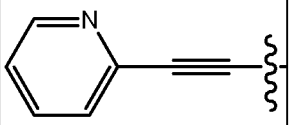
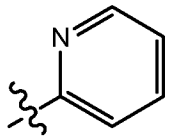
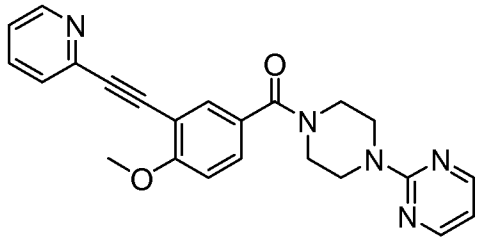
339	5-bromo-4-methoxy-2-{4-[3-(pyridin-2-ylethynyl)-4-(trifluoromethoxy)benzoyl]piperazin-1-yl}pyrimidine		$COCF_3$	
340	1-pyridin-2-yl-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethoxy)phenyl]carbonyl}piperazine		$COCF_3$	

TABLE 17A

Cmpd	Name	LCMS data		Biological Activity	
		Mass	Ion	Median Ki (μM)	IC50 (uM)
335	2-{4-[3-(pyridin-2-ylethynyl)-4-(trifluoromethoxy)benzoyl]piperazin-1-yl}pyrazine	454.1	M+H	0.176	0.273
336	1-(3-chloropyridin-2-yl)-4-[3-(pyridin-2-ylethynyl)-4-(trifluoromethoxy)benzoyl]piperazine	487.0	M+H	1.066	
337	1-[3-(pyridin-2-ylethynyl)-4-(trifluoromethoxy)benzoyl]-4-[3-(trifluoromethyl)phenyl]piperazine	520.1	M+H	1.569	
338	3-{4-[3-(pyridin-2-ylethynyl)-4-(trifluoromethoxy)benzoyl]piperazin-1-yl}-1,2-benzisoxazole	493.1	M+H	0.001	0.016
339	5-bromo-4-methoxy-2-{4-[3-(pyridin-2-ylethynyl)-4-(trifluoromethoxy)benzoyl]piperazin-1-yl}pyrimidine	562.0	M+H	0.702	
340	1-pyridin-2-yl-4-{[3-(pyridine-2-ylethynyl)-4-(trifluoromethoxy)phenyl]carbonyl}piperazine	453.2	M+H	0.002	0.007

EXAMPLE 18:

2-{4-[4-Methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine (Compound 353)



Step 1: Methyl 4-methoxy-3-((trimethylsilyl)ethynyl)benzoate

The title compound was prepared from methyl 3-bromo-4-methoxybenzoate and ethynyltrimethylsilane in substantially the same manner as described in Example 3, step 3.

Step 2: Methyl 3-ethynyl-4-methoxybenzoate

A mixture of methyl 4-methoxy-3-((trimethylsilyl)ethynyl)benzoate (4.2 g, 16.0 mmol) and potassium carbonate (1.3 g, 9.6 mmol) in a mixed solvent of methanol and tetrahydrofuran (1:1; 20 mL) was stirred at room temperature for 2 h. After the reaction was complete the reaction mixture was dried with anhydrous Na_2SO_4, filtered and evaporated to yield the title compound as an oil (3.7 g, 64% yield).

Step 3: 3-Ethynyl-4-methoxybenzoic acid

The title compound was prepared from methyl 3-ethynyl-4-methoxybenzoate (step 2) in substantially the same manner as described in Example 3, step 4.

Step 4: (3-Ethynyl-4-methoxyphenyl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone

The title compound was prepared from 3-Ethynyl-4-methoxybenzoic acid (step 3) and 2-(piperazin-1-yl)pyrimidine in substantially the same manner as described in Example 3, step 5.

Step 5: 2-{4-[4-Methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine

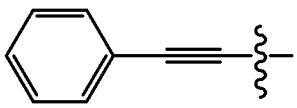
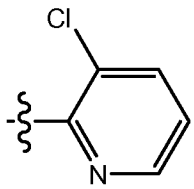
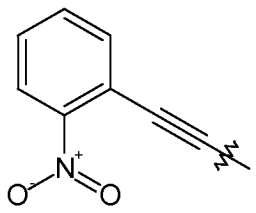
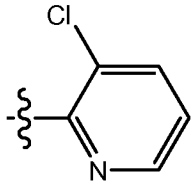
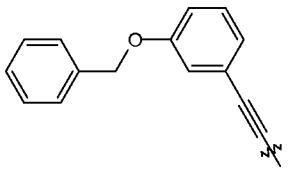
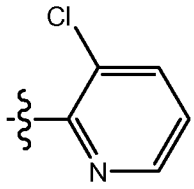
The title compound was prepared from methyl (3-ethynyl-4-methoxyphenyl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone (step 4) in substantially the same manner as described in Example 3, step 3.

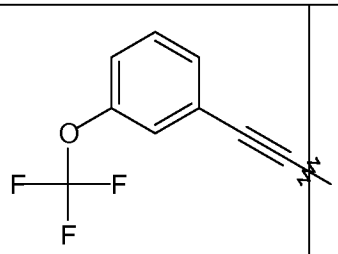
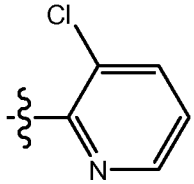
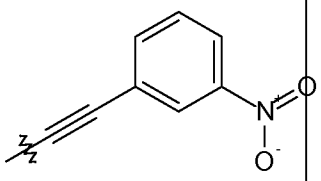
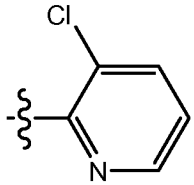
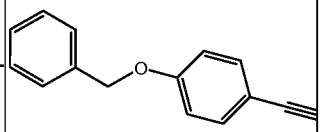
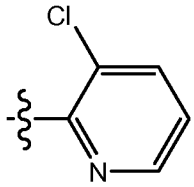
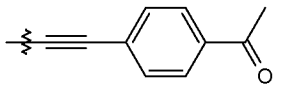
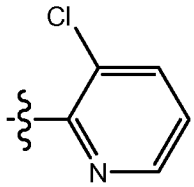
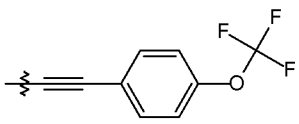
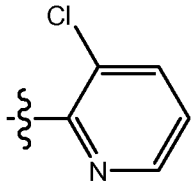
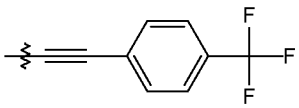
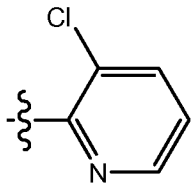
Compounds 341-364 were synthesized according to Example 18.

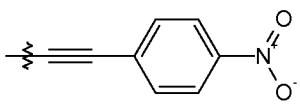
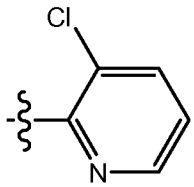
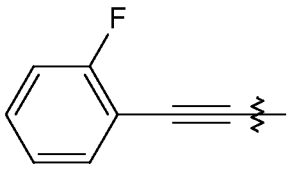
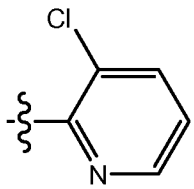
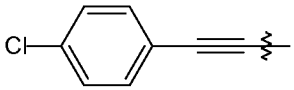
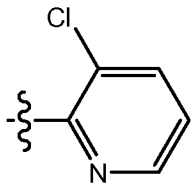
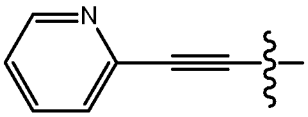
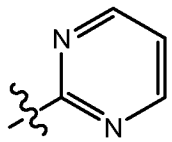
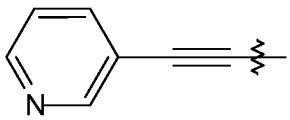
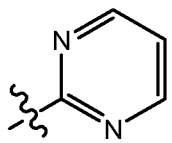
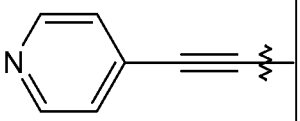
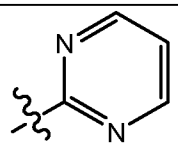
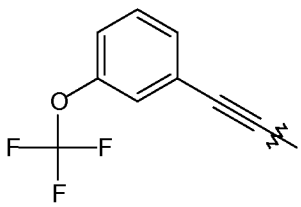
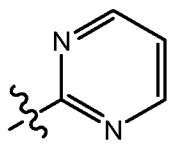
UNLESS NOTED OTHERWISE THE FOLLOWING VALUES REFER TO FORMULA I

WHEREIN R_1, R_4, R_{4a}, R_5, R_{5a} = H; X_1 = COMe, X_2 = CH; Z = CO

TABLE 18

Cmpd	Name	R_2	Noted Values	R_6
341	1-(3-chloropyridin-2-yl)-4-[4-methoxy -3-(phenyl ethynyl) benzoyl] piperazine		COMe	
342	1-(3-chloropyridin-2-yl)-4-{4-methoxy-3-[(2-nitro phenyl)ethynyl]benzoyl} piperazine		COMe	
343	1-(3-{[3-(benzyloxy)phenyl] ethynyl}-4-methoxy benzoyl)-4-(3-chloropyridin-2-yl)piperazine		COMe	

344	1-(3-chloropyridin-2-yl)-4-(4-methoxy-3-{[3-(trifluoromethoxy)phenyl]ethynyl}benzoyl)piperazine		COMe	
345	1-(3-chloropyridin-2-yl)-4-{4-methoxy-3-[(3-nitrophenyl)ethynyl]benzoyl}piperazine		COMe	
346	1-(3-{[4-(benzyloxy)phenyl]ethynyl}-4-methoxybenzoyl)-4-(3-chloropyridin-2-yl)piperazine		COMe	
347	1-{4-[(5-{[4-(3-chloropyridin-2-yl)piperazin-1-yl]carbonyl}-2-methoxyphenyl)ethynyl]phenyl}ethanone		COMe	
348	1-(3-chloropyridin-2-yl)-4-(4-methoxy-3-{[4-(trifluoromethoxy)phenyl]ethynyl}benzoyl)piperazine		COMe	
349	1-(3-chloropyridin-2-yl)-4-(4-methoxy-3-{[4-(trifluoromethyl)phenyl]ethynyl}benzoyl)piperazine		COMe	

350	1-(3-chloropyridin-2-yl)-4-{4-methoxy-3-[(4-nitrophenyl)ethynyl]benzoyl}piperazine		COMe	
351	1-(3-chloropyridin-2-yl)-4-{3-[(2-fluorophenyl)ethynyl]-4-methoxybenzoyl}piperazine		COMe	
352	1-{3-[(4-chlorophenyl)ethynyl]-4-methoxybenzoyl}-4-(3-chloropyridin-2-yl)piperazine		COMe	
353	2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine		COMe	
354	2-{4-[4-methoxy-3-(pyridin-3-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine		COMe	
355	2-{4-[4-methoxy-3-(pyridin-4-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine		COMe	
356	2-[4-(4-methoxy-3-{[3-(trifluoromethoxy)phenyl]ethynyl}benzoyl)piperazin-1-yl]pyrimidine		COMe	

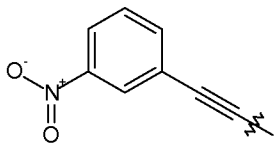
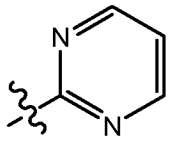
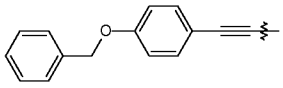
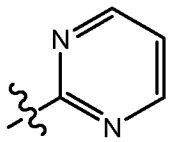
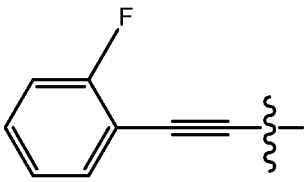
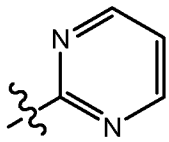
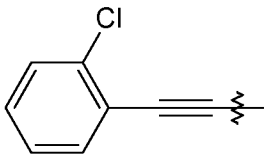
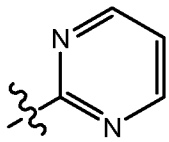
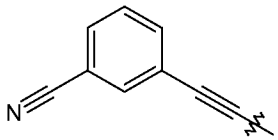
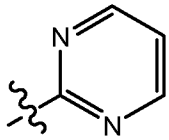
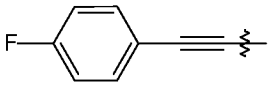
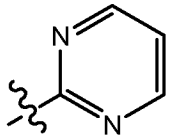
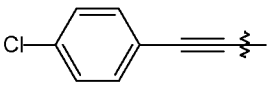
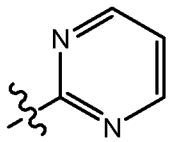
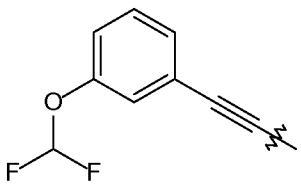
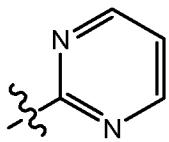
357	2-(4-{4-methoxy-3-[(3-nitrophenyl)ethynyl]benzoyl}piperazin-1-yl)pyrimidine		COME	
358	2-[4-(3-{[4-(benzyloxy)phenyl]ethynyl}-4-methoxybenzoyl)piperazin-1-yl]pyrimidine		COMe	
359	2-(4-{3-[(2-fluoro phenyl)ethynyl]-4-methoxybenzoyl}piperazin-1-yl) pyrimidine		COMe	
360	2-(4-{3-[(2-chloro phenyl)ethynyl]-4-methoxybenzoyl}piperazin-1-yl) pyrimidine		COMe	
361	3-({2-methoxy-5-[(4-pyrimidin-2-ylpiperazin-1-yl)carbonyl]phenyl}ethynyl) benzo nitrile		COMe	
362	2-(4-{3-[(4-fluorophenyl)ethynyl]-4-methoxy benzoyl}piperazin-1-yl)pyrimidine		COMe	
363	2-(4-{3-[(4-chloro phenyl)ethynyl]-4-methoxybenzoyl}piperazin-1-yl) pyrimidine		COMe	
364	2-[4-(3-{[3-(difluoromethoxy)phenyl]ethynyl}-4-methoxybenzoyl)piperazin-1-yl] pyrimidine		COMe	

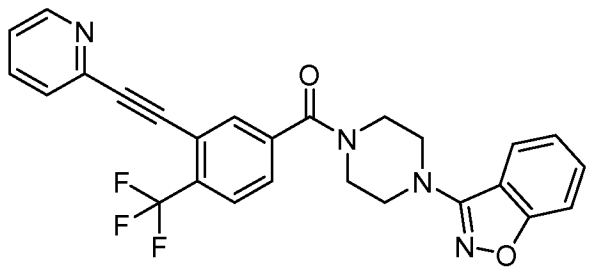
TABLE 18A

Cmpd	Name	LCMS data		Biological Activity	
		Mass	Ion	Median Ki (μM)	IC50 (uM)
341	1-(3-chloropyridin-2-yl)-4-[4-methoxy-3-(phenylethynyl) benzoyl]piperazine	432.1	M+H	1.130	
342	1-(3-chloropyridin-2-yl)-4-{4-methoxy-3-[(2-nitrophenyl) ethynyl]benzoyl}piperazine	477.0	M+H	IC50 >10 Um	
343	1-(3-{[3-(benzyloxy)phenyl] ethynyl}-4-methoxybenzoyl)-4-(3-chloropyridin-2-yl) piperazine	538.1	M+H	IC50 >10 uM	
344	1-(3-chloropyridin-2-yl)-4-(4-methoxy-3-{[3-(trifluoromethoxy)phenyl]ethynyl}benzoyl) piperazine	516.0	M+H	IC50 >10 uM	
345	1-(3-chloropyridin-2-yl)-4-{4-methoxy-3-[(3-nitrophenyl)ethynyl]benzoyl}piperazine	447.0	M+H	3.207	
346	1-(3-{[4-(benzyloxy)phenyl] ethynyl}-4-methoxybenzoyl)-4-(3-chloropyridin-2-yl) piperazine	538.0	M+H	IC50 >10 Um	
347	1-{4-[(5-{[4-(3-chloropyridin-2-yl)piperazin-1-yl]carbonyl}-2-methoxyphenyl)ethynyl] phenyl}ethanone	474.1	M+H	IC50 >10 uM	
348	1-(3-chloropyridin-2-yl)-4-(4-methoxy-3-{[4-(trifluoro methoxy)phenyl]ethynyl} benzoyl)piperazine	516.0	M+H	IC50 >10 uM	
349	1-(3-chloropyridin-2-yl)-4-(4-methoxy-3-{[4-(trifluoromethyl)phenyl]ethynyl} benzoyl)piperazine	500.0	M+H	IC50 >10 uM	
350	1-(3-chloropyridin-2-yl)-4-{4-methoxy-3-[(4-nitrophenyl)ethynyl]benzoyl}piperazine	477.0	M+H	IC50 >10 uM	
351	1-(3-chloropyridin-2-yl)-4-{3-[(2-fluorophenyl)ethynyl]-4-methoxybenzoyl}piperazine	450.0	M+H	4.301	

352	1-{3-[(4-chlorophenyl) ethynyl]-4-methoxybenzoyl}-4-(3-chloropyridin-2-yl) piperazine	466.0	M+H	3.192	
353	2-{4-[4-methoxy-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}pyrimidine	400.1	M+H	0.031	0.072
354	2-{4-[4-methoxy-3-(pyridin-3-ylethynyl) benzoyl]piperazin-1-yl}pyrimidine	400.1	M+H	4.972	
355	2-{4-[4-methoxy-3-(pyridin-4-ylethynyl) benzoyl]piperazin-1-yl}pyrimidine	400.1	M+H	1.568	
356	2-[4-(4-methoxy-3-{[3-(trifluoromethoxy) phenyl]ethynyl}benzoyl)piperazin-1-yl]pyrimidine	483.1	M+H	0.290	
357	2-(4-{4-methoxy-3-[(3-nitrophenyl) ethynyl]benzoyl}piperazin-1-yl)pyrimidine	444.1	M+H	0.239	
358	2-[4-(3-{[4-(benzyloxy)phenyl] ethynyl}-4-methoxybenzoyl) piperazin-1-yl]pyrimidine	505.1	M+H	IC50 >10 uM	
359	2-(4-{3-[(2-fluorophenyl) ethynyl]-4-methoxybenzoyl} piperazin-1-yl)pyrimidine	417.1	M+H	0.287	
360	2-(4-{3-[(2-chlorophenyl) ethynyl]-4-methoxybenzoyl} piperazin-1-yl)pyrimidine	433.0	M+H	4.498	
361	3-({2-methoxy-5-[(4-pyrimidin-2-ylpiperazin-1-yl)carbonyl] phenyl}ethynyl) benzonitrile	424.1	M+H	0.064	0.056
362	2-(4-{3-[(4-fluorophenyl) ethynyl]-4-methoxybenzoyl} piperazin-1-yl)pyrimidine	417.1	M+H	0.068	1.450
363	2-(4-{3-[(4-chlorophenyl) ethynyl]-4-methoxybenzoyl} piperazin-1-yl)pyrimidine	433.0	M+H	0.891	
364	2-[4-(3-{[3-(difluoromethoxy) phenyl] ethynyl}-4-methoxy benzoyl)piperazin-1-yl] pyrimidine	465.1	M+H	0.230	

Example 19

3-(4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazin-1-yl)-1,2-benzisoxazole (Compound 374)



Step 1: Methyl 3-amino-4-(trifluoromethyl)benzoate

A solution of 3-amino-4-(trifluoromethyl)benzoic acid (10 g, 48.8 mmol) and concentrated HCl (36 %, 5.5 mL) in methanol (42 mL) was heated at 70 °C for 10 hours. After the reaction is complete, the reaction mixture was cooled down and concentrated *in vacuo* to afford methyl 3-amino-4-(trifluoromethyl)benzoate, HCl salt as a white solid (8.9 g, 34.8 mmol; 71% yield).

Step 2: Methyl 3-iodo-4-(trifluoromethyl)benzoate

A solution of sodium nitrite (1.34 g 19.3 mmol) in water (7.0 mL) was added dropwise to a rapidly stirred suspension of methyl 3-amino-4-(trifluoromethyl)benzoate, HCl salt (4.5 g, 17.5 mmol) from step 1 in 6 N aqueous HCl (11 mL) at –5 to 0 °C over a period of five min. After the reaction was stirred at –5 °C for 30 min., a solution of potassium iodide (2.9 g, 17.5 mmol) in water (6.0 mL) and a small crystal of iodine were added slowly to the diazonium chloride formed in the reaction suspension. The resulting dark red solution was allowed to warm to room temperature and heated at 90 °C for one hour. The reaction mixture was extracted with ethyl acetate. The collected ethyl acetate extracts were washed with water. Separation and evaporation afforded

methyl 3-iodo-4-(trifluoromethyl)benzoate as a dark brown solid (5.2 g, 15.8 mmol; 90% yield).

Step 3: Methyl 3-(pyridin-2-ylethynyl)-4-(trifluoromethyl) benzoate

A mixture of methyl 3-iodo-4-(trifluoromethyl)benzoate (3 g, 9.1 mmol) from step 2, 2-ethynylpyridine (1.42 mL, 13.6 mmol), dichlorobistriphenylphosphine palladium(II) (1.28 g, 1.8 mmol), copper iodide (0.36 g, 1.82 mmol) and triethylamine (2.6 mL, 18.2 mmol) in toluene (46 mL) was stirred at 100 °C for six hours. The reaction mixture was monitored by LC-MS. After the reaction was complete, the reaction mixture was then allowed to cool down to room temperature. The reaction mixture was concentrated to yield a semi-solid residue. This residue was dissolved in ethyl acetate and the un-dissolved dark solid was removed by filtration. The ethyl acetate filtrate was washed with water and brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to provide a brown crude solid. This material was purified by flash chromatography on SiO_2 (gradient elution using 0-3% MeOH in CH_2Cl_2) to yield the title compound as a brown solid (1.5 g, 4.9 mmol; 54% yield).

Step 4: 3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)benzoic acid

A 1.0 N solution of aqueous sodium hydroxide (7.3 mL, 7.3 mmol) was added to a solution of methyl 3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)benzoate (1.1 g, 3.7 mmol) from step 3 in a mixed solvent of methanol and tetrahydrofuran (1:1; 20 mL) with stirring at room temperature. The reaction was complete in six hours. The reaction was acidified with 2.0 N aqueous HCl (3.7 mL, 7.3 mmol) to pH = 1. The suspended mixture was filtered and evaporated to afford a light brown solid (1.5 g, 3.7 mmol; 100% yield) as a di-sodium chloride salt, which was used for the next reaction without any further purification.

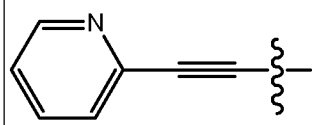
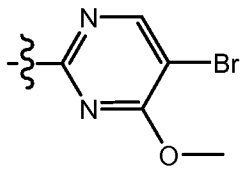
Step 5: 3-(4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl] carbonyl}piperazin-1-yl)-1,2-benzisoxazole

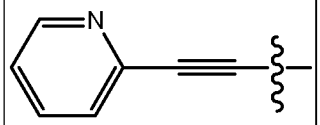
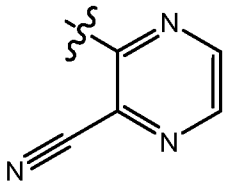
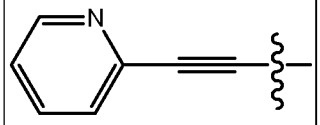
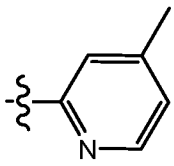
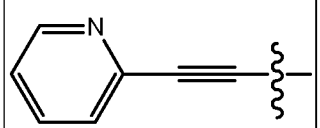
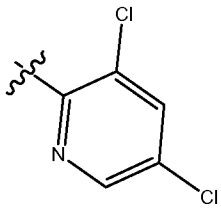
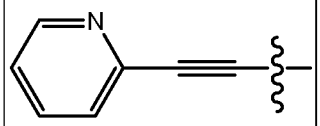
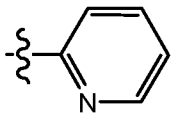
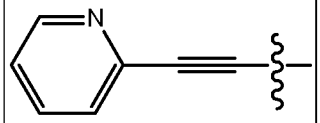
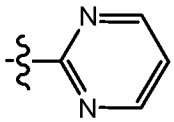
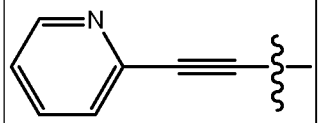
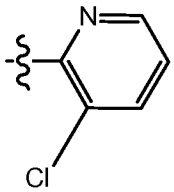
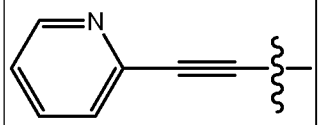
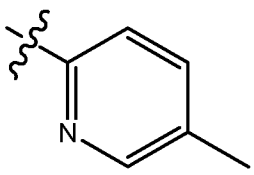
Triethylamine (1.1 mL, 8.1 mmol) was added to a mixture of 3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)benzoic acid (di-sodium chloride salt, 1.1 g, 2.7 mmol) from step 4, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.62 g, 3.2 mmol), 1-hydroxy-7-azabenzotriazole (0.44 mg, 3.2 mmol) and 3-(piperazin-1-yl)benzo[d]isoxazole (0.62 g, 3.0 mmol) in dichloromethane (20 mL) with stirring at room temperature under an atmosphere of nitrogen. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with a small amount of water. Solvents were removed and the residue was purified by flash chromatography on SiO_2 (gradient elution using 40-60% EtOAc in hexane) to yield the title compound as a white solid (0.87 g, 67% yield).

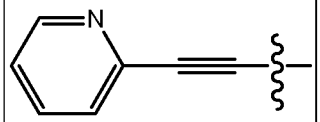
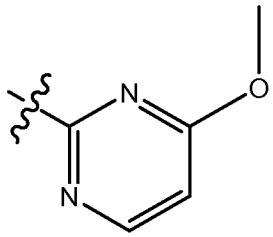
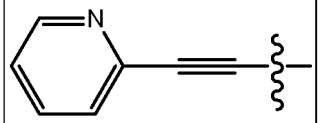
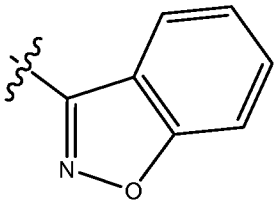
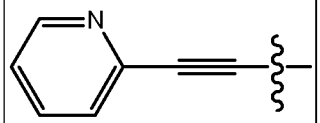
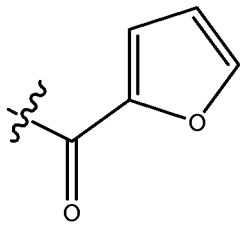
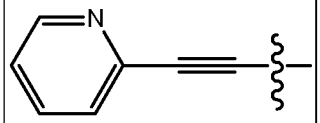
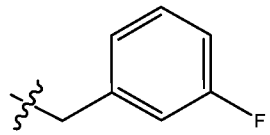
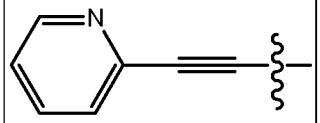
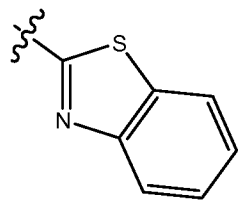
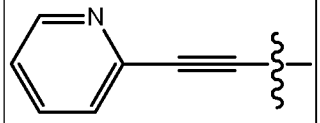
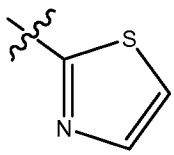
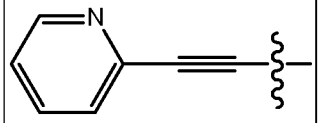
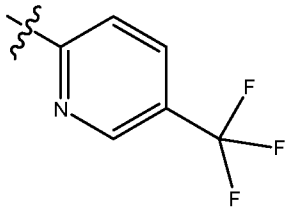
Compounds 365-381 were synthesized according to Example 19.

UNLESS NOTED OTHERWISE THE FOLLOWING
VALUES REFER TO FORMULA I
WHEREIN R_1, R_4, R_{4a}, R_5, R_{5a} = H; X_2 = CH; Z = CO

TABLE 19

Cmpd	Name	R_2	X_1	R_6
365	5-bromo-4-methoxy-2-(4-{[3-(pyridin-2-yl ethynyl)-4-(trifluoro methyl)phenyl]carbon yl}piperazin-1-yl) pyrimidine		CCF_3	

366	3-(4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazin-1-yl) pyrazine-2-carbonitrile		CCF_3	
367	1-(4-methylpyridin-2-yl)-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazine		CCF_3	
368	1-(3,5-dichloropyridin-2-yl)-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazine		CCF_3	
369	1-pyridin-2-yl-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl) phenyl]carbonyl}piperazine		CCF_3	
370	2-(4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazin-1-yl) pyrimidine		CCF_3	
371	1-(3-chloropyridin-2-yl)-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazine		CCF_3	
372	1-(5-methylpyridin-2-yl)-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazine		CCF_3	

373	4-methoxy-2-(4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl) phenyl]carbonyl}piperazin-1-yl)pyrimidine		CCF_3	
374	3-(4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazin-1-yl)-1,2-benzisoxazole		CCF_3	
375	1-(furan-2-ylcarbonyl)-4-{[3-(pyridin-2-yl ethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazine		CCF_3	
376	1-(3-fluorobenzyl)-4-{[3-(pyridin-2-yl ethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazine		CCF_3	
377	2-(4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazin-1-yl)-1,3-benzothiazole		CCF_3	
378	1-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}-4-(1,3-thiazol-2-yl)piperazine		CCF_3	
379	1-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}-4-[5-(trifluoromethyl) pyridin-2-yl] piperazine		CCF_3	

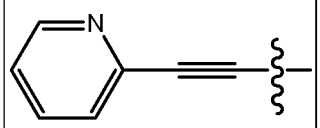
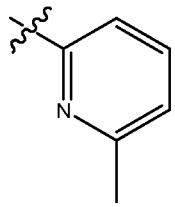
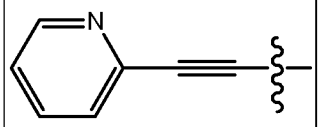
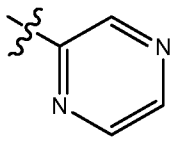
380	1-(6-methylpyridin -2-yl)-4-{[3-(pyridine-2-ylethynyl)-4-(trifluoro methyl)phenyl]carbon yl} piperazine		CCF_3	
381	2-(4-{[3-(pyridin-2-ylethynyl)-4-(trifluoro methyl)phenyl]carbon yl}piperazin-1-yl) pyrazine		CCF_3	

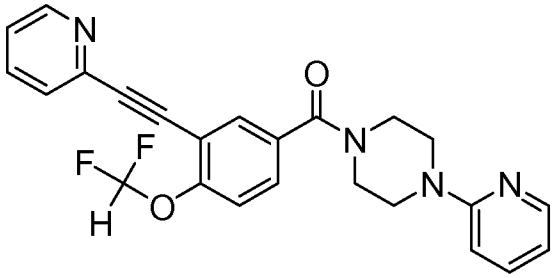
TABLE 19A

Cmpd	Name	LCMS data		Biological Activity	
		Mass	Ion	Median Ki (μM)	IC50 (uM)
365	5-bromo-4-methoxy-2-(4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazin-1-yl)pyrimidine	546.0	M+H	IC50 >10 uM	
366	3-(4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl] carbonyl}piperazin-1-yl) pyrazine-2-carbonitrile	463.1	M+H	0.459	
367	1-(4-methylpyridin-2-yl)-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazine	462.0	M+H	0.008	0.016
368	1-(3,5-dichloropyridin-2-yl)-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazine	505.0	M+H	2.924	
369	1-pyridin-2-yl-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazine	437.1	M+H	0.031	0.030
370	2-(4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl] carbonyl}piperazin-1-yl)pyrimidine	438.1	M+H	0.164	

371	1-(3-chloropyridin-2-yl)-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazine	471.1	M+H	1.001	
372	1-(5-methylpyridin-2-yl)-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazine	451.1	M+H	0.292	
373	4-methoxy-2-(4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl) phenyl]carbonyl}piperazin-1-yl)pyrimidine	468.1	M+H	0.040	0.034
374	3-(4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl] carbonyl}piperazin-1-yl)-1,2-benzisoxazole	477.1	M+H	0.004	0.053
375	1-(furan-2-ylcarbonyl)-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazine	454.1	M+H	0.029	0.040
376	1-(3-fluorobenzyl)-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazine	468.1	M+H	0.811	
377	2-(4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl] carbonyl}piperazin-1-yl)-1,3-benzothiazole	493.1	M+H	IC50 >10 uM	
378	1-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}-4-(1,3-thiazol-2-yl)piperazine	443.1	M+H	0.049	0.043
379	1-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}-4-[5-(trifluoromethyl) pyridin-2-yl]piperazine	505.1	M+H	3.126	
380	1-(6-methylpyridin-2-yl)-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazine	451.1	M+H	0.352	
381	2-(4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl] carbonyl}piperazin-1-yl)pyrazine	438.1	M+H	0.162	

Example 20

1-{[4-(Difluoromethoxy)-3-(pyridin-2-ylethynyl)phenyl]carbonyl}-4-pyridin-2-ylpiperazine (Compound 385)



Step 1: Methyl 4-(difluoromethoxy)-3-iodobenzoate

A cold solution of difluoroiodomethane (5.0 g, 28.0 mmol) in DMF (15 mL) was added to a stirred suspension of potassium carbonate (5.2 g, 37.4 mmol) and methyl 4-hydroxy-3-iodobenzoate (5.4 g, 97%, 18.7 mmol) in DMF (65 mL) at 0 °C under an atmosphere of nitrogen. After the reaction was stirred at 0 °C for 30 min., the reaction mixture was stirred at room temperature for 2.5 hours. After the reaction was complete, solid material was removed by filtration and the filtrate was concentrated to yield a semi-solid residue. This residue was purified by flash chromatography on SiO_2 (gradient elution using EtOAc/hexane 15/85) to yield the title compound as a white solid (5.0 g, 81% yield).

Step 2: Methyl 4-(difluoromethoxy)-3-(pyridin-2-ylethynyl) benzoate

A mixture of methyl 4-(difluoromethoxy)-3-iodobenzoate (2 g, 6.1 mmol) from step 1, 2-ethynylpyridine (0.94 mL, 9.2 mmol), dichlorobistriphenylphosphine palladium(II) (0.86 g, 1.2 mmol), copper iodide (0.23 g, 1.2 mmol) and triethylamine (1.7 mL, 12.2 mmol) in toluene (30 mL) was stirred at 100 °C under an atmosphere of nitrogen for six hours. After the reaction was complete, the reaction mixture was

concentrated to yield a semi-solid residue. This residue was purified by flash chromatography on SiO_2 (gradient elution using EtOAc/hexane 20/80) to yield the title compound as a white solid (1.47 g, 80% yield).

Step 3: 4-(difluoromethoxy)-3-(pyridin-2-ylethynyl)benzoic acid

A 1.0 N solution of aqueous sodium hydroxide (9.6 mL, 9.6 mmol) was added to a solution of methyl 4-(difluoromethoxy)-3-(pyridin-2-ylethynyl)benzoate (1.5 g, 4.8 mmol) from step 2 in a mixed solvent of methanol and tetrahydrofuran (1:1; 26 mL) with stirring at room temperature. The reaction was complete in three hours. The reaction was acidified with 2.0 N aqueous HCl (5.0 mL, 10.0 mmol) to pH = 1. The suspended mixture was evaporated to afford a grey solid (1.84 g, 95% yield) containing two equivalents of sodium chloride, which was used for the next reaction without any further purification.

Step 4: 1-{[4-(difluoromethoxy)-3-(pyridin-2-ylethynyl)phenyl] carbonyl}-4-pyridin-2-ylpiperazine

Triethylamine (0.48 mL, 3.5 mmol) was added to a mixture of 4-(difluoromethoxy)-3-(pyridin-2-ylethynyl)benzoic acid containing two equivalents of sodium chloride (700 mg, 1.72 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.43 g, 2.24 mmol), 1-hydroxy-7-azabenzotriazole (0.31 g, 2.24 mmol) and 2-(piperazin-1-yl)pyrazine (0.31 mL, 2.1 mmol) in dichloromethane (26 mL) with stirring at room temperature under an atmosphere of nitrogen. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with small amount of water. The solvents were removed and the residue was purified by flash chromatography on SiO_2 (column diam: 60 mm; fraction size: 100 mL; gradient elution using 0-8% methanol in dichloromethane). Fractions 30-33 were combined and

evaporated to give an oil, which was dissolved in methanol (20 mL). Aqueous HCl (2.0 N, 1.8 mL) was added to this methanol solution. The mixture was then stirred at room temperature for 20 min. Evaporation yielded a semi-solid, which was triturated with dichloromethane (3X) and dried *in vacuo* at 50 °C for 7 hours to afford the di-HCl product as a light green solid (0.81 g, 93 % yield).

Compounds 382-385 were synthesized according to Example 20.

UNLESS NOTED OTHERWISE THE FOLLOWING
VALUES REFER TO FORMULA I
WHEREIN R_1, R_4, R_{4a}, R_5, R_{5a} = H; X_2 = CH; Z = CO

TABLE 20

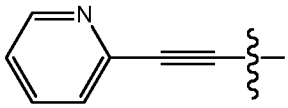
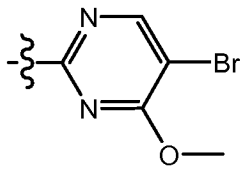
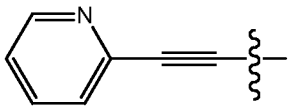
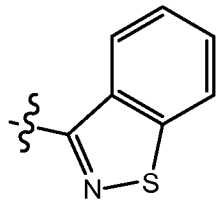
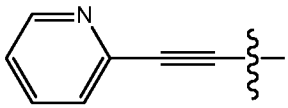
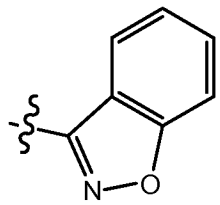
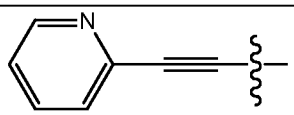
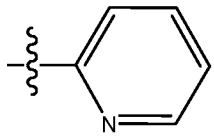
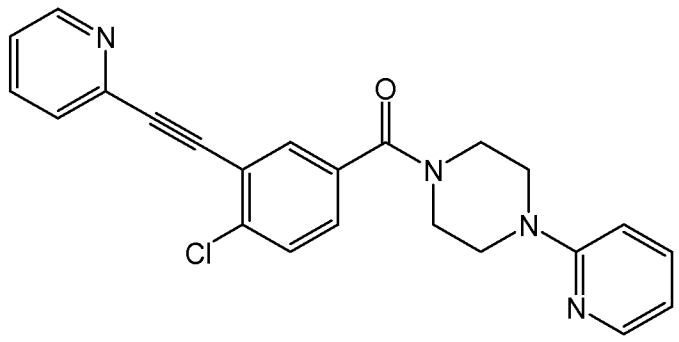
Cmpd	Name	R_2	X_1	R_6
382	5-bromo-2-(4-{[4-(difluoromethoxy)-3-(pyridin-2-ylethynyl) phenyl]carbonyl}piperazin-1-yl)-4-methoxy pyrimidine		$COCHF_2$	
383	3-(4-{[4-(difluoro methoxy)-3-(pyridin-2-ylethynyl)phenyl]carbonyl}piperazin-1-yl)-1,2-benzisothiazole		$COCHF_2$	
384	3-(4-{[4-(difluoro methoxy)-3-(pyridin-2-ylethynyl)phenyl]carbonyl}piperazin-1-yl)-1,2-benzisoxazole		$COCHF_2$	
385	1-{[4-(difluoromethoxy) -3-(pyridin-2-ylethynyl) phenyl]carbonyl}-4-pyridin-2-ylpiperazine		$COCHF_2$	

TABLE 20A

Cmpd	Name	LCMS data		Biological Activity	
		Mass	Ion	Median Ki (μM)	IC50 (uM)
382	5-bromo-2-(4-{[4-(difluoro methoxy)-3-(pyridin-2-yl ethynyl)phenyl]carbonyl} piperazin-1-yl)-4-methoxy pyrimidine	544.0	M+H	0.035	0.104
383	3-(4-{[4-(difluoromethoxy)-3-(pyridin-2-ylethynyl)phenyl] carbonyl}piperazin-1-yl)-1,2-benzisothiazole	491.1	M+H	0.001	0.041
384	3-(4-{[4-(difluoromethoxy)-3-(pyridin-2-ylethynyl)phenyl] carbonyl}piperazin-1-yl)-1,2-benzisoxazole	475.1	M+H	0.001	0.016
385	1-{[4-(difluoromethoxy)-3-(pyridin-2-ylethynyl)phenyl] carbonyl}-4-pyridin-2-ylpiperazine	453.0	M+H	0.007	0.013

Example 21

1-[4-chloro-3-(pyridin-2-ylethynyl)benzoyl]-4-pyridin-2-ylpiperazine (Compound 386)



Step 1: methyl 4-chloro-3-(pyridin-2-ylethynyl)benzoate

Methyl 3-bromo-4-chlorobenzoate (1.758 g, 7.089 mmol), 2-ethynyl pyridine (1.40 mL, 13.9 mmol), and triethylamine (2.20 mL, 15.8 mmol) were dissolved

in 34 mL dry toluene. Nitrogen gas was bubbled through the mixture for 10 minutes, and then dichlorobis(triphenylphosphine)-palladium(II) (1.00 g, 1.42 mmol) and copper(I) iodide (0.268 g, 1.41 mmol) were added to the mixture. Nitrogen was bubbled through the mixture for another 5 minutes, and then the mixture was then heated to 100 °C for 6 hours. The mixture was cooled, and then filtered through a pad of Celite. The Celite pad was washed with ethyl acetate (2X) and then ~5% methanol/methylene chloride (2X). The combined filtrate was evaporated and the residue was chromatographed on silica gel using a gradient elution of ethyl acetate in methylene chloride. Methyl 4-chloro-3-(pyridin-2-ylethynyl)benzoate is obtained (0.843 g, 3.11 mmol; 44% yield) as a light brown-gray solid.

Step 2: 4-chloro-3-(pyridin-2-ylethynyl)benzoic acid

Methyl 4-chloro-3-(pyridin-2-ylethynyl)benzoate (0.413 g, 1.52 mmol) was dissolved in 6 mL of methanol. Aqueous 2N NaOH (1.52 mL, 3.05 mmol) was added, and the mixture was stirred 24 hours at room temperature. Aqueous 2N HCl (1.52 mL, 3.05 mmol) was added, and the mixture was stirred 5 minutes at room temperature. The mixture was evaporated to dryness to afford 4-chloro-3-(pyridin-2-ylethynyl)benzoic acid (0.580 g) as a light gray solid containing 2 equivalents of sodium chloride. This material was used as is for subsequent reactions.

Step 3: 1-[4-chloro-3-(pyridin-2-ylethynyl)benzoyl]-4-pyridin-2-yl piperazine

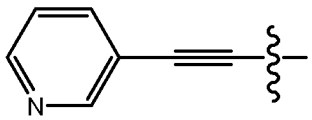
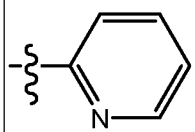
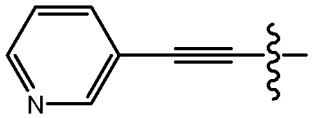
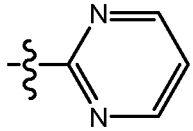
4-Chloro-3-(pyridin-2-ylethynyl)benzoic acid containing 2 equivalents of sodium chloride (0.040 g, 0.107 mmol) was dissolved in 0.8 mL dimethylformamide. N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide hydrochloride (EDCI, 0.027 g, 0.141 mmol) was added, followed by 1-hydroxy-7-azabenzotriazole (HOAt, 0.019 g, 0.140 mmol) and then 1-(2-pyridyl)-piperazine (0.016 mL, 0.110 mmol). Triethylamine (0.045

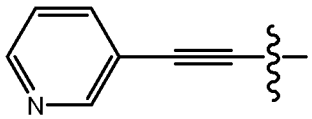
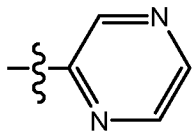
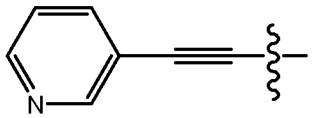
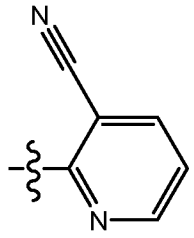
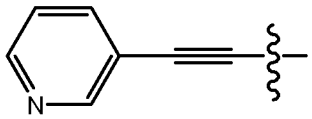
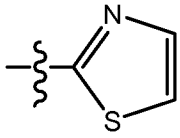
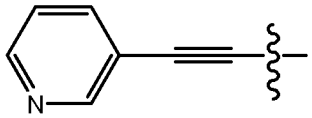
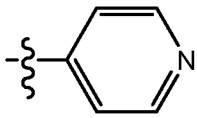
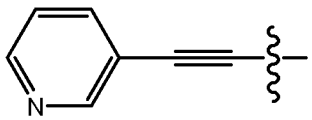
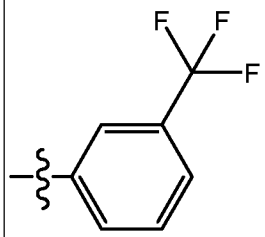
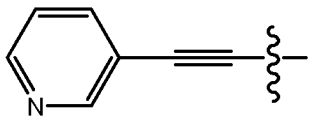
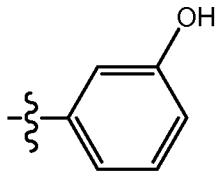
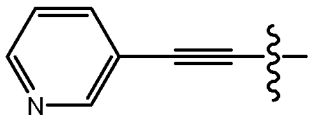
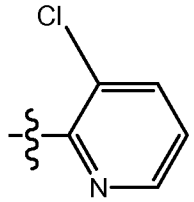
mL, 0.323 mmol) was added, and the mixture was stirred overnight at room temperature. The mixture was then partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic phase was pumped dry, and was purified by prep HPLC using a Gilson reversed-phase HPLC with TFA modified water and acetonitrile as eluant. The solid obtained from the fractions containing the desired product was taken up in 0.7 mL methanol, and 2N HCl (0.050 mL, 0.100 mmol) was added. The mixture was stirred at room temperature for 5 minutes, and was then pumped dry to afford the HCl salt of 1-[4-chloro-3-(pyridin-2-ylethynyl)benzoyl]-4-pyridin-2-ylpiperazine (0.026 g, 0.055 mmol; 51% yield) as a light greenish-white solid.

Compounds 386-396, shown in Table 21 below, were prepared using the procedure of Example 21 described above.

UNLESS NOTED OTHERWISE THE FOLLOWING
VALUES REFER TO FORMULA I
WHEREIN R_1, R_4, R_{4a}, R_5, R_{5a} = H; X_2 = CH; Z = CO

TABLE 21

Cmpd	Name	R_2	X_1	R_6
386	1-[4-chloro-3-(pyridin-2-ylethynyl)benzoyl]-4-pyridin-2-yl piperazine		CCl	
387	2-{4-[4-chloro-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}pyrimidine		CCl	

388	2-{4-[4-chloro-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}pyrazine		CCl	
389	2-{4-[4-chloro-3-(pyridin-2-ylethynyl) benzoyl]piperazin-1-yl}nicotinonitrile		CCl	
390	1-[4-chloro-3-(pyridin-2-ylethynyl)benzoyl]-4-(1,3-thiazol-2-yl) piperazine		CCl	
391	1-[4-chloro-3-(pyridin-2-ylethynyl)benzoyl]-4-pyridin-4-yl piperazine		CCl	
392	1-[4-chloro-3-(pyridin-2-ylethynyl)benzoyl]-4-[3- (trifluoromethyl) phenyl]piperazine		CCl	
393	3-(4-{[4-chloro-3-(pyridin-2-ylethynyl) phenyl]carbonyl}piperazin-1-yl)phenol		CCl	
394	1-(3-chloropyridin-2-yl)-4-{[4-chloro-3-(pyridin-2-ylethynyl) phenyl]carbonyl} piperazine		CCl	

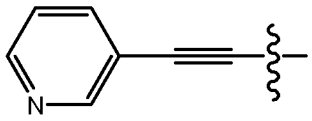
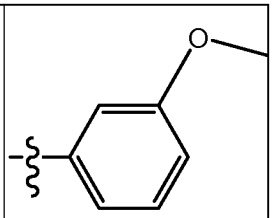
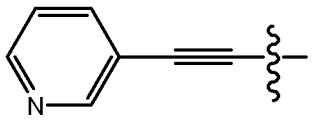
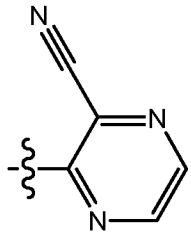
395	1-{[4-chloro-3-(pyridin-2-ylethynyl) phenyl]carbonyl}-4-(3-methoxyphenyl) piperazine		CCl	
396	3-(4-{[4-chloro-3-(pyridin-2-ylethynyl) phenyl]carbonyl}piperazin-1-yl)pyrazine-2-carbonitrile		CCl	

TABLE 21A

Cmpd	Name	LCMS data		Biological Activity	
		Mass	Ion	Median Ki (μM)	IC50 (uM)
386	1-[4-chloro-3-(pyridin-2-ylethynyl)benzoyl]-4-pyridin-2-ylpiperazine	403.1	M+H	0.003	0.039
387	2-{4-[4-chloro-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine	404.1	M+H	0.010	0.131
388	2-{4-[4-chloro-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrazine	404.1	M+H	0.013	0.094
389	2-{4-[4-chloro-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}nicotinonitrile	428.1	M+H	0.063	0.239
390	1-[4-chloro-3-(pyridin-2-ylethynyl)benzoyl]-4-(1,3-thiazol-2-yl)piperazine	409.1	M+H	0.007	0.039
391	1-[4-chloro-3-(pyridin-2-ylethynyl)benzoyl]-4-pyridin-4-ylpiperazine	403.1	M+H	0.079	1.494
392	1-[4-chloro-3-(pyridin-2-ylethynyl)benzoyl]-4-[3- (trifluoromethyl)phenyl]piperazine	470.1	M+H	0.120	

393	3-(4-{[4-chloro-3-(pyridin-2-ylethynyl)phenyl]carbonyl}piperazin-1-yl)phenol	418.1	M+H	0.012	0.144
394	1-(3-chloropyridin-2-yl)-4-{[4-chloro-3-(pyridin-2-ylethynyl)phenyl]carbonyl}piperazine	437.1	M+H	0.021	0.145
395	1-{[4-chloro-3-(pyridin-2-ylethynyl)phenyl]carbonyl}-4-(3-methoxyphenyl)piperazine	432.1	M+H	0.019	0.113
396	3-(4-{[4-chloro-3-(pyridin-2-ylethynyl)phenyl]carbonyl}piperazin-1-yl)pyrazine-2-carbonitrile	429.1	M+H	0.017	0.047

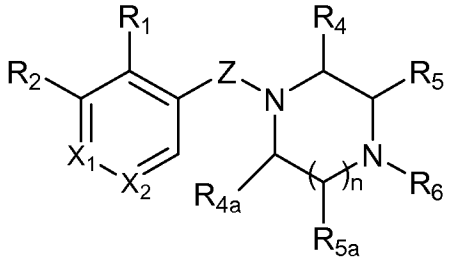
Variations, modifications, and other implementations of what is described herein will occur to those of ordinary skill in the art without departing from the spirit and the essential characteristics of the present teachings. Accordingly, the invention is intended to include all such modifications and implementations, and their equivalents.

Each reference cited in the present application, including books, patents, published applications, journal articles and other publications, is incorporated herein by reference in its entirety.

This application claims the benefit under 35 USC 119(e) of U.S. provisional application 61/055,671 filed on May 23, 2008, which is incorporated herein by reference in its entirety.

WHAT IS CLAIMED IS:

1. A compound of Formula I:



I

wherein:

R_1 is each independently selected from H, C_{1-6} alkyl, halogen, OH, and OC_{1-6} alkyl;

R_2 is selected from $-(L_1)_a-(Y)_c-(L_2)_b-Q_3$, $-L_3-Q_4$ and $-L_4-Q_5$;

L_3 is C_{2-12} alkynyl optionally substituted with 1-3 substituents selected from OH and halogen;

L_1 and L_2 are each independently C_{1-3} alkyl;

L_4 is C_{2-12} alkenyl optionally substituted with 1-3 substituents selected from OH and halogen;

n is 1 or 2

R_4, R_{4a}, R_5, and R_{5a} are each independently selected from H, (=O) and C_{1-6} alkyl; or R_4 and one of R_{5a} together can form a bridging methylene; or R_5 can be together with the carbon to which it is attached –C(=O)

R_6 is selected from H, CH_3, $-(L_5)-$(3- to 14-membered heterocycle), $-(L_5)-$(5 to 14 membered heteroaromatic), $(L_5)-$(3- to 10-membered cycloalkyl), $(L_5)-(C_{6-14}$ aryl) and $-(L_5)-C_{1-6}$ alkyl each of which except H can be optionally substituted with 1 to 3 substituents independently selected from H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, $-C(=O)O-(C_{1-6}$ alkyl), NO_2, C_{1-3} haloalkyl, $-S-C_{1-6}$ alkyl, CN, (5- to 14-membered heteroaromatic), NR_1R_1, SO_2C_{1-6} alkyl, SO_2, $SO_2NR_1R_1$, C_{1-6}alkylaryl, COC_{1-6} alkyl, and (3- to 14-membered heterocycle) optionally substituted with NO_2.

L_5 is selected from a bond, C_{1-3} alkyl, -C(=O)-, SO_2, (3- to 6-membered heterocycle) and (5- to 14-membered heteroaromatic).

X_1, X_2 are independently CR_3 or N;

each R_3 is independently H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, SO_2, 3- to 14-membered heterocycle or 5- to 14-membered heteroaromatic, wherein each of C_{1-6} alkyl or OC_{1-6} alkyl can be optionally substituted with 1 to 3 substituents independently selected from halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), cycloalkyl, NR_1R_1, or CN;

Z is CO;

Y is CR_7R_8, NR_9, O, or S;

R_7, R_8, R_9 are independently H, C_{1-6} alkyl, halogen, OH, or OC_{1-6} alkyl

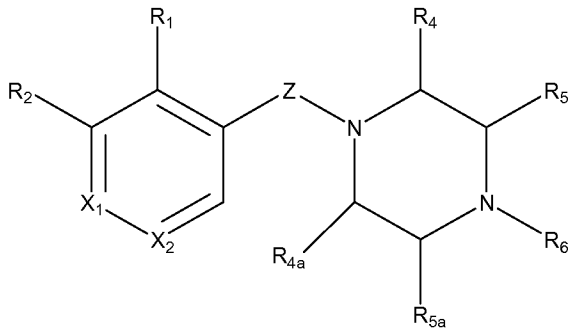
a, b, c are independently 0 or 1; and

Q_3 is C_{6-14} aryl, 5 to 14 membered heterocyclic, 5 to 14 membered heteroaromatic, or 4 to 9 membered carbocyclic; each of which can be optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), OC_{1-3} haloalkyl, OC_{1-6} alkylaryl and CN;

Q_4 is H, C_{6-14} aryl, 5 to 14 membered heterocyclic, 5 to 14 membered heteroaromatic, or 4 to 9 membered carbocyclic; each of which except H can be optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), -C(=O)C_{1-6} alkyl, NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), OC_{1-3}haloalkyl, OC_{1-6}alkylaryl and CN;

Q_5 is C_{6-14} aryl, 5 to 14 membered heterocyclic, 5 to 14 membered heteroaromatic, or 4 to 9 membered carbocyclic; each of which can be optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), OC_{1-3}haloalkyl, OC_{1-6}alkylaryl and CN.

2. A compound of Formula I:



I

wherein:

R_1 is H, C_{1-6} alkyl, halogen, OH, or OC_{1-6} alkyl;

R_2 is $-(L_1)_a-(Y)_c-(L_2)_b-Q_3$, $-L_3-Q_4$ or $-L_4-Q_5$;

L_3 is C_{2-12} alkynyl optionally substituted with 1-3 substituents selected from OH and halogen;

L_1 and L_2 are each independently C_{1-3} alkyl;

L_4 is C_{2-12} alkenyl optionally substituted with 1-3 substituents selected from OH and halogen;

R_4, R_{4a}, R_5, and R_{5a} are each independently H or C_{1-6} alkyl;

R_6 is selected from H, CH_3, $-(L_5)$-2-pyridyl, $-(L_5)$-4-pyridyl, $-(L_5)$-pyrazinyl, $-(L_5)$-phenyl, $-(L_5)$-(3-14 membered heterocyclic), $-(L_5)$-(5 to 14 membered heteroaromatic), and (L_5)-(C_{6-14} aryl) each of which except H can be optionally substituted with 1 to 3 substituents independently selected from H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, $-C(=O)O-(C_{1-6}$ alkyl), NO_2, C_{1-3} haloalkyl, $-S-C_{1-6}$ alkyl, COC_{1-6} alkyl and CN;

X_1, X_2 are independently CR_3 or N;

L_5 is selected from a bond, C_{1-3} alkyl, -C(=O)-, SO_2, (3- to 6-membered heterocycle) and (5- to 14-membered heteroaromatic).

X_1, X_2 are independently CR_3 or N;

each R_3 is independently H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, SO_2, 3- to 14-membered heterocycle or 5- to 14-membered heteroaromatic, wherein each of C_{1-6} alkyl or OC_{1-6} alkyl can be optionally substituted with 1 to 3 substituents independently selected from halogen, OH, OC_{1-6} alkyl, $-C(=O)O-(C_{1-6}$ alkyl), NO_2, C_{1-3} haloalkyl, $-S-C_{1-6}$ alkyl $-NH_2$, $-NH-(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)(C_{1-6} alkyl), cycloalkyl, NR_1R_1, or CN;

Z is CO;

Y is CR_7R_8, NR_9, O, or S;

R_7, R_8, R_9 are independently H, C_{1-6} alkyl, halogen, OH, or OC_{1-6} alkyl

a, b, c are independently 0 or 1; and

Q_3 is C_{6-14} aryl, 5 to 14 membered heterocyclic, 5 to 14 membered heteroaromatic, or 4 to 9 membered carbocyclic; each of which can be optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen,

OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), OC_{1-3} haloalkyl, OC_{1-6} alkylaryl and CN;

Q_4 is H, C_{6-14} aryl, 5 to 14 membered heterocyclic, 5 to 14 membered heteroaromatic, or 4 to 9 membered carbocyclic; each of which except H can be optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), -C(=O)C_{1-6} alkyl, NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), OC_{1-3}haloalkyl, OC_{1-6}alkylaryl and CN;

Q_5 is C_{6-14} aryl, 5 to 14 membered heterocyclic, 5 to 14 membered heteroaromatic, or 4 to 9 membered carbocyclic; each of which can be optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), OC_{1-3}haloalkyl, OC_{1-6}alkylaryl and CN.

3. The compound of claim 1 or 2, wherein R_2 is -L_3-Q_4.

4. The compound of claim 1 or 2, wherein R_6 is selected from -(L_5)-2-pyridyl, -(L_5)-4-pyridyl, -(L_5)-pyrazinyl, and -(L_5)-phenyl.

5. The compound of any one of claims 1-4 wherein X_1 is $COCHF_2$ or $COCF_3$.

6. The compound of any one of claims 1-5, wherein R_3 is selected from H, methyl, methoxy or halogen.

7. The compound of any one of claims 1-5, wherein R_3 is selected from $OCHF_2$, OCF_3, ethoxy, cyclopropylmethyloxy, and CF_3.

8. The compound of any one of claims 1-7, wherein R_1, R_4, R_{4a}, R_5, and R_{5a}, are each H.

9. The compound of any one of claims 1-8 wherein the 3-14 membered heterocycle of R_6 is selected from aziridinyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothienyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl,

dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, dihydro-1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydroquinolinyl, and tetrahydroisoquinolinyl.

10. The compound of any one of claims 1-8 wherein the 5 to 14 membered heteroaromatic of R_6 is selected from furyl, thienyl, pyridyl, pyrrolyl, oxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, isoxazolyl, triazolyl, oxadiazolyl, pyrimidinyl, pyrazinyl, indolyl, benzimidazolyl, benzothiophenyl, quinolinyl, isoquinolinyl, quinoxalinyl, and benzothiazolyl

11. The compound of any one of claims 1 to 10, wherein L_5 is selected from a bond, SO_2 and –C(=O)-.

12. The compound according to any one of claims 1 to 11, wherein X_1 is CR_3; X_2 is CH, R_6 is –(L_5)-2-pyridyl optionally substituted with halogen or C_{1-6}alkyl, wherein L_5 is a bond, R_{4a} and R_5 form a bridging methylene, R_2 is -L_3-Q_4, L_3 is C_2 alkynyl, and Q_4 is 2-pyridyl or phenyl optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl) and CN.

13. The compound of any of claims 1-12, wherein R_3 is OC_{1-6} alkyl.

14. The compound of any of claims 1-12, wherein R_2 is -L_3-Q_4 and L_3 is C_{2-3} alkynyl.

15. The compound of any one of claims 1-14, wherein Q_4 is selected from C_{6-14} aryl, 5- to 14-membered heterocycle and 5- to 14-membered heteroaromatic optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl) and CN.

16. The compound of claim 15, wherein Q_4 is pyridinyl optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), -C(=O)C_{1-6} alkyl, NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), OC_{1-3}haloalkyl, OC_{1-6}alkylaryl and CN

17. The compound of claim 15, wherein R_6 is 5-to 14-membered heteroaromatic optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl and CN.

18. The compound of claim 1 or 2, wherein:
R_2 is selected from methyl-5-phenylethynyl-pyridine and methyl-2-phenylethynyl-pyridine; and
R_6 is selected from phenyl, 2-pyridyl, methyl-pyrimidine, methyl-nicotinonitrile, methyl-5-trifluoromethyl-pyridine, 2,4-dimethyl-pyridine, 2,6-dimethyl pyridine, methyl-6-trifluoromethyl-pyridine, methyl-pyrazine, methyl-3-trifluoromethyl-pyridine, methyl-nicotinonitrile, methyl-pyrimidine, and 4-pyridyl.

19. The compound of claim 1, wherein the compound is selected from 1-{[5-(phenyl ethynyl)pyridin-3-yl]carbonyl}-4-pyridin-2-ylpiperazine; 2-{4-[2-(phenylethynyl) isonicotinoyl]piperazin-1-yl}pyrimidine; 1-[2-(phenylethynyl)isonicotinoyl]-4-pyridin-2-ylpiperazine; 6-{4-[2-(phenylethynyl)isonicotinoyl]piperazin-1-yl}nicotinonitrile; 1-[2-(phenylethynyl)isonicotinoyl]-4-[5-(trifluoromethyl)pyridin-2-yl]piperazine; 1-(4-methyl pyridin-2-yl)-4-[2-(phenylethynyl)isonicotinoyl]piperazine; 1-(6-methylpyridin-2-yl)-4-[2-(phenylethynyl)isonicotinoyl]piperazine; 1-[2-(phenylethynyl)isonicotinoyl]-4-[6-(trifluoromethyl)pyridin-2-yl]piperazine; 2-{4-[2-(phenylethynyl)isonicotinoyl]piperazin-1-yl}pyrazine; 2-(4-{[5-(phenylethynyl)pyridin-3-yl]carbonyl}piperazin-1-yl)pyrimidine; 6-(4-{[5-(phenylethynyl)pyridin-3-yl]carbonyl}piperazin-1-yl)nicotinonitrile; 1-{[5-(phenylethynyl)pyridin-3-yl]carbonyl}-4-[5-(trifluoromethyl)pyridin-2-yl]piperazine; 1-(4-methylpyridin-2-yl)-4-{[5-(phenylethynyl)pyridin-3-yl]carbonyl}piperazine; 1-{[5-(phenylethynyl)pyridin-3-yl]carbonyl}-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine; 2-(4-{[5-(phenylethynyl)pyridin-3-yl]carbonyl}piperazin-1-yl)nicotinonitrile; 4,6-dimethyl-2-(4-{[5-(phenylethynyl)pyridin-3-yl]carbonyl}piperazin-1-yl)pyrimidine; 2-(4-{[5-

(phenylethynyl)pyridin-3-yl]carbonyl}piperazin-1-yl)pyrazine; 1-{[5-(phenylethynyl) pyridin-3-yl]carbonyl}-4-pyridin-4-ylpiperazine; 2-{4-[2-(phenylethynyl)isonicotinoyl] piperazin-1-yl}nicotinonitrile; 1-(6-methylpyridin-2-yl)-4-{[5-(phenylethynyl)pyridin-3-yl]carbonyl}piperazine; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-pyridin-2-ylpiperazine or 1-[2-(phenylethynyl)isonicotinoyl]-4-pyridin-4-ylpiperazine.

20. The compound of claim 1, wherein the compound is 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-[5-(trifluoromethyl)pyridin-2- yl]piperazine; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-[3-(trifluoromethyl)pyridin-2- yl]piperazine; 1-(3,5-dichloropyridin-2-yl)-4-[4-methoxy-3-(pyridin-2- ylethynyl)benzoyl]piperazine; 1-(3-chloropyridin-2-yl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-[3- (trifluoromethyl)phenyl] piperazine; 1-(5-chloropyridin-2-yl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-(3-chlorophenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-4-[4-methoxy-3-(pyridin-2- ylethynyl)benzoyl]piperazine; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(4-methylpyridin-2-yl)piperazine; 2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-4,6- dimethylpyrimidine; 3-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrazine-2- carbonitrile; 2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-4- (trifluoromethyl)pyrimidine; 3-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}phenol; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(3-methylphenyl)piperazine; 5-bromo-4-methoxy-2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1- yl}pyrimidine; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(6-methylpyridin-2-yl)piperazine; (1R,4S)-2-(4-chlorophenyl)-5-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-2,5-diazabicyclo[2.2.1]heptane; 4-methoxy-2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1- yl}pyrimidine; 3-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-1,2- benzisothiazole; 6-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-1,4-diazepan-1- yl}nicotinonitrile or 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(5-methylpyridin-2-yl)piperazine; 2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-6-methylpyrazine; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-pyridin-2-yl-1,4-diazepane; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-[5-(trifluoromethyl)-1,3,4- thiadiazol-2-yl]piperazine; (1R,4S)-2-(3-fluorophenyl)-5-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-2,5-

diazabicyclo[2.2.1]heptane; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(3-methylpyridin-2-yl)piperazine; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-[3-(trifluoromethyl)pyridin-2- yl]-1,4-diazepane; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-[5-(trifluoromethyl)pyridin-2- yl]-1,4-diazepane; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(6-methylpyridin-2-yl)-1,4- diazepane; 1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-4-[4-methoxy-3-(pyridin-2- ylethynyl)benzoyl]-1,4-diazepane; 1-(6-methoxypyridin-2-yl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-1,4-diazepan-1- yl}nicotinonitrile; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(5-nitropyridin-2-yl)-1,4- diazepane; 1-(2-chlorophenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-(4-chlorophenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-(3,4-dichlorophenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-(2,3-dimethylphenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 2-isopropyl-4-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-6- methylpyrimidine; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(2-methylphenyl)piperazine; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(4-methylphenyl)piperazine; or 1-(3-fluorophenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine, 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(phenylsulfonyl)piperazine; 1-[(5-chloro-2-thienyl)sulfonyl]-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; (1R,4S)-2-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-5-(4-methylphenyl)-2,5- diazabicyclo[2.2.1]heptane; (1S,4R)-2-(4-fluorophenyl)-5-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-2,5- diazabicyclo[2.2.1]heptane; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-[4- (trifluoromethyl)phenyl]piperazine; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(5-nitropyridin-2-yl)piperazine; 1-(2-methoxyphenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-(4-fluorophenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(4-nitrophenyl)piperazine; 1-(4-methoxyphenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-(benzylsulfonyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-(2,3-dihydro-1,4-benzodioxin-6-ylsulfonyl)-4-[4-methoxy-3-(pyridin-2- ylethynyl)benzoyl]piperazine; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-pyridin-4-ylpiperazine; 1-(4-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}phenyl)ethanone; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-[4- (methylsulfonyl)phenyl]piperazine; 1-[(3,4-

dichlorophenyl)sulfonyl]-4-[4-methoxy-3-(pyridin-2- ylethynyl)benzoyl]piperazine; 1-[4-fluoro-2-(methylsulfonyl)phenyl]-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-(3-methoxyphenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-(2,5-dimethylphenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-[(4-chlorophenyl)sulfonyl]-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-benzoyl-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-(ethylsulfonyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-[2-(trifluoromethyl)phenyl]piperazine; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(1,3-thiazol-2-yl)piperazine; 1-(cyclopropylcarbonyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(tetrahydrofuran-2- ylcarbonyl)piperazine; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-2-methyl-4-phenylpiperazine; 3-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-1,2-benzisoxazole; 6-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}nicotinonitrile; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-[(4- methylphenyl)sulfonyl]piperazine; 5-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-4-nitrothiophene- 2-sulfonamide; 1-(6-chloropyridin-2-yl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-1,3-benzothiazole; 2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-1,3-benzoxazole; 1-(2-furoyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-(1,3-benzodioxol-5-ylmethyl)-4-[4-methoxy-3-(pyridin-2- ylethynyl)benzoyl]piperazine; 1-(1,3-benzodioxol-5-ylmethyl)-4-[4-methoxy-3-(pyridin-2- ylethynyl)benzoyl]piperazine; 1-(1,3-benzodioxol-5-ylmethyl)-4-[4-methoxy-3-(pyridin-2- ylethynyl)benzoyl]piperazine; 7-bromo-3-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1- yl}isoquinoline; 5-bromo-2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine; 1-(2-methoxybenzoyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-(3-methoxybenzoyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-(4-methoxybenzoyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-(2-fluorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-(3-fluorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-(4-fluorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-[(5-bromo-2-thienyl)sulfonyl]-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-[(3,5-dimethylisoxazol-4-yl)sulfonyl]-4-[4-methoxy-3-

(pyridin-2- ylethynyl)benzoyl] piperazine; 1-(3,5-dichlorophenyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl] piperazine; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-{[3-methoxy-4-(1H-tetrazol-1- yl)phenyl]sulfonyl}piperazine; 5-({4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}sulfonyl)-N,N- dimethylnaphthalen-1-amine; 1-(3-chlorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-(4-chlorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(5-nitro-1,3,4-thiadiazol-2- yl)piperazine; 1-(2,6-dichlorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-[(2-chlorophenyl)sulfonyl]-4-[4-methoxy-3-(pyridin-2- ylethynyl)benzoyl]piperazine; 1-[(3-chlorophenyl)sulfonyl]-4-[4-methoxy-3-(pyridin-2- ylethynyl)benzoyl]piperazine; 1-(2,4-dichlorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(3-phenyl-1,2,4-thiadiazol-5- yl)piperazine; 2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-6-nitro-1,3- benzothiazole; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-[5-(1-methyl-5-nitro-1H-imidazol- 2-yl)-1,3,4-thiadiazol-2-yl]piperazine; The compound of claim 1, wherein the compound is 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-{[4-(1H-tetrazol-1-yl)phenyl]sulfonyl}piperazine; 1-(4-bromo-2-fluorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; tert-butyl 4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine-1-carboxylate; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(2-naphthylsulfonyl)piperazine; 1-(3,4-dichlorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-(2-chloro-6-fluorobenzyl)-4-[4-methoxy-3-(pyridin-2- ylethynyl)benzoyl]piperazine; 1-(1-benzothiophen-2-yl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-(5-phenyl-4H-1,2,4-triazol-3- yl)piperazine; 1-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-phenylpiperazine; 4-amino-2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine-5-carbonitrile; 4-chloro-6-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-2-(methylthio)pyrimidine; 2-chloro-5-fluoro-4-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine; 4-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-2-(methylthio)pyrimidine; 4-chloro-6-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-2-methylpyrimidine; 5-fluoro-2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine; 5-fluoro-2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine; 5-fluoro-2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-

yl}pyrimidin-4-amine; 3-methoxy-6-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyridizine; 6-chloro-3-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-4-methylpyridazine; 2-chloro-3-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrazine; 2,4-dimethoxy-6-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-1,3,5-triazine; 1-chloro-4-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}phthalazine; 3-{4-[4-methyl-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-1,2-benzisoxazole; 4-methoxy-2-{4-[4-methyl-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine; 2-{4-[4-methyl-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine; 1-(3,5-dichloropyridin-2-yl)-4-[4-methyl-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-(3-chloropyridin-2-yl)-4-[4-methyl-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 2-{4-[4-fluoro-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine; 1-[4-fluoro-3-(pyridin-2-ylethynyl)benzoyl]-4-pyridin-2-ylpiperazine; 1-(3,5-dichloropyridin-2-yl)-4-[4-fluoro-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 1-(3-chloropyridin-2-yl)-4-[4-fluoro-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 3-{4-[4-fluoro-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1-yl}-1,2-benzisoxazole; 2-{4-[4-fluoro-3-(pyridin-2-ylethynyl)benzoyl] piperazin-1-yl}-4-methoxypyrimidine; 1-[4-ethoxy-3-(pyridin-2-ylethynyl)benzoyl]-4-pyridin-2-ylpiperazine; 1-(3,5-dichloropyridin-2-yl)-4-[4-ethoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 2-{4-[4-ethoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-4-methoxypyrimidine; 1-(3-chloropyridin-2-yl)-4-[4-ethoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazine; 3-{4-[4-ethoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}-1,2-benzisoxazole; 1-{[4-(cyclopropylmethoxy)-3-(pyridin-2-ylethynyl)phenyl] carbonyl}-4-pyridin-2-ylpiperazine; 3-(4-{[4-(cyclopropylmethoxy)-3-(pyridin-2-ylethynyl)phenyl]carbonyl}piperazin-1-yl)-1,2-benzisoxazole; 2-(4-{[4-(cyclopropylmethoxy)-3-(pyridin-2-ylethynyl)phenyl]carbonyl}piperazin-1-yl)pyrimidine; 1-(4-chlorophenyl)-4-{[4-methoxy-3-(pyridin-2-ylethynyl)phenyl]carbonyl}piperazin-2-one; 1-(3-chlorophenyl)-4-{[4-methoxy-3-(pyridin-2-ylethynyl)phenyl]carbonyl}piperazin-2-one; 1-(2-chlorophenyl)-4-{[4-methoxy-3-(pyridin-2-ylethynyl)phenyl]carbonyl}piperazin-2-one; 4-{[4-methoxy-3-(pyridin-2-ylethynyl)phenyl]carbonyl}-1-phenylpiperazin-2-one; 4-{[4-methoxy-3-(pyridin-2-ylethynyl)phenyl]carbonyl}-1-pyridin-2-ylpiperazin-2-one; 1-benzyl-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-2-one; 1-(2-chlorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-2-one; 1-(3-chlorobenzyl)-4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-2-one; 1-(4-chlorobenzyl)-4-[4-

methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-2-one; 2-{4-[3-(pyridin-2-ylethynyl)-4-(trifluoromethoxy)benzoyl]piperazin-1-yl}pyrazine; 1-(3-chloropyridin-2-yl)-4-[3-(pyridin-2-ylethynyl)-4-(trifluoromethoxy)benzoyl]piperazine; 1-[3-(pyridin-2-ylethynyl)-4-(trifluoromethoxy)benzoyl]-4-[3-(trifluoromethyl)phenyl]piperazine; 3-{4-[3-(pyridin-2-ylethynyl)-4-(trifluoromethoxy)benzoyl]piperazin-1-yl}-1,2-benzisoxazole; 5-bromo-4-methoxy-2-{4-[3-(pyridin-2-ylethynyl)-4-(trifluoromethoxy)benzoyl]piperazin-1-yl}pyrimidine; 1-pyridin-2-yl-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethoxy)phenyl]carbonyl}piperazine; 1-(3-chloropyridin-2-yl)-4-[4-methoxy-3-(phenylethynyl)benzoyl]piperazine; 1-(3-chloropyridin-2-yl)-4-{4-methoxy-3-[(2-nitrophenyl)ethynyl]benzoyl}piperazine or 1-(3-{[3-(benzyloxy)phenyl]ethynyl}-4-methoxybenzoyl)-4-(3-chloropyridin-2-yl)piperazine, 1-(3-chloropyridin-2-yl)-4-(4-methoxy-3-{[3-(trifluoromethoxy)phenyl]ethynyl}benzoyl)piperazine; 1-(3-chloropyridin-2-yl)-4-{4-methoxy-3-[(3-nitrophenyl)ethynyl]benzoyl}piperazine; 1-(3-{[4-(benzyloxy)phenyl]ethynyl}-4-methoxybenzoyl)-4-(3-chloropyridin-2-yl)piperazine; 1-{4-[(5-{[4-(3-chloropyridin-2-yl)piperazin-1-yl]carbonyl}-2-methoxyphenyl)ethynyl]phenyl} ethanone; 1-(3-chloropyridin-2-yl)-4-(4-methoxy-3-{[4-(trifluoromethane)phenyl]ethynyl}benzoyl)piperazine; 1-(3-chloropyridin-2-yl)-4-{4-methoxy-3-[(4-nitrophenyl)ethynyl]benzoyl}piperazine; 1-(3-chloropyridin-2-yl)-4-{3-[(2-fluorophenyl)ethynyl]-4-methoxybenzoyl}piperazine; 1-{3-[(4-chlorophenyl)ethynyl]-4-methoxybenzoyl}-4-(3-chloropyridin-2-yl)piperazine; 2-{4-[4-methoxy-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine; 2-{4-[4-methoxy-3-(pyridin-3-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine; 2-{4-[4-methoxy-3-(pyridin-4-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine; 2-[4-(4-methoxy-3-{[3-(trifluoromethoxy)phenyl]ethynyl}benzoyl)piperazin-1-yl]pyrimidine; 2-(4-{4-methoxy-3-[(3-nitrophenyl)ethynyl]benzoyl}piperazin-1-yl)pyrimidine; 2-[4-(3-{[4-(benzyloxy)phenyl]ethynyl}-4-methoxybenzoyl)piperazin-1-yl]pyrimidine; 2-(4-{3-[(2-fluorophenyl)ethynyl]-4-methoxybenzoyl}piperazin-1-yl)pyrimidine; 2-(4-{3-[(2-chlorophenyl)ethynyl]-4-methoxybenzoyl}piperazin-1-yl)pyrimidine; 3-({2-methoxy-5-[(4-pyrimidin-2-ylpiperazin-1-yl)carbonyl]phenyl}ethynyl)benzonitrile; 2-(4-{3-[(4-fluorophenyl)ethynyl]-4-methoxybenzoyl}piperazin-1-yl)pyrimidine; 2-(4-{3-[(4-chlorophenyl)ethynyl]-4-methoxybenzoyl}piperazin-1-yl)pyrimidine; 2-[4-(3-{[3-(difluoromethoxy)phenyl]ethynyl}-4-methoxybenzoyl)piperazin-1-yl]pyrimidine, 5-bromo-4-methoxy-2-(4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}

piperazin-1-yl)pyrimidine, 3-(4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl] carbonyl}piperazin-1-yl)pyrazine-2-carbonitrile; 1-(4-methylpyridin-2-yl)-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazine; 1-(3,5-dichloropyridin-2-yl)-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazine; 1-pyridin-2-yl-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazine; 2-(4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazin-1-yl)pyrimidine; 1-(3-chloropyridin-2-yl)-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl} piperazine; 1-(5-methylpyridin-2-yl)-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl) phenyl]carbonyl}piperazine; 4-methoxy-2-(4-{[3-(pyridin-2-ylethynyl)-4-(trifluoro methyl)phenyl]carbonyl}piperazin-1-yl)pyrimidine; 3-(4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazin-1-yl)-1,2-benzisoxazole; 1-(furan-2-ylcarbonyl)-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl} piperazine; 1-(3-fluorobenzyl)-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl] carbonyl} piperazine; 2-(4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl} piperazin-1-yl)-1,3-benzothiazole; 1-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl) phenyl]carbonyl} -4-(1,3-thiazol-2-yl)piperazine; 1-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl] carbonyl}-4-[5-(trifluoromethyl)pyridin-2-yl]piperazine; 1-(6-methylpyridin-2-yl)-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl} piperazine; 2-(4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethyl)phenyl]carbonyl}piperazin-1-yl)pyrazine; 5-bromo-2-(4-{[4-(difluoromethoxy)-3-(pyridin-2-ylethynyl)phenyl] carbonyl}piperazin-1-yl)-4-methoxypyrimidine; or 3-(4-{[4-(difluoromethoxy)-3-(pyridin-2-ylethynyl)phenyl] carbonyl}piperazin-1-yl)-1,2-benzisothiazole; 3-(4-{[4-(difluoromethoxy)-3-(pyridin-2-ylethynyl)phenyl]carbonyl}piperazin-1-yl)-1,2-benzisoxazole; 1-{[4-(difluoromethoxy)-3-(pyridin-2-ylethynyl)phenyl]carbonyl}-4-pyridin-2-ylpiperazine; 1-[4-chloro-3-(pyridin-2-ylethynyl)benzoyl]-4-pyridin-2-ylpiperazine; 2-{4-[4-chloro-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrimidine; 2-{4-[4-chloro-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}pyrazine; 2-{4-[4-chloro-3-(pyridin-2-ylethynyl)benzoyl]piperazin-1-yl}nicotinonitrile; 1-[4-chloro-3-(pyridin-2-ylethynyl)benzoyl]-4-(1,3-thiazol-2-yl)piperazine; 1-[4-chloro-3-(pyridin-2-ylethynyl)benzoyl]-4-pyridin-4-ylpiperazine; 1-[4-chloro-3-(pyridin-2-ylethynyl)benzoyl]-4-[3- (trifluoromethyl)phenyl]piperazine; 1-[4-chloro-3-(pyridin-2-ylethynyl)benzoyl]-4-[3- (trifluoromethyl)phenyl]piperazine; 3-(4-{[4-chloro-3-(pyridin-2-ylethynyl)phenyl]carbonyl}piperazin-1-yl)phenol; 1-(3-chloropyridin-2-yl)-4-{[4-chloro-3-

(pyridin-2- ylethynyl)phenyl]carbonyl}piperazine; 1-(4-chloropyridin-2-yl)-4-{[4-chloro-3-(pyridin-2- ylethynyl)phenyl]carbonyl}piperazine or 3-(4-{[4-chloro-3-(pyridin-2-ylethynyl)phenyl]carbonyl}piperazin-1-yl)pyrazine- 2-carbonitrile

21. The compound of claim 20, wherein the compound is selected from 1-pyridin-2-yl-4-{[3-(pyridin-2-ylethynyl)-4-(trifluoromethoxy)phenyl] carbonyl}piperazine and 1-{[4-(difluoromethoxy)-3-(pyridin-2-ylethynyl)phenyl]carbonyl}-4-pyridin-2-ylpiperazine.

22. The compound of claim 1 or 2, wherein Y is O, and Q_3 and Q_5 are each phenyl optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl) and CN.

23. The compound of claim 1 or 2, wherein R_2 is –CH=CH-, –CH_2-O- or –O-CH_2-; Y is O; and Q_3 and Q_5 are each phenyl optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl) and CN.

24. The compound of claim 1 or 2, wherein the compound is 3-({3-[(4-pyridin-2-ylpiperazin-1-yl)methyl]phenyl}ethynyl)phenol; 1-[3-(cyclohex-1-en-1-ylethynyl) benzyl]-4-pyridin-2-ylpiperazine; 1-[3-(3-phenylprop-1-yn-1-yl)benzyl]-4-pyridin-2-ylpiperazine; 3-({3-[(4-pyridin-2-yl piperazin-1-yl)methyl]phenyl}ethynyl)aniline; and 1-{3-[(3-methoxyphenyl) ethynyl]benzyl}-4-pyridin-2-ylpiperazine.

25. The compound of claim 1 or 2, wherein the compound is 3-({3-[(4-pyridin-2-ylpiperazin-1-yl)sulfonyl]phenyl}ethynyl)phenol; 1-{[3-(cyclohex-1-en-1-ylethynyl)phenyl]sulfonyl}-4-pyridin-2-ylpiperazine; 1-{[3-(3-phenylprop-1-yn-1-yl)phenyl]sulfonyl}-4-pyridin-2-ylpiperazine; 1-({3-[(3-methoxyphenyl)ethynyl]phenyl}sulfonyl)-4-pyridin-2-ylpiperazine; or 1-{[3-(phenylethynyl)phenyl]sulfonyl}-4-pyridin-2-yl-piperazine.

26. The compound of claim 1 or 2, wherein:

R_2 is $-L_3-Q_4$;

Q_4 is 5 to 14 membered heteroaromatic optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, $-C(=O)O-(C_{1-6}$ alkyl), NO_2, C_{1-3} haloalkyl, $-S-C_{1-6}$ alkyl $-NH_2$, $-NH-(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)(C_{1-6} alkyl) and CN; and

R_6 is $-(L_5)-$(5 to 14 membered heteroaromatic) optionally substituted with 1 to 3 substituents independently selected from H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, $-C(=O)O-(C_{1-6}$ alkyl), NO_2, C_{1-3} haloalkyl, $-S-C_{1-6}$ alkyl and CN.

27. The compound of any one of claims 1- 26, wherein Q_4 is pyridyl optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, $-C(=O)O-(C_{1-6}$ alkyl), NO_2, C_{1-3} haloalkyl, $-S-C_{1-6}$ alkyl $-NH_2$, $-NH-(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)(C_{1-6} alkyl) and CN.

28. The compound of any one of claims 1-26, wherein:

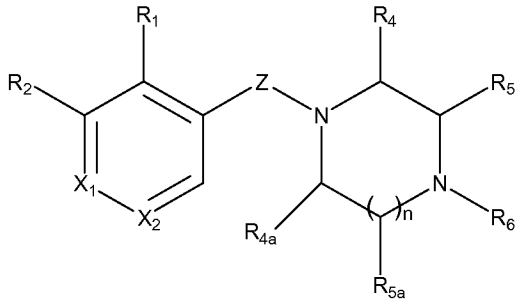
Q_4 is pyrid-2-yl; and

R_6 is $-(L_5)-$(pyrid-2-yl) optionally substituted with 1 to 3 substituents independently selected from H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, $-C(=O)O-(C_{1-6}$ alkyl), NO_2, C_{1-3} haloalkyl, $-S-C_{1-6}$ alkyl and CN.

29. The compound of claim 25-28, wherein X_1 is CR_3 and X_2 is CH.

30. Use of the compound of any of claims 1-29 for manufacturing a medicament for treating a patient suffering from a chronic condition selected from schizophrenia, paranoia, depression, manic-depressive illness, anxiety, panic disorders, social anxiety, obsessive compulsive disorders, generalized anxiety disorders, phobias, post-traumatic stress disorder, bipolar disorder, Asperger's syndrome, pervasive developmental disorders, gastrointestinal disorders such as gastroesophageal reflux disease, dyspepsia, irritable bowel syndrome, functional bloating, functional diarrhea, chronic constipation, functional disturbances of the biliary tract, migraine, chronic pain, fibromyalgia, neuropathic pain, post-herpatic neuropathic pain, addiction, Parkinson's disease, senile dementia, levadopa-induced dyskinesia, Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis, multiple sclerosis, Down

Syndrome, fragile-X syndrome, autistic spectrum disorders, attention deficit hyperactivity disorder, stroke, ischemic injury, epilepsy, hypoglycemia and obesity comprising providing a therapeutically effective amount of compound of Formula I:



I

wherein:

R_1 is each independently selected from H, C_{1-6} alkyl, halogen, OH, and OC_{1-6} alkyl;

R_2 is selected from $-(L_1)_a-(Y)_c-(L_2)_b-Q_3$, $-L_3-Q_4$ and $-L_4-Q_5$;

L_3 is C_{2-12} alkynyl optionally substituted with 1-3 substituents selected from OH and halogen;

L_1 and L_2 are each independently C_{1-3} alkyl;

L_4 is C_{2-12} alkenyl optionally substituted with 1-3 substituents selected from OH and halogen;

n is 1 or 2

R_4, R_{4a}, R_5, and R_{5a} are each independently selected from H, (=O) and C_{1-6} alkyl; or R_4 and one of R_{5a} together can form a bridging methylene; or R_5 can be together with the carbon to which it is attached –C(=O)

R_6 is selected from H, CH_3, $-(L_5)-$(3- to 14-membered heterocycle), $-(L_5)-$(5 to 14 membered heteroaromatic), $(L_5)-$(3- to 10-membered cycloalkyl), $(L_5)-(C_{6-14}$ aryl) and $-(L_5)-C_{1-6}$ alkyl each of which except H can be optionally substituted with 1 to 3 substituents independently selected from H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, $-C(=O)O-(C_{1-6}$ alkyl), NO_2, C_{1-3} haloalkyl, $-S-C_{1-6}$ alkyl, CN, (5- to 14-membered heteroaromatic), NR_1R_1, SO_2C_{1-6} alkyl, SO_2, $SO_2NR_1R_1$, C_{1-6}alkylaryl, COC_{1-6} alkyl, and (3- to 14-membered heterocycle) optionally substituted with NO_2.

L_5 is selected from a bond, C_{1-3} alkyl, -C(=O)-, SO_2, (3- to 6-membered heterocycle) and (5- to 14-membered heteroaromatic).

X_1, X_2 are independently CR_3 or N;

each R_3 is independently H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, SO_2, 3- to 14-membered heterocycle or 5- to 14-membered heteroaromatic, wherein each of C_{1-6} alkyl or OC_{1-6} alkyl can be optionally substituted with 1 to 3 substituents independently selected from halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl $-NH_2$, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), cycloalkyl, NR_1R_1, or CN;

Z is CO;

Y is CR_7R_8, NR_9, O, or S;

R_7, R_8, R_9 are independently H, C_{1-6} alkyl, halogen, OH, or OC_{1-6} alkyl

a, b, c are independently 0 or 1; and

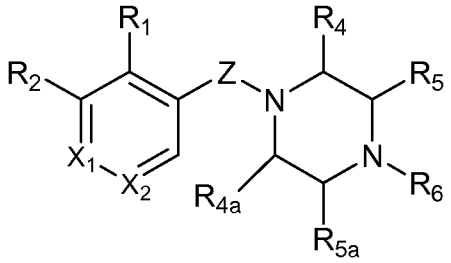
Q_3 is C_{6-14} aryl, 5 to 14 membered heterocyclic, 5 to 14 membered heteroaromatic, or 4 to 9 membered carbocyclic; each of which can be optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl $-NH_2$, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), OC_{1-3} haloalkyl, OC_{1-6} alkylaryl and CN;

Q_4 is H, C_{6-14} aryl, 5 to 14 membered heterocyclic, 5 to 14 membered heteroaromatic, or 4 to 9 membered carbocyclic; each of which except H can be optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), -C(=O)C_{1-6} alkyl, NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl $-NH_2$, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), OC_{1-3}haloalkyl, OC_{1-6}alkylaryl and CN;

Q_5 is C_{6-14} aryl, 5 to 14 membered heterocyclic, 5 to 14 membered heteroaromatic, or 4 to 9 membered carbocyclic; each of which can be optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl $-NH_2$, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), OC_{1-3}haloalkyl, OC_{1-6}alkylaryl and CN.

31. Use of the compound of any one of claims 1-29, for manufacturing a medicament for treating a patient suffering from a chronic condition selected from schizophrenia, paranoia, depression, manic-depressive illness, anxiety, panic disorders, social anxiety, obsessive compulsive disorders, generalized anxiety disorders, phobias, post-traumatic stress disorder, bipolar disorder, Asperger's

syndrome, pervasive developmental disorders, gastrointestinal disorders such as gastroesophageal reflux disease, dyspepsia, irritable bowel syndrome, functional bloating, functional diarrhea, chronic constipation, functional disturbances of the biliary tract, migraine, chronic pain, fibromyalgia, neuropathic pain, post-herpatic neuropathic pain, addiction, Parkinson's disease, senile dementia, levadopa-induced dyskinesia, Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis, multiple sclerosis, Down Syndrome, fragile-X syndrome, autistic spectrum disorders, attention deficit hyperactivity disorder, stroke, ischemic injury, epilepsy, hypoglycemia and obesity comprising providing a therapeutically effective amount of compound of Formula I:



I

wherein:

R_1 is H, C_{1-6} alkyl, halogen, OH, or OC_{1-6} alkyl;

R_2 is $-(L_1)_a-(Y)_c-(L_2)_b-Q_3$, $-L_3-Q_4$ or $-L_4-Q_5$;

L_3 is C_{2-12} alkynyl optionally substituted with 1-3 substituents selected from OH and halogen;

L_1 and L_2 are each independently C_{1-3} alkyl;

L_4 is C_{2-12} alkenyl optionally substituted with 1-3 substituents selected from OH and halogen;

R_4, R_{4a}, R_5, and R_{5a} are each independently H or C_{1-6} alkyl;

R_6 is selected from H, CH_3, $-(L_5)$-2-pyridyl, $-(L_5)$-4-pyridyl, $-(L_5)$-pyrazinyl, $-(L_5)$-phenyl, $-(L_5)$-(3-14 membered heterocyclic), $-(L_5)$-(5 to 14 membered heteroaromatic) and (L_5)-(C_{6-14} aryl), each of which except H can be optionally substituted with 1 to 3 substituents independently selected from H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, $-C(=O)O-(C_{1-6}$ alkyl), NO_2, C_{1-3} haloalkyl, $-S-C_{1-6}$ alkyl, COC_{1-6} alkyl and CN;

X_1, X_2 are independently CR_3 or N;

L_5 is selected from a bond, C_{1-3} alkyl, -C(=O)-, SO_2, (3- to 6-membered heterocycle) and (5- to 14-membered heteroaromatic).

X_1, X_2 are independently CR_3 or N;

each R_3 is independently H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, SO_2, 3- to 14-membered heterocycle or 5- to 14-membered heteroaromatic, wherein each of C_{1-6} alkyl or OC_{1-6} alkyl can be optionally substituted with 1 to 3 substituents independently selected from halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), cycloalkyl, NR_1R_1, or CN;

Z is CO;

Y is CR_7R_8, NR_9, O, or S;

R_7, R_8, R_9 are independently H, C_{1-6} alkyl, halogen, OH, or OC_{1-6} alkyl

a, b, c are independently 0 or 1; and

Q_3 is C_{6-14} aryl, 5 to 14 membered heterocyclic, 5 to 14 membered heteroaromatic, or 4 to 9 membered carbocyclic; each of which can be optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), OC_{1-3} haloalkyl, OC_{1-6} alkylaryl and CN;

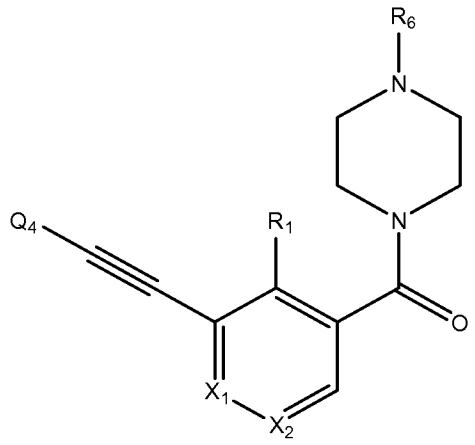
Q_4 is H, C_{6-14} aryl, 5 to 14 membered heterocyclic, 5 to 14 membered heteroaromatic, or 4 to 9 membered carbocyclic; each of which except H can be optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), -C(=O)C_{1-6} alkyl, NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), OC_{1-3}haloalkyl, OC_{1-6}alkylaryl and CN;

Q_5 is C_{6-14} aryl, 5 to 14 membered heterocyclic, 5 to 14 membered heteroaromatic, or 4 to 9 membered carbocyclic; each of which can be optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), OC_{1-3}haloalkyl, OC_{1-6}alkylaryl and CN.

32. Use of the compound of claim 30 or 31, wherein the patient is a human.

33. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound according to any one of claims claim 1 - 29.

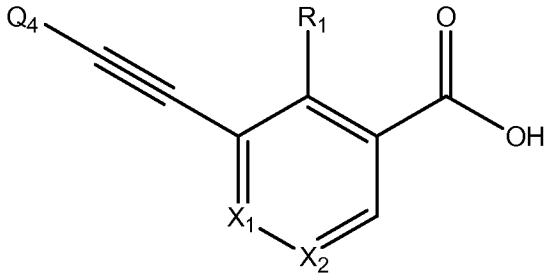
34. A synthetic process for preparing a compound of Formula IV:



IV

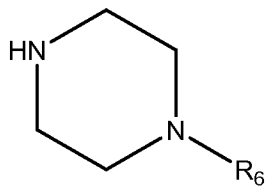
comprising:

reacting a compound of Formula III:



III

with an N-substituted piperazine of Formula IIIa:



IIIa

for a time and under conditions effective to form the compound of Formula IV;

wherein:

X_1 and X_2 are each independently CR_3 or N;

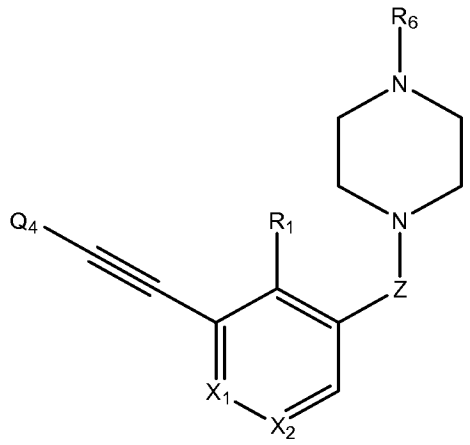
R_1 is H, $C_{1\text{-}6}$alkyl, halogen, OH, or $OC_{1\text{-}6}$alkyl;

each R_3 is independently H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, SO_2, 3- to 14-membered heterocycle or 5- to 14-membered heteroaromatic, wherein each of C_{1-6} alkyl or OC_{1-6} alkyl can be optionally substituted with 1 to 3 substituents independently selected from halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), cycloalkyl, NR_1R_1, or CN;

R_6 is selected from H, CH_3, -(L_5)-(3- to 14-membered heterocycle), -(L_5)-(5 to 14 membered heteroaromatic), (L_5)-(3- to 10-membered cycloalkyl), (L_5)-(C_{6-14} aryl) and –(L_5)-C_{1-6} alkyl each of which except H can be optionally substituted with 1 to 3 substituents independently selected from H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl, CN, (5- to 14-membered heteroaromatic), NR_1R_1, SO_2C_{1-6} alkyl, SO_2, $SO_2NR_1R_1$, C_{1-6}alkylaryl, COC_{1-6} alkyl, and (3- to 14-membered heterocycle) optionally substituted with NO_2; and

Q_4 is H, C_{6-14} aryl, 5 to 14 membered heterocyclic, 5 to 14 membered heteroaromatic, or 4 to 9 membered carbocyclic; each of which except H can be optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), -C(=O)C_{1-6} alkyl, NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), OC_{1-3}haloalkyl, OC_{1-6}alkylaryl and CN.

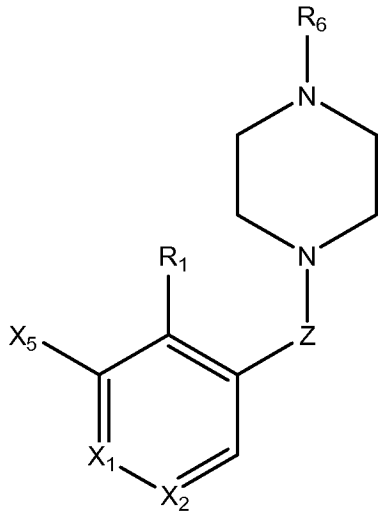
35. A synthetic process for preparing a compound of Formula IV:



IV

comprising:

reacting a compound of Formula VI:



VI

where X_5 is halogen, with an acetylene of Formula Q_4-CCH; in the presence of a palladium triphenyphosphine-containing catalyst for a time and under conditions effective to form the compounds of Formula IV;

wherein:

X_1 and X_2 are each independently CR_3 or N;

R_1 is H, C_{1-6}alkyl, halogen, OH, or OC_{1-6}alkyl;

each R_3 is independently H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, SO_2, 3- to 14-membered heterocycle or 5- to 14-membered heteroaromatic, wherein each of C_{1-6} alkyl or OC_{1-6} alkyl can be optionally substituted with 1 to 3 substituents independently selected from halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), cycloalkyl, NR_1R_1, or CN;

R_6, is selected from H, CH_3, -(L_5)-2-pyridyl, -(L_5)-4-pyridyl, -(L_5)-pyrazinyl, -(L_5)-phenyl, -(L_5)-(3-14 membered heterocyclic), and -(L_5)-(5 to 14 membered heteroaromatic), each of which except H can be optionally substituted with 1 to 3 substituents independently selected from H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl, COC_{1-6} alkyl and CN;

Z is CO;

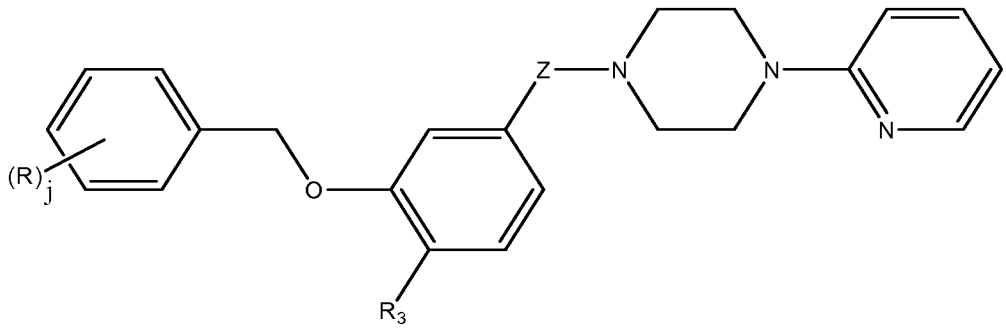
L_5 is a bond or C_{1-3} alkyl; and

Q_4 is H, C_{6-14} aryl, 5 to 14 membered heterocyclic, 5 to 14 membered heteroaromatic, or 4 to 9 membered carbocyclic; each of which except H can be optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), -C(=O)C_{1-6} alkyl, NO_2, C_{1-3} haloalkyl, -S-

C_{1-6} alkyl $-NH_2$, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), OC_{1-3}haloalkyl, OC_{1-6}alkylaryl and CN.

36. The process of claim 35, wherein X_5 is bromine, and the palladium triphenyphosphine-containing catalyst is Pd $(PPh_3)_2Cl_2$.

37. A synthetic process for preparing a compound of Formula IX:



IX

wherein:

each R_3 is independently H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, SO_2, 3- to 14-membered heterocycle or 5- to 14-membered heteroaromatic, wherein each of C_{1-6} alkyl or OC_{1-6} alkyl can be optionally substituted with 1 to 3 substituents independently selected from halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl $-NH_2$, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), cycloalkyl, NR_1R_1, or CN;

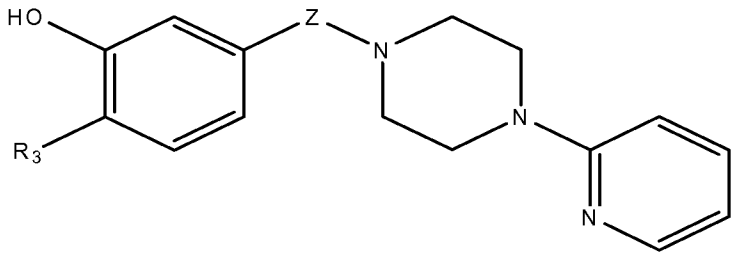
Z is CO;

each R is independently C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl $-NH_2$, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl) or CN; and

j is 0, 1, 2, or 3

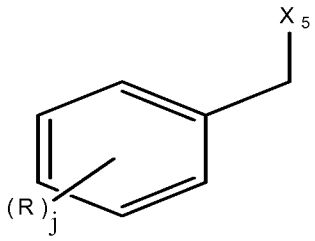
comprising:

reacting a compound of Formula VIII:



VIII

with a benzyl halide derivative of formula VIIIa:

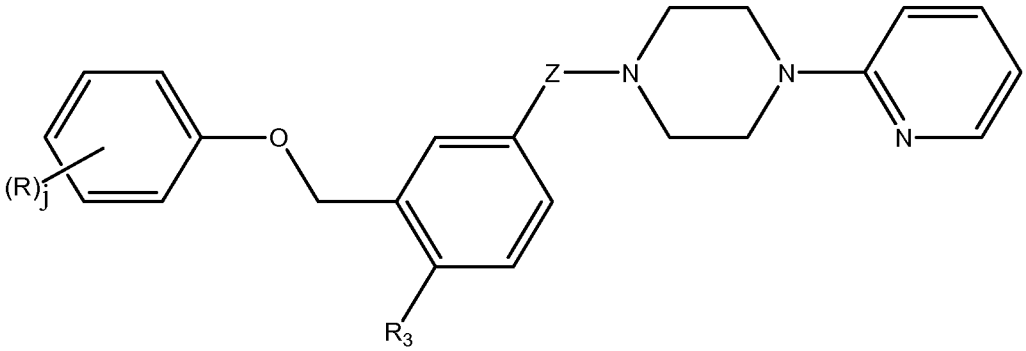


VIIIa

where X_5 is halogen, for a time and under conditions effective to form the compound of Formula IX.

38. The process of claim 37, wherein X_5 is bromine.

39. A synthetic process for preparing a compound of Formula XI:



XI

wherein:

Z is CO;

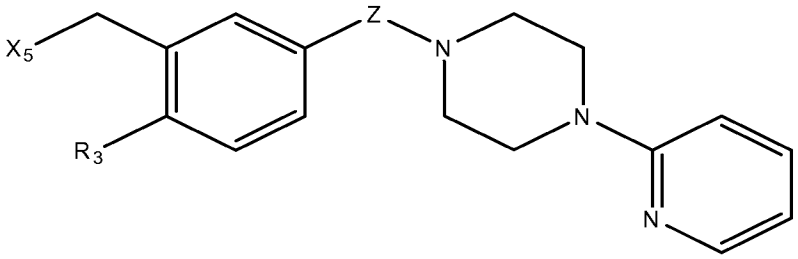
each R_3 is independently H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, SO_2, 3- to 14-membered heterocycle or 5- to 14-membered heteroaromatic, wherein each of C_{1-6} alkyl or OC_{1-6} alkyl can be optionally substituted with 1 to 3 substituents independently

selected from halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl -NH_2, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), cycloalkyl, NR_1R_1, or CN; and

j is 0, 1, 2, or 3;

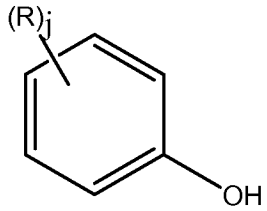
comprising:

reacting a compound of Formula X,



X

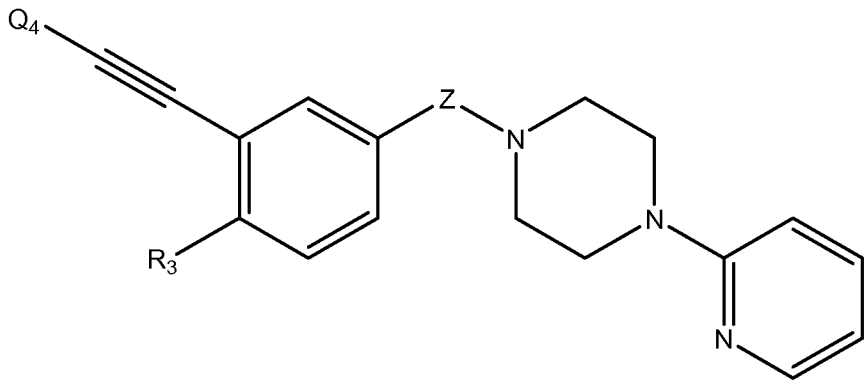
wherein X_5 is halogen, with a phenol derivative of Formula Xa:



Xa

for a time and under conditions effective to form the compound of Formula XI.

40. A synthetic process for preparing a compound of Formula XIII:



XIII

wherein:

Q_4 is H, C_{6-14} aryl, 5 to 14 membered heterocyclic, 5 to 14 membered heteroaromatic, or 4 to 9 membered carbocyclic; each of which except H can be

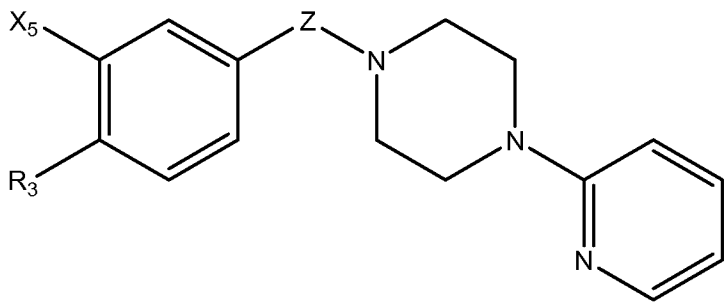
optionally substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), -C(=O)C_{1-6} alkyl, NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl $-NH_2$, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), OC_{1-3}haloalkyl, OC_{1-6}alkylaryl and CN; and

each R_3 is independently H, C_{1-6} alkyl, halogen, OH, OC_{1-6} alkyl, SO_2, 3- to 14-membered heterocycle or 5- to 14-membered heteroaromatic, wherein each of C_{1-6} alkyl or OC_{1-6} alkyl can be optionally substituted with 1 to 3 substituents independently selected from halogen, OH, OC_{1-6} alkyl, -C(=O)O-(C_{1-6} alkyl), NO_2, C_{1-3} haloalkyl, -S-C_{1-6} alkyl $-NH_2$, -NH-(C_{1-6} alkyl), -N(C_{1-6} alkyl)(C_{1-6} alkyl), cycloalkyl, NR_1R_1, or CN;

Z is CO;

comprising:

reacting a compound of Formula XII:



XII

wherein X_5 is halogen, with an acetylene of Formula Q_4-CCH, in the presence of a palladium triphenyphosphine-containing catalyst for a time and under conditions effective to form the compounds of Formula XII.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/044938

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/74 C07D241/20 C07D401/12 C07D295/192 A61K31/496
A61P25/00

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)
C07D A61K A61P

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 practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2007/078523 A (ASTRAZENECA AB [SE]; NPS PHARMA INC [US]; SLASSI ABDELMALIK [CA]; JOSE) 12 July 2007 (2007-07-12) pages 31-32; example 10.10	1-40
Y	WO 2006/062110 A (BANYU PHARMA CO LTD [JP]; SATOH ATSUSHI [JP]; NAGATOMI YASUSHI [JP]; K) 15 June 2006 (2006-06-15) abstract; examples	1-40
Y	WO 02/40466 A (ORTHO MCNEIL PHARM INC [US]) 23 May 2002 (2002-05-23) pages 9-11; examples	1-40

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* 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 document 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
13 October 2009	23/10/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Lauro, Paola

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/044938

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2007/090617 A (REMYND NV [BE]; GRIFFIOEN GERARD [BE]; COUPET KRISTEL MARIE EDITH [BE]) 16 August 2007 (2007-08-16) pages 1-3; examples	1-40
Y	BACH, ISAAC, SLASSI: "Metabotropic glutamate receptor 5 modulators and their potential therapeutic applications" EXPERT OPIN. THERAP. PATENTS, vol. 17, no. 4, 2007, pages 371-384, XP002549979 cited in the application the whole document	1-40
E	EP 2 065 369 A (ASTELLAS PHARMA INC [JP]) 3 June 2009 (2009-06-03) the whole document	1
X	& WO 2008/023720 A (ASTELLAS PHARMA INC [JP]; ISHII TAKAHIRO [JP]; SUGANE TAKASHI [JP]; KA) 28 February 2008 (2008-02-28) page 60	1
X	WO 2008/002820 A (JANSSEN PHARMACEUTICA NV [BE]; ALLISON BRETT [US]; CURTIS MICHAEL P [U) 3 January 2008 (2008-01-03) page 70	1
X	EP 1 652 842 A (KYOWA HAKKO KOGYO KK [JP]) 3 May 2006 (2006-05-03) example 36	1
X	EP 1 849 773 A (ASTELLAS PHARMA INC [JP]) 31 October 2007 (2007-10-31) examples 131,132	1
X	GB 2 068 961 A (SANKYO CO) 19 August 1981 (1981-08-19) abstract; examples 35,36	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/044938

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007078523 A	12-07-2007	AR 057218 A1	21-11-2007
		CN 101426773 A	06-05-2009
		EP 1994016 A2	26-11-2008
		JP 2009519929 T	21-05-2009
		US 2009012089 A1	08-01-2009
		US 2007275966 A1	29-11-2007
		UY 29988 A1	31-07-2007
WO 2006062110 A	15-06-2006	NONE	
WO 0240466 A	23-05-2002	AU 3976102 A	27-05-2002
		BG 107789 A	27-02-2004
		BR 0114983 A	23-09-2003
		CA 2427296 A1	23-05-2002
		CN 1483030 A	17-03-2004
		CZ 20031386 A3	18-02-2004
		EE 200300167 A	15-08-2003
		EP 1334098 A2	13-08-2003
		HR 20030340 A2	30-04-2005
		HU 0400832 A2	28-07-2004
		JP 2004513944 T	13-05-2004
		MX PA03003817 A	15-10-2004
		NO 20031903 A	25-06-2003
		NZ 525547 A	26-11-2004
		PL 361947 A1	18-10-2004
		SK 6112003 A3	06-04-2004
		UA 75899 C2	15-08-2003
		ZA 200304064 A	26-08-2004
WO 2007090617 A	16-08-2007	AU 2007213954 A1	16-08-2007
		CA 2641453 A1	16-08-2007
		CN 101378757 A	04-03-2009
		EA 200870233 A1	27-02-2009
		EP 1981504 A2	22-10-2008
		JP 2009526000 T	16-07-2009
EP 2065369 A	03-06-2009	CA 2665804 A1	28-02-2008
		WO 2008023720 A1	28-02-2008
WO 2008023720 A	28-02-2008	CA 2665804 A1	28-02-2008
		EP 2065369 A1	03-06-2009
WO 2008002820 A	03-01-2008	AU 2007265242 A1	03-01-2008
		CA 2656089 A1	03-01-2008
		CN 101511785 A	19-08-2009
		EP 2049473 A2	22-04-2009
		US 2009137562 A1	28-05-2009
		US 2008045509 A1	21-02-2008
EP 1652842 A	03-05-2006	AU 2004260756 A1	10-02-2005
		BR PI0408876 A	11-04-2006
		CA 2518950 A1	10-02-2005
		CN 1777590 A	24-05-2006
		WO 2005012257 A1	10-02-2005
		KR 20060119705 A	24-11-2006
		MX PA05011420 A	12-12-2005
		US 2009082348 A1	26-03-2009
		US 2007117856 A1	24-05-2007

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/044938

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1652842 A		ZA 200509952 A	27-09-2006
EP 1849773 A	31-10-2007	AU 2006215080 A1	24-08-2006
		CA 2598294 A1	24-08-2006
		WO 2006088075 A1	24-08-2006
		KR 20070107122 A	06-11-2007
		US 2008306046 A1	11-12-2008
GB 2068961 A	19-08-1981	CA 1154765 A1	04-10-1983
		CH 644857 A5	31-08-1984
		DE 3105330 A1	17-12-1981
		ES 8207169 A1	01-12-1982
		FR 2475548 A1	14-08-1981
		IT 1172225 B	18-06-1987
		NL 8100726 A	16-09-1981
		US 4426382 A	17-01-1984