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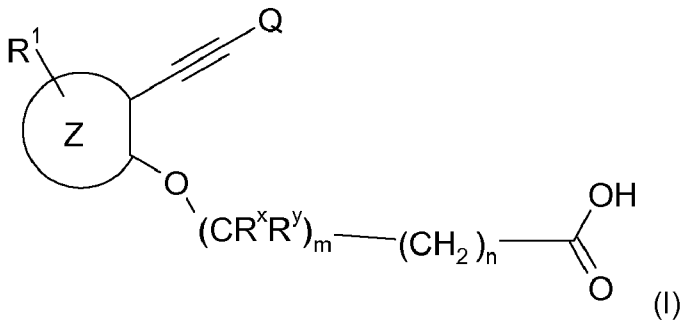
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(54) Title: PHENOXY ACETIC ACID DERIVATIVES



(I)

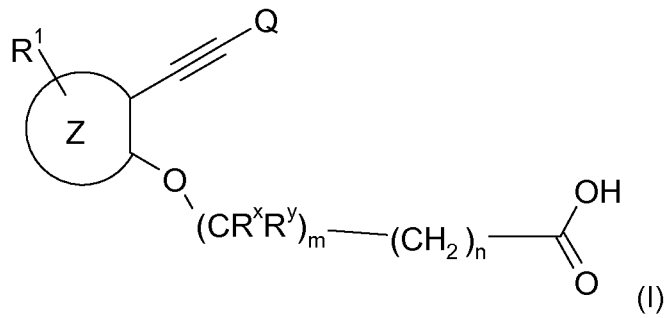
(57) Abstract: The present invention provides phenoxyacetic acid derivatives of Formula (I) for the treatment of CRTH2 related disorders and disease selected from asthma, atopic dermatitis and inflammatory dermatoses.

WO 2010/092043 A1

Phenoxy acetic acid derivatives

The present invention relates to phenoxy acetic acid derivatives of Formula (I) and its ester derivatives, for use as pharmaceutical active compounds, as well as pharmaceutical formulations containing such phenoxy acetic acids. Said derivatives are useful for the treatment and/or prevention of diseases such as asthma, atopic dermatitis and inflammatory dermatoses. Specifically, the present invention is related to the use of phenoxy acetic acid derivatives for the modulation of CRTH2 activity. The present invention furthermore relates to methods of the preparation of phenoxy acetic acid derivatives.

In one aspect, the invention provides compounds of Formula (I)



(I)

as well as its ester derivatives, its geometrical isomers, its optically active enantiomers, diastereoisomers and its racemates forms, and tautomers, or a pharmaceutically acceptable derivative thereof,

wherein :

R^1 is H, Hal, A, CN, NO_2, OA, CF_3, OCF_3, Ar or Het,

Q is Ar, Het,

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

m is 0, 1 or 2 wherein n+m is not 0,

Z is phenyl, naphthyl or pyridinyl,

A is branched or linear alkyl having 1 to 12 C-atoms, wherein one or more, preferably 1 to 7 H-atoms may be replaced by Hal, OR^3, CN or $N(R^3)_2$ and wherein one or more, preferably 1 to 7 non-adjacent CH_2-groups may be replaced by O, NR^3 or S and/or by CH=CH- or -C≡C- groups, or denotes cycloalkyl or cycloalkylalkylen having 3 to 7 ring C atoms,

Hal is F, Cl, Br or I,

Ar denotes a monocyclic or bicyclic, unsaturated or aromatic carbocyclic ring having 6 to 14 carbon atoms which may be unsubstituted or monosubstituted, disubstituted or trisubstituted or tetrasubstituted by Hal, A, $-CH_2OA$, $-CH_2OR^3$, $-CH_2SO_2A$, $-OR^3$, CF_3, $-OCF_3$, $-N(R^3)_2$, NO_2, -CN, $-NR^3COA$, $-NR^3COAr'$, $-NR^3SO_2A$, $-COR^3$, $CON(R^3)_2$, COHet, $-SO_2N(R^3)_2$, -SOA, $-SO_2A$, Het, or by SO_2T , SOT , Ar',

T denotes $-(CH_2)_p$-Ar' or $-(CH_2)_p$-Het',

p is 0, 1, 2, 3 or 4,

Ar' denotes a monocyclic or bicyclic, unsaturated or aromatic carbocyclic ring having 6 to 14 carbon atoms which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, $-CH_2OA$, $-CH_2OR^3$, $-OR^3$, $-CF_3$, $-OCF_3$,

Het' denotes a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic ring, having 1 to 4 N, O and/or S atoms, which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, CH_2OA, OR^3, CF_3, OCF_3,

Het denotes a monocyclic or bicyclic or tricyclic, saturated, unsaturated or aromatic heterocyclic ring, having 1 to 4 N, O, S atoms, and/or 1 SO_2 and/or CO groups and/or NO groups, which may be unsubstituted or monosubstituted, disubstituted or trisubstituted or tetrasubstituted by Hal, A, CH_2OA, OR^3, CF_3, OCF_3, $N(R^3)_2$, NO_2, CN, NR^3COA, NR^3SO_2A, COR^3, $SO_2N(R^3)_2$, SOA, SO_2A, SO_2T,

R^3 is H or A,

R^x, R^y independently denote H, a linear or branched alkyl having 1 to 8 carbon atoms optionally substituted with OH, Hal, CN, or R^x and R^y together form a carbocyclic ring having 3 to 7 carbon atoms, optionally substituted by OH, Hal, CN,

BACKGROUND OF THE INVENTION

Prostaglandin D2 (PGD2) has long been associated with inflammatory and atopic conditions, specifically allergic diseases such as asthma, rhinitis, conjonctivitis and atopic dermatitis (Lewis et al. (1982) J. Immunol. 129, 1627). PGD2 belongs to a class of compounds derived from the 20-carbon fatty acid skeleton of arachidonic acid. In response to an antigen challenge, PGD2 is released in large amounts into the airway as well as to the skin during an acute allergic response. The DP receptor, which is a member of the G-protein coupled receptor (GPCR) subfamily, has long been thought to be the only receptor of PGD2. DP's role in allergic asthma has been demonstrated with DP deficient mice (Matsuoka et al. (2000) Science 287, 2013-2017). However, despite intense interest in the role of PGD2 in the inflammatory response, a direct link between DP receptor activation and PGD2-stimulated eosinophil migration has not been established (Woodward et al. (1990) Invest. Ophthalomol Vis. Sci. 31, 138-146; Woodward et al. (1993) Eur. J. Pharmacol. 230, 327-333).

More recently, another G-protein coupled receptor, referred to as "Chemoattractant Receptor-Homologous molecule expressed on T-Helper 2 cells" (CRTH2) (Nagata et al. (1999) J. Immunol. 162, 1278-1286, Hirai et al. (2001) J Exp. Med. 193, 255-261) has been identified as a receptor for PGD2 and this discovery has begun to shed light on the mechanism of action of PGD2. CRTH2, which is also referred to as DP2, GPR44 or DLIR, shows little structural similarity with the DP receptor and other prostanoid receptors. However, CRTH2 possesses similar affinity for PGD2. Among peripheral blood T lymphocytes, human CRTH2 is selectively expressed on Th2 cells and is highly expressed on cell types associated with allergic inflammation such as eosinophils, basophiles and Th2 cells. In addition, CRTH2 mediates PGD2 dependent cell migration of blood eosinophils and basophiles. Furthermore, increased numbers of circulating T cells expressing CRTH2 have been correlated with the severity of atopic dermatitis (Cosmi et al. (2000) Eur. J. Immunol. 30, 2972-2979). The interaction of CRTH2 with PGD2 plays a critical role in the allergen-induced recruitment of Th2 cells in the target tissues of allergic inflammation. Compounds that inhibit the binding of CRTH2 and PGD2 should therefore be useful for the treatment of allergic diseases.

Allergic disease, like asthma, and inflammatory dermatoses represent a major class of complex, and typically chronic, inflammatory diseases that currently affect about 10% of the population and that number appears to be increasing (Bush, R.K., Georgitis J.W., Handbook of asthma and rhinitis. Ist ed. (1997), Abingdon: Blackwell Science. 270).

Atopic dermatitis is a chronic skin disease, wherein the skin becomes extremely itchy. It accounts for 10 to 20 percent of all visits to dermatologists. The increasing incidence of allergic diseases and inflammatory dermatoses worldwide underscores the need for new therapies to effectively treat or prevent these diseases. Currently, numerous classes of pharmaceutical agents are widely used to treat these diseases, for example, antihistamines, decongestants, anticholinergics, methylxanthines, cromolyns, corticosteroids, and leukotriene modulators. However, the usefulness of these agents is often limited by side effects and low efficacy.

It has been reported recently that 3-sulphur-substituted indole derivatives (A) exhibit CRTH2 activity (WO 04/106302, AstraZeneca AB) and are potentially useful for the treatment of various respiratory diseases.

WO 04/096777 (Bayer Healthcare AG) relates to pyrimidine derivatives, which are useful for the treatment of diseases mediated by CRTH2.

WO 04/035543 and WO 05/102338 (Warner-Lambert Company LLC) disclose tetrahydrochinoline derivatives as CRTH2 antagonists (C), which are also described to be effective in the treatment of neuropatic pain.

Specific tetrahydrochinoline derivatives as CRTH2 modulators are also provided by WO 04/032848 (Millennium Pharmaceutical Inc.) and WO 05/007094 (Tularik Inc.). These tetrahydrochinoline derivatives are said to be useful for treating disorders associated with allergic inflammation processes.

Patent applications WO2005115382, WO2007062678, and WO2007062773 also provides phenoxyacetic acid derivatives as ligands of CRTH2 receptors.

The invention further provides a pharmaceutical composition comprising a compound of Formula (I), together with a pharmaceutically acceptable excipient or carrier.

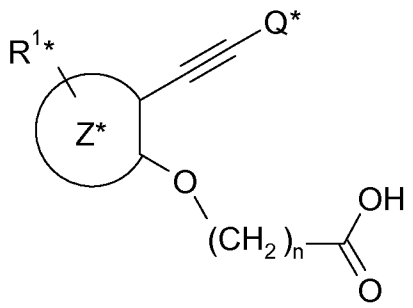
The invention further relates to a kit or a set comprising at least one compound of Formula (I), preferably in combination with immunomodulating agents. Alternativelly, the kit consists of separate packs of :

(a) an effective amount of a compound of the formula (I) and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and
(b) an effective amount of a further medicament active ingredient.

The invention further relates to the use of compounds of Formula (I) for the preparation of a medicament for the treatment and/or prevention of diseases selected from allergic diseases such as allergic asthma, allergic rhinitis, allergic conjunctivitis, systemic anaphylaxis or hypersensitivity responses, and inflammatory dermatoses such as atopic dermatitis, eczema, allergic contact dermatitis, and urticaria, myositis, neurodegenerative disorders such as neuropatic pain, and other inflammatory diseases such as chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, multiple sclerosis, osteoarthritis, and inflammatory bowel disease (IBD) such as ulcerative colitis and Crohn disease and other diseases or disorders associated with CRTH2 activity. Specifically the present invention is related to the use of compounds of Formula (I) for the modulation, notably the inhibition of CRTH2 activity.

The invention further relates to a method for treating and/or preventing a patient suffering from a disease selected from allergic diseases such as allergic asthma, allergic rhinitis, allergic conjunctivitis, systemic anaphylaxis or hypersensitivity responses, and inflammatory dermatoses such as atopic dermatitis, eczema, allergic contact dermatitis, and urticaria, myositis, neurodegenerative disorders such as neuropatic pain, and other inflammatory diseases such as chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, multiple sclerosis, osteoarthritis, and inflammatory bowel disease (IBD) such as ulcerative colitis and Crohn disease and other diseases and disorders associated with CTRH2 activity, by administering a compound according to Formula (I).
The invention further relates to the use of compounds of Formula I for the preparation of a pharmaceutical composition.
The invention finally relates to novel compounds of Formula I as well as to methods to synthesize these molecules.

In another embodiment, the present invention provides compounds of Formula (IA)



(IA)

As well as its ester derivatives, its geometrical isomers, its optically active enantiomers, diastereoisomers and its racemates forms, and tautomers, or a pharmaceutically acceptable derivative thereof.

Wherein

R^{1*} is H, Hal, A, CN, NO_2, OA, CF_3, OCF_3,

Q* is Ar*, Het*,

n is 1, 2, 3, or 4,

Z* is phenyl or pyridinyl,

A is branched or linear alkyl having 1 to 12 C-atoms, wherein one or more, preferably 1 to 7 H-atoms may be replaced by Hal, OR^3, CN or $N(R^3)_2$ and wherein one or more, preferably 1 to 7 non-adjacent CH_2-groups may be replaced by O, NR^3 or S and/or by CH=CH- or -C≡C- groups, or denotes cycloalkyl or cycloalkylalkylen having 3 to 7 ring C atoms,

Hal is F, Cl, Br or I,

Ar* denotes a monocyclic or bicyclic, unsaturated or aromatic carbocyclic ring having 6 to 14 carbon atoms which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, CH_2OA, $-CH_2OR^3$, OR^3, CF_3, OCF_3, $N(R^3)_2$, NO_2, CN, NR^3COA, NR^3SO_2A, COR^3, $SO_2N(R^3)_2$, SOA, SO_2A, Het, or by SO_2T,

T denotes $-(CH_2)_p$-Ar' or $-(CH_2)_p$-Het',

p is 0, 1, 2, 3 or 4,

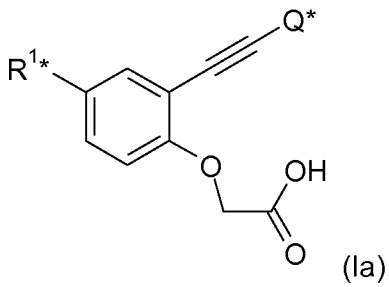
Ar' denotes a monocyclic or bicyclic, unsaturated or aromatic carbocyclic ring having 6 to 14 carbon atoms which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, $-CH_2OA$, $-CH_2OR^3$, $-OR^3$, $-CF_3$, $-OCF_3$,

Het' denotes a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic ring, having 1 to 4 N, O and/or S atoms, which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, CH_2OA, OR^3, CF_3, OCF_3,

Het* denotes a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic ring, having 1 to 4 N, O and/or S atoms, which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, CH_2OA, OR^3, CF_3, OCF_3, $N(R^3)_2$, NO_2, CN, NR^3COA, NR^3SO_2A, COR^3, $SO_2N(R^3)_2$, SOA, SO_2A, SO_2T,

R^3 is H or A,

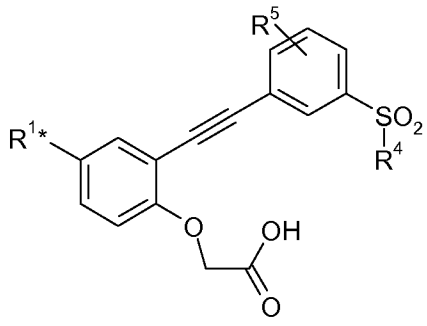
In a preferred embodiment, the invention provides compounds of Formula (Ia):



(Ia)

wherein R^{1*} and Q* are as above defined,
as well as their ester derivatives, their geometrical isomers, their optically active enantiomers, diastereoisomers and its racemates forms, and tautomers, or a pharmaceutically acceptable derivative thereof.

In a preferred embodiment, the invention provides compounds of Formula (Ib):



(Ib)

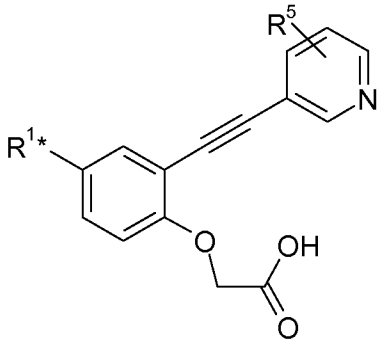
Wherein R^1 is as above defined

R^4 is $N(R^3)_2$, A or T,

R^5 is H, Hal, A, CF_3, SO_2A, $SO_2N(R^3)_2$, or SO_2T,
with A, T and R^3 being as above defined,

as well as their ester derivatives, their geometrical isomers, their optically active enantiomers, diastereoisomers and its racemates forms, and tautomers, or a pharmaceutically acceptable derivative thereof.

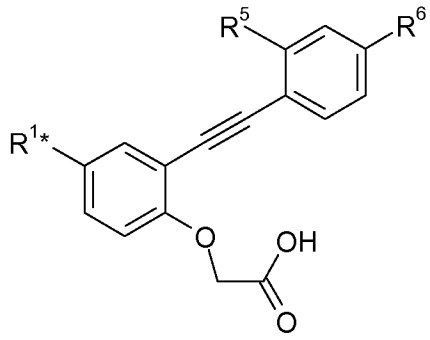
In another preferred embodiment, the invention provides compounds of Formula (Ic):



(Ic)

wherein R^{1*} and R^5 are as above defined

In another preferred embodiment, the invention provides compounds of Formula (Id) :

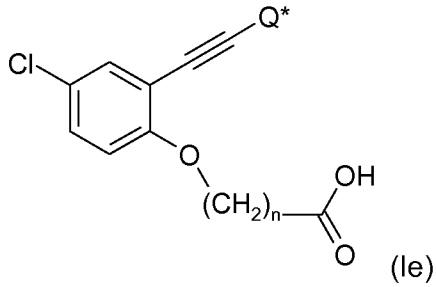


(Id)

wherein R^{1*} is as defined above, R^5 is Hal, and R^6 is A, CH_2OA,

as well as their ester derivatives, their geometrical isomers, their optically active enantiomers, diastereoisomers and its racemates forms, and tautomers, or a pharmaceutically acceptable derivative thereof.

In another preferred embodiment, the invention provides compounds of Formula (Ie):

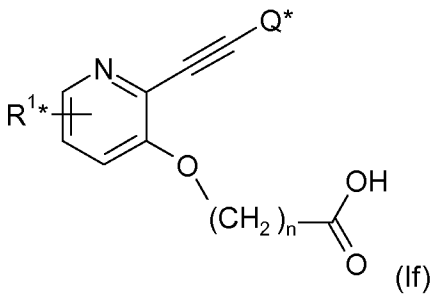


(Ie)

wherein Q* and n are as above defined,

as well as their ester derivatives, their geometrical isomers, their optically active enantiomers, diastereoisomers and its racemates forms, and tautomers, or a pharmaceutically acceptable derivative thereof.

In another preferred embodiment, the invention provides compounds of Formula (If)

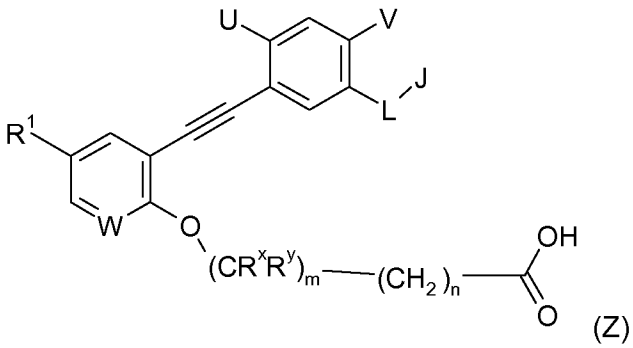


(If)

wherein Q*, R^{1*} and n are as above defined,

as well as their ester derivatives, their geometrical isomers, their optically active enantiomers, diastereoisomers and its racemates forms, and tautomers, or a pharmaceutically acceptable derivative thereof.

In another preferred embodiment, the invention provides compounds of Formula (Z):



(Z)

Wherein R^1, R^x, R^y, m and n are as defined under Formula (I),

L denotes SO_2, SO, or O, preferably SO_2;

W denotes C or N, preferably C,

U denotes H, Hal, R^Z,

V denotes H, Ar', R^Z, COR^Z, $CONHR^Z$, and if linked to J also –CO-, $-CONR^Z$, or an arylen,

J denotes R^Z, NHR^Z, $N(R^Z)_2$, $(CH_2)_sAr'$, whereby s is 0 or 1; and if linked to V also – NR^Z, or $(CH_2)_sAr''$; whereby an arylen denotes a di-, tri-, or tetravalent Ar' group, or when L is O, J also denotes H,

and wherein J and V may be linked to each other to form a ring.

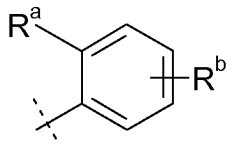
R^Z denotes a linear or branched alkyl or alkenyl having 1 to 6 carbon atoms, optionally substituted by OH, or OCH_3;

Ar'' denotes an arylen which may be further substituted by 1 or 2 groups selected from OR^3, Hal, CF_3 wherein R^3 is as above defined.

as well as their ester derivatives, their geometrical isomers, their optically active enantiomers, diastereoisomers and their racemates forms, and tautomers, or a pharmaceutically acceptable derivative thereof.

Ar preferably denotes a monocyclic or bicyclic aromatic carbocyclic ring having 6 to 14 carbon atoms which may be unsubstituted, monosubstituted or disubstituted by Hal, A, CH_2OA, OR^3, CF_3, OCF_3, $N(R^3)_2$, NO_2, CN, NR^3COA, NR^3SO_2A, COR^3, $SO_2N(R^3)_2$, SOA, SO_2A, SO_2T, wherein T is as defined above.

More preferably, Ar is selected from the following groups:

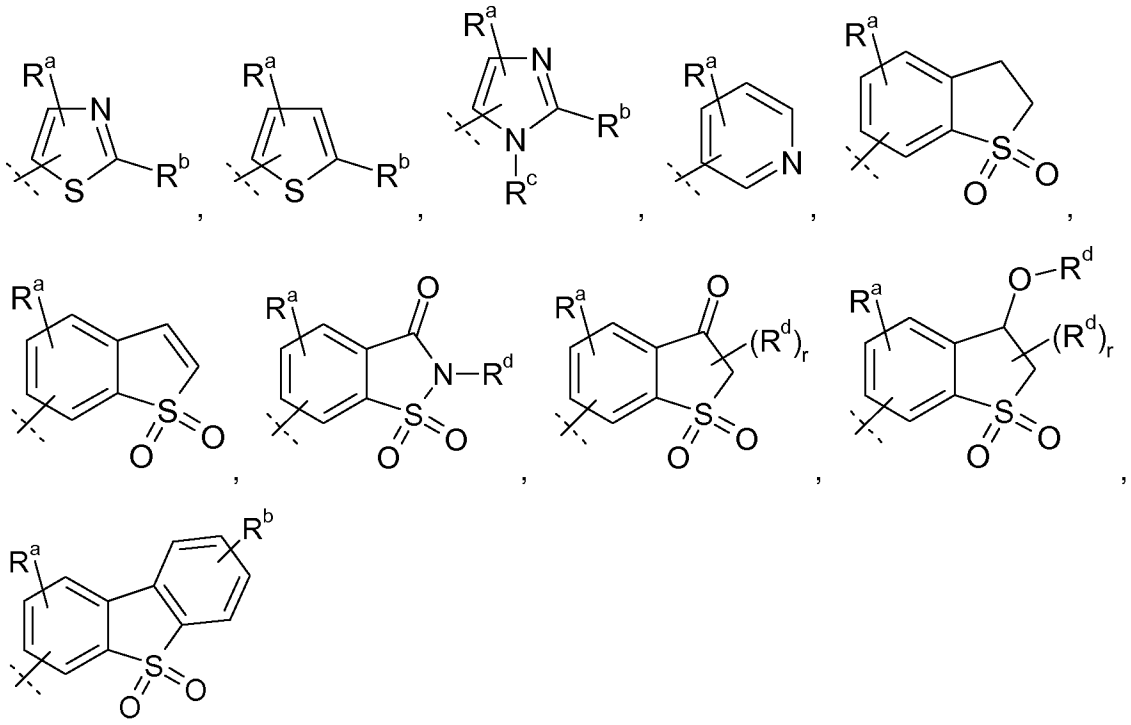


wherein R^a denotes H, alkyl having 1 to 6 carbon atoms, Hal, CF_3, $-OR^3$, and R^b denotes H, Hal, CF_3, $-SO_2N(R^3)_2$, $-SO_2R^3$, CH_2OR^3, SO_2T.

Het preferably denotes a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic ring, having 1 to 3 N, O and/or S atoms, which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, CH_2OA, OR^3, CF_3, OCF_3, $N(R^3)_2$, NO_2, CN, NR^3COA, NR^3SO_2A, COR^3, $SO_2N(R^3)_2$, SOA, SO_2A, SO_2T, wherein T is as above defined.

More preferably, Het denotes a monocyclic, unsaturated or aromatic heterocyclic ring, having 1 to 3 N, and/or S atoms, which may be unsubstituted, monosubstituted or disubstituted by Hal, A, CH_2OA, OR^3, CF_3, OCF_3, $N(R^3)_2$, NO_2, CN, NR^3COA, NR^3SO_2A, COR^3, $SO_2N(R^3)_2$, SOA, SO_2A, SO_2T, wherein T is as above defined.

More preferably, Het denotes one of the following groups:



wherein R^a, R^b independently from one another denotes an alkyl group having 1 to 6 carbon atoms, H, Hal, CN, CF_3, -OMe, -OEt, $(CH_2)_qCH_3$, $-SO_2NH(CH_2)_qCH_3$, $-SO_2(CH_2)_qCH_3$, $-SO_2NH(CH_2)_qOH$, $-SO_2(CH_2)_qOH$, , $-SO_2NH(CH_2)_qO(CH_2)_qCH_3$, $-SO_2(CH_2)_qO(CH_2)_qCH_3$, or SO_2T wherein q denotes 0, 1, 2, 3 or 4;

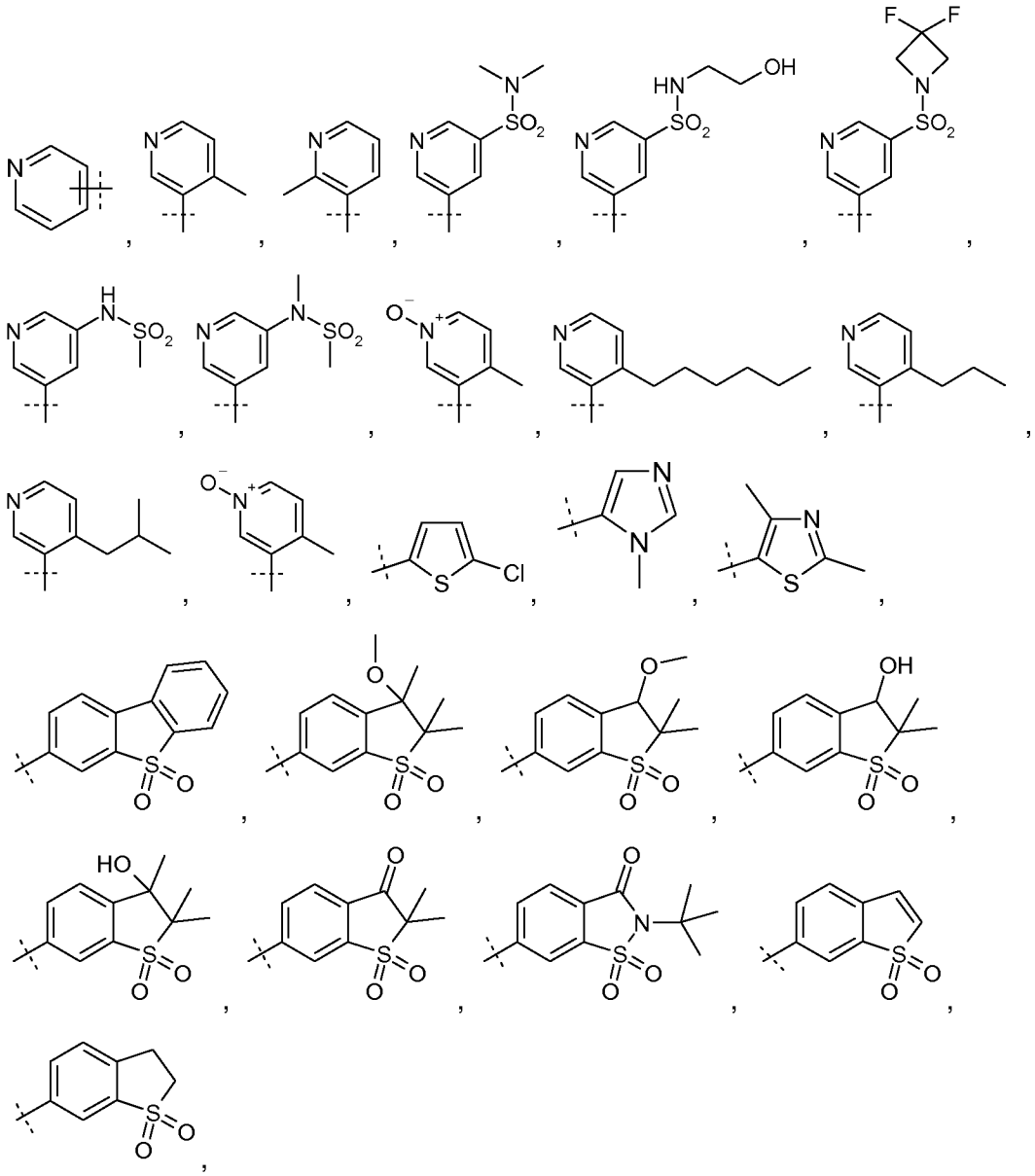
R^c denotes H, Me, or Et,

R^d denotes H or a branched or linear alkyl having 1 to 6 carbon atoms,

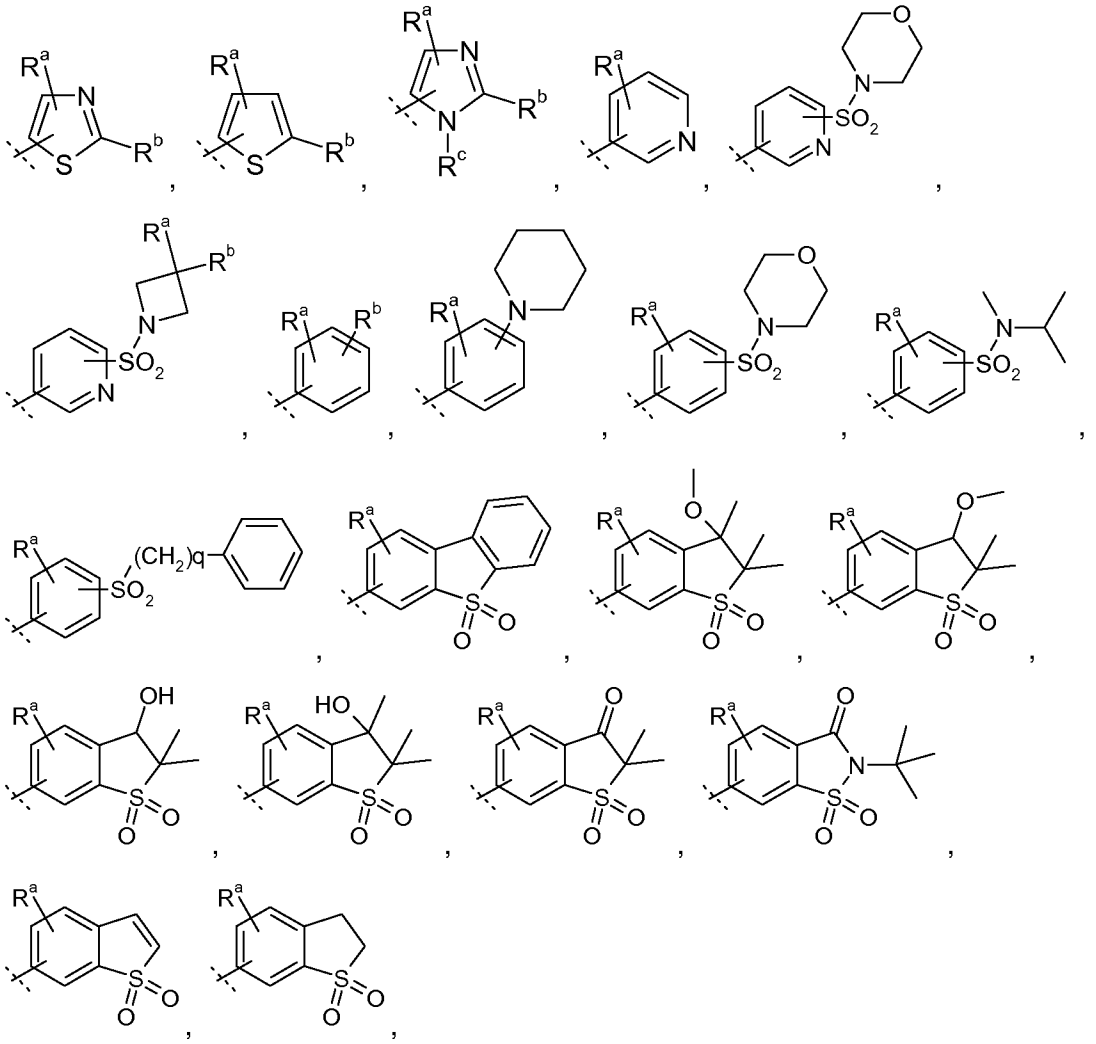
and r is 0, 1, 2 or 3.

Q is preferably Ar, more preferably a phenyl group.

Most preferably, when Q is Het, Het denotes one of the following groups:

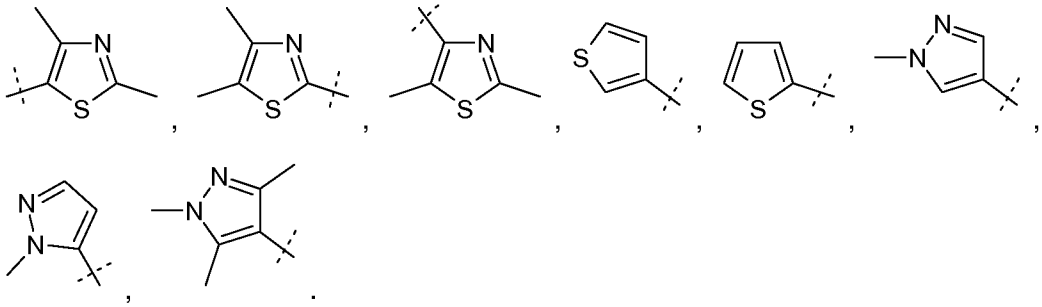


In another preferred embodiment, the invention provides compounds of Formula (I) wherein Q is selected from the following groups:



Wherein R^a, R^b independently from one another denotes H, Hal, CN, OH, CF_3, -OMe, -OEt, $(CH_2)_qCH_3$, $-(CH_2)_q(CH)(CH_3)_2$, $-SO_2NH(CH_2)_qCH_3$, $-SO_2NH(CH_2)_qC(CH_3)_3$, $-SO_2N(C_2H_5)_2$, $-SO_2(CH_2)_qCH_3$, $-SO_2(CH)(CH_3)_2$, $SO_2(CH_2)_qCH(CH_3)_2$, $-SO_2NH(CH_2)_qOH$, $-SO_2(CH_2)_qOH$, $-SO_2NH(CH_2)_qO(CH_2)_qCH_3$, $-SO_2(CH_2)_qO(CH_2)_qCH_3$, $N(CH_3)-SO_2-(CH_2)_qCH_3$, -Ar', $-(CH_2)Ar'$, or SO_2T, wherein q denotes 0, 1, 2, 3 or 4,
and wherein R^c denotes H, Me, Et.

Most preferrably, when R^1 is Het, R^1 denotes one of the following groups:

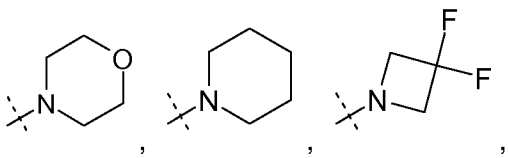


Otherwise R^1 preferrably denotes H, Cl, F, CN, $-CH_3$, $-CF_3$, or a phenyl group optionally substituted by an alkyl having 1 to 6 carbon atoms, and most preferrably H, Cl, or a phenyl group optionally substituted by an alkyl having 1 to 6 carbon atoms.

A preferably denotes a branched or linear alkyl having 1 to 6 C-atoms, wherein one or more, preferably 1 to 7 H-atoms may be replaced by Hal, OR^3, CN or $N(R^3)_2$ and wherein one or more, preferably 1 to 7 non-adjacent CH_2-groups may be replaced by O, NR^3 or S.

Het' preferably denotes a monocyclic saturated, heterocyclic ring, having 1 to 3 N, and/or O atoms, which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, CH_2OA, OR^3, CF_3, OCF_3

Most preferably, Het' denotes one of the following groups:



Ar' preferably denotes a phenyl group.

n is preferably 1 or 2

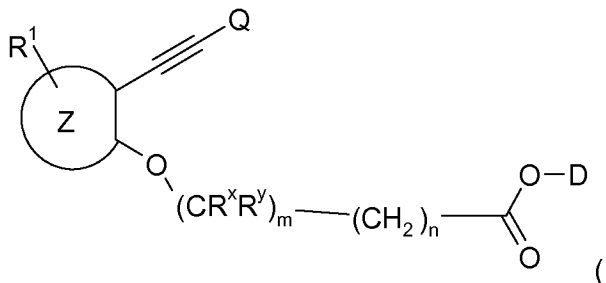
$-OR^3$ preferably denotes one of the following groups: -OH, $O(C_1-C_6)$alkyl, most preferably, OH or OMe.

An “alkyl” or “alky group” denotes a linear or branched carbon chain having 1 to 6 carbon atoms. Preferably, an “alkyl” or an “alkyl group” denotes a linear or branched carbon chain having 1 to 4 carbon atoms.

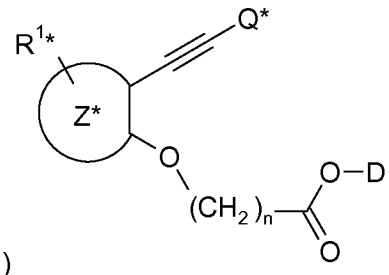
The term “ester” or “ester derivatives” refers to compounds of Formula (I) wherein one or more carboxylic function is protected with an alkyl, Ar, Het or benzyl group, preferably with a *tert*-butyl group.

The terme “arylen” refers to a divalent monocyclic or bicyclic, unsaturated or aromatic carbocyclic ring, having 6 to 14 carbon atoms. “Arylen” preferrably refers to a phenylene group optionally substituted with OR^3, Hal, and/or CF_3, wherein R^3 is as above defined.

In a preferred embodiment, the invention also provides compounds of Formula (I’) or (IA’)



(I')



(IA’)

wherein D denotes an alkyl, a benzyl group, Ar or Het.
D preferably denotes an alkyl, preferably tert-butyl, or a benzyl group.

In another preferred embodiment, the invention provides compounds of Formula (IA) wherein R^{1*} is as defined under (IA) and wherein Q* denotes a phenyl optionally substituted with Hal, -OMe, CN, CF_3, $-SO_2NH(CH_2)_qCH_3$, $-SO_2(CH_2)_qCH_3$, $-SO_2NH(CH_2)_qOR_3$, $-SO_2(CH_2)_qOR_3$, $-(CH_2)_qCH_3$, $-(CH_2)_qOR_3$, wherein q and R^3 are as above defined.

In another preferred embodiment, the invention provides compounds of Formula (IA) wherein R^{1*} is as defined under Formula (IA) and wherein Q* denotes a phenyl optionally substituted with an alkyl having 1 to 6 carbon atoms.

In another preferred embodiment, the invention provides compounds of Formula (IA) wherein R^{1*} is as defined under Formula (IA) and wherein Q* denotes a pyridinyl optionally substituted with Hal, -OMe, CN, CF_3, $-SO_2NH(CH_2)_qCH_3$, $-SO_2(CH_2)_qCH_3$, $-SO_2NH(CH_2)_qOR_3$, $-SO_2(CH_2)_qOR_3$, $-(CH_2)_qCH_3$, $-(CH_2)_qOR^3$, wherein q and R^3 are as above defined.

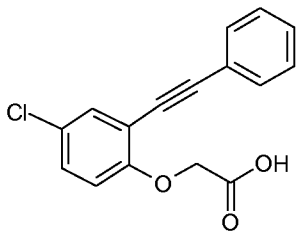
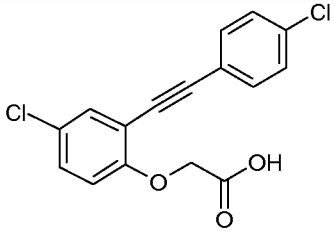
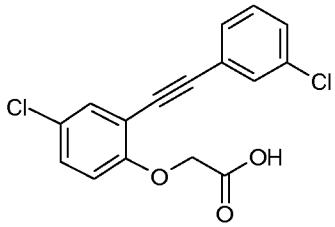
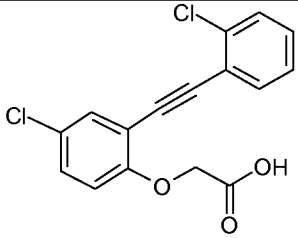
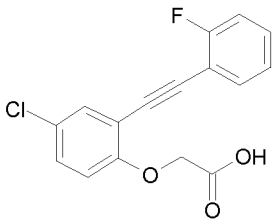
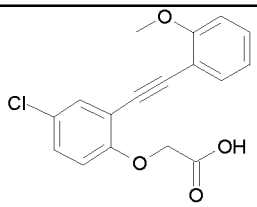
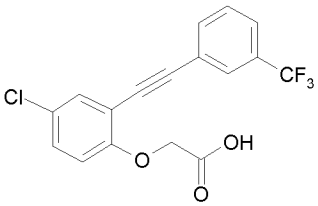
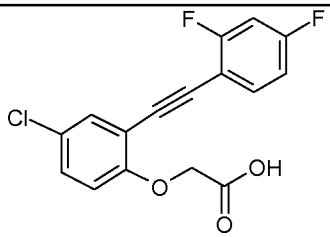
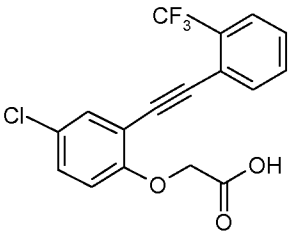
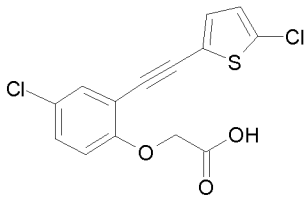
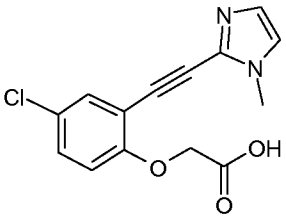
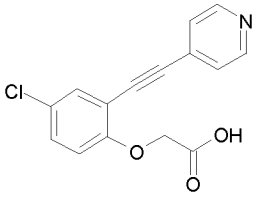
In another embodiment, the invention provides compounds of Formula (IA) wherein R^{1*} is as defined under Formula (IA) and wherein Q* denotes a thienyl optionally substituted with Hal, -OMe, CN, CF_3, $-SO_2NH(CH_2)_qCH_3$, $-SO_2(CH_2)_qCH_3$, $-SO_2NH(CH_2)_qOR_3$, $-SO_2(CH_2)_qOR_3$, $-(CH_2)_qCH_3$, $-(CH_2)_qOR^3$, wherein q and R^3 are as above defined.

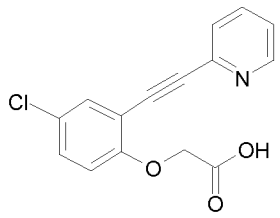
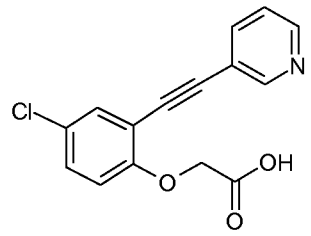
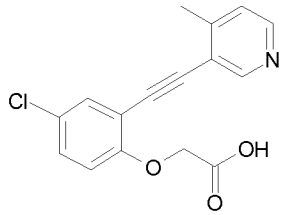
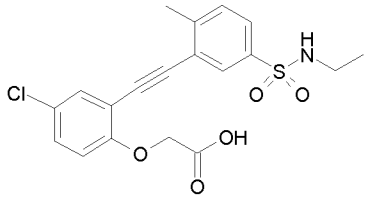
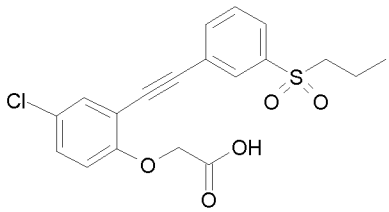
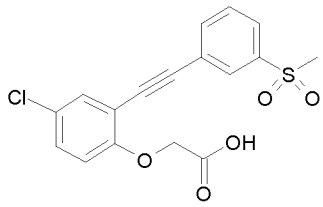
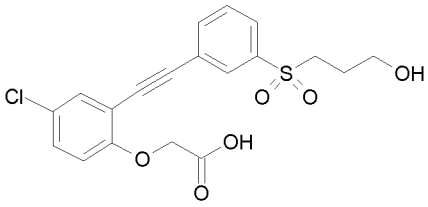
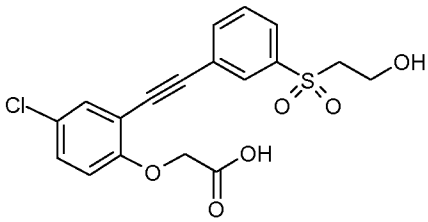
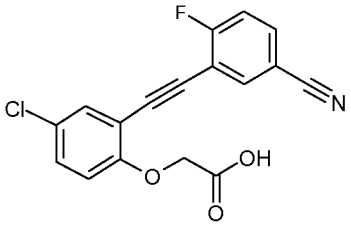
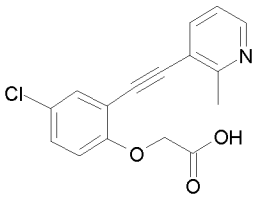
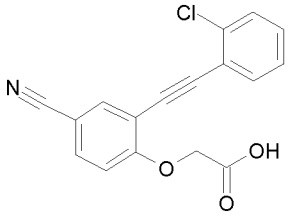
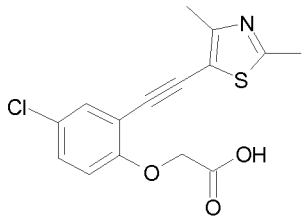
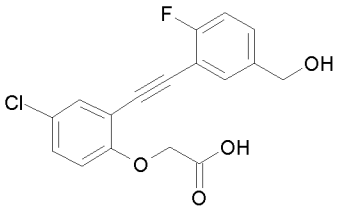
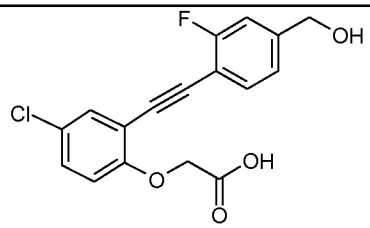
In another embodiment, the invention provides compounds of Formula (IA) wherein R^{1*} is as defined under Formula (IA) and wherein Q* denotes an imidazol optionally substituted with Hal, -OMe, CN, CF_3, $-SO_2NH(CH_2)_qCH_3$, $-SO_2(CH_2)_qCH_3$, $-SO_2NH(CH_2)_qOR_3$, $-SO_2(CH_2)_qOR_3$, $-(CH_2)_qCH_3$, $-(CH_2)_qOR^3$, wherein q and R^3 are as above defined.

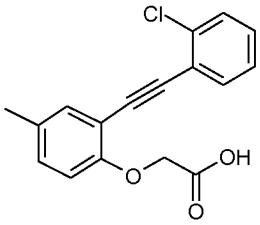
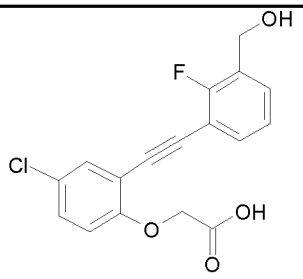
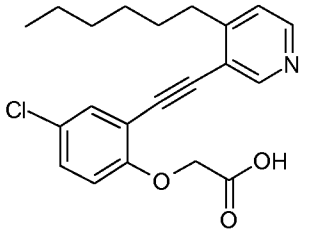
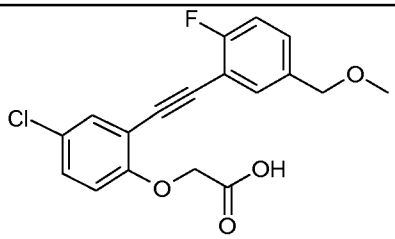
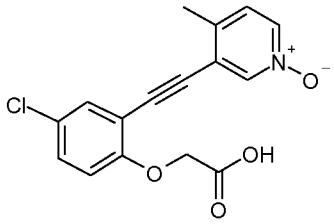
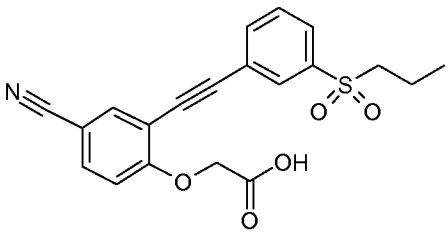
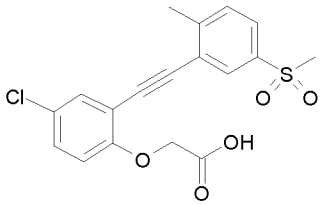
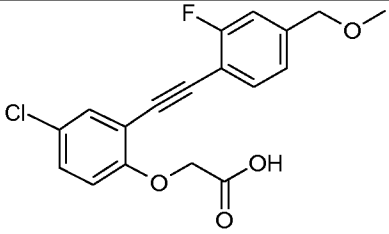
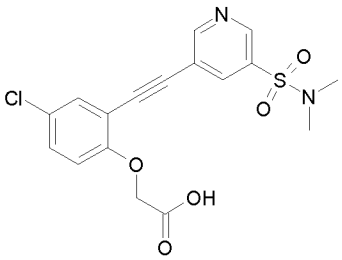
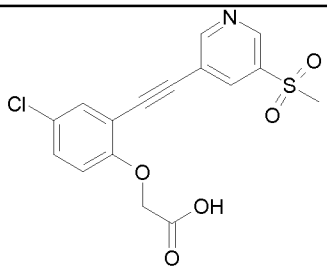
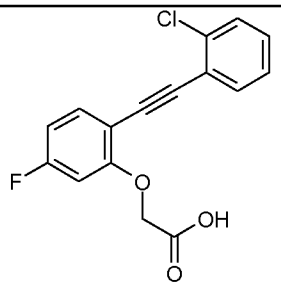
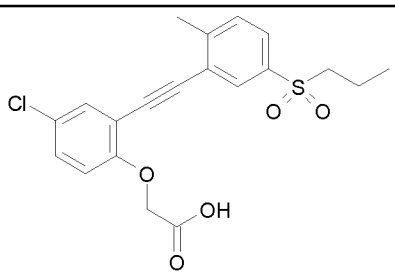
In another preferred embodiment, the invention provides compounds of Formula (IA) and related formulae wherein Q* is as defined above and wherein R^{1*} is Hal, $-(CH_2)_qCH_3$, CN, CF_3, $-O(CH_2)_qCH_3$, wherein q is 0, 1, 2, 3, or 4, preferably 0, 1 or 2.

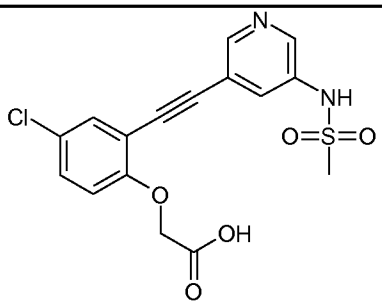
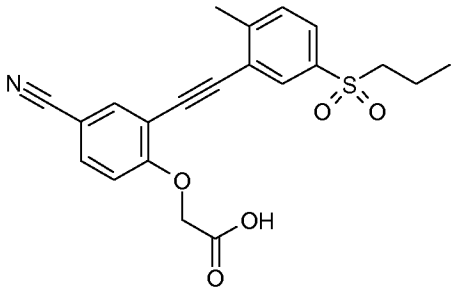
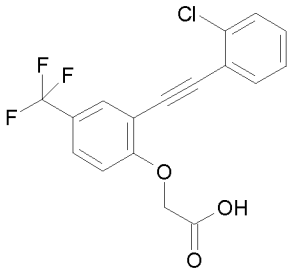
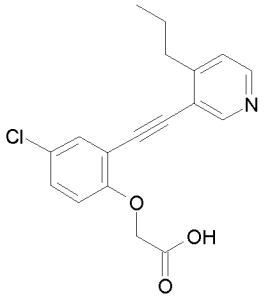
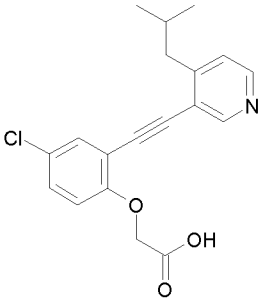
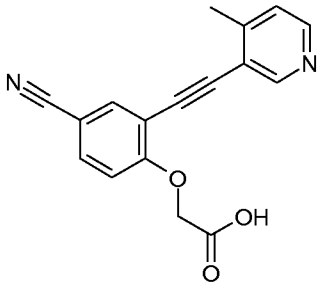
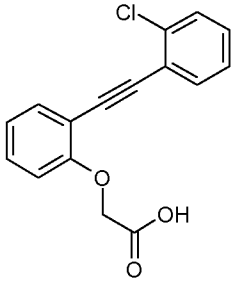
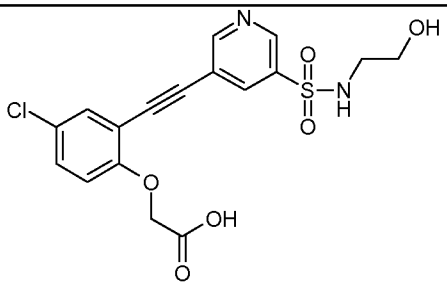
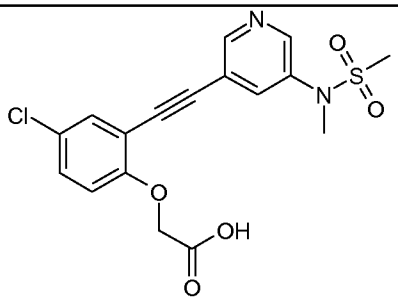
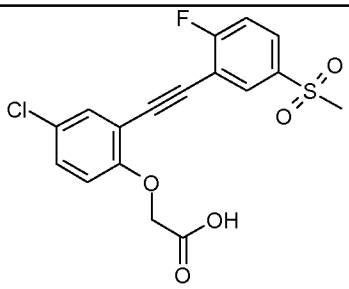
In another preferred embodiment, the invention provides compounds of Formula (I) wherein Q denotes a phenyl or a pyridinyl optionally substituted with Hal, -OMe, -OH, -CN, $-CF_3$, $-SO_2NH(CH_2)_qCH_3$, $-SO_2(CH_2)_qCH_3$, $-SO_2NH(CH_2)_qOR^3$, $-SO_2NR^3(CH_2)_qOR^3$, $-SO_2(CH_2)_qOR^3$, $-(CH_2)_qCH_3$, $-(CH_2)_qOR^3$, $-SO_2(CH_2)_qC(CH_3)_2$, $SO_2(CH_2)_qAr$, $SO_2N(CH_3)_2$, $NR^3CO(CH_2)_qCH_3$, wherein q and R^3 are as defined under Formula (I).

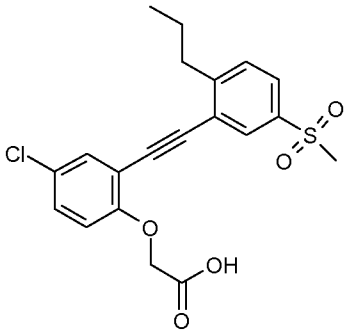
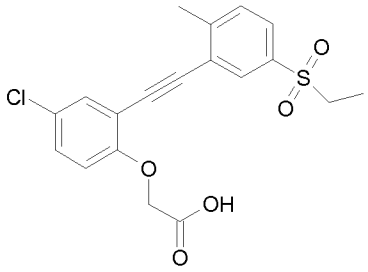
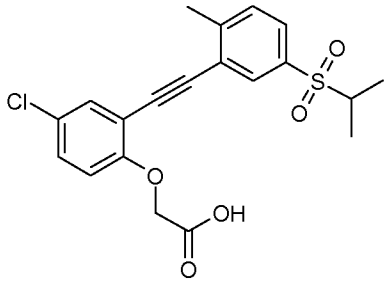
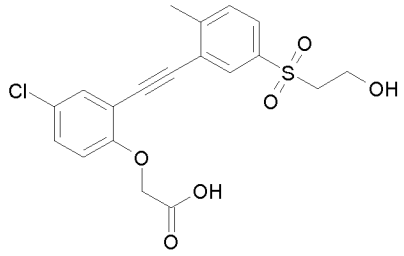
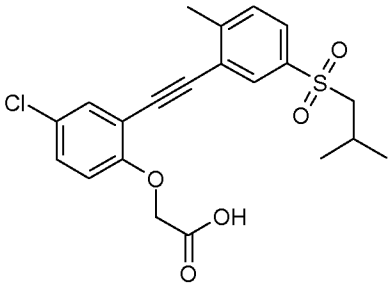
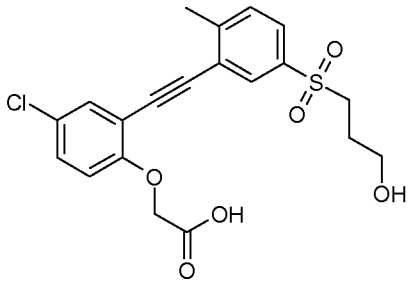
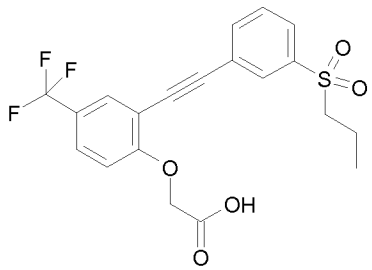
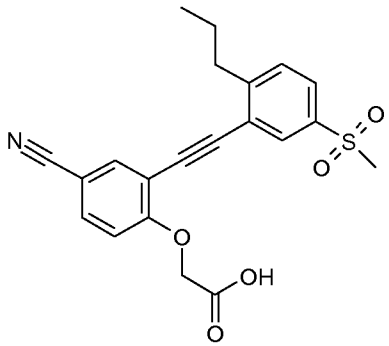
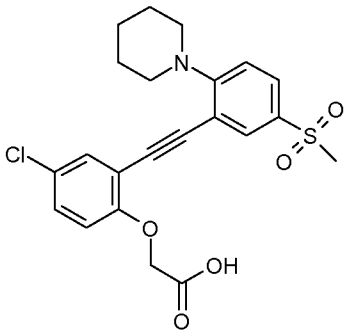
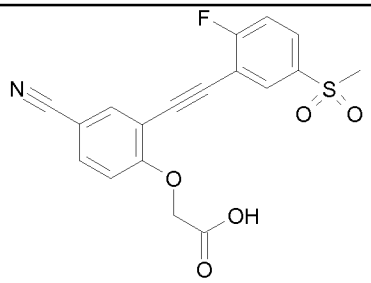
The preferred compounds of the invention are selected from the following group:

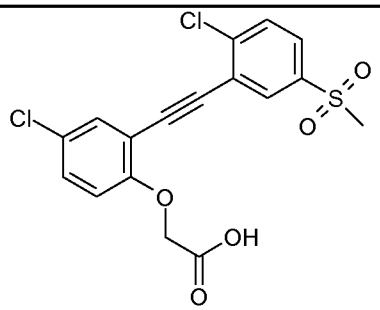
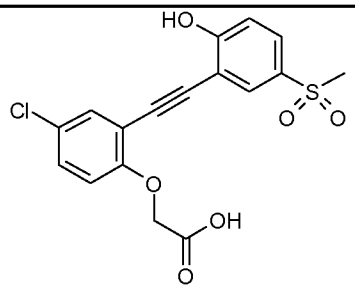
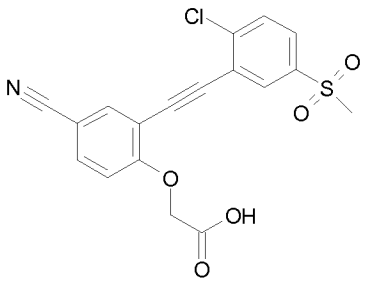
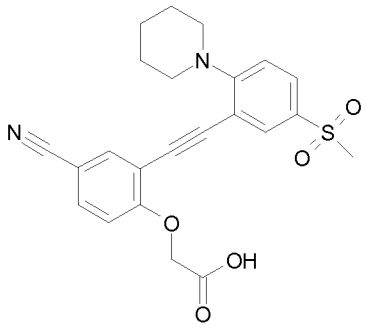
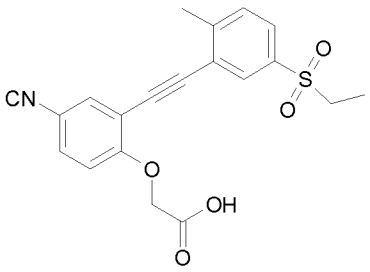
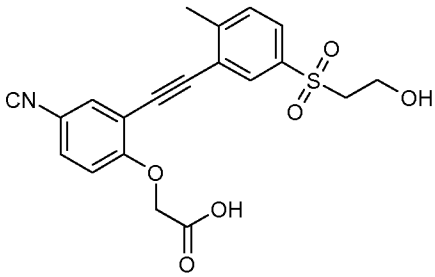
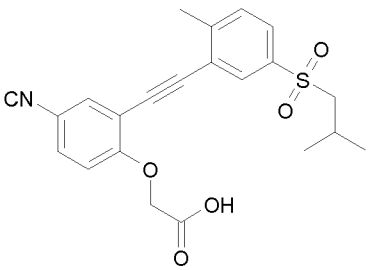
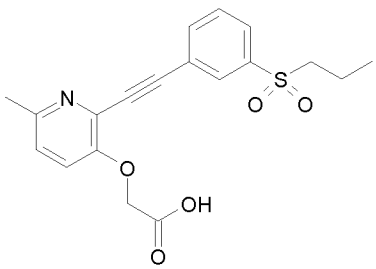
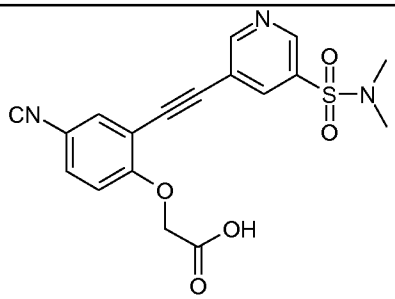
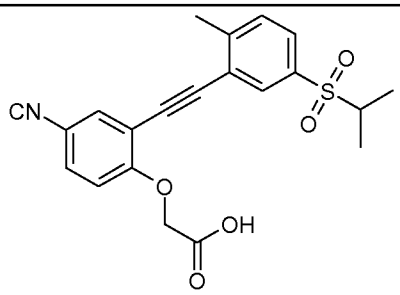
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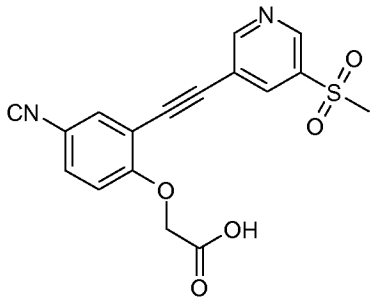
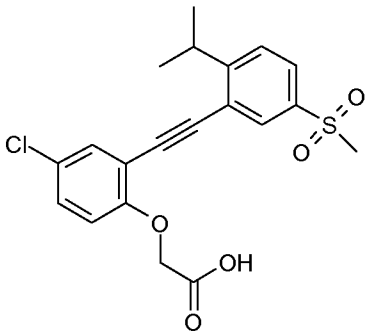
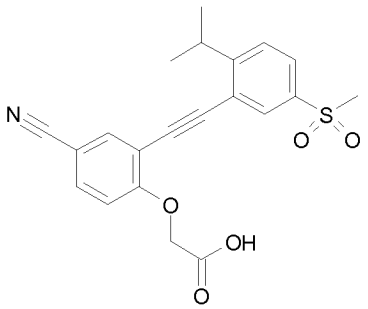
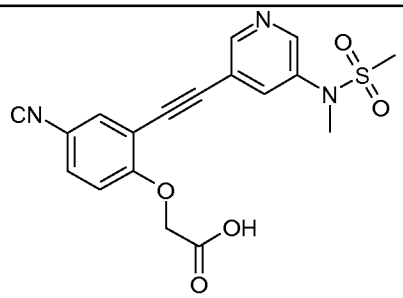
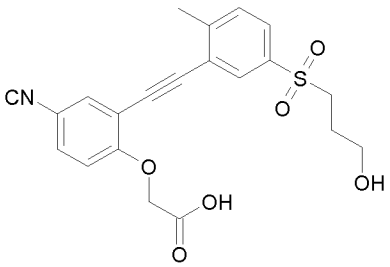
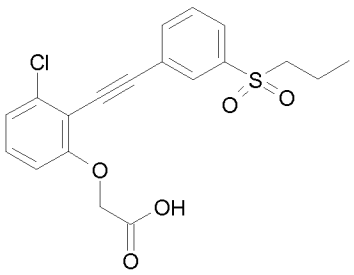
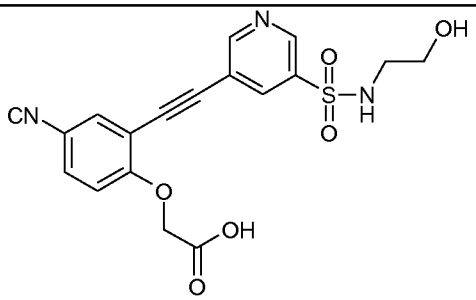
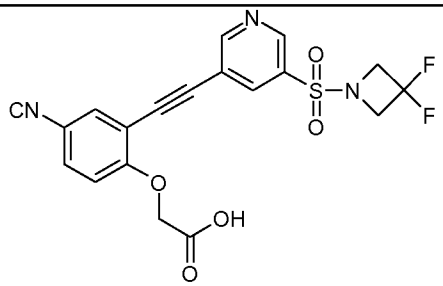
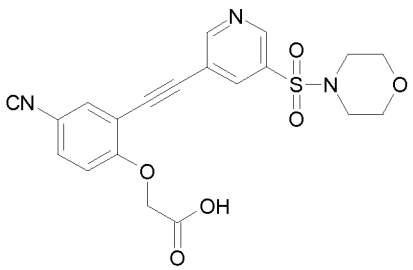
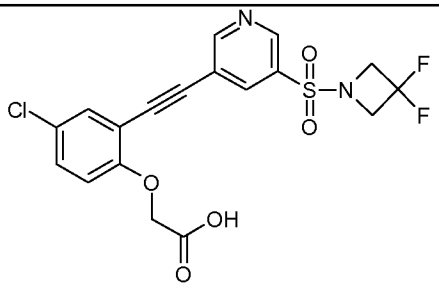
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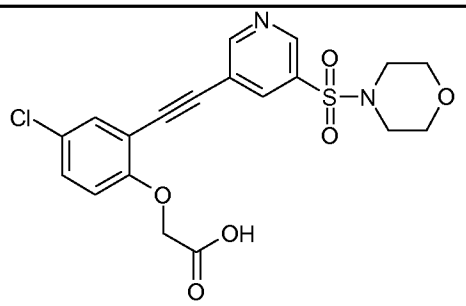
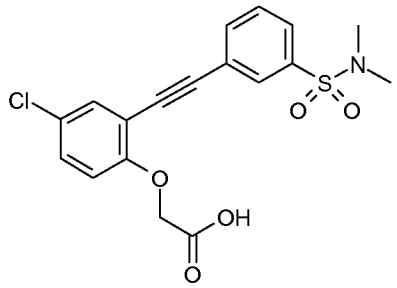
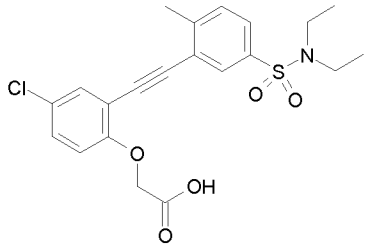
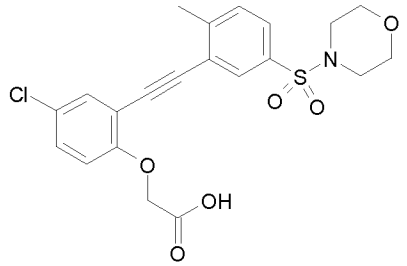
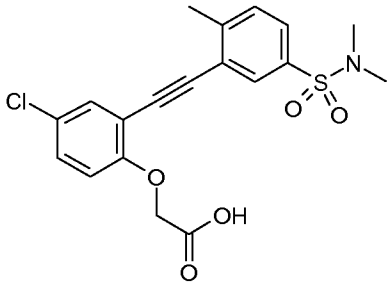
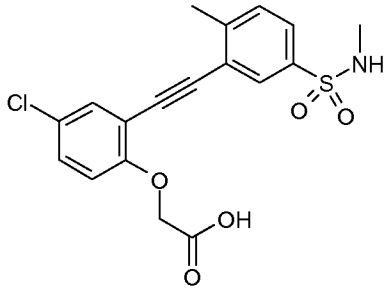
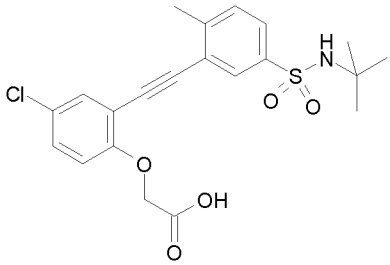
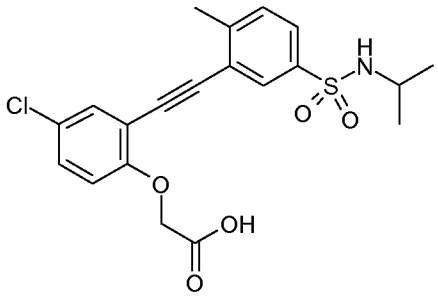
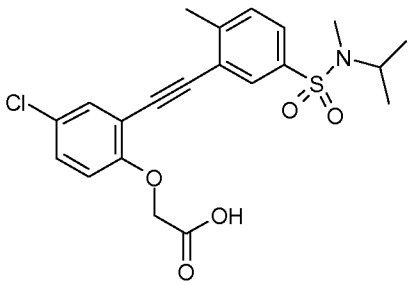
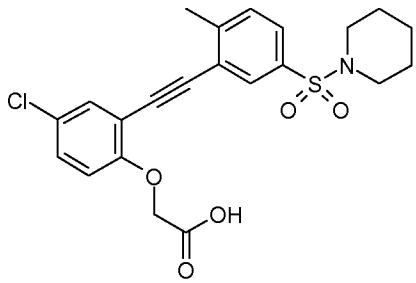
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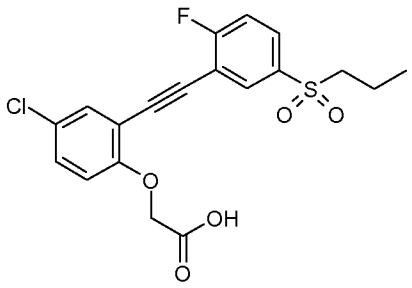
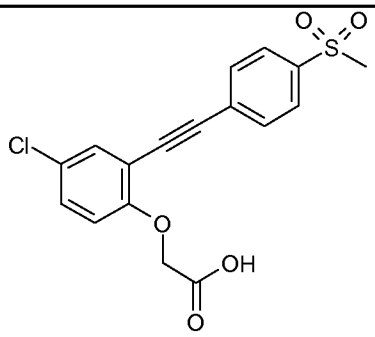
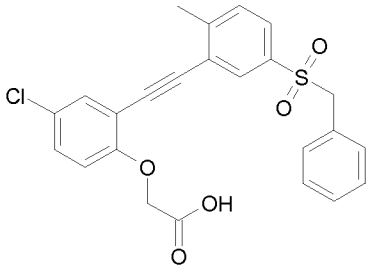
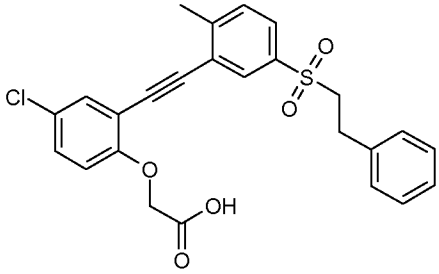
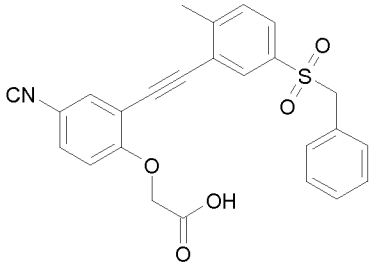
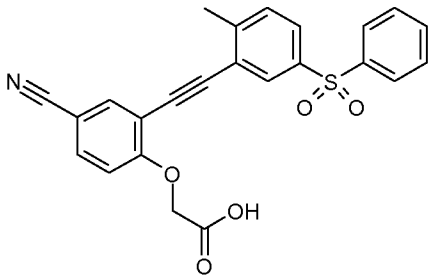
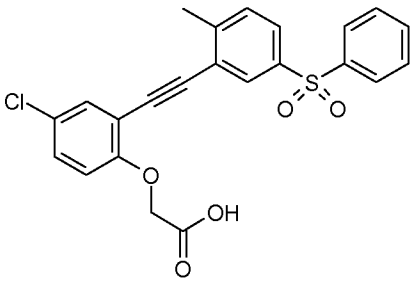
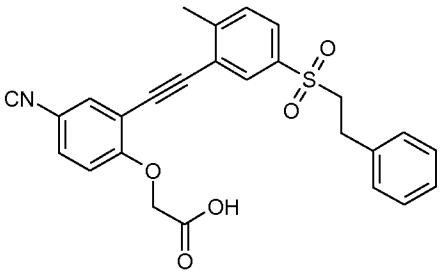
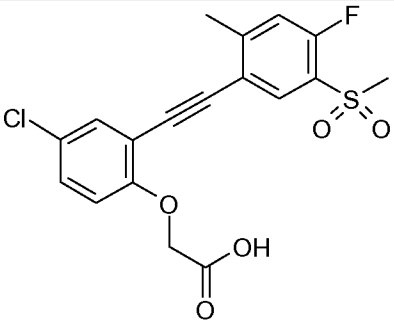
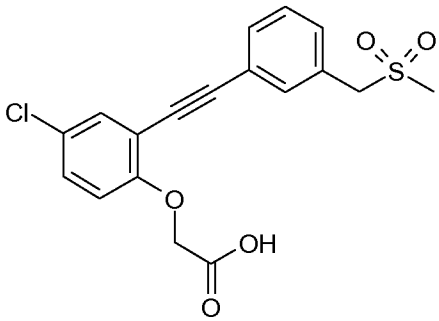
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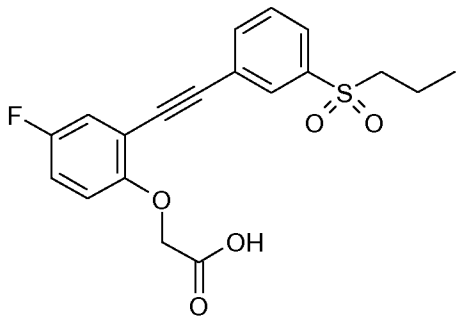
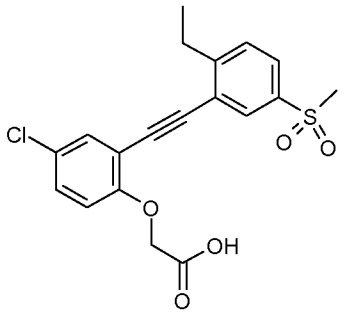
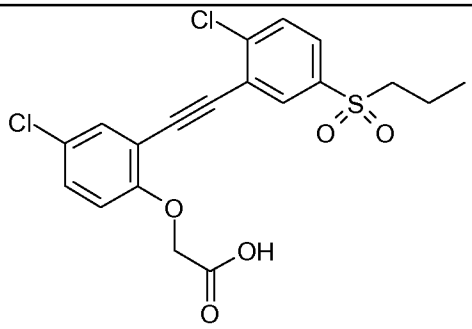
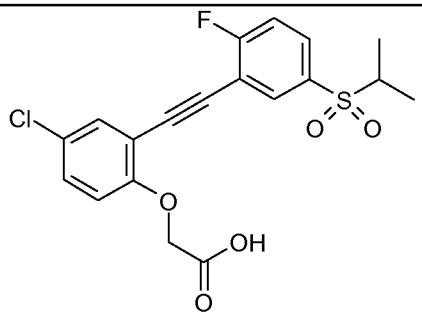
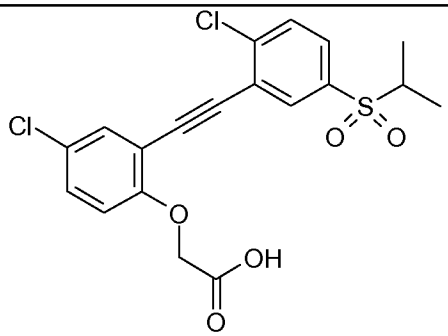
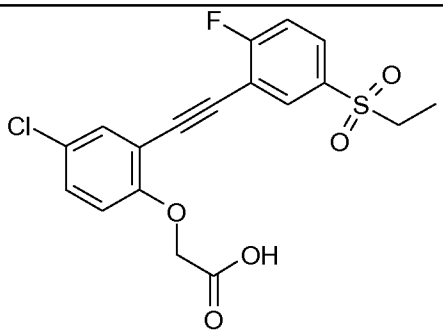
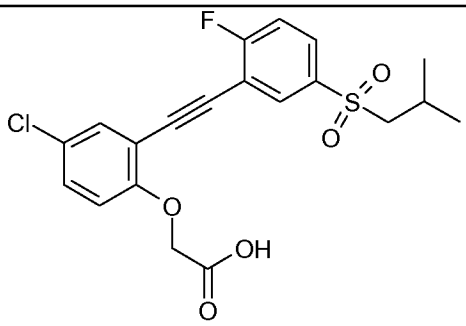
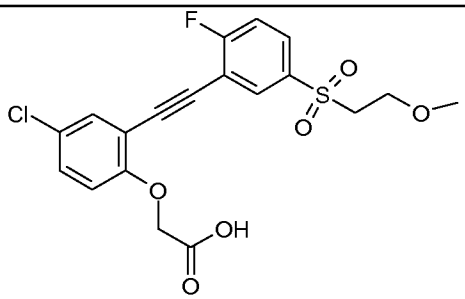
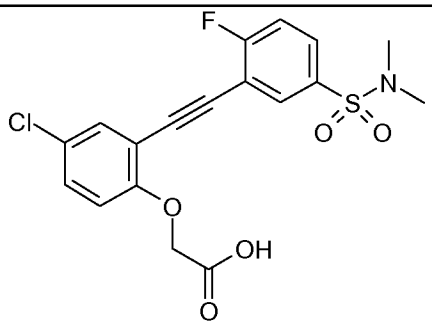
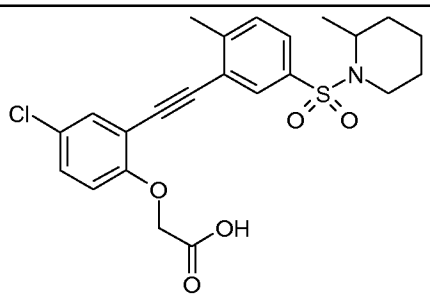
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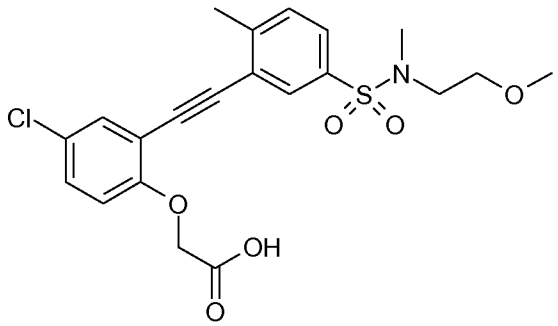
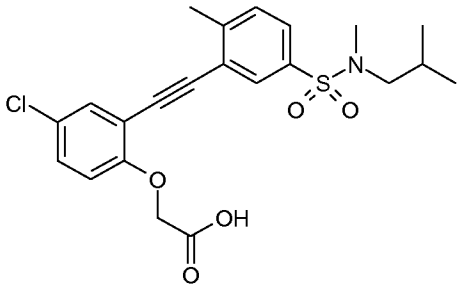
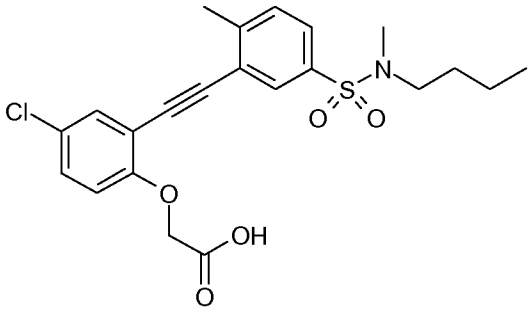
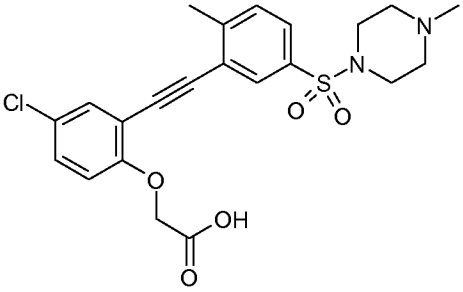
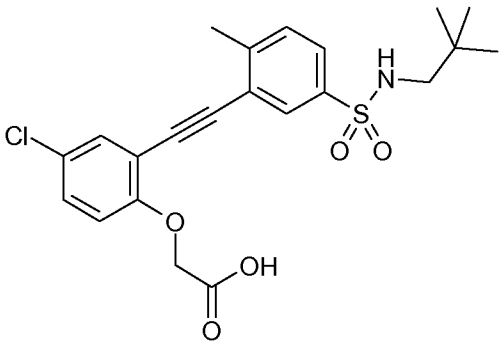
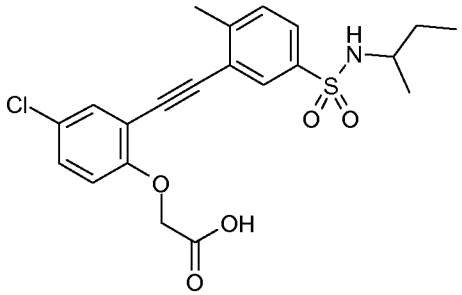
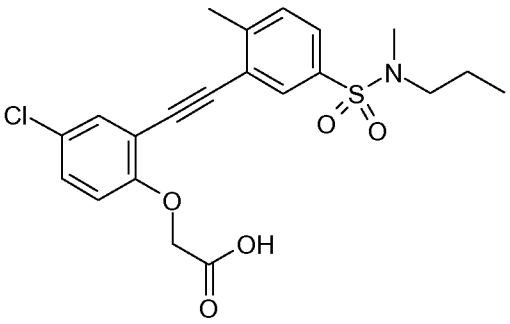
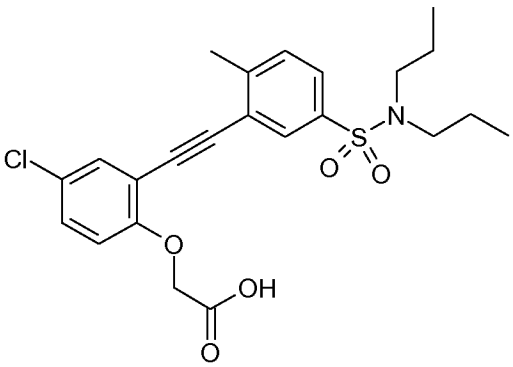
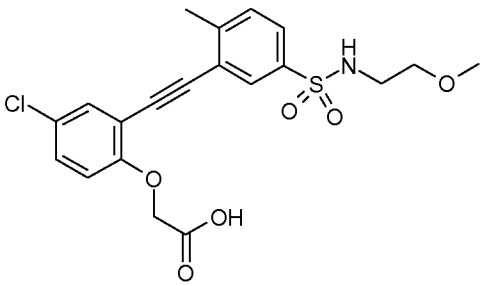
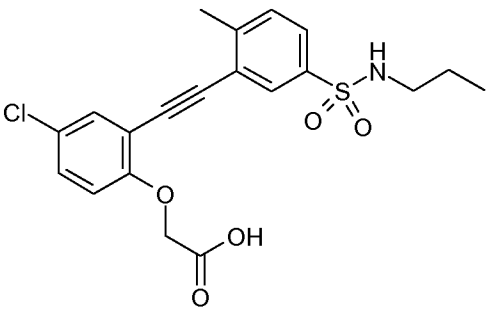
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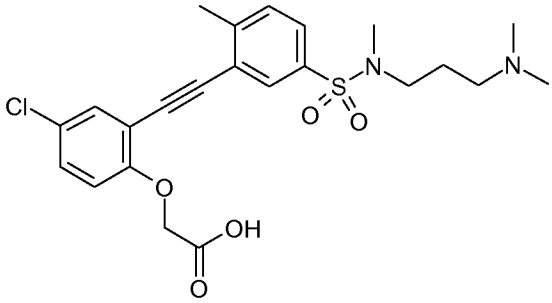
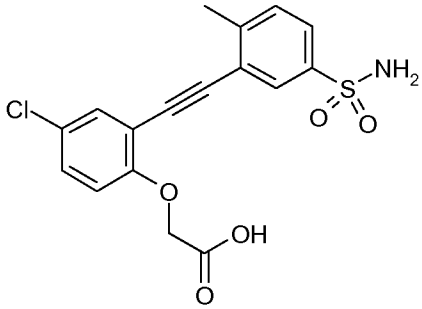
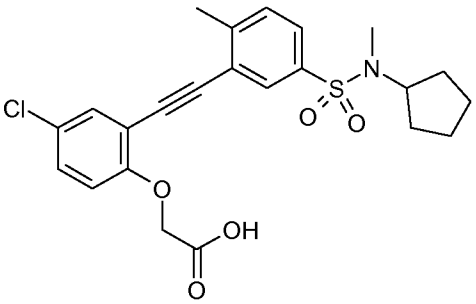
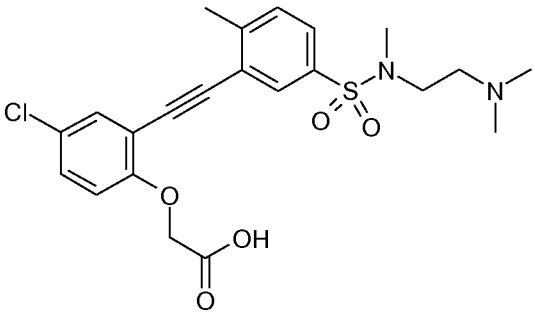
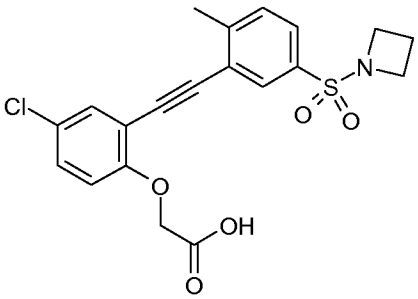
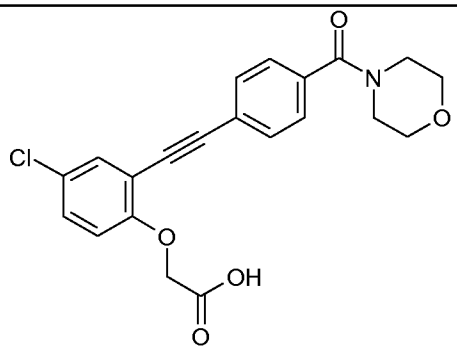
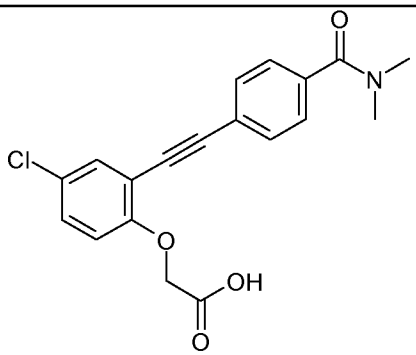
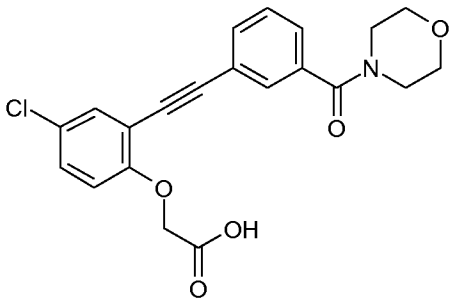
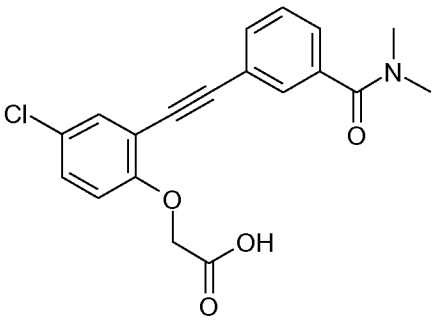
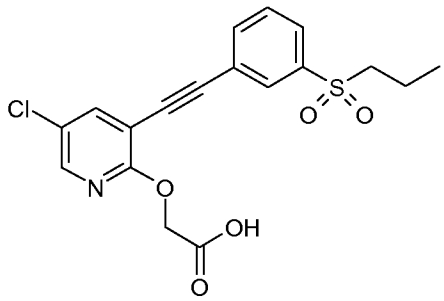
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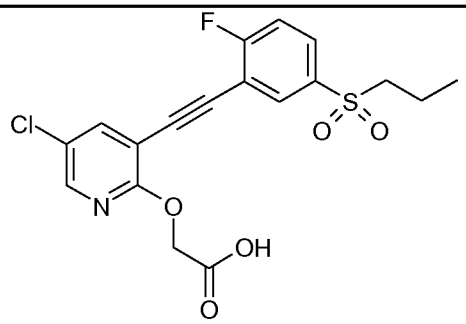
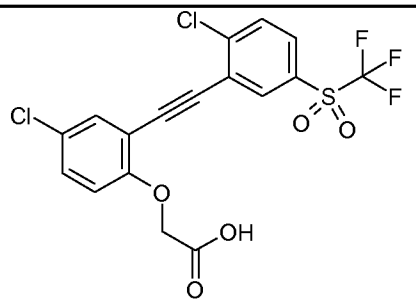
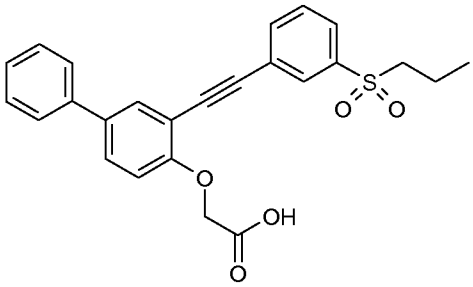
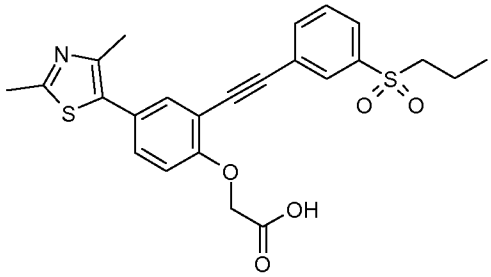
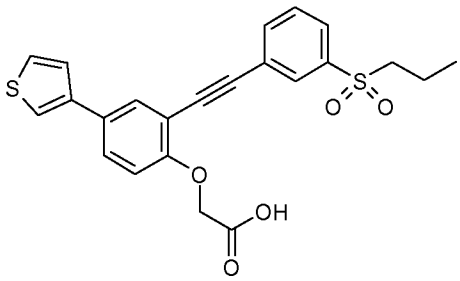
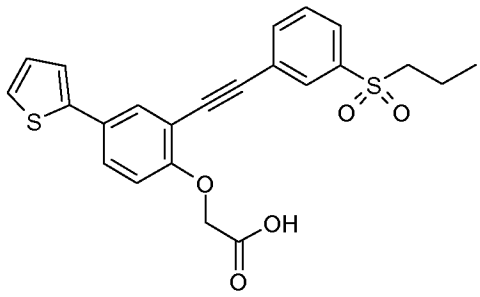
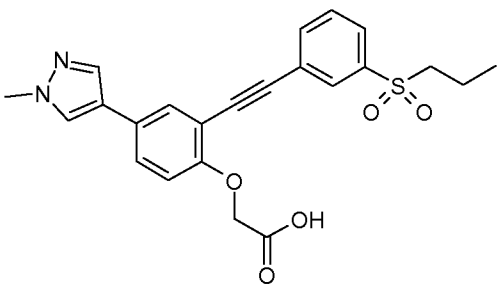
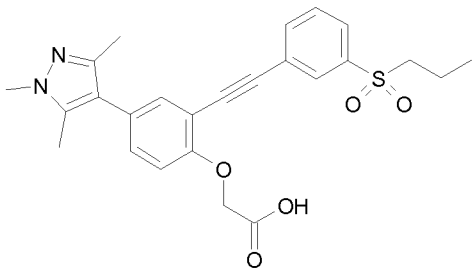
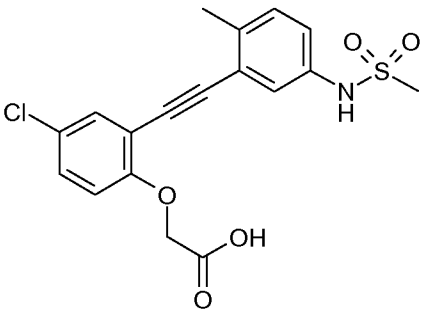
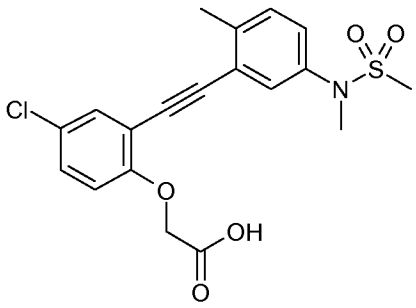
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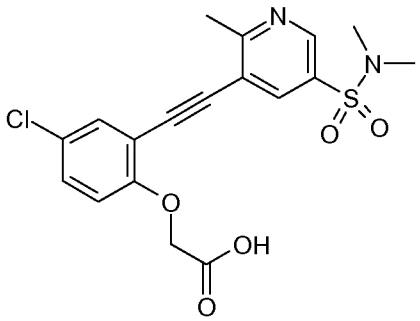
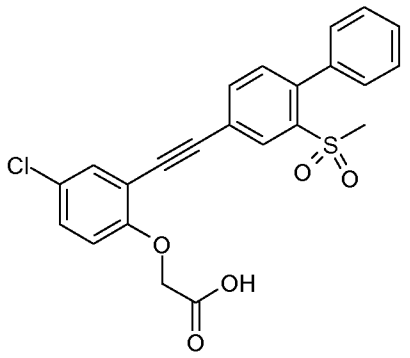
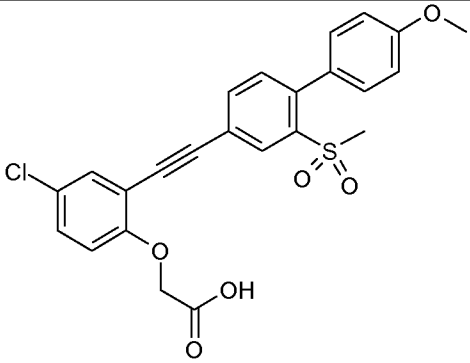
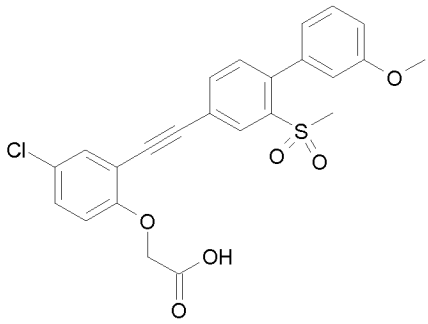
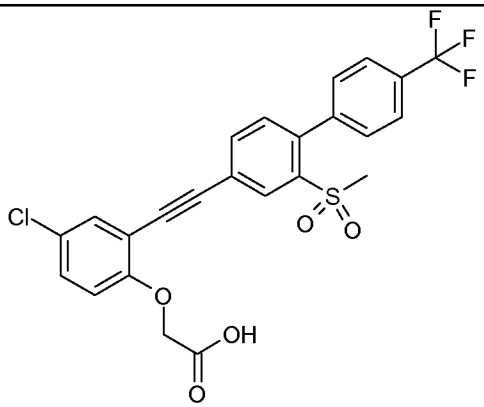
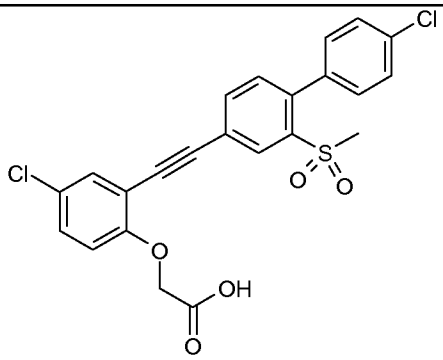
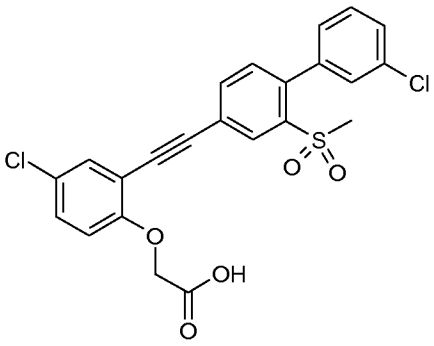
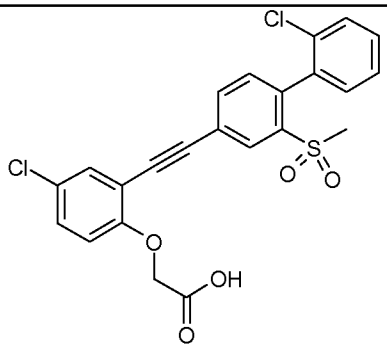
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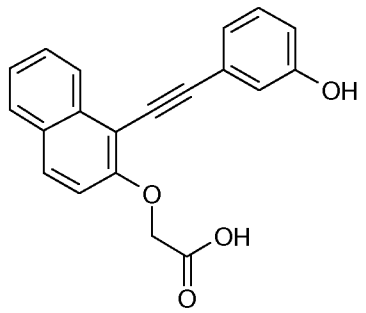
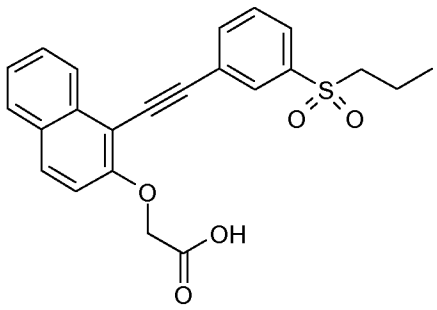
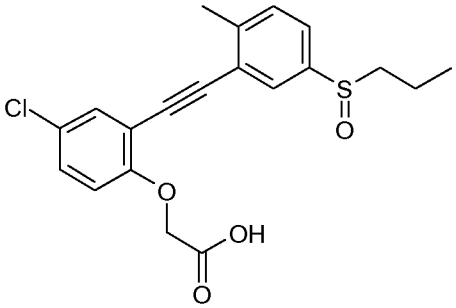
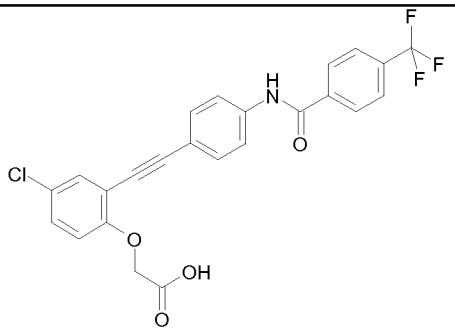
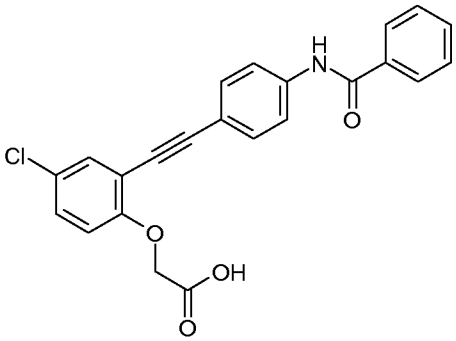
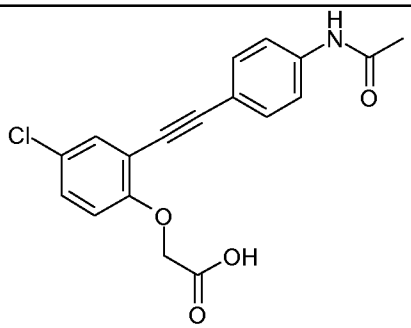
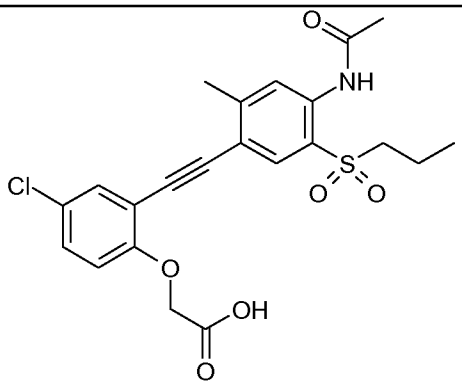
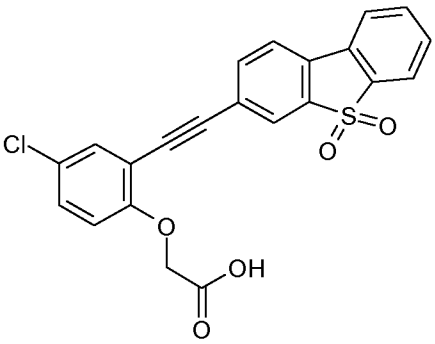
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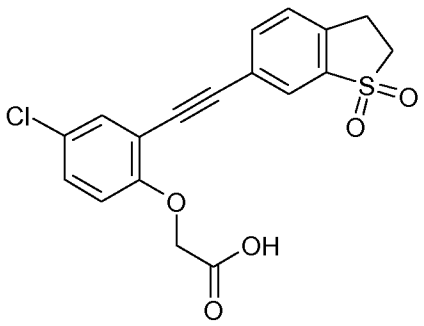
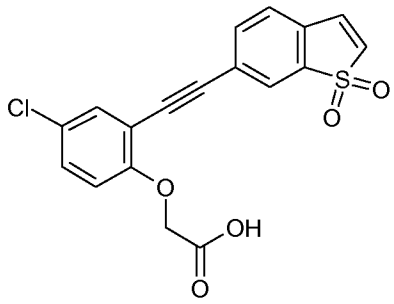
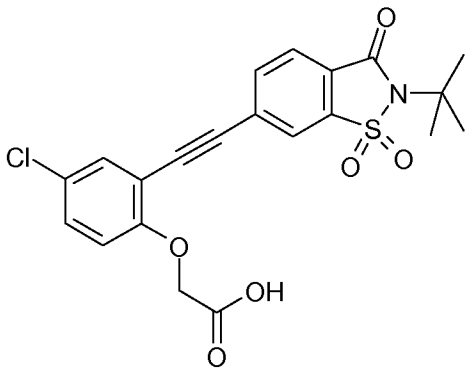
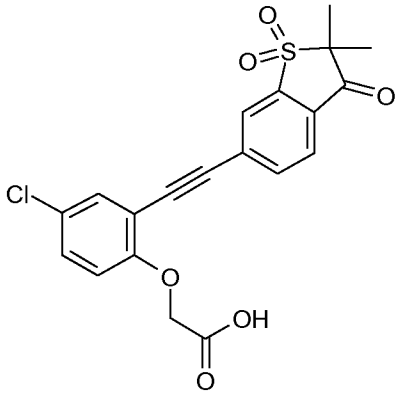
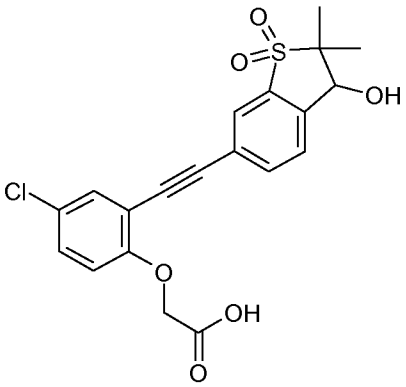
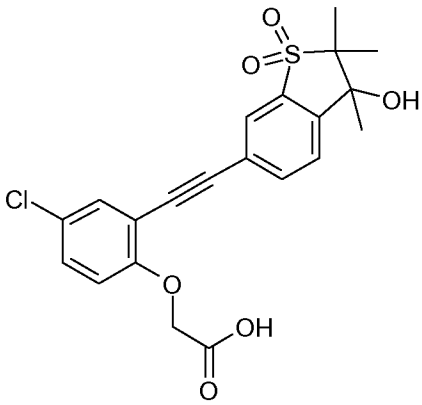
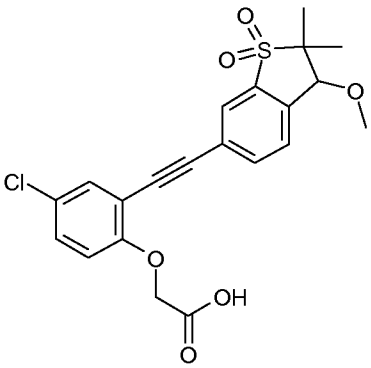
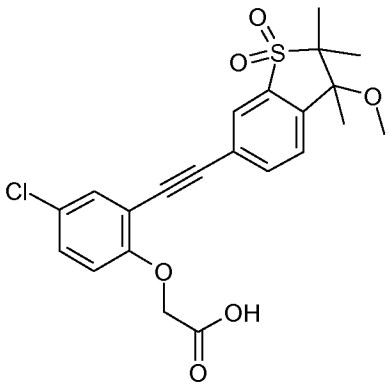
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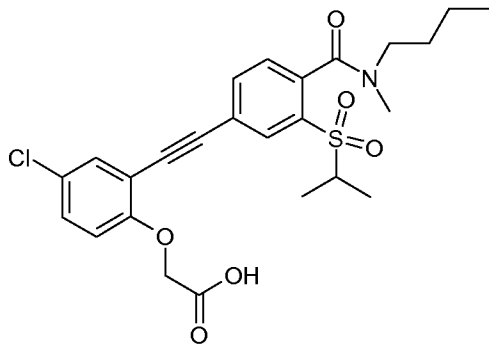
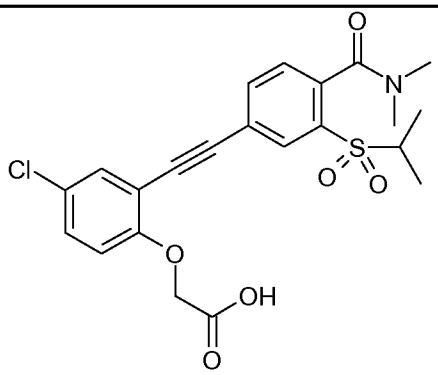
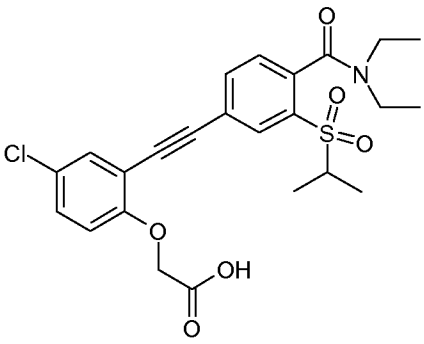
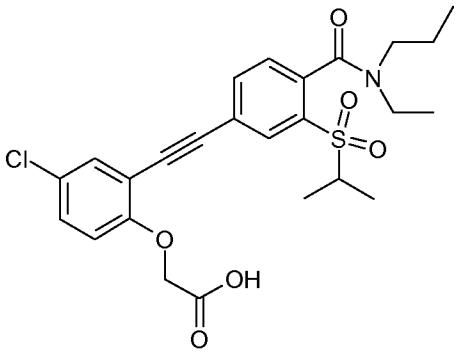
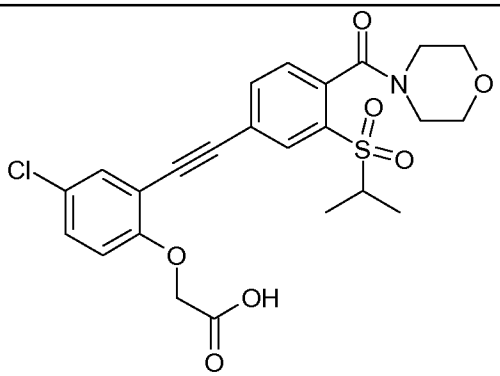
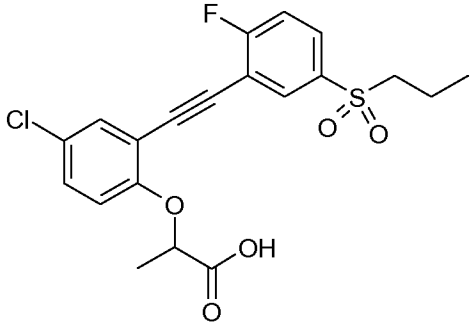
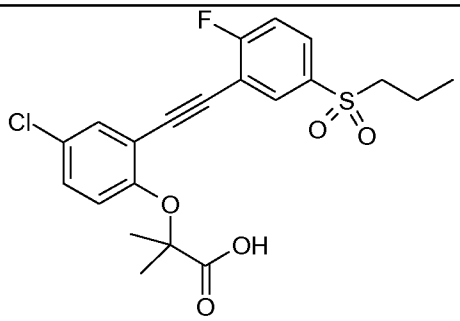
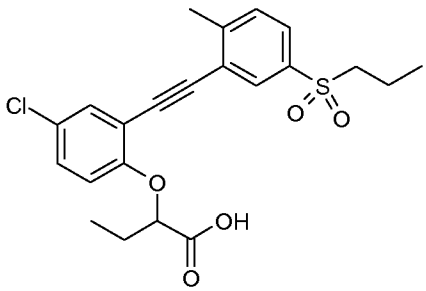
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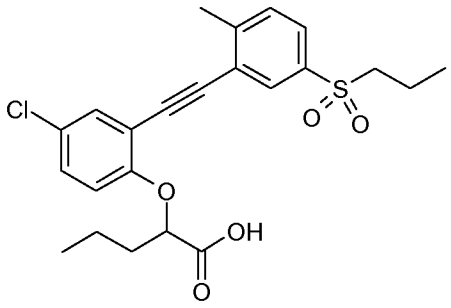
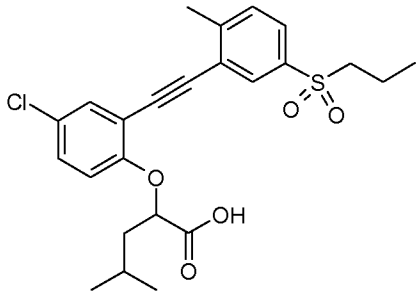
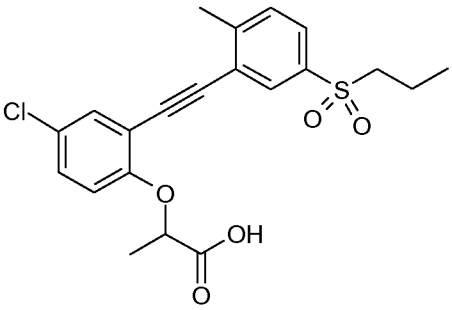
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"Pharmaceutically acceptable cationic salts or complexes" is intended to define such salts as the alkali metal salts, (e.g. sodium and potassium), alkaline earth metal salts (e.g. calcium or magnesium), aluminium salts, ammonium salts and salts with organic amines such as with methylamine, dimethylamine, trimethylamine, ethylamine, triethylamine, morpholine, N-Me-D-glucamine, N,N'-bis(phenylmethyl)-1,2-ethanediamine, ethanolamine, diethanolamine, ethylenediamine, N-methylmorpholine, piperidine, benzathine (N,N'-dibenzylethylenediamine), choline, ethylene-diamine, meglumine (N-methylglucamine), benethamine (N-benzylphenethylamine), diethylamine, piperazine, thromethamine (2-amino-2-hydroxymethyl-1,3-propanediol), procaine as well as amines of formula –NR,R',R'' wherein R, R', R'' is independently hydrogen, alkyl or benzyl. Especially preferred salts are sodium and potassium salts.

"Pharmaceutically acceptable salts or complexes" refers to salts or complexes of the below-identified compounds of Formula I that retain the desired biological activity. Examples of such salts include, but are not restricted to, acid addition salts formed with inorganic acids (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, fumaric acid, maleic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalene

sulfonic acid, naphthalene disul-fonic acid, and poly-galacturonic acid. Said compounds can also be administered as pharmaceutically acceptable quaternary salts known by a person skilled in the art, which specifically include the quarternary ammonium salt of the Formula –NR,R',R" $^{+}$ Z^{-}, wherein R, R', R" is independently hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, fumarate, citrate, tartrate, ascorbate, cinnamoate, mandeloate, and diphenylacetate).

"Pharmaceutically active derivative" refers to any compound that, upon administration to the recipient, is capable of providing directly or indirectly, the activity disclosed herein. The compounds of the present invention according to Formula (I) are useful in the treatment and/or prevention of diseases selected from allergic diseases such as allergic asthma, allergic rhinitis, allergic conjunctivitis, systemic anaphylaxis or hypersensitivity responses, and inflammatory dermatoses such as atopic dermatitis, eczema, allergic contact dermatitis, and urticaria, myositis, neurodegenerative disorders such as neuropatic pain, and other inflammatory diseases such as chronic obstructive pulmonary disease (COPD) rheumatoid arthritis, multiple sclerosis, osteoarthritis, and inflammatory bowel disease (IBD) such as ulcerative colitis and Crohn disease.

In one aspect the compounds according to Formula (I) are suitable as modulators, notably as antagonists, of CRTH2. Therefore, the compounds of the present invention are also particularly useful for the treatment and/or prevention of disorders, which are mediated by CRTH2 activity. Said treatment involves the modulation of CRTH2, notably an inhibition of CRTH2 or an antagonizing effect of CRTH2 in mammals, and in particular in humans. The modulators of CRTH2 are selected from the group consisting of an antagonist, an inverse agonist, a partial agonist and an agonist of CRTH2.
In another embodiment, the modulators of CRTH2 are antagonists of CRTH2.
In one embodiment, the modulators of CRTH2 are inverse agonists of CRTH2.
In another embodiment, the modulators of CRTH2 are partial agonists of CRTH2.
In another embodiment, the modulators of CRTH2 are agonists of CRTH2.
The compounds according to Formula (I) are suitable for use as a medicament.

Compounds of Formula (I) include also their geometrical isomers, their optically active forms as enantiomers, diastereomers, its racemate forms and tautomers, as well as pharmaceutically acceptable salts thereof, wherein:

In a second aspect, the invention provides a pharmaceutical composition comprising a compound according to Formula (I), together with a pharmaceutically acceptable excipient or carrier.

In a third aspect, the invention provides the use of a compound according to formulae (I) for the preparation of a medicament for the treatment and/or prevention of a disease selected from allergic diseases such as allergic asthma, allergic rhinitis, allergic conjunctivitis, systemic anaphylaxis or hypersensitivity responses, and inflammatory dermatoses such as atopic dermatitis, eczema, allergic contact dermatitis, and urticaria, myositis and other diseases with an inflammatory component such as chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, osteoarthritis, and inflammatory bowel disease (IBD) such as ulcerative colitis and Crohn disease and other diseases and disorders associated with CTRH2 activity.

In a fourth aspect, the invention provides a method for treating and/or preventing a patient suffering from a disease selected from allergic diseases such as allergic asthma, allergic rhinitis, allergic conjunctivitis, systemic anaphylaxis or hypersensitivity responses, and inflammatory dermatoses such as atopic dermatitis, eczema, allergic contact dermatitis, and urticaria, myositis, neurodegenerative disorders such as neuropatic pain, and other inflammatory diseases such as chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, multiple sclerosis, osteoarthritis, and inflammatory bowel disease (IBD) such as ulcerative colitis and Crohn disease and other diseases and disorders associated with CTRH2 activity, by administering a compound according to Formula (I).

The term “preventing”, as used herein, should be understood as partially or totally preventing, inhibiting, alleviating, or reversing one or more symptoms or cause(s) of allergic disease or inflammatory dermatitis.

In a fifth aspect, the invention provides the use of a compound of Formula (I) for the preparation of a pharmaceutical composition useful for a variety of therapies, including preventing and/or treating a disease selected from allergic diseases such as allergic asthma, allergic rhinitis, allergic conjunctivitis, systemic anaphylaxis or hypersensitivity responses, and inflammatory dermatoses such as atopic dermatitis, eczema, allergic contact dermatitis, and urticaria, myositis, neurodegenerative disorders such as neuropatic pain, and other inflammatory diseases such as chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, multiple sclerosis, osteoarthritis, and inflammatory bowel disease (IBD) such as ulcerative colitis and Crohn disease and other diseases and disorders associated with CTRH2 activity.

The invention provides further the use of a compound of Formula (I) for preventing and/or treating a disease selected from allergic diseases such as allergic asthma, allergic rhinitis, allergic conjunctivitis, systemic anaphylaxis or hypersensitivity responses, and inflammatory dermatoses such as atopic dermatitis, eczema, allergic contact dermatitis, and urticaria, myositis, neurodegenerative disorders such as neuropatic pain, and other inflammatory diseases such as chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, multiple sclerosis, osteoarthritis, and inflammatory bowel disease (IBD) such as ulcerative colitis and Crohn disease and other diseases and disorders associated with CTRH2 activity.

The compounds of the invention, together with a conventionally employed adjuvant, carrier, diluent or excipient may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, or in the form of sterile injectable solutions for parenteral (including subcutaneous use). Such pharmaceutical compositions and unit dosage forms thereof may comprise ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

The compounds according to Formula (I) of the present invention are typically administered in form of a pharmaceutical composition. Such compositions can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. Generally, the compounds of this invention are administered in a

pharmaceutically effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

The pharmaceutical compositions of these inventions can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled, premeasured ampoules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the substituted methylene amide derivative according to the invention is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

Liquid forms suitable for oral administration may include a suitable aqueous or non-aqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatine; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as pepper-mint, methyl salicylate, or orange flavoring.

Injectable compositions are typically based upon injectable sterile saline or phosphate buffered saline or other injectable carriers known in the art. As above mentioned, substituted methylene amide derivatives of Formula (I) in such compositions is typically a minor component, frequently ranging between 0.05 to 10% by weight with the remainder being the injectable carrier and the like.

The above-described components for orally administered or injectable compositions are merely representative. Further materials as well as processing techniques and the like are set out in Part 5 of *Remington's Pharmaceutical Sciences*, 20th Edition, 2000, Marck Publishing Company, Easton, Pennsylvania, which is incorporated herein be reference. The compounds of this invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can also be found in the incorporated materials in *Remington's Pharmaceutical Sciences*.

The compounds according to formula (I) can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred experimental conditions (i.e. reaction temperatures, time, moles of reagents, solvents etc.) are given, other experimental conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by the person skilled in the art, using routine optimisation procedures.

The following abbreviations refer respectively to the definitions below:
aq (aqueous), h (hour), g (gram), L (liter), mg (milligram), MHz (Megahertz), min. (minute), mm (millimeter), mmol (millimole), mM (millimolar), m.p. (melting point), eq (equivalent), mL (milliliter), µL (microliter), ACN (acetonitrile), BOC (tert-butoxy-carbonyl), CBZ (carbobenzoxy), $CDCl_3$ (deuterated chloroform), CD_3OD (deuterated methanol), CH_3CN (acetonitrile), c-hex (cyclohexane), DCC (dicyclohexyl carbodiimide), DCM (dichloromethane), DIC (diisopropyl carbodiimide), DIEA (diisopropylethyl-amine), DMF (dimethylformamide), DMSO (dimethylsulfoxide), DMSO-d_6 (deuterated dimethylsulfoxide), EDC (1-(3-dimethyl-amino-propyl)-3-ethylcarbodiimide), ESI (Electro-spray ionization), EtOAc (ethyl acetate), Et_2O (diethyl ether), EtOH (ethanol), FMOC (fluorenylmethyloxycarbonyl), HATU (dimethylamino-([1,2,3]triazolo[4,5-b]pyridin-3-yloxy)-methylene]-dimethyl-ammonium hexafluorophosphate), HPLC (High Performance Liquid Chromatography), i-PrOH (2-propanol), K_2CO_3 (potassium carbonate), LC (Liquid Chromatography), MeOH (methanol), $MgSO_4$ (magnesium sulfate), MS (mass spectrometry), MTBE (Methyl tert-butyl ether), Mtr. (4-Methoxy-2, 3, 6-trimethylbenzensulfonyl), $NaHCO_3$ (sodium bicarbonate), $NaBH_4$ (sodium borohydride), NMM (N-methyl morpholine), NMR (Nuclear

Magnetic Resonance), POA (phenoxyacetate), PyBOP® (benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate), RT (room temperature), Rt (retention time), SPE (solid phase extraction), TBAF (tetrabutylammonium fluoride), TBTU (2-(1-H-benzotriazole-1-yl)-1,1,3,3-tetramethyluromium tetrafluoro borate), TEA (triethylamine), TFA (trifluoroacetic acid), THF (tetrahydrofuran), TLC (Thin Layer Chromatography), UV (Ultraviolet).

"O-PG" denotes a protecting group, preferably for acyl groups, i.e an acyl-protecting group. O-PG denotes preferably an O-alkyl group like tert-butoxy, methoxyl, ethoxy or benzyloxy group.

The term "protecting group" is known in general terms and relates to groups which are suitable for protecting a functional group against chemical reactions, but are easy to remove after the desired chemical reaction has been carried out elsewhere in the molecule. The nature and size of the protecting groups are not crucial since they are removed again after the desired chemical reaction or reaction sequence; preference is given to groups having 1-20, in particular 1-10, carbon atoms.

In general, compounds according to Formula (I) of this invention can be prepared from readily available starting materials. If such starting materials are not commercially available they can be prepared by standard synthetic techniques. The following general methods and procedures described hereinafter in the examples can be employed to prepare compounds of Formula (I).

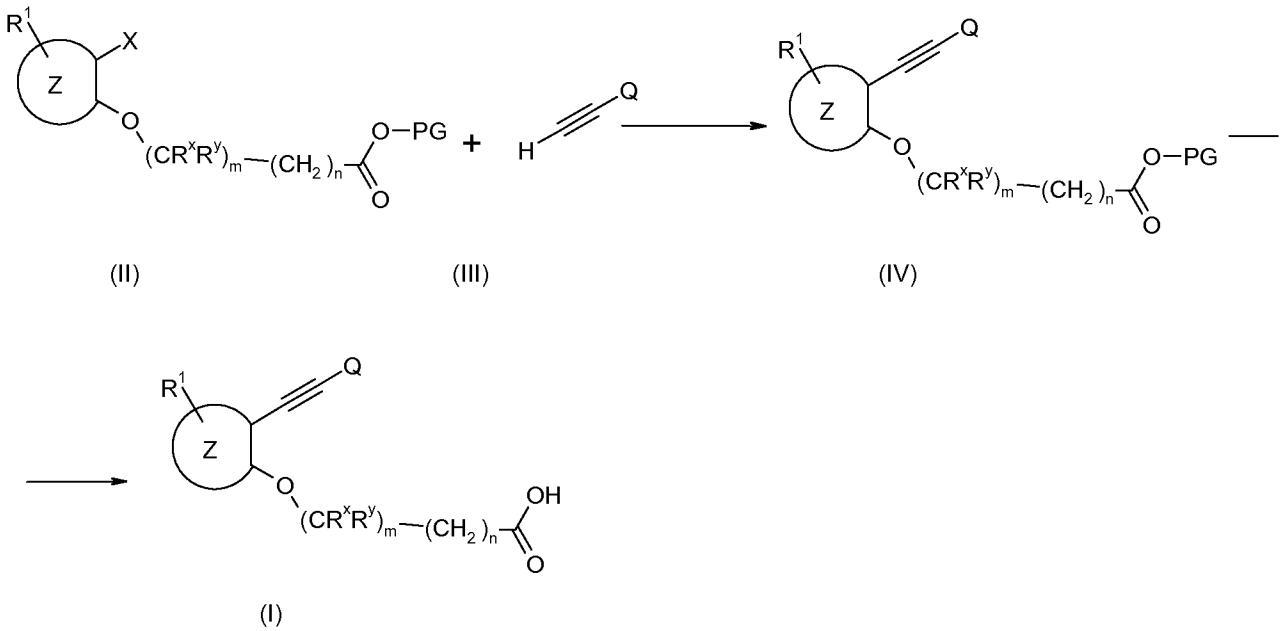
Depending on the nature of R^1, R^x, R^y, Q, m and n in formula (I), different synthetic strategies may be selected for the synthesis of compounds of Formula I. In the process illustrated in the following schemes R^1, R^x, R^y, Q, X, m and n are as defined in the description.

Generally, compounds of Formula (I), wherein R^1, R^x, R^y, Z, Q, m and n are defined as above, can be obtained in 2 steps as outlined in Scheme 1. The first step consists in coupling a compound of Formula (II), wherein R^1, R^x, R^y, Z, Q, m and n are defined as above, X denotes Cl, Br, I, preferably Br or I, or trifluoromethanesulfonyl and wherein PG denotes a protecting group such as tert-butyl, with an alkyne of Formula (III), wherein Q

is defined as above. General protocols for such coupling are given below in the Examples, using conditions and methods well known to those skilled in the art to perform such coupling. The reaction can optionally be performed with an appropriate catalyst such as but not limited to dichlorobis(triphenylphosphine)palladium(II) or 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II), $Pd(OAc)_2$, $Pd_2(dba)_3$, or Pd/C in the presence or absence of an additional ligand, such as but not limited to $P(tBu)_3$, $P(oTol)_3$, PPh_3, BINAP. Additionally, the reaction can optionally be performed in the presence of a suitable copper salt such as but not limited to copper (I) iodide, copper (I) bromide or copper (I) chloride. The reaction can be performed in the presence or absence of bases such as TEA, DIEA, NMM, piperidine, Cs_2CO_3, sodium phosphate, in the presence or absence of a suitable solvent such as THF, ACN, DMF, acetone at a temperature between about 20 °C to about 100 °C, preferably at about 70 °C, for a few hours, e.g. one hour to 24 h. For a list of conditions described for the coupling of an aryl alkyne with an aryl or heteroaryl triflate or halide, see also Rafael Chinchilla and Carmen Najera, *Chem. Rev.* **2007**, *107*, 874-892.

Conversion of compounds of Formula (IV) to give compounds of Formula (I) can be achieved using conditions and methods well known to those skilled in the art for the conversion of an ester to a carboxylic acid, such as but not limited to treatment with a base or an appropriate acid, such as trifluoroacetic acid or hydrochloric acid, in the presence of a suitable solvent such as DCM, dioxane, THF at a temperature between about 20 °C to about 100 °C, preferably at about 20 °C, for a few hours, e.g. one hour to 24 h.

Scheme 1

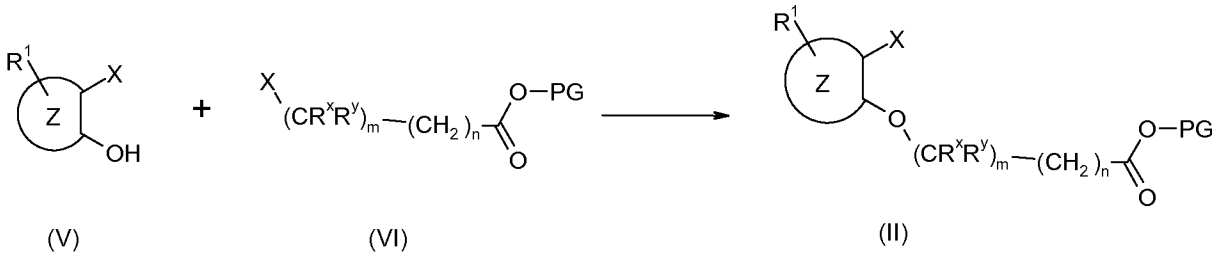


(II) (III) (IV)

(I)

Compounds of Formula (II), wherein R^1, R^x, R^y, Z, X , PG, m and n are defined as above, can be prepared by alkylation of a compound of Formula (V), wherein R^1, Z and X are defined as above, with a compound of Formula (VI), wherein R^x, R^y, X , PG, m and n are as defined above, as outlined in Scheme 2. The reaction can be performed in the presence of a suitable base, such as potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, sodium *tert*-butoxide, in the presence of a suitable solvent such as DCM, dioxane, THF, in the presence or absence of water. The reaction can be carried out at a temperature between about 20 °C to about 100 °C, preferably at about 20 °C, for a few hours, e.g. one hour to 24 h. Alternatively, the Compounds of Formula (II) can be prepared by reaction of a compound of Formula (V) with an opportunely protected hydroxyalkyl carboxylic acid under Mitsunobu conditions, using conditions and methods well known to those skilled in the art such as in the presence of a phosphine, such as but not limited to triphenylphosphine, and an azadicarboxylate, such as but not limited to diisopropylazadicarboxylate.

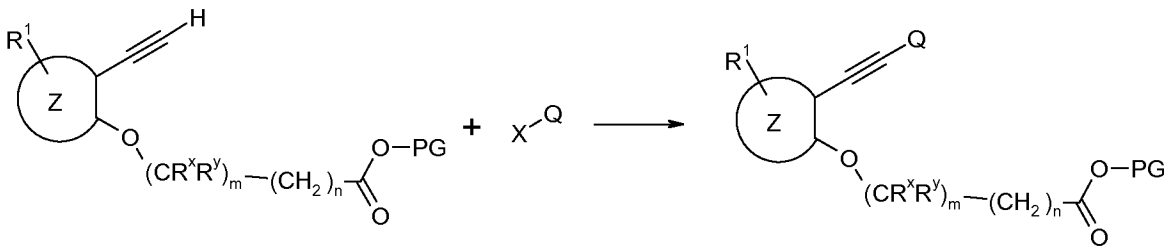
Scheme 2



(V) (VI) (II)

Compounds of Formula (IV) wherein Q, Z, R^1, R^x, R^y, PG, m and n are as above defined can be obtained by coupling a compound of Formula (VII) wherein Z, R^1, R^x, R^y, PG, m and n are as above defined, with a compound of Formula (VIII) wherein Q is as above defined and wherein X denotes a triflate or an halide, preferably a bromide or an iodide, as outlined in Scheme 3. General protocols for such coupling are given below in the Examples, using conditions and methods well known to those skilled in the art to perform such coupling. This reaction is preferably performed with an appropriate catalyst such as but not limited to dichlorobis(triphenylphosphine)palladium(II) or 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II), $Pd(OAc)_2$, $Pd_2(dba)_3$, $Pd(Cl)_2$ or Pd/C in the presence or absence of an additionnal ligand, such as but not limited to $P(t\text{Bu})_3$, $P(o\text{Tol})_3$, PPh_3, BINAP. The reaction can also be performed in the presence of a suitable copper salt such as but not limited to copper (I) iodide, copper (I) bromide or copper (I) chloride. The reaction can be performed in the presence or absence of bases such as TEA, DIEA, NMM, piperidine, Cs_2CO_3, sodium phosphate, in the presence or absence of a suitable solvent such as THF, ACN, DMF or acetone. This coupling reaction can be carried out at a temperature between about 20 °C to about 100 °C, preferably at about 70 °C, for a few hours, e.g. one hour to 24 h.

Scheme 3



(VII) (VIII) (IV)

The method for preparing the compounds of Formula (IV) selected below:

tert-butyl {4-chloro-2-[(4-methylpyridin-3-yl)ethynyl]phenoxy}acetate
tert-butyl {4-chloro-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate
tert-butyl {4-chloro-2-[(5-cyano-2-fluorophenyl)ethynyl]phenoxy}acetate
tert-butyl {4-chloro-2-[(2-methylpyridin-3-yl)ethynyl]phenoxy}acetate
tert-butyl (4-chloro-2-{[2-fluoro-5-(hydroxymethyl)phenyl]ethynyl}phenoxy)acetate
tert-butyl (4-chloro-2-{[2-fluoro-4-(hydroxymethyl)phenyl]ethynyl}phenoxy)acetate
tert-butyl (4-chloro-2-{[2-fluoro-3-(hydroxymethyl)phenyl]ethynyl}phenoxy)acetate
tert-butyl (4-chloro-2-{[2-fluoro-5-(methoxymethyl)phenyl]ethynyl}phenoxy)acetate
tert-butyl {4-chloro-2-[(4-methyl-1-oxidopyridin-3-yl)ethynyl]phenoxy}acetate
tert-butyl (4-cyano-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate
tert-butyl (4-chloro-2-{[2-methyl-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate
tert-butyl (4-chloro-2-{[2-fluoro-4-(methoxymethyl)phenyl]ethynyl}phenoxy)acetate
tert-butyl (4-chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate
tert-butyl {4-chloro-2-[(4-propylpyridin-3-yl)ethynyl]phenoxy}acetate
tert-butyl {4-chloro-2-[(4-isobutylpyridin-3-yl)ethynyl]phenoxy}acetate
tert-butyl {4-cyano-2-[(4-methylpyridin-3-yl)ethynyl]phenoxy}acetate
tert-butyl {2-[(2-chlorophenyl)ethynyl]phenoxy}acetate
tert-butyl (4-chloro-2-{[5-(methylsulfonyl)-2-propylphenyl]ethynyl}phenoxy)acetate
tert-butyl [2-{[3-(propylsulfonyl)phenyl]ethynyl}-4-(trifluoromethyl)phenoxy]acetate
tert-butyl (4-cyano-2-{[5-(methylsulfonyl)-2-propylphenyl]ethynyl}phenoxy)acetate
tert-butyl (4-chloro-2-{[5-(methylsulfonyl)-2-piperidin-1-ylphenyl]ethynyl}phenoxy)acetate
tert-butyl (4-cyano-2-{[2-fluoro-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate
tert-butyl (4-chloro-2-{[2-chloro-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate
tert-butyl (4-chloro-2-{[2-hydroxy-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate
tert-butyl (2-{[2-chloro-5-(methylsulfonyl)phenyl]ethynyl}-4-cyanophenoxy)acetate
tert-butyl (4-cyano-2-{[5-(methylsulfonyl)-2-piperidin-1-ylphenyl]ethynyl}phenoxy)acetate
tert-butyl [(6-methyl-2-{[3-(propylsulfonyl)phenyl]ethynyl}pyridin-3-yl)oxy]acetate
tert-butyl (4-chloro-2-{[2-isopropyl-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate
tert-butyl (4-cyano-2-{[2-isopropyl-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate
tert-butyl (3-chloro-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate
tert-butyl [4-chloro-2-({3-[(dimethylamino)sulfonyl]phenyl}ethynyl)phenoxy]acetate

tert-butyl [4-chloro-2-({5-[(diethylamino)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetate

tert-butyl (4-chloro-2-{[2-methyl-5-(morpholi*N*-4-ylsulfonyl)phenyl]ethynyl}phenoxy)acetate

tert-butyl [4-chloro-2-({5-[(dimethylamino)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetate

tert-butyl [4-chloro-2-({2-methyl-5-[(methylamino)sulfonyl]phenyl}ethynyl)phenoxy]acetate

tert-butyl [2-({5-[(*tert*-butylamino)sulfonyl]-2-methylphenyl}ethynyl)-4-chlorophenoxy]acetate

tert-butyl [4-chloro-2-({5-[(isopropylamino)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetate

tert-butyl {4-chloro-2-[(5-{[isopropyl(methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetate

tert-butyl (4-chloro-2-{[2-fluoro-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate

tert-butyl (4-chloro-2-{[4-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate

tert-butyl (4-cyano-2-{[2-methyl-5-(phenylsulfonyl)phenyl]ethynyl}phenoxy)acetate

tert-butyl (4-chloro-2-{[2-methyl-5-(phenylsulfonyl)phenyl]ethynyl}phenoxy)acetate

tert-butyl (4-chloro-2-{[4-fluoro-2-methyl-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate

tert-butyl [4-chloro-2-({3-[(methylsulfonyl)methyl]phenyl}ethynyl)phenoxy]acetate

tert-butyl (4-fluoro-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate

tert-butyl (4-chloro-2-{[2-ethyl-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate

tert-butyl (4-chloro-2-{[2-chloro-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate

tert-butyl (4-chloro-2-{[2-fluoro-5-(isopropylsulfonyl)phenyl]ethynyl}phenoxy)acetate

tert-butyl (4-chloro-2-{[2-chloro-5-(isopropylsulfonyl)phenyl]ethynyl}phenoxy)acetate

tert-butyl (4-chloro-2-{[5-(ethylsulfonyl)-2-fluorophenyl]ethynyl}phenoxy)acetate

tert-butyl (4-chloro-2-{[2-fluoro-5-(isobutylsulfonyl)phenyl]ethynyl}phenoxy)acetate

tert-butyl [4-chloro-2-({2-fluoro-5-[(2-methoxyethyl)sulfonyl]phenyl}ethynyl)phenoxy]acetate

tert-butyl (4-chloro-2-{[2-methyl-5-(piperidin-1-ylsulfonyl)phenyl]ethynyl}phenoxy)acetate

tert-butyl [4-chloro-2-({5-[(dimethylamino)sulfonyl]-2-fluorophenyl}ethynyl)phenoxy]acetate

tert-butyl [4-chloro-2-({2-methyl-5-[(2-methylpiperidin-1-yl)sulfonyl]phenyl}ethynyl)phenoxy]acetate

tert-butyl {4-chloro-2-[(5-{[(2-methoxyethyl)(methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetate

tert-butyl {4-chloro-2-[(5-{[isobutyl(methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetate

tert-butyl {2-[(5-{[butyl(methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]-4-chlorophenoxy}acetate

tert-butyl [4-chloro-2-({2-methyl-5-[(4-methylpiperazi*N*-1-yl)sulfonyl]phenyl}ethynyl)phenoxy]acetate

tert-butyl {4-chloro-2-[(5-{[(2,2-dimethylpropyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetate

tert-butyl [2-({5-[(*sec*-butylamino)sulfonyl]-2-methylphenyl}ethynyl)-4-chlorophenoxy]acetate

tert-butyl {4-chloro-2-[(2-methyl-5-{[methyl(propyl)amino]sulfonyl}phenyl)ethynyl]phenoxy}acetate

tert-butyl [4-chloro-2-({5-[(dipropylamino)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetate

tert-butyl {4-chloro-2-[(5-{[(2-methoxyethyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetate

tert-butyl [4-chloro-2-({2-methyl-5-[(propylamino)sulfonyl]phenyl}ethynyl)phenoxy]acetate

tert-butyl {4-chloro-2-[(5-{[[3-(dimethylamino)propyl](methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetate

tert-butyl (2-{[5-(aminosulfonyl)-2-methylphenyl]ethynyl}-4-chlorophenoxy)acetate

tert-butyl {4-chloro-2-[(5-{[cyclopentyl(methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetate

tert-butyl {4-chloro-2-[(5-{[[2-(dimethylamino)ethyl](methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetate

tert-butyl (2-{[5-(azetidin-1-ylsulfonyl)-2-methylphenyl]ethynyl}-4-chlorophenoxy)acetate

tert-butyl (4-chloro-2-{[4-(morpholi*N*-4-ylcarbonyl)phenyl]ethynyl}phenoxy)acetate

tert-butyl [4-chloro-2-({4-[(dimethylamino)carbonyl]phenyl}ethynyl)phenoxy]acetate

tert-butyl (4-chloro-2-{[3-(morpholi*N*-4-ylcarbonyl)phenyl]ethynyl}phenoxy)acetate

tert-butyl [4-chloro-2-({3-[(dimethylamino)carbonyl]phenyl}ethynyl)phenoxy]acetate

tert-butyl [(5-chloro-3-{[3-(propylsulfonyl)phenyl]ethynyl}pyridin-2-yl)oxy]acetate

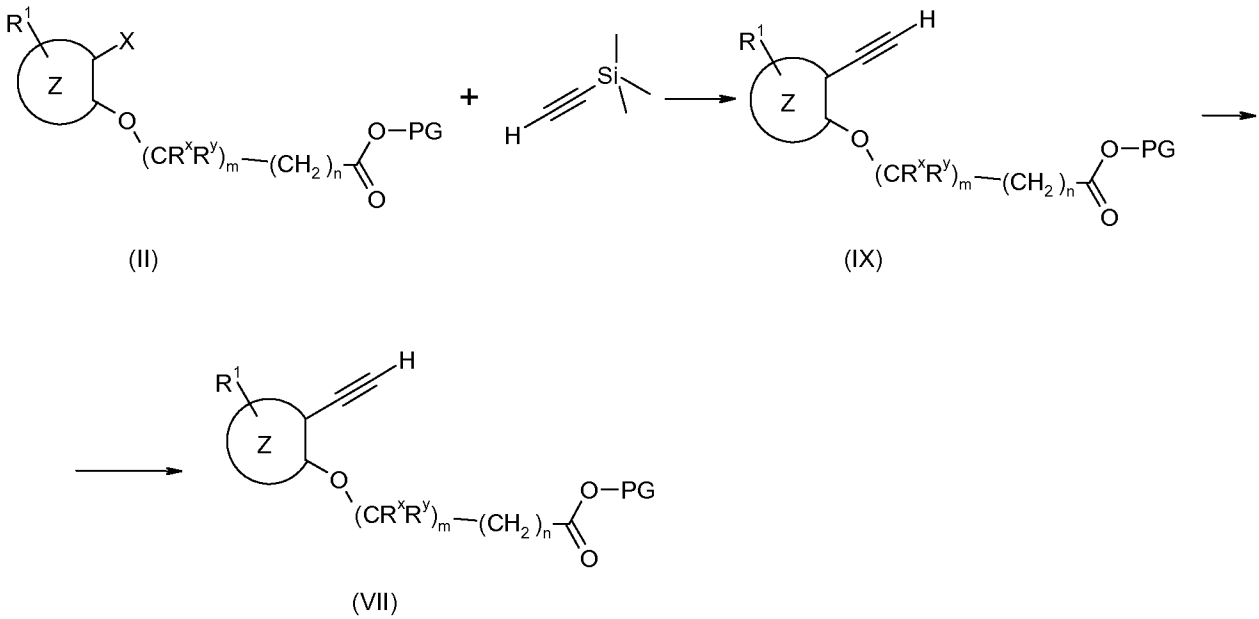
tert-butyl [(5-chloro-3-{[2-fluoro-5-(propylsulfonyl)phenyl]ethynyl}pyridin-2-yl)oxy]acetate
tert-butyl [4-chloro-2-({2-chloro-5-[(trifluoromethyl)sulfonyl]phenyl}ethynyl)phenoxy]acetate
tert-butyl (4-bromo-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate
tert-butyl (4-(2,4-dimethyl-1,3-thiazol-5-yl)-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate
tert-butyl [2-{[3-(propylsulfonyl)phenyl]ethynyl}-4-(2-thienyl)phenoxy]acetate
tert-butyl (4-(1-methyl-1*H*-pyrazol-4-yl)-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate
tert-butyl [2-{[3-(propylsulfonyl)phenyl]ethynyl}-4-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)phenoxy]acetate
tert-butyl [4-chloro-2-({2-methyl-5-[(methylsulfonyl)amino]phenyl}ethynyl)phenoxy]acetate
tert-butyl [4-chloro-2-({2-methyl-5-[methyl(methylsulfonyl)amino]phenyl}ethynyl)phenoxy]acetate
tert-butyl [4-chloro-2-({5-[(dimethylamino)sulfonyl]-2-methylpyridin-3-yl}ethynyl)phenoxy]acetate
tert-butyl (4-chloro-2-{[2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetate
tert-butyl (4-chloro-2-{[4'-methoxy-2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetate
tert-butyl (4-chloro-2-{[3'-methoxy-2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetate
tert-butyl (4-chloro-2-{[2-(methylsulfonyl)-4'-(trifluoromethyl)biphenyl-4-yl]ethynyl}phenoxy)acetate
tert-butyl (4-chloro-2-{[4'-chloro-2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetate
tert-butyl (4-chloro-2-{[3'-chloro-2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetate
tert-butyl (4-chloro-2-{[2'-chloro-2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetate
tert-butyl [(1-{[3-(propylsulfonyl)phenyl]ethynyl}-2-naphthyl)oxy]acetate
methyl (4-chloro-2-{[2-methyl-5-(propylsulfinyl)phenyl]ethynyl}phenoxy)acetate
tert-butyl {4-chloro-2-[(4-{[4-(trifluoromethyl)benzoyl]amino}phenyl)ethynyl]phenoxy}acetate
tert-butyl (2-{[4-(benzoylamino)phenyl]ethynyl}-4-chlorophenoxy)acetate
tert-butyl (2-{[4-(acetylamino)phenyl]ethynyl}-4-chlorophenoxy)acetate

tert-butyl (2-{[4-(acetylamino)-2-methyl-5-(propylsulfonyl)phenyl]ethynyl}-4-chlorophenoxy)acetate
tert-butyl {4-chloro-2-[(5,5-dioxidodibenzo[b,d]thien-3-yl)ethynyl]phenoxy}acetate
tert-butyl {4-chloro-2-[(1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetate
tert-butyl {4-chloro-2-[(1,1-dioxido-1-benzothien-6-yl)ethynyl]phenoxy}acetate
tert-butyl {4-chloro-2-[(2,2-dimethyl-1,1-dioxido-3-oxo-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetate
tert-butyl {4-chloro-2-[(3-hydroxy-2,2-dimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetate
tert-butyl {4-chloro-2-[(3-hydroxy-2,2,3-trimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetate
tert-butyl {4-chloro-2-[(3-methoxy-2,2-dimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetate
tert-butyl {4-chloro-2-[(3-methoxy-2,2,3-trimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetate
tert-butyl (2-{[4-{[butyl(methyl)amino]carbonyl}-3-(isopropylsulfonyl)phenyl]ethynyl}-4-chlorophenoxy)acetate
tert-butyl (4-chloro-2-{[4-[(dimethylamino)carbonyl]-3-(isopropylsulfonyl)phenyl]ethynyl}phenoxy)acetate
tert-butyl (4-chloro-2-{[4-[(diethylamino)carbonyl]-3-(isopropylsulfonyl)phenyl]ethynyl}phenoxy)acetate
tert-butyl (4-chloro-2-{[4-{[ethyl(propyl)amino]carbonyl}-3-(isopropylsulfonyl)phenyl]ethynyl}phenoxy)acetate
tert-butyl (4-chloro-2-{[3-(isopropylsulfonyl)-4-(morpholi*N*-4-ylcarbonyl)phenyl]ethynyl}phenoxy)acetate
ethyl 2-(4-chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)butanoate
ethyl 2-(4-chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)pentanoate
ethyl 2-(4-chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)-4-methylpentanoate
is more particularly described in the examples.

Compounds of Formula (VII) wherein Z, R^1, R^x, R^y, PG, X, m and n are as above defined can be obtained in a 2-step protocol as outlined in Scheme 4. The first step consists in

the coupling of a compound of Formula (II) wherein Z, R^1, R^x, R^y, PG, m and n are as above defined and wherein X is preferably Br, with trimethylsilylacetylene using conditions and methods well known to those skilled in the art. This reaction can be performed with or without a catalyst such as but not limited to dichlorobis(triphenylphosphine)palladium(II) or 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II), $Pd(OAc)_2$, $Pd_2(dba)_3$, or Pd/C in the presence or absence of an additional ligand, such as but not limited to $P(tBu)_3$, $P(oTol)_3$, PPh_3, BINAP. The reaction is preferably performed in the presence of a suitable copper salt such as but not limited to copper (I) iodide, copper (I) bromide or copper (I) chloride. The reaction can be performed in the presence or absence of bases such as TEA, DIEA, NMM, piperidine, in the presence or absence of a suitable solvent such as THF, ACN, DMF. The reaction can be carried out at a temperature between about 20 °C to about 100 °C, preferably at about 70 °C, for a few hours, e.g. one hour to 24 h. The second step consists in the removal of the trimethylsilyl protecting group, which can be accomplished by treatment with strong acids, or with potassium carbonate in methanol, or with a source of fluoride ions, such as but not limited to tetrabutylammonium fluoride or pyridinium fluoride, in the presence or absence of a suitable solvent such as THF, at a temperature between about 20 °C to about 100 °C, preferably at about 70 °C, for a few hours, e.g. one hour to 24 h.

Scheme 4



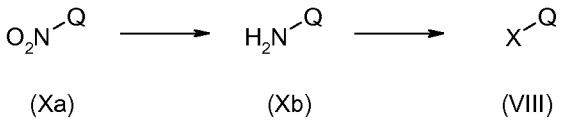
(II) (IX)

(VII)

Compounds of Formula (VIII) wherein Q is as above defined and X represents a halogen, preferably bromine or iodine, can be obtained as shown in Scheme 5. The first step consists in the reduction of an aryl or hetaryl nitro compound of Formula (Xa). General protocols for such coupling are given below in the Examples, using conditions and methods well known to those skilled in the art to perform such coupling. This reaction can be performed by hydrogenolysis, with an appropriate catalyst such as but not limited to Pd/C, Pt/C, PtO_2, Ni Raney, in the presence of hydrogen gas or of a source of hydrogen gas such as cyclohexadiene or ammonium formate, in a suitable solvent such as MeOH, EtOH, EtOAc, THF, DMF. This coupling reaction can be carried out at a temperature between about 20 °C to about 100 °C, preferably at about 20 °C, for a few hours, e.g. one hour to 24 h. The reduction can also be carried out using a metal as reducing agent, such as iron or zinc, in the presence or absence of acetic acid, at a temperature between about 20 °C to about 100 °C, preferably at about 20 °C, for a few hours, e.g. one hour to 24 h.

The second step consists in the conversion of the compounds of Formula (Xb) to the corresponding compounds of Formula (VIII), using methods well known to those skilled in the art for the conversion of an aryl or hetaryl amine to an aryl or hetaryl halide (Sandmeyer reaction and variants thereof), such as using sodium nitrite or *tert*-butyl nitrite and CuBr, CuI, KI or another suitable source of bromine or iodine, in a suitable solvent, such as an aqueous HCl solution, at a temperature between about 20 °C to about 100 °C, preferably at about 20 °C, for a few hours, e.g. one hour to 24 h.

Scheme 5



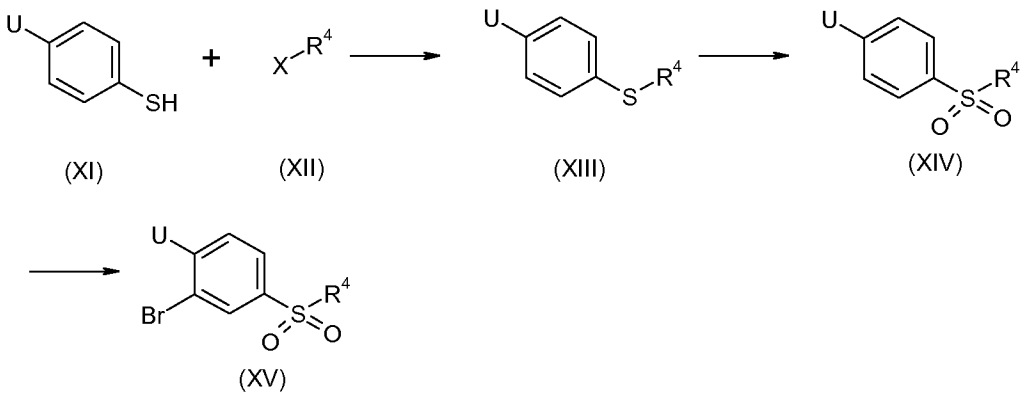
(Xa) (Xb) (VIII)

Compounds of Formula (XV), wherein U is as above defined, R^4 is $-CH_2$-A wherein A is as defined above or T with p>0 and X represents an halogen or a triflate, can be obtained as shown in Scheme 6. An aromatic thiol of Formula (XI) can be alkylated with an alkyl halide of Formula (XII) in presence of a suitable base, such as but not limited to K_2CO_3, Cs_2CO_3, Na_2CO_3, NaOH, KOH, NaH, in a suitable solvent such as DMF, acetone, THF, in the presence of absence of water as a co-solvent, at a temperature between about 20 °C to about 100 °C, preferably at about 20 °C, for a few hours, e.g. one hour to 24 h.

The second step consists in the oxidation of the thioether group to a sulfone group, to give compounds of Formula (XIV), using oxidizing agents well known to those skilled in the art, such as but not limited to oxone®, sodium periodate, hydrogen peroxide, 3-chloroperbenzoic acid, hydrogen peroxide in the presence of acetic acid, in a suitable solvent depending on the nature of the oxidant.

The third step consists in an aromatic bromination reaction, using a suitable source of bromine such as Br_2 or NBS, in the presence of a suitable solvent such as concentrated sulphuric acid, at a temperature between about 20 °C to about 100 °C, preferably at about 20 °C, for a few hours, e.g. one hour to 24 h.

Scheme 6



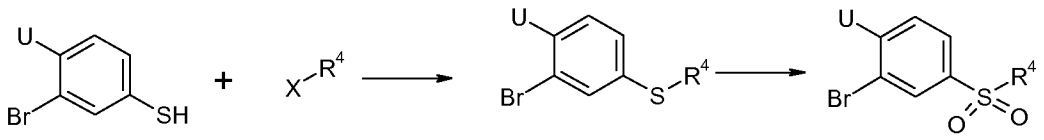
(XI) (XII) (XIII) (XIV) (XV)

Alternatively, the compounds of Formula (XV), defined as above, can be obtained as shown in Scheme 7. Compounds of Formula (XVI) can be alkylated with a compound of

Formula (XII), in presence of a suitable base, such as but not limited to K_2CO_3, Cs_2CO_3, Na_2CO_3, NaOH, KOH, NaH, in a suitable solvent such as DMF, acetone, THF, in the presence or absence of a water as a co-solvent, at a temperature between about 0 °C to about 100 °C, preferably at about 20 °C, for a few hours, e.g. one hour to 24 h.

The compounds of Formula (XV) could be obtained by oxidation, using oxidizing agents well known to those skilled in the art, such as but not limited to oxone®, sodium periodate, hydrogen peroxide, m-chloroperbenzoic acid, hydrogen peroxide in the presence of acetic acid, in a suitable solvent depending on the nature of the oxidant.

Scheme 7



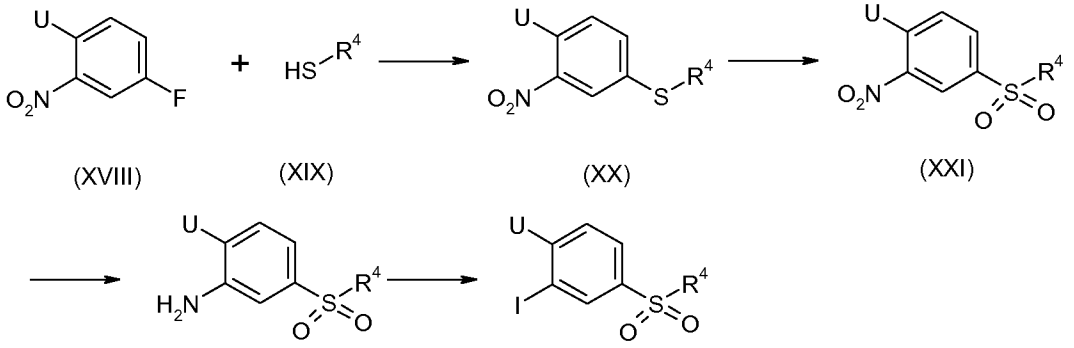
(XVI) (XII) (XVII) (XV)

Compounds of Formula (XXIII), wherein U and R^4 are as above defined, can be prepared as shown in Scheme 8. A compound of Formula (XVIII), wherein U is as defined above, can be coupled with a compound of Formula (XIX), in the presence of a suitable base, such as K_2CO_3, Cs_2CO_3, Na_2CO_3, NaOH, KOH, NaH, in a suitable solvent such as DMF, acetone, THF, DMSO in the presence of absence of water as a co-solvent, at a temperature between about 20 °C to about 150 °C, preferably at 20 °C, for a few hours, e.g. one hour to 24 h. The compounds of Formula (XX) can be oxidized as described above, to yield the corresponding compounds of Formula (XXI).

The reduction of compounds of Formula (XXI) to afford compounds of Formula (XXII) can be performed by hydrogenolysis, with an appropriate catalyst such as but not limited to Pd/C, Pt/C, PtO_2, Ni raney, in the presence of hydrogen gas or of a source of hydrogen gas such as cyclohexadiene or ammonium formiate, in the a suitable solvent such as MeOH, EtOH, EtOAc, THF, DMF. This coupling reaction can be carried out at a temperature between about 20 °C to about 100 °C, preferably at about 20 °C, for a few hours, e.g. one hour to 24 h. The reduction can also be carried out using a metal as reducing agent, such as iron or zinc, in the presence or absence of acetic acid, at a temperature between about 20 °C to about 100 °C, preferably at about 20 °C, for a few hours, e.g. one hour to 24 h.

The last step consists in the conversion of the compounds of Formula (XXII) to the corresponding compounds of Formula (XXIII), using methods well known to those skilled in the art for the conversion of an aryl or hetaryl amine to an aryl or hetaryl halide (Sandmeyer reaction and variants thereof), such as using sodium nitrite or *tert*-butyl nitrite and CuBr, CuI, KI or another suitable source of bromine or iodine, in a suitable solvent, such as an aqueous HCl solution, at a temperature between about 20 °C to about 100 °C, preferably at about 20 °C, for a few hours, e.g. one hour to 24 h.

Scheme 8



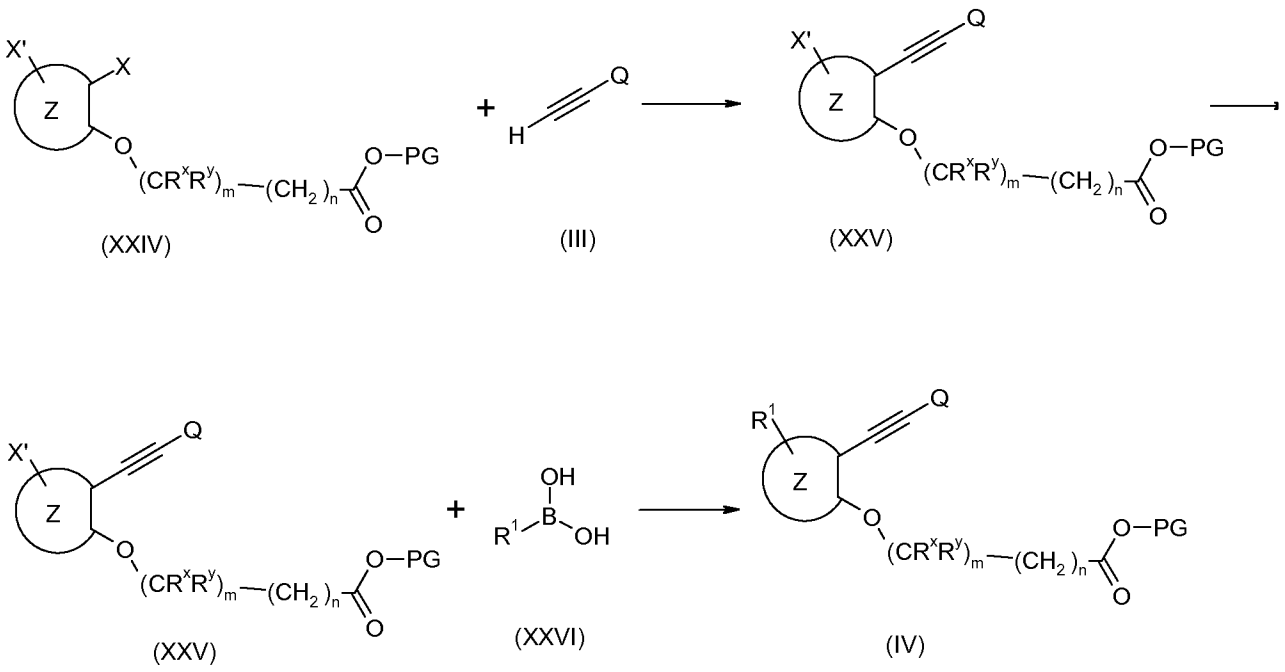
Compounds of Formula (IV), wherein Q, Z, R^1, R^x, R^y, PG, m and n are as defined above and R^1 is Ar or Het can be obtained as described in Scheme 9. Compounds of Formula (XXIV), wherein Z, R^1, R^x, R^y, PG, m and n are as defined above, and X and X' denote suitably selected halogens or a triflate group, with X being preferentially iodine and X' being preferentially bromine, can be coupled with compounds of Formula (III), wherein Q is as defined above.

General protocols for such coupling are given below in the Examples, using conditions and methods well known to those skilled in the art to perform such coupling. This reaction is preferably performed with an appropriate catalyst such as but not limited to dichlorobis(triphenylphosphine)palladium(II) or 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II), $Pd(OAc)_2$, $Pd_2(dba)_3$, $Pd(Cl)_2$ or Pd/C in the presence or absence of an additionnal ligand, such as but not limited to $P(tBu)_3$, $P(oTol)_3$, PPh_3, BINAP. The reaction can also be performed in the presence of a suitable copper salt such as but not limited to copper (I) iodide, copper (I) bromide or copper (I) chloride. The reaction can be performed in the presence or absence of bases such as TEA, DIEA, NMM, piperidine, Cs_2CO_3, sodium phosphate, in the presence or absence of a suitable solvent such as THF, ACN, DMF or acetone. This coupling

reaction can be carried out at a temperature between about 20 °C to about 100 °C, preferably at about 70 °C, for a few hours, e.g. one hour to 24 h.

Compounds of Formula (XXV) can be coupled with aryl or heteroaryl boronic acids of Formula (XXVI), wherein R^1 is Ar or Het, or the corresponding boronate esters. General protocols for such coupling are given below in the Examples, using conditions and methods well known to those skilled in the art to perform such coupling. This reaction is performed with an appropriate catalyst such as but not limited to dichlorobis(triphenylphosphine)palladium(II), $Pd(PPh_3)_4$ or 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II), $Pd(OAc)_2$, $Pd_2(dba)_3$, $Pd(Cl)_2$ or Pd/C in the presence or absence of an additionnal ligand, such as but not limited to $P(tBu)_3$, $P(oTol)_3$, PPh_3, BINAP. The reaction is performed in the presence of a base such as Cs_2CO_3, K_2CO_3, CsF, in the presence of a suitable solvent such as THF, toluene or dioxane, in the presence or absence of water as a co-solvent. This coupling reaction can be carried out at a temperature between about 20 °C to about 150 °C, preferably at about 120 °C, for a few minutes to a few hours, possibly under microwave irradiation.

Scheme 9



The above set out general synthetic methods may be modified to obtain compounds of Formula (I), since various suitable methods of preparation known by a person skilled in the art are available.

According to a further general process, compounds of Formula (I) can be converted to alternative compounds of Formula (I), employing suitable interconversion techniques well known by a person skilled in the art.

Suitable methods of preparation for the compounds and intermediates of the invention as known by a person skilled in the art should be used. In general, the synthesis pathways for any individual compound of Formula (I) will depend on the specific substitutents of each molecule and upon the ready availability of intermediates necessary; again such factors being appreciated by those of ordinary skill in the art.

General:

The HPLC data provided in the examples described below were obtained as followed.

Condition A: Column Waters Xbridge™ C_8 50 mm x 4.6 mm at a flow of 2 mL/min; 8 min gradient from 0.1 % TFA in H_2O to 0.07 % TFA in CH_3CN.

Condition B: Column Waters ACQUITY UPLC® BEH C_{18} 50 mm x 2.1 mm 1.7 µm at a flow of 1 mL/min; 3 min gradient from 95% (10 mM NH_4OAc in H_2O) / 5% CH_3CN to 100% CH_3CN.

Condition C: Column Waters ACQUITY UPLC® BEH C_{18} 50 mm x 2.1 mm 1.7 µm at a flow of 1 mL/min; 3 min gradient from 60% (10 mM NH_4OAc in H_2O) / 40% CH_3CN to 100% CH_3CN.

Condition D: Column Waters ATLANTIS® C_{18} 75 mm x 4.6 mm, 5 µm at a flow of 0.8 mL/min; gradient from 0.1 % TFA in H_2O to CH_3CN.

Condition E: Column Grace Vidac GENESIS® C_{18} 50 mm x 4.6mm 5 µm at a flow of 1.0 mL/min;gradient from 0.1 % HCOOH in H_2O to CH_3CN.

Condition F: Column Waters ATLANTIS C_{18} 75 mm x 4.6 mm, 5 µm at a flow of 1.0 mL/min; gradient from 0.1 % HCOOH in H_2O to CH_3CN.

UV detection (maxplot) for all conditions.

The MS data provided in the examples described below were obtained as followed:

Mass spectrum: LC/MS Waters ZMD (ESI) or a Waters Acquity SQD (ESI)

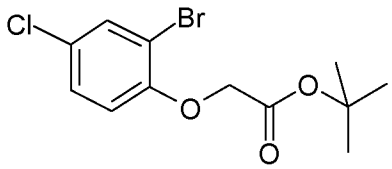
The NMR data provided in the examples described below were obtained as followed: ^{1}H-NMR: Bruker DPX-300MHz or a Bruker DPX 400 MHz.

The microwave chemistry was performed on a single mode microwave reactor Emrys™ Optimiser from Personal Chemistry

Preparative HPLC purifications were performed with a mass directed autopurification Fractionlynx from Waters equipped with a Sunfire Prep C18 OBD column 19x100 mm 5 μm, unless otherwise reported. All HPLC purifications were performed with a gradient of ACN/H_2O or ACN/H_2O/HCOOH (0.1%).

The compounds of invention have been named according to the standards used in the program „ACD/Name Batch" from Advanced Chemistry Development Inc., ACD/Labs (7.00 Release). Product version: 7.10, build: 15 Sep 2003

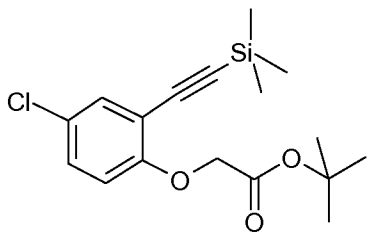
Intermediate 1: *tert*-butyl (2-bromo-4-chlorophenoxy)acetate



A solution of 2-bromo-4-chlorophenol (Aldrich; 13.11 g; 63.2 mmol) in acetone (100 mL) was treated with potassium carbonate (9.61 g; 69.5 mmol), stirred for 10 minutes then treated with *tert*-butyl bromoacetate (Aldrich; 9.34 mL; 63.2 mmol). The reaction mixture was stirred at 65 °C for 18 hours, then the mixture was filtered, the solid was washed with acetone and the filtrate was concentrated to dryness under vacuum to give the title compound as a yellow sticky solid (19.4 g, 95%).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.68 (1H, d, *J*= 2.6Hz), 7.39 (1H, dd, *J*= 9.0 Hz; *J*= 2.6 Hz), 7.37 (1H, d, *J*= 9.0 Hz), 4.80 (2H, s), 1.41 (9H, s). MS (ESI$^+$): 340.1 (M+NH_4^+). HPLC (Condition A): Rt 5.06 min (HPLC purity 96.8%).

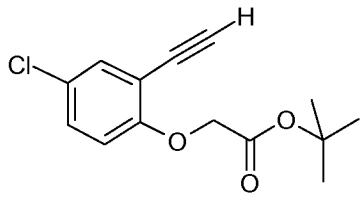
Intermediate 2: *tert*-butyl {4-chloro-2-[(trimethylsilyl)ethynyl]phenoxy}acetate



A solution of *tert*-butyl (2-bromo-4-chlorophenoxy)acetate (Intermediate 1; 19.40 g; 60.3 mmol) and 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) (2.65 g; 3.62 mmol) in THF (290 mL) was degassed during 2 minutes under nitrogen then triethylamine (12.5 mL; 91 mmol) and (trimethylsilyl)acetylene (Aldrich; 10.2 mL; 72.4 mmol) were added. The reaction mixture was stirred under nitrogen for 10 minutes before being treated with copper iodide (689 mg; 3.62 mmol) and triethlyamine (12.5 mL, 90.5 mmol) and stirred at 60 °C for 24h. The reaction mixture was filtered through Celite and the cake of Celite was washed with EtOAc. The resulting filtrate was washed with HCl 1N and brine, dried over $MgSO_4$, filtered and concentrated to dryness affording a dark brown sticky solid, which was suspended in petroleum ether (350 mL). The resulting precipitate was filtered, washed with petroleum ether (2x150 mL) and the filtrated was concentrated to dryness affording the crude product (17.7 g, 87%) as a brown oil.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.43 (1H, d, *J*= 2.7 Hz), 7.38 (1H, dd, *J*= 8.9, *J*= 2.7 Hz), 6.92 (1H, d, *J*= 8.9 Hz), 4.74 (s, 2H), 1.43 (s, 9H), 0.23 (s, 9H). MS (ESI$^+$): 356.2 (M+NH_4^+). HPLC (Condition A): Rt 6.32 min.

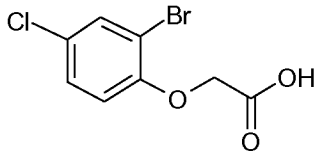
Intermediate 3: *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate



A solution of *tert*-butyl {4-chloro-2-[(trimethylsilyl)ethynyl]phenoxy}acetate (Intermediate 2, 17.70 g; 52.2 mmol) in THF (180 mL) was treated with tetrabutylammonium fluoride trihydrate (16.48 g; 52.2 mmol). The reaction mixture was stirred for 4 hours, then ethyl acetate (450 mL) was added and the organic phase was washed with water (750 mL) then with brine (750 mL), dried over $MgSO_4$, filtered and concentrated under vacuum to give a brown oily residue which was purified by flash chromatography (silica) eluting with cyclohexane containing increasing amounts of ethyl acetate. The title compound was obtained as a brown oil which solidified after prolonged standing.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.47 (1H, d, *J*= 2.7 Hz), 7.39 (1H, dd, *J*= 9.0, *J*= 2.7 Hz), 6.93 (1H, d, *J*= 9.0 Hz), 4.77 (2H, s), 4.39 (1H, s), 1.42 (9H, s). MS (ESI$^+$): 267.1. HPLC (Condition A): Rt 4.79 min (HPLC purity 95.5%).

Intermediate 4: (2-bromo-4-chlorophenoxy)acetic acid

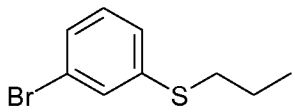


A cooled (0 °C) solution of *tert*-butyl (2-bromo-4-chlorophenoxy)acetate (1.00 g; 3.11 mmol) in DCM (22 mL) was treated with trifluoroacetic acid (2.38 mL; 31.1 mmol). The reaction mixture was stirred at room temperature for 5 hours, the solvents were removed under vacuum to give the title compound (825 mg, quant.).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.16 (1 H, s), 7.71 (1 H, d, *J*= 2.7 Hz), 7.39 (1 H, dd, *J*= 8.9, *J*= 2.7 Hz), 7.03 (1 H, d, *J*= 8.9 Hz), 4.83 (2 H, s). MS (ESI$^-$): 264.9. HPLC (Condition A): Rt 3.56 min (HPLC purity 91.5%).

Intermediate 5: 1-(Bromomethyl)-3-(propylsulfonyl) benzene

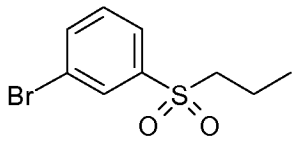
Step-1: 1-Bromo-3-(propylthio)benzene



A solution of 3-bromobenzenethiol (5.00 g, 26.4 mmol) in anhydrous DMF (30 mL) was treated with K_2CO_3 (7.30 g, 52.8 mmol) followed by 1-bromopropane (3.90 g, 31.7 mmol) and the mixture was heated to about 50 °C under nitrogen for 12h. The solvent was distilled out completely, and the residue was dissolved in DCM and washed with water and brine. The organic layer was dried over sodium sulphate and evaporated to afford 5.50 g (90%) of the title compound as pale yellow liquid.

^{1}H NMR (400MHz, $CDCl_3$) δ [ppm] 7.44 (1H, s), 7.29-7.27 (1H, m), 7.24-7.21 (1H, m), 7.15-7.11 (1H, m), 2.90 (2H, t) 1.64-1.73 (2H, m), 1.04 (3H, t).

Step-2: 1-(Bromomethyl)-3-(propylsulfonyl) benzene



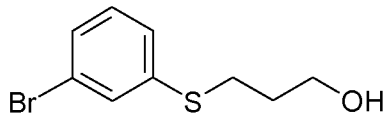
A solution of 1-bromo-3-(propylthio) benzene (5.50 g, 23.7 mmol) in DCM (75 mL) was treated with *m*-chloroperbenzoic acid (12.3 g, 71.3 mmol) and stirred at RT for 5h. The solid formed was filtered off and the filtrate was washed with 10% solution of sodium

bicarbonate, water and brine. The organic layer was dried over Na_2SO_4 and evaporated to afford 5.7 g (91%) of the title compound as yellow liquid.

^{1}H NMR (400MHz, $CDCl_3$) δ [ppm] 8.05 (1H, s), 7.85-7.83 (1H, m), 7.80-7.77 (1H, m), 7.45 (1H, t), 3.10-3.06 (2H, m), 1.80-1.71 (2H, m), 1.02 (3H, t). HPLC (Condition D): Rt 3.54 min (HPLC purity 97.4%).

Intermediate 6: 3-[(3-bromophenyl)sulfonyl]propan-1-ol

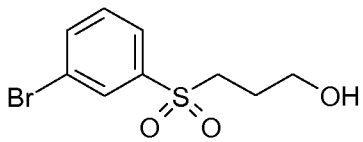
Step-1: 3-[(3-Bromophenyl)thio]propan-1-ol



A solution of 3-bromobenzenethiol (5.00 g, 26.4 mmol) in anhydrous DMF (30 mL) was treated with Cs_2CO_3 (17.2 g, 52.9 mmol) followed by 3-bromopropan-1-ol (4.40 g, 31.6 mmol). The mixture was heated to 50 °C under nitrogen for 12h. DMF was distilled out completely, and the residue was dissolved in DCM and washed with water, brine and dried over Na_2SO_4. The solvent was evaporated to afford 6.4 g (98%) of the title compound as pale yellow liquid.

^{1}H NMR (400MHz, $CDCl_3$) δ [ppm] 7.46 (1H, s), 7.30-7.25 (2H, m), 7.16-7.12 (1H, m), 3.78 (2H, t), 3.07-2.99 (2H, m) 1.93-1.87 (2H, m). MS (ESI^-): 247.1. HPLC (Condition E): Rt 3.36 min.

Step-2: 3-[(3-bromophenyl)sulfonyl]propan-1-ol

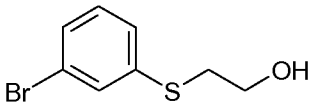


A solution of 3-[(3-bromophenyl) thio] propan-1-ol (7.00 g, 49.2 mmol) in DCM (75 mL) was treated with *m*-chloroperbenzoic acid (25.4 g, 148 mmol) and stirred at RT for 5 h. The solid formed was removed by filtration and the filtrate was washed with sodium-bicarbonate solution, water and brine. Organic layer was dried over Na_2SO_4 and evaporated to afford 6.7 g (93%) of the title compound as yellow semi-solid.

^{1}H NMR (400MHz, $CDCl_3$) δ [ppm] 8.06 (1H, s), 7.85 (1H, dd), 7.79 (1H, dd), 7.46 (1H, dd), 3.76-3.73 (2H, m), 3.27-3.23 (2H, m), 2.02-1.97 (2H, m). MS (ESI^+): 281.1. HPLC (Condition E): Rt 3.15 min (HPLC purity 99.3%).

Intermediate 7: 2-[(3-Bromophenyl)sulfonyl]ethanol

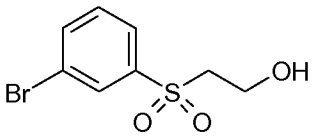
Step-1: 2-[(3-Bromophenyl) thio] ethanol



A solution of 3-bromobenzenethiol (5.00 g, 26.4 mmol) in anhydrous DMF (30 mL) was treated with Cs_2CO_3 (17.2 g, 52.8 mmol) and 2-bromoethanol (3.90 g, 31.7mol) and heated to about 50 °C under nitrogen for 12h. DMF was distilled out completely and the residue was dissolved in DCM and washed with water and brine. Organic layer was dried over Na_2SO_4, evaporated and purified by column chromatography (silica) to afford 5.5 g (90%) of the title compound as pale yellow solid.

^{1}H NMR (400MHz, $CDCl_3$) δ [ppm] 7.53 (1H, s), 7.36(1H, m), 7.34 (1H, m), 7.16 (1H, t), 3.78 (2H, t), 3.14 (2H, t). MS (ESI^-): 217.1. HPLC (Condition F): Rt 3.87 min (HPLC purity 99.8%).

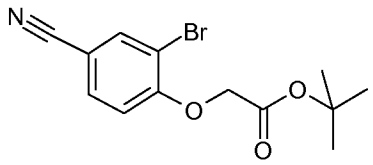
Step-2: 2-[(3-Bromophenyl)sulfonyl]ethanol



A solution of 2-[(3-bromophenyl) thio] ethanol (5.50 g, 23.5 mmol) in DCM (75 mL) was treated with *m*-chloroperbenzoic acid (12.2 g, 70.7 mmol) and stirred at RT for 5h. The solid formed was filtered and washed with cold DCM and the filtrate was washed with 10% sodium hydroxide, water and brine. Organic layer was dried over Na_2SO_4, evaporated and passed through column chromatography using silica gel (60-120 mesh) to afford the title compound as off white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ [ppm] 8.04 (1H, s), 7.94-7.88 (2H, m), 7.61-7.53 (1H, m), 4.89 (1H, t), 3.70-3.66 (2H, m), 3.52 (2H, t). MS (ESI^+): 310.6. HPLC (Condition F): Rt 2.04 min (HPLC purity 95.6%).

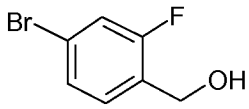
Intermediate 8: *tert*-butyl (2-bromo-4-cyanophenoxy)acetate



A solution of 3-bromo-4-hydroxybenzonitrile (Lancaster; 3.00 g; 15.2 mmol) in acetone (30 mL) was treated with potassium carbonate (2.30 g; 16.7 mmol), stirred for 10 minutes then treated with *tert*-butyl bromoacetate (2.24 mL; 15.2 mmol). The reaction mixture was stirred at 65 °C for 18 hours, then the mixture was filtered, the solid was washed with acetone and the filtrate was concentrated to dryness under vacuum to give the title compound as a yellow sticky solid (4.75 g, quant).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.18 (1 H, d, *J*= 2.0 Hz), 7.84 (1 H, dd, *J*= 8.7, 2.0 Hz), 7.17 (1 H, d, *J*= 8.7 Hz), 4.95 (2 H, s), 1.42 (9 H, s).

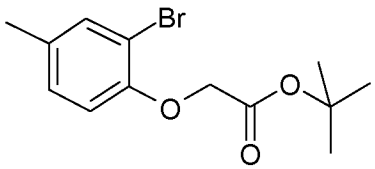
Intermediate 9: (4-bromo-3-fluorophenyl)methanol



A cooled (0 °C) suspension of lithium aluminum hydride (88 mg; 2.3 mmol) in anhydrous THF (10 mL) was treated dropwise with a solution of methyl 4-bromo-3-fluorobenzoate (Combi-Blocks; 300 mg; 1.29 mmol) dissolved in anhydrous Et_2O (10 mL), and the reaction mixture was stirred at RT for 2 days. The reaction mixture was treated with a saturated aqueous solution of sodium thiosulfate. The organic phase was separated, dried over $MgSO_4$, filtered and concentrated to dryness affording the title compound as a yellow liquid (247 mg, 94%).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.64 (1H, dd, *J*= 8.1, *J*= 7.5 Hz), 7.28 (1H, m), 7.11 (1H, m), 5.40 (1H, t, *J*= 5.8 Hz), 4.48 (2H, d, *J*= 5.8 Hz). HPLC (Condition A): Rt 2.78 min (HPLC purity 90.2%).

Intermediate 10: *tert*-butyl (2-bromo-4-methylphenoxy)acetate

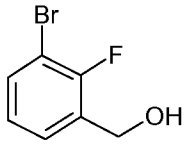


A solution of 2-bromo-4-methylphenol (Alfa; 3.00 g; 16.0 mmol) in acetone (30 mL) was treated with potassium carbonate (2.44 g; 17.6 mmol), stirred for 10 minutes then treated

with *tert*-butyl bromoacetate (2.37 mL; 16.0 mmol). The reaction mixture was stirred at 65 °C for 18 hours, then the mixture was filtered, the solid was washed with acetone and the filtrate was concentrated to dryness under vacuum to give the title compound as a pale yellow liquid (4.8 g, 99%).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.18 (1 H, d, *J*= 2.1 Hz), 7.84 (1 H, dd, *J*= 8.7, 2.1 Hz), 7.17 (1 H, d, *J*= 8.7 Hz), 4.95 (2 H, s), 2.23 (3H, s), 1.42 (9 H, s). MS (ESI$^+$): 320.1 (M+NH_4^+).

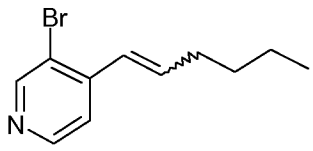
Intermediate 11: (3-bromo-2-fluorophenyl)methanol



A cooled (0 °C) solution of 3-bromo-2-fluorobenzoic acid (Fluorochem; 500 mg; 2.28 mmol) in anhydrous THF (4 mL) was slowly treated with borane-tetrahydrofuran complex (3.42 mL; 1.00 M; 3.42 mmol) and the resulting solution was stirred at RT for 2 days. Borane-tetrahydrofuran complex (3.42 mL; 1.00 M; 3.42 mmol) was added and the reaction mixture was stirred at RT for a further 3 hours. The reaction was carefully quenched with water and the mixture was concentrated. The residue was dissolved in Et_2O, and the aqueous phase was saturated with K_2CO_3. The organic layer was separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with water and brine, dried over $MgSO_4$ and concentrated to dryness affording the title compound as a colorless oil.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.60 (1H, m), 7.45 (1H, m), 7.15 (1H, t, *J*= 7.1 Hz), 5.42 (1H, s), 4.57 (2H, s). HPLC (Condition A): Rt 2.67 min (HPLC purity 97.6%).

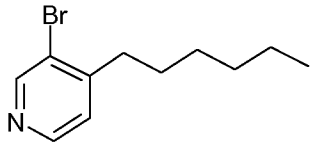
Intermediate 12: 3-bromo-4-(hex-1-en-1-yl)pyridine



A cooled (0 °C) suspension of *n*-pentyl-triphenylphosphonium bromide (Acros; 1200 mg; 2.90 mmol) in anhydrous THF (20 mL) was slowly treated with a solution (1.6 M) of butyllithium in hexane (2 700 µL; 4.35 mmol). The mixture was stirred for 1 hour, then a solution of 3-bromo-4-pyridinecarboxaldehyde (Aldrich; 567 mg; 3.05 mmol) in

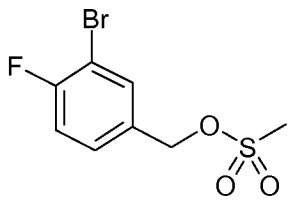
anhydrous THF (10 mL) was added. After stirring for one hour, the reaction was quenched by addition of a saturated aqueous solution of ammonium chloride. After addition of EtOAc the phases were separated and the organic phase washed with brine, dried over $MgSO_4$ and concentrated under vacuum to afford a crude product, which was purified by column chromatography, eluting with cyclohexane containing increasing amounts of EtOAc to afford the title compound as a mixture of cis and trans isomers. MS (ESI^-): 240.1.

Intermediate 13: 3-bromo-4-hexylpyridine



A mixture of 3-bromo-4-(hex-1-en-1-yl)pyridine (Intermediate 12; 360 mg; 1.50 mmol) and platinum dioxide (34 mg; 0.15 mmol) in EtOAc (35 mL) was hydrogenated at 7 atm for 1 hour in a PARR apparatus. The reaction mixture was filtered, evaporated and purified by flash column chromatography, eluting with cyclohexane containing increasing amounts of EtOAc, affording the title compound as a colorless liquid.
^1H NMR (300MHz, DMSO-d_6) δ [ppm] 8.67 (1H, s), 8.45 (1H, d, *J*= 5.0 Hz), 7.40 (1H, d, *J*= 5.0 Hz), 2.70 (2H, t, *J*= 7.8 Hz), 1.52-1.62 (2H, m), 1.28-1.34 (6H, m), 0.87 (3H, t, *J*= 7.0 Hz). MS (ESI^+): 242.1. HPLC (Condition A): Rt 3.79 min (HPLC purity 98.0%).

Intermediate 14: 3-bromo-4-fluorobenzyl methanesulfonate

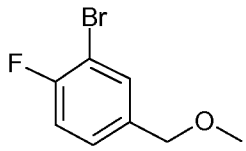


A cooled (-20 °C) solution of 3-bromo-4-fluorobenzyl alcohol (Oakwood; 500 mg; 2.44 mmol) and methanesulfonyl chloride (123 µL; 1.59 mmol) in DCM (5 mL) was treated with a solution of triethylamine (255 µL; 1.83 mmol) in DCM (2.5 mL). The reaction mixture was allowed to warm to RT and stirred for 30 minutes before being quenched with water. The phases were separated and the organic phase was washed with HCl (0.1N in water) and brine, dried over $MgSO_4$, filtered and concentrated to dryness affording a residue, which was purified by flash column chromatography), eluting with

cyclohexane containing increasing amounts of EtOAc, to give the title compound as a colorless liquid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.84 (1H, dd, *J*= 6.7, *J*= 2.1 Hz), 7.54 (1H, ddd, *J*= 8.7, *J*= 4.9, *J*= 2.1 Hz), 7.45 (1H, d, *J*= 8.7 Hz), 5.25 (2H, s), 3.27 (3H, s).

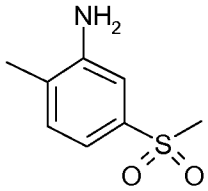
Intermediate 15: 2-bromo-1-fluoro-4-(methoxymethyl)benzene



A solution of 3-bromo-4-fluorobenzyl methanesulfonate (Intermediate 14, 330 mg; 1.17 mmol) and 2,6-lutidine (176 µL; 1.52 mmol) in methanol (4 mL) was stirred for 16 hours at RT. Additional aliquots of 2,6-lutidine (176 µL; 1.52 mmol each) were added once a day for a total of three days, during which stirring was continued at RT. The mixture was taken up in Et_2O, washed with water, HCl (0.1N in water) and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated with moderate vacuum and without heating affording the title compound as a pale yellow liquid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.66 (1H, d, *J*= 7.3 Hz), 7.38 (2H, m), 4.41 (2H, s), 3.30 (3H, s).

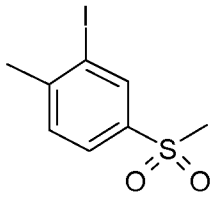
Intermediate 16: 2-methyl-5-(methylsulfonyl)aniline



A mixture of 4-methylsulfonyl-2-nitrotoluene (Alfa; 4.00 g; 18.6 mmol) and platinum oxide (120 mg; 0.53 mmol) in EtOAc (200 mL) was hydrogenated in a PARR apparatus at 5 atm for 75 minutes. The mixture was filtered through a pad of celite and the solvent was evaporated to afford the title compound as a colorless oil (3.41 g, 99%).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.16 (1 H, d, *J*= 7.8 Hz), 7.11 (1 H, d, *J*= 1.9 Hz), 6.95 (1 H, dd, *J*= 7.7, 1.9 Hz), 5.42 (2 H, bs), 3.07 (3 H, s), 2.12 (3 H, s). MS (ESI$^+$): 186.1.

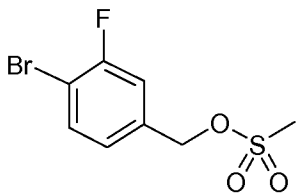
Intermediate 17: 2-iodo-1-methyl-4-(methylsulfonyl)benzene



A cooled (0 °C) solution of 2-methyl-5-(methylsulfonyl)aniline (Intermediate 16; 556 mg; 3.00 mmol) in aqueous hydrogen chloride (5 M, 10 mL; 50 mmol) was treated with sodium nitrite (248 mg; 3.60 mmol) and the resulting mixture was stirred at 0 °C for 30 minutes, before being treated with a solution of potassium iodide (4.98 g; 30 mmol) in water (8 mL). The resulting mixture was stirred at RT for 1 hour, the EtOAc was added and the phases separated. The organic layer was washed twice with an aqueous, saturated sodium thiosulfate solution, then with brine, dried over $MgSO_4$ and concentrated to afford a residue which was purified by column chromatography, eluting with cyclohexane containing increasing amounts of EtOAc to afford the title compound (649 mg, 73%) as a colorless liquid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.28 (1 H, d, *J*= 2.0 Hz), 7.85 (1 H, dd, *J*= 8.0, 2.0 Hz), 7.60 (1 H, d, *J*= 8.0 Hz), 3.24 (3 H, s), 2.47 (3 H, s). HPLC (Condition A): Rt 3.23 min (HPLC purity 100%).

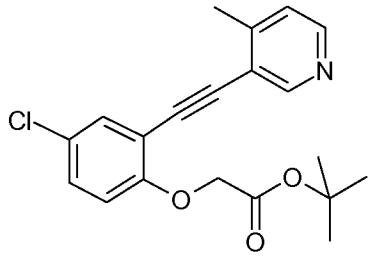
Intermediate 18: 4-bromo-3-fluorobenzyl methanesulfonate



A cooled (0 °C) solution of (4-bromo-3-fluorophenyl)methanol (Intermediate 9; 299 mg; 1.46 mmol) and methanesulfonyl chloride (147 µL; 1.90 mmol) in DCM (3 mL) was treated slowly with a solution of triethylamine (305 µL; 2.19 mmol) in DCM (1.5 mL). The reaction mixture was allowed to warm to RT and stirred for 45 minutes before being quenched by addition of water. The organic phase was washed with HCl (0.1N in water) and brine, dried over $MgSO_4$, filtered and concentrated to dryness affording a residue, which was purified by flash column chromatography, eluting with cyclohexane containing increasing amounts of EtOAc to give the title compound as a colourless liquid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.77 (1H, dd, *J*= 8.2, *J*= 7.5 Hz), 7.48 (1H, dd, *J*= 9.7, *J*= 2.0 Hz), 7.26 (1H, dd, *J*= 8.2, *J*= 2.0 Hz), 5.26 (2H, s), 3.27 (3H, s).

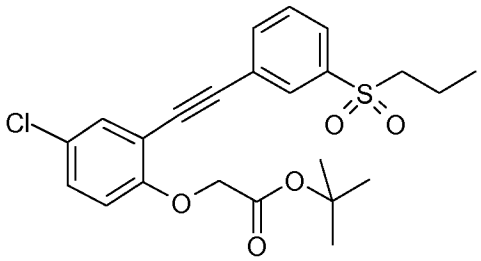
Intermediate 19: *tert*-butyl {4-chloro-2-[(4-methylpyridin-3-yl)ethynyl]phenoxy}acetate



A mixture of 3-bromo-4-methylpyridine (Apollo; 355 mg; 2.06 mmol), *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (Intermediate 3, 500 mg; 1.87 mmol), dichlorobis(triphenylphosphine)palladium(II) (82 mg; 0.11 mmol), copper(I) iodide (21 mg; 0.11 mmol) was degassed during two minutes under nitrogen then THF (7.5 mL) and triethylamine (520 µL; 3.75 mmol) were added and reaction mixture was stirred at 60 °C for 16 hours. The solvents were removed under vacuum affording a dark brown residue, which was purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc. The title compound was obtained as a dark brown sticky solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.63 (1H, s), 8.44 (1H, d, *J*= 5.0 Hz), 7.61 (1H, d, *J*= 2.6 Hz), 7.44 (1H, dd, *J*= 9.0, *J*= 2.6 Hz), 7.38 (1H, d, *J*= 5.0 Hz), 7.02 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s), 2.48 (3H, s), 1.43 (9H, s). MS (ESI$^+$): 358.3. HPLC (Condition A): Rt 3.74 min (HPLC purity 99.8%).

Intermediate 20: *tert*-butyl {4-chloro-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate

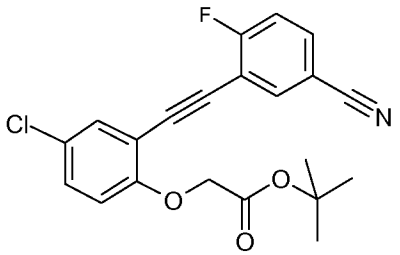


A mixture of 1-bromo-3-(propane-1-sulfonyl)-benzene (Intermediate 5; 493 mg, 1.87 mmol), *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (Intermediate 3, 500 mg; 1.87 mmol), dichlorobis(triphenylphosphine)palladium(II) (52 mg; 0.07 mmol) and piperidine (550 µL; 5.6 mmol) was heated at 70 °C for 18 hours. The reaction mixture was taken up

in EtOAc, washed twice with citric acid (0.5 M aqueous solution) and once with brine. The organic phase was dried over $MgSO_4$, filtered and concentrated to dryness affording a crude, which was purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc. The title compound was obtained as a dark orange sticky solid (640 mg, 76%).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.04 (1 H, t, *J*= 1.7 Hz), 7.96-7.88 (2 H, m), 7.75 (1 H, t, *J*= 7.8 Hz), 7.67 (1 H, d, *J*= 2.7 Hz), 7.47 (1 H, dd, *J*= 9.0, 2.7 Hz), 7.03 (1 H, d, *J*= 9.0 Hz), 4.84 (2 H, s), 3.42-3.34 (2 H, m), 1.66-1.51 (2 H, m), 1.51-1.37 (9 H, m), 0.94 (3 H, t, *J*= 7.4 Hz). MS (ESI$^+$): 466.3 (M+NH_4^+). HPLC (Condition A): Rt 5.48 min (HPLC purity 94.5%).

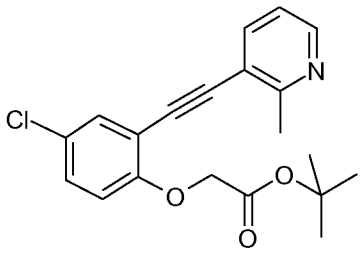
Intermediate 21: *tert*-butyl {4-chloro-2-[(5-cyano-2-fluorophenyl)ethynyl]phenoxy}acetate



Following the general method as outlined in Intermediate 19, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (Intermediate 3) and 3-bromo-4-fluorobenzonitrile (ABCR), the title compound was obtained as a beige solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.22 (1H, dd, *J*= 6.7, *J*= 2.3 Hz), 8.01 (1H, m), 7.58-7.64 (2H, m), 7.48 (1H, dd, *J*= 9.0, *J*= 2.7 Hz), 7.02 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 1.43 (9H, s). MS (ESI$^+$): 403.2 (M+NH_4^+). HPLC (Condition A): Rt 5.47 min (HPLC purity 99.4%).

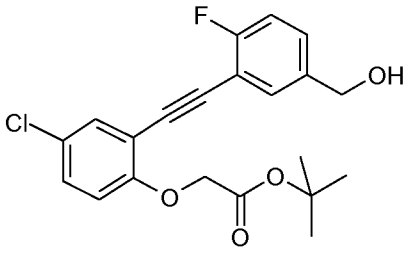
Intermediate 22: *tert*-butyl {4-chloro-2-[(2-methylpyridin-3-yl)ethynyl]phenoxy}acetate



Following the general method as outlined in Intermediate 19, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (Intermediate 3) and 3-bromo-2-methylpyridine (Synchem-OHG), the title compound was obtained as a yellow sticky solid after purification by preparative HPLC.

MS (ESI^+): 358.2. HPLC (Condition C): Rt 2.24 min (HPLC purity 100%).

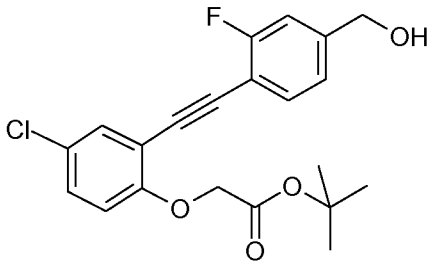
Intermediate 23: *tert*-butyl (4-chloro-2-{[2-fluoro-5-(hydroxymethyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 19, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (Intermediate 3) and 3-bromo-4-fluorobenzyl alcohol (Oakwood), the title compound was obtained as a dark brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

MS (ESI^+): 408.3 ($M+NH_4^+$). HPLC (Condition A): Rt 7.81 min (HPLC purity 97.2%).

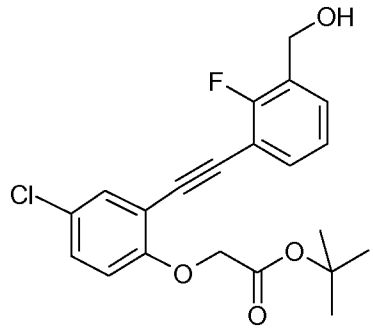
Intermediate 24: *tert*-butyl (4-chloro-2-{[2-fluoro-4-(hydroxymethyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 19, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (Intermediate 3) and (4-bromo-3-fluorophenyl)methanol (Intermediate 9), the title compound was obtained as a dark brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

MS (ESI^+): 408.3 ($M+NH_4^+$). HPLC (Condition C): Rt 2.16 min (HPLC purity 100%).

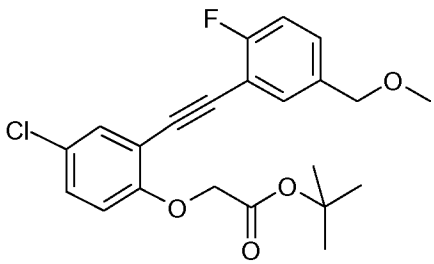
Intermediate 25: *tert*-butyl (4-chloro-2-{[2-fluoro-3-(hydroxymethyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 19, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (Intermediate 3) and (3-bromo-2-fluorophenyl)methanol (Intermediate 11), the title compound was obtained as a dark brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

MS (ESI^+): 408.3. HPLC (Condition C): Rt 1.62 min (HPLC purity 100%).

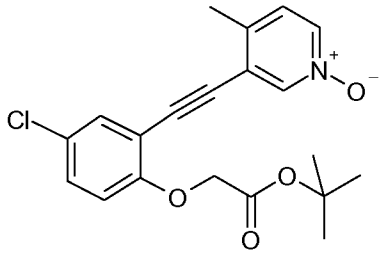
Intermediate 26: *tert*-butyl (4-chloro-2-{[2-fluoro-5-(methoxymethyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 19, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (Intermediate 3) and 2-bromo-1-fluoro-4-(methoxymethyl)benzene (Intermediate 15), the title compound was obtained as a dark yellow sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

MS (ESI^+): 422.3.

Intermeditate 27: *tert*-butyl {4-chloro-2-[(4-methyl-1-oxidopyridin-3-yl)ethynyl]phenoxy}acetate

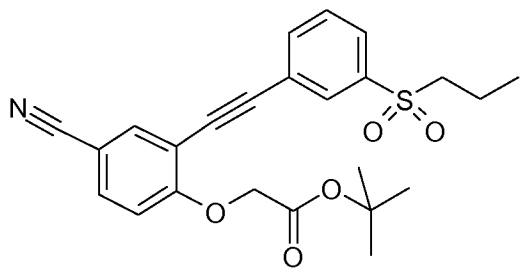


A solution of *tert*-butyl {4-chloro-2-[(4-methylpyridin-3-yl)ethynyl]phenoxy}acetate (Intermediate 19; 110 mg; 0.31 mmol) in DCM (5 mL) was treated with 3-chloroperbenzoic acid (91 mg; 0.37 mmol) and stirred at RT for 2 hours. The solvents were removed under vacuum, the residue was taken up in EtOAc and the organic phase washed with a saturated bicarbonate solution twice, then with brine. The organic layer was then dried over $MgSO_4$ and concentrated under vacuum to afford the title compound (110 mg, 96%) as a white solid.

^1H NMR (300MHz, DMSO-d_6) δ [ppm] 8.26 (1 H, d, *J*= 1.9 Hz), 8.01 (1 H, dd, *J*= 6.6, 1.9 Hz), 7.41 (1 H, d, *J*= 2.6 Hz), 7.22 (1 H, dd, *J*= 8.9, 2.6 Hz), 7.06 (1 H, d, *J*= 6.6 Hz), 6.66 (1 H, d, *J*= 8.9 Hz), 4.53 (2 H, s), 2.44 (3 H, s), 1.41 (9 H, s). MS (ESI^+): 374.2.

HPLC (Condition A): Rt 4.27 min (HPLC purity 92.2%).

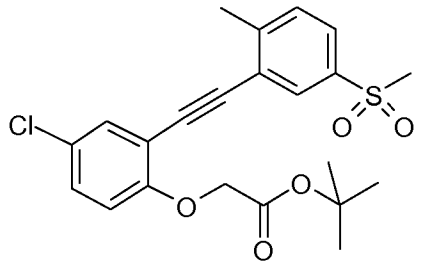
Intermediate 28: *tert*-butyl (4-cyano-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 8) and 1-bromo-3-(propane-1-sulfonyl)-benzene (Intermediate 5), the title compound was obtained as a colourless oil after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.11 (1 H, d, *J*= 2.1 Hz), 8.04 (1 H, s), 7.98-7.85 (3 H, m), 7.75 (1 H, t, *J*= 7.8 Hz), 7.19 (1 H, d, *J*= 8.8 Hz), 4.96 (2 H, s), 3.38 (2 H, m), 1.63-1.49 (2 H, m), 1.44 (9 H, s), 0.93 (3 H, t, *J*= 7.4 Hz). MS (ESI$^+$): 457.3. HPLC (Condition A): Rt 4.95 min (HPLC purity 88.4%).

Intermediate 29: *tert*-butyl (4-chloro-2-{[2-methyl-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate

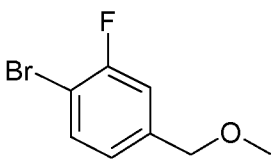


Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 2-iodo-1-methyl-4-(methylsulfonyl)benzene (Intermediate 17), the title compound was obtained as a colorless oil after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.01 (1 H, d, *J*= 2.0 Hz), 7.85 (1 H, dd, *J*= 8.0, 2.0 Hz), 7.65 (1 H, d, *J*= 2.7 Hz), 7.63 (1 H, d, *J*= 8.0 Hz), 7.46 (1 H, dd, *J*= 9.0, 2.7 Hz), 7.04 (1 H, d, *J*= 9.0 Hz), 4.83 (2 H, s), 3.25 (3 H, s), 2.58 (3 H, s), 1.43 (9 H, s). MS (ESI$^+$): 452.3. HPLC (Condition A): Rt 5.23 min (HPLC purity 94.8%).

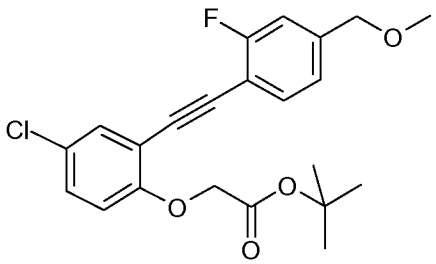
Intermediate 30: *tert*-butyl (4-chloro-2-{[2-fluoro-4-(methoxymethyl)phenyl]ethynyl}phenoxy)acetate

Step-1: 1-bromo-2-fluoro-4-(methoxymethyl)benzene



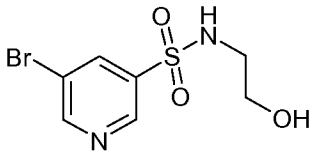
A solution of 4-bromo-3-fluorobenzyl methanesulfonate (Intermediate 18, 286 mg; 1.01 mmol) and 2,6-lutidine (234 µL; 2.0 mmol) in methanol (4 mL) was stirred for 16 hours at RT. Additional aliquots of 2,6-lutidine (234 µL; 2.0 mmol each) were added once a day for a total of three days, during which stirring was continued at RT. The mixture was taken up in Et_2O, washed with water, HCl (0.1N in water) and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated with moderate vacuum and without heating affording the title compound in a mixture with ethyl ether.
HPLC (Condition C): Rt 1.34 min.

Step 2: *tert*-butyl (4-chloro-2-{[2-fluoro-4-(methoxymethyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 1-bromo-2-fluoro-4-(methoxymethyl)benzene (obtained in Step 1), the title compound was obtained as a dark orange sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.62 (1H, d, *J*= 7.7 Hz), 7.59 (1H, d, *J*= 2.6 Hz), 7.45 (1H, dd, *J*= 9.0, *J*= 2.6 Hz), 7.28 (1H, dd, *J*= 10.3, *J*= 1.4 Hz), 7.24 (1H, dd, *J*= 8.0, *J*= 1.4 Hz), 7.01 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 4.49 (2H, s), 3.34 (3H, s), 1.44 (9H, s).
MS (ESI$^+$): 422.3 (M+NH_4^+). HPLC (Condition A): Rt 5.62 min.

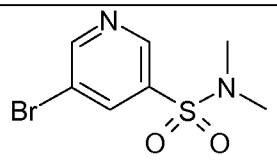
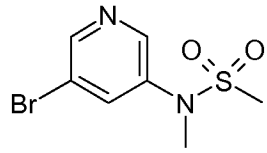
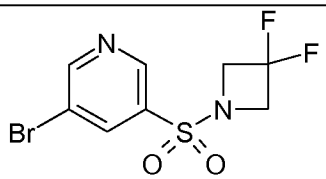
Intermediate 31: 5-bromo-*N*-(2-hydroxyethyl)pyridine-3-sulfonamide



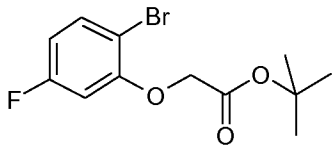
A cooled (0 °C) solution of 5-bromopyridine-3-sulfonyl chloride hydrochloride (3.00 g, 10.2 mmol) in DCM (50 ml) was slowly treated with triethylamine (4.3 ml) and stirred until a clear solution was obtained. This solution was treated dropwise with 2-hydroxyethylamine (0.68 g, 0.68 mL) and stirred at RT for 16 hours. The reaction mixture was washed successively with water and brine, the organic layer was dried with sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography (silica) eluting with 20% ethyl acetate in petroleum ether, to give the title compound.

^{1}H NMR (400MHz, DMSO-d_6) δ [ppm] 8.97 (d, *J*= 2.1 Hz, 1H), 8.91 (d, *J*= 1.9 Hz, 1H), 8.37 (t, *J*= 2.1 Hz, 1H), 7.99 (bs, 1H), 4.73 (t, *J*= 5.4 Hz, 1H), 3.39-3.32 (m, 2H), 2.90-2.86 (m, 2H). HPLC (Condition A), Rt: 2.07 (purity: 93.7%). MS (ESI$^+$): 280.8.

The compounds in the table below were all prepared following the general method as outlined in Intermediate 31:

Intermediate	**Structure**	**Chemical name**	**^{1}H NMR 300MHz, DMSO-d_6) δ [ppm]**
32		5-bromo-pyridine-3-sulfonic acid dimethylamide	9.05 (d, *J*= 2.0 Hz, 1H), 8.90 (d, *J*= 2.0 Hz, 1H), 8.39 (t, *J*= 2.0 Hz, 1H), 2.69 (s, 6H)
33		*N*-(5-bromopyridin-3-yl)-*N*-methylmethanesulfonamide	8.62-8.60 (m, 2H), 8.16 (t, *J* = 2.1 Hz, 1H), 3.28 (s, 3H), 3.05 (s, 3H)
34		3-bromo-5-[(3,3-difluoroazetidin-1-yl)sulfonyl]pyridine	MS (ESI$^+$): 313.8

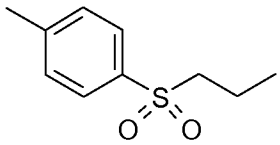
Intermediate 35: *tert*-butyl (2-bromo-5-fluorophenoxy)acetate



Following the general method as outlined in Intermediate 1, starting from 2-bromo-5-fluorophenol and *tert*-butyl bromoacetate (Aldrich), the title compound was obtained as a white solid in 95% yield.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.62 (dd, *J*= 6.3, *J*= 8.8 Hz, 1H), 6.98 (dd, *J*= 2.7, *J*= 11.0 Hz, 1H), 6.80 (ddd, *J*= 2.7; *J*= 8.3, *J*= 8.8 Hz, 1H), 4.83 (s, 2H), 1.42 (s, 9H). HPLC (Condition A) Purity 94.4%; Rt 4.7 min.

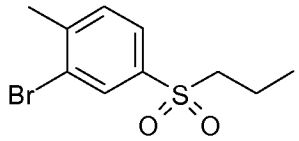
Intermediate 36: 1-methyl-4-(propylsulfonyl)benzene



A cooled (0 °C) solution of 4-methylthiophenol (Aldrich; 20.0 g; 161 mmol) in MeOH (400 ml) was treated with a 5 N solution of NaOH in water (40 mL) and with 1-iodopropane (18.0 ml; 185 mmol). The reaction was stirred at at 0 °C for 1 h then concentrated under reduced pressure. The concentrated solution was diluted with EtOAc then washed with brine. The organic phase was dried on $MgSO_4$, filtered and concentrated under reduced pressure to give a residue, which was dissolved in DCM (200 ml) and cooled to at 0 °C. This solution was treated over 20 min with a suspension of 3-chloroperbenzoic acid (83.12 g; 337.2 mmol) in DCM (600 ml). The reaction suspension was stirred at 0 °C for 3 h then treated with a further portion of 3-chloroperbenzoic acid (18.86 g; 76.52 mmol) in DCM (150 ml). The reaction was warmed to RT and stirred for 16 h. The reaction solution was filtered and the filtrate reduced in volume under reduced pressure and diluted with EtOAc, then washed twice with a 1 N solution of NaOH in water and then brine. The organic phase was dried on $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound (24.80 g, 78%) as an oil which solidified upon standing

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.76 (d, *J*= 8.1 Hz, 2H), 7.45 (d, *J*= 8.1 Hz, 2H), 3.31-3.15 (m, 2H), 2.41 (s, 3H), 1.63-1.42 (m, 2H), 0.89 (t, *J*= 7.4 Hz, 3H). HPLC (Condition A) Purity 95.4%; Rt 1.4 min.

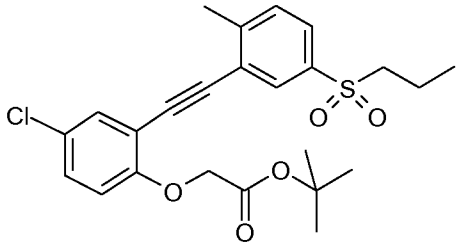
Intermediate 37: 2-bromo-1-methyl-4-(propylsulfonyl)benzene



A finely ground mixture of 1-methyl-4-(propylsulfonyl)benzene (Intermediate 36; 24.80 g; 0.13 mol) and *N*-bromosuccinimide (26.8 g; 0.15 mol) was treated with conc. sulfuric acid (115 ml; 2.15 mol). The reaction mixture was stirred for 16 h then treated with a further portion of *N*-bromosuccinimide (1.33 g; 0.01 mol). The reaction solution was stirred 1 h then carefully poured into 800 mL of crushed ice. The aqueous solution was extracted with 400 mL of AcOEt. The layers were separated and the organic phase was washed first with ca. 300 mL of brine, then twice with a 1N solution of NaOH in water and twice with brine. The organic phase was dried on $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound (29.3 g, 85%) as a brown oil which solidified upon standing.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.03 (d, *J*= 1.9 Hz, 1H), 7.80 (dd, *J*= 8.0, 1.9 Hz, 1H), 7.64 (d, *J*= 8.0 Hz, 1H), 3.39-3.28 (m, 2H), 2.45 (s, 3H), 1.63-1.47 (m, 2H), 0.92 (t, *J*= 7.4 Hz, 3H). HPLC (Condition A) Rt 3.8 min.

Intermediate 38: *tert*-butyl (4-chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate

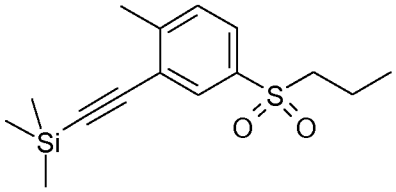


A mixture of 2-bromo-1-methyl-4-(propylsulfonyl)benzene (Intermediate 37; 14.86 g, 53.6 mmol), *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (Intermediate 3, 13.00 g; 48.7 mmol), dichlorobis(triphenylphosphine)palladium(II) (1.37 g; 1.95 mmol) and piperidine (14.5 mL) was heated at 70 °C for 18 hours. The reaction mixture was taken up in EtOAc, washed twice with ammonium chloride and once with brine. The organic phase was dried over $MgSO_4$, filtered and concentrated to dryness affording a crude, which was purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc. The compound thus obtained as a brown sticky

solid was recrystallized twice from EtOAc / petroleum ether to afford the title compound as a beige solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.95 (1H, d, *J*= 1.9 Hz), 7.80 (1H, dd, *J*= 8.0 Hz, *J*= 1.9 Hz), 7.65 (1H, d, *J*= 2.7 Hz), 7.62 (1H, d, *J*= 8.0 Hz), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 3.31 (2H, m), 2.58 (3H, s), 1.55 (2H, sext., *J*= 7.5 Hz), 1.43 (9H, s), 0.92 (3H, t, *J*= 7.5 Hz). HPLC (Condition A) Purity 98.5%; Rt 5.8 min.

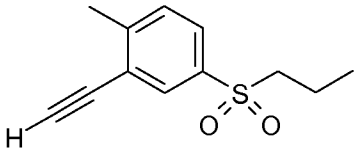
Intermediate 39: 2-Trimethylsilylethynyl-1-methyl-4-(propylsulfonyl) benzene



Following the general method as outlined in Intermediate 2, starting from 2-bromo-1-methyl-4-(propylsulfonyl)benzene (Intermediate 37) and trimethylsilylacetilene, the title compound was obtained as a brown liquid in 75% yield.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.05 (s, 1H), 7.79 (d, 1H, *J*= 8.0 Hz), 7.45 (d, 1H, *J*= 8.0 Hz), 3.07 (t, 2H, *J*= 8.0 Hz), 2.61 (s, 3H), 1.78-1.72 (m, 2H), 1.57 (s, 9H), 1.03-1.00 (t, 3H, *J*= 7.4 Hz).

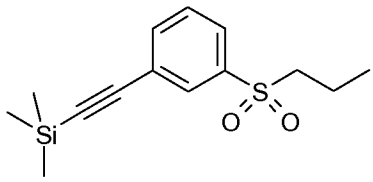
Intermediate 40: 2-ethynyl-1-methyl-4-(propylsulfonyl) benzene



Following the general method as outlined in Intermediate 3, starting from 2-trimethylsilylethynyl-1-methyl-4-(propylsulfonyl) benzene (Intermediate 39), the title compound was obtained as a brown liquid after purification by column chromatography (silica) eluting with petroleum ether and ethyl acetate.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.86 (s, 1H), 7.78 (d, 1H, *J*= 8.1 Hz), 7.57 (d, 1H, *J*= 8.1 Hz), 4.63 (s, 1H), 3.29 (t, 2H, *J*= 8 Hz), 2.48 (s, 3H), 1.56-1.54 (m, 2H), 1.51 (t, 3H, *J*= 7.6 Hz). MS (ESI$^+$): 223. HPLC (Condition A) Purity 99.7%; Rt 4.23 min.

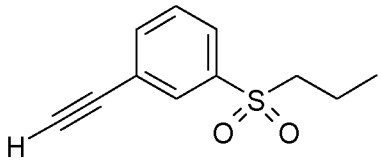
Intermediate 41: 1-(2-Trimethylsilyl-1-ethynyl)-3-(propylsulfonyl)benzene



A solution of 1-bromo-3-(propylsulfonyl) benzene (Intermediate 5; 23g, 88 mmol) in THF (450 ml) was treated with $Pd(dppf)Cl_2$ (3.9 g, 5.3 mmol), triethylamine (13.4 g, 132 mmol) and trimethylsilyl acetylene (8.64 g, 88 mmol). The reaction mixture was stirred at RT for 10 minutes, then cuprous iodide (1.0 g, 5.3 mmol) was added, the reaction mixture was heated at 60 °C for 24h. The reaction mixture was filtered to remove the solid and the filtrate was concentrated under reduced pressure. The crude material was purified by column chromatography using petroleum ether and ethyl acetate (98:2) as a eluent to afford the title compound as a brown oil.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.88 (2H, m), 7.79 (1H, t), 7.66 (1H, q), 3.34 (2H, m), 1.53 (2H, m), 0.92 (3H, t), 0.22 (9H, s).

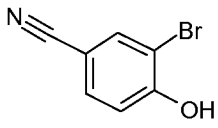
Intermediate 42: 1-Ethynyl-3-(propylsulfonyl)benzene



Following the general method as outlined in Intermediate 3, starting from 1-(2-trimethylsilyl-1-ethynyl)-3-(propylsulfonyl)benzene (Intermediate 41), the title compound was obtained as a brown liquid in 70% yield after purification by column chromatography (silica) eluting with petroleum ether and ethyl acetate.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.89 (1H, t), 7.84 (1H, p), 7.67 (1H, t), 4.45 (1H, s), 3.33 (2H, p), 1.53 (2H, m), 0.90 (3H, t). MS (ESI^+): 208.8. HPLC (Condition A) Purity 98.6%; Rt 3.89 min.

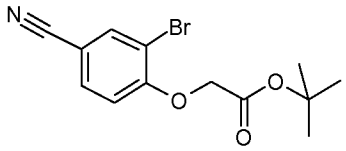
Intermediate 43: 3-Bromo-4-hydroxybenzonitrile



A solution of 4-cyanophenol (30.0 g, 252 mmol) in acetic acid (450 ml) was treated with *N*-bromosuccinimide (44.8 g, 252 mmol). The reaction mixture was stirred at RT for 18h, filtered and the filtrate was concentrated under reduced pressure. The crude material was purified by column chromatography (silica) eluting with chloroform and methanol (99:1) to afford the title compound as a brown solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 11.54 (1H, s), 8.04 (1H, d, *J*= 2.0), 7.66 (1H, dd, *J*= 2.0, *J*= 8.5), 7.06 (1H, d, *J*=8.5).

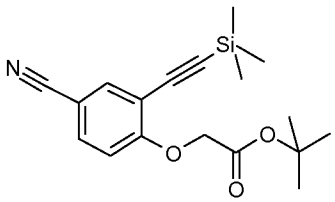
Intermediate 44: *tert*-Butyl (2-bromo-4-cyanophenoxy)acetate



A solution of 3-bromo-4-hydroxybenzonitrile (Intermediate 43; 25.0 g, 126 mmol) in anyhdrous acetone (400 ml) was treated with Potassium carbonate (20.8 g, 151 mmol) and dropwise with *tert*-butyl bromoacetate (24.5 g, 126 mmol). The reaction mixture was heated at 60 °C for 10h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The crude material was purified by column chromatography (silica) eluting with petroleum ether and ethyl acetate (90:10) to afford the title compound as a brown solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.16 (1H, d, *J*= 2.1), 7.82 (1H, dd, *J*= 2.1, *J*=8.6), 7.16 (1H, d, *J*= 8.6), 4.93 (2H, s), 1.40 (9H, s).

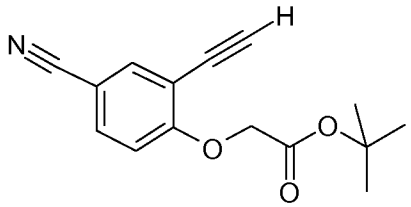
Intermediate 45: *tert*-butyl {4-cyano-2-[(trimethylsilyl)ethynyl]phenoxy}acetate



Following the general method as outlined in Intermediate 2, starting from *tert*-butyl (2-bromo-4-cyanophenoxy)acetate (Intermediate 44) and (trimethylsilyl)acetylene (Aldrich), the title compound was obtained as a dark brown sticky solid in 87% yield.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.89 (1H, d, *J*= 2.1 Hz), 7.81 (1H, dd, *J*= 2.1 Hz, *J*= 8.8 Hz), 7.09 (1H, d, *J*=8.8 Hz), 4.88 (2H, s), 1.42 (9H, s), 0.22 (9H, s).

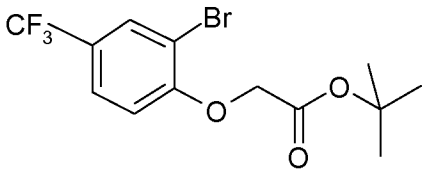
Intermediate 46: *tert*-butyl (4-cyano-2-ethynylphenoxy)acetate



Following the general method as outlined in Intermediate 3, starting from *tert*-butyl {4-cyano-2-[(trimethylsilyl)ethynyl]phenoxy}acetate (Intermediate 45), the title compound was obtained as an oil in 72% yield.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.93 (1H, d, *J*=2.1 Hz), 7.82 (1H, dd, *J*=2.1 Hz, *J*=8.8 Hz), 7.11 (1H, d, *J*=8.8 Hz), 4.89 (2H, s), 4.46(1H, s), 1.41 (9H, s). MS (ESI$^+$): 199.7. HPLC (Condition A) Purity 98.0 %; Rt 4.82 min.

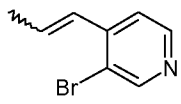
Intermediate 47: *tert*-butyl [2-bromo-4-(trifluoromethyl)phenoxy]acetate



Following the general method as outlined in Intermediate 1, starting from 2-bromo-4-(trifluoromethyl)phenol and *tert*-butyl bromoacetate (Aldrich), the title compound was obtained as a dark orange sticky solid in quantitative yield.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.99 (dd, *J*= 0.6, *J*= 2.2 Hz, 1H), 7.74 (ddd, *J*= 0.6, *J*= 2.2, *J*= 8.6 Hz, 1H), 7.19 (d, *J*= 8.6 Hz, 1H), 4.94 (s, 2H), 1.44 (s, 9H). HPLC (Condition A) Purity 92.3%; Rt 5.2 min.

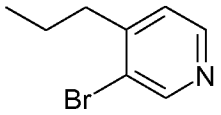
Intermediate 48: 3-bromo-4-[prop-1-en-1-yl]pyridine



Following the general method as outlined in Intermediate 12, starting from 3-bromo-4-pyridinecarboxaldehyde (Aldrich) and ethyltriphenylphosphonium bromide, the title compound (mixture of *cis* and *trans* isomers) was obtained as a colorless liquid after purification by flash column chromatography, eluting with cyclohexane containing increasing amounts of EtOAc.

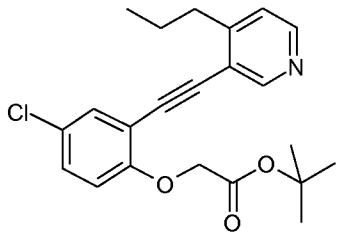
MS (ESI$^-$): 198.0

Intermediate 49: 3-bromo-4-propylpyridine



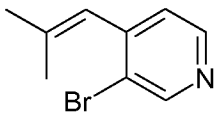
Following the general method as outlined in Intermediate 13, starting from 3-bromo-4-(prop-1-en-1-yl)pyridine (Intermediate 48), the title compound was obtained as a dark orange sticky solid in 79% yield after purification by flash column chromatography, eluting with cyclohexane containing increasing amounts of EtOAc.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.68 (s, 1H), 8.46 (d, *J*= 4.9 Hz, 1H), 7.40 (d, *J*= 4.9 Hz, 1H), 2.69 (m, 2H), 1.62 (sext., *J*= 7.5 Hz, 2H), 0.95 (t, *J*= 7.5 Hz, 3H). HPLC (Condition A) Rt 1.8 min.

Intermediate 50: *tert*-butyl {4-chloro-2-[(4-propylpyridin-3-yl)ethynyl]phenoxy}acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 3-bromo-4-propylpyridine (Intermediate 49), the title compound was obtained as a dark orange sticky solid after purification by flash column chromatography, eluting with cyclohexane containing increasing amounts of EtOAc.
MS (ESI$^+$): 386.3. HPLC (Condition A) Purity 94.1%; Rt 4.2 min.

Intermediate 51: 3-bromo-4-(2-methylprop-1-en-1-yl)pyridine

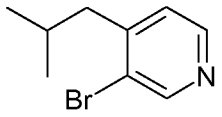


Following the general method as outlined in Intermediate 12, starting from 3-bromo-4-pyridinecarboxaldehyde (Aldrich) and isopropyltriphenylphosphonium iodide, the title

compound was obtained as a yellow liquid after purification by flash column chromatography, eluting with cyclohexane containing increasing amounts of EtOAc.

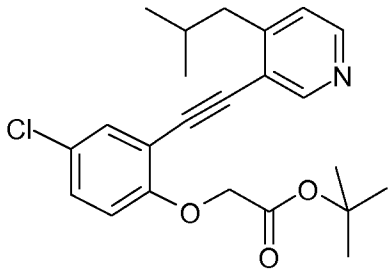
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.73 (s, 1H), 8.50 (d, *J*= 5.0 Hz, 1H), 7.36 (d, *J*= 5.0 Hz, 1H), 6.21 (s, 1H), 1.96 (d, *J*= 1.3 Hz, 3H), 1.80 (d, *J*= 1.3 Hz, 3H). HPLC (Condition A) Purity 100.0%; Rt 1.9 min.

Intermediate 52: 3-bromo-4-isobutylpyridine



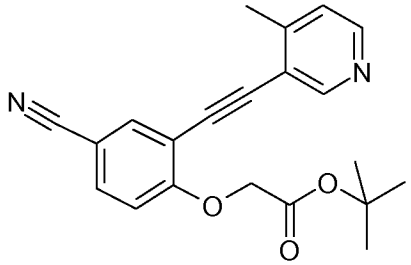
Following the general method as outlined in Intermediate 13, starting from 3-bromo-4-(2-methylprop-1-en-1-yl)pyridine (Intermediate 51), the title compound was obtained as a colorless liquid after purification by flash column chromatography, eluting with cyclohexane containing increasing amounts of EtOAc.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.69 (s, 1H), 8.46 (d, *J*= 4.9 Hz, 1H), 7.37 (d, *J*= 4.9 Hz, 1H), 2.61 (d, *J*= 7.3 Hz, 1H), 1.96 (m, 1H), 0.91 (d, *J*= 6.6 Hz, 6H). HPLC (Condition A) Rt 2.3 min.

Intermediate 53: *tert*-butyl {4-chloro-2-[(4-isobutylpyridin-3-yl)ethynyl]phenoxy}acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 3-bromo-4-isobutylpyridine (Intermediate 52), the title compound was obtained as a dark orange sticky solid after purification by preparative HPLC.
MS (ESI$^+$): 400.4. HPLC (Condition A) Purity 94.7%; Rt 4.4 min.

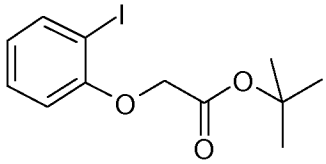
Intermediate 54: *tert*-butyl {4-cyano-2-[(4-methylpyridin-3-yl)ethynyl]phenoxy}acetate



Following the general method as outlined in Intermediate 20, starting from *tert*-butyl (4-cyano-2-ethynylphenoxy)acetate (Intermediate 46) and 3-bromo-4-methylpyridine (53), the title compound was obtained as a dark orange sticky solid after purification by flash column chromatography, eluting with cyclohexane containing increasing amounts of EtOAc.

MS (ESI^+): 349.3. HPLC (Condition A) Purity 88.7%; Rt 3.2 min.

Intermediate 55: *tert*-butyl (2-iodophenoxy)acetate

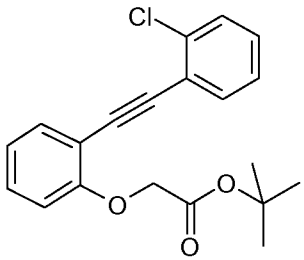


Following the general method as outlined in Intermediate 1, starting from 2-iodophenol and *tert*-butyl bromoacetate (Aldrich), the title compound was obtained as a yellow liquid in quantitative yield.

^1H NMR (300MHz, DMSO-d_6) δ [ppm] 7.80 (dd, *J*= 7.6, *J*= 1.6 Hz, 1H), 7.35 (m, 1H), 6.88 (dd, 8.3, *J*= 1.3 Hz, 1H), 6.79 (dd, *J*= 7.6, *J*= 1.3 Hz, 1H), 4.77 (s, 2H), 1.44 (s, 9H).

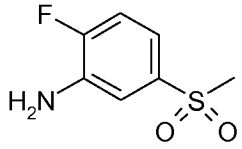
HPLC (Condition A) Purity 97.8%; Rt 4.8 min.

Intermediate 56: *tert*-butyl {2-[(2-chlorophenyl)ethynyl]phenoxy}acetate



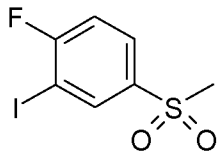
Following the general method as outlined in Intermediate 20, starting *tert*-butyl (2-iodophenoxy)acetate (Intermediate 55) and 2'-chlorophenyl acetylene (ABCR), the title compound was obtained as a dark orange sticky solid after purification by flash column chromatography, eluting with cyclohexane containing increasing amounts of EtOAc.
HPLC (Condition A) Rt 5.5 min.

Intermediate 57: 2-fluoro-5-(methylsulfonyl)aniline



A mixture of 4-fluoro-3-nitrophenyl methyl sulfone (ABCR; 1.50 g; 6.84 mmol) and 10% Pd/C (100 mg) in MeOH (30 ml) was placed in a PARR reactor and treated with a pressure of 15 atm of hydrogen for 2 hours. The reaction mixture was filtered through Celite and the filtrate was concentrated to dryness affording the title compound (1.04 g, 80%).
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.31 (dd, *J*= 2.4, *J*= 8.4 Hz, 1H), 7.26 (dd, *J*= 8.4, *J*= 11.4 Hz, 1H), 7.05 (ddd, *J*= 2.4, *J*= 4.2, *J*= 8.4 Hz, 1H), 5.75 (s, 2H), 3.14 (s, 3H).

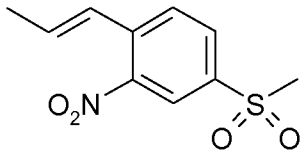
Intermediate 58: 1-fluoro-2-iodo-4-(methylsulfonyl)benzene



2-Fluoro-5-(methylsulfonyl)aniline (Intermediate 57; 500 mg; 2.64 mmol) was treated with a 5 N solution of hydrochloric acid in water (8.98 ml; 44.92 mmol) and the solution cooled to 0 °C. The solution was treated with sodium nitrite (219 mg; 3.17 mmol) and stirred at 0 °C for 30 minutes, then treated with a solution of potassium iodide (4.39 g; 26.43 mmol) in water (8 mL) and stirred at RT for 1 hour. EtOAc was added, the phases were separated and the organic phase was washed with a saturated sodium thiosulfate solution twice, then with brine. The organic phase was dried on $MgSO_4$, filtered and concentrated under reduced pressure to give a residue which was purified by by flash column chromatography, eluting with cyclohexane containing increasing amounts of EtOAc. The title compound was obtained as a white solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.37 (dd, *J*= 5.8, *J*= 2.3 Hz, 1H), 8.00 (ddd, *J*= 2.3, *J*= 4.8, *J*= 8.6 Hz, 1H), 7.56 (dd, *J*= 0.4, *J*= 8.1 Hz, 1H), 3.30 (s, 3H).

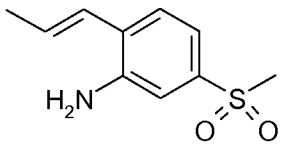
Intermediate 59: 4-(methylsulfonyl)-2-nitro-1-[(1*E*)-prop-1-en-1-yl]benzene



A mixture of 2-bromo-5-methylsulfonylnitrobenzene (1.50 g; 5.36 mmol), trans-propenylboronic acid (690 mg; 8.03 mmol), caesium fluoride (2.44 g; 16.1 mmol) and bis(triphenylphosphine)palladium(II) chloride (376 mg; 0.54 mmol) was degassed with nitrogen, then treated with dioxane (30 ml) and water (15 ml). The resulting reaction mixture was heated at 80 °C for 2 hours, taken up in EtOAc and washed with water and brine. The organic phase was dried on $MgSO_4$, filtered and concentrated under reduced pressure to give a residue which was purified by by flash column chromatography, eluting with cyclohexane containing increasing amounts of EtOAc. The title compound was obtained as an off-white solid (1.10 g, 85%).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.40 (1H, d, *J*= 1.9 Hz), 8.14 (1H, dd, *J*= 8.3 Hz, *J*= 1.9 Hz), 8.05 (1H, d, *J*= 8.3 Hz), 6.68-6.59 (2H, m), 3.32 (3H, s), 1.95 (1H, dd, *J*= 6.1 Hz, *J*= 0.9 Hz).

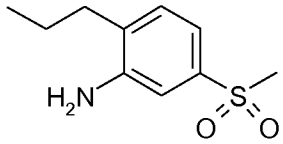
Intermediate 60: 5-(methylsulfonyl)-2-[(1*E*)-prop-1-en-1-yl]aniline



A solution of 4-(methylsulfonyl)-2-nitro-1-[(1*E*)-prop-1-en-1-yl]benzene (Intermediate 59; 1.10 g; 4.56 mmol) in AcOH (7 ml) was treated with powdered iron (3.82 g; 68.4 mmol) and the reaction mixture was stirred at 90 °C for 25 min. Further AcOH was added (20 mL), the solid was filterered off and rinsed with EtOAc. The solvents were removed under reduced pressure, the residue was taken up in EtOAc and washed with saturated $NaHCO_3$ solution twice the with brine. The organic phase was dried on $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound as a brown oil (784 mg, 81%).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.40 (1H, d, *J*= 8.0 Hz), 7.13 (1H, d, *J*= 2.0 Hz), 6.96 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 6.58 (1H, dd, *J*= 5.5 Hz, *J*= 1.6 Hz), 6.20 (1H, m), 5.60 (2H, s), 3.09 (3H, s), 1.88 (1H, dd, *J*= 6.6 Hz, *J*= 1.5 Hz).

Intermediate 61: 5-(methylsulfonyl)-2-propylaniline

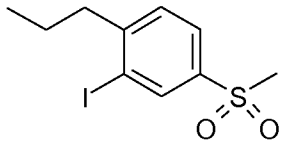


A mixture of 5-(methylsulfonyl)-2-[(1*E*)-prop-1-en-1-yl]aniline (Intermediate 60; 1.50 g; 6.84 mmol) and 10% Pd/C (196 mg) in MeOH (39 ml) was placed in a PARR reactor and treated with a pressure of 20 atm of hydrogen for 3 hours.

The reaction mixture was filtered through Celite and the filtrate was concentrated to dryness affording the title compound (600 g, 76%).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.14-7.11 (2H, m), 6.96 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 5.42 (2H, s), 3.08 (3H, s), 2.50-2.40 (2H, m), 1.60-1.48 (2H, m), 0.93 (1H, t, *J*= 7.3 Hz).

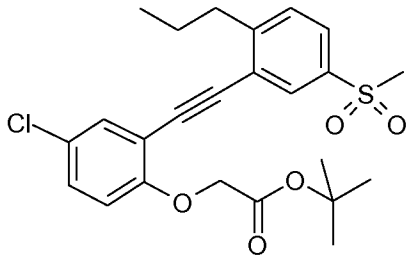
Intermediate 62: 2-iodo-4-(methylsulfonyl)-1-propylbenzene



Following the general method as outlined in Intermediate 58, starting from 5-(methylsulfonyl)-2-propylaniline (Intermediate 61), the title compound was obtained as a yellow liquid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.27 (1H, d, *J*= 2.0 Hz), 7.87 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.55 (1H, d, *J*= 8.0 Hz), 3.25 (3H, s), 2.74 (2H, m), 1.58 (2H, m), 0.96 (1H, t, *J*= 7.3 Hz).

Intermediate 63: *tert*-butyl (4-chloro-2-{[5-(methylsulfonyl)-2-propylphenyl]ethynyl}phenoxy)acetate

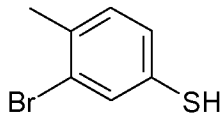


Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 2-iodo-4-(methylsulfonyl)-1-propylbenzene (Intermediate 62), the title compound was obtained as a white solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.01 (1H, d, *J*= 1.5 Hz), 7.86 (1H, dd, *J*= 8.0 Hz, *J*= 1.5 Hz), 7.62-7.59 (2H, m), 7.45 (1H, dd, *J*= 8.8 Hz, *J*= 2.0 Hz), 7.05 (1H, d, *J*= 8.8 Hz), 4.83 (2H, s), 3.26 (3H, s), 2.91 (2H, t, *J*= 7.5 Hz), 1.68 (2H, sextet, *J*= 7.5 Hz), 1.42 (9H, s), 0.94 (3H, t, *J*= 7.5 Hz).

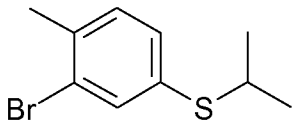
Intermediate 64: 2-bromo-4-(isopropylsulfonyl)-1-methylbenzene

Step 1: 3-bromo-4-methylbenzenethiol



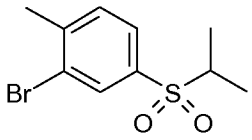
A cooled (-15 °C) solution of 3-bromo-4-methylaniline (ABCR; 2.0 g) in a 6N solution of HCl in water (30 mL) was treated drop-wise with a solution of sodium nitrite (1.78 g) in water (10 mL). The reaction mixture was stirred for 30 mins. The resulting clear solution was added dropwise to a stirred solution of *O*-ethyl xanthic acid potassium salt (6.1 g) in water (25 mL). The mixture was then heated to 80 °C for 15 minutes. The mixture was then cooled and extracted with diethyl ether twice. The solvents were evaporated under reduced pressure to give a residue, which was treated with a solution of KOH (6.1 g) in 95% ethanol (55 mL) and heated to reflux for 10 h. The reaction mixture was diluted with water and acidified with conc. HCl to pH 3 and extracted with diethyl ether. The organic layer was washed with water, brine and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel), eluting with petroleum ether. This product obtained was triturated with hexane to give the title compound (1.5g, 70%) as an off-white solid.

Step 2: 2-bromo-4-(isopropylthio)-1-methylbenzene



A stirred suspension of NaH (40 mg) in anhydrous DMF (5 mL) was treated with a solution of 3-bromo-4-methylbenzenethiol (200 mg) in anhydrous DMF (3 ml). The reaction mixture was stirred for 30 minutes at RT, then 2-iodo propane (0.14 ml) was added to the reaction mixture and the reaction mixture was heated to 55 °C for 3 hours. The reaction mixture was quenched with ice and extracted with diethylether. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (Silica gel), eluting with hexane, to give the title compounds.

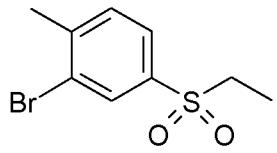
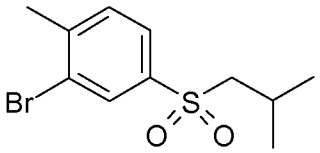
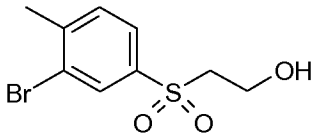
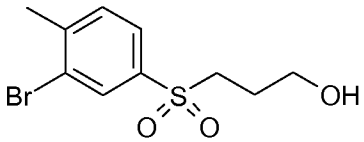
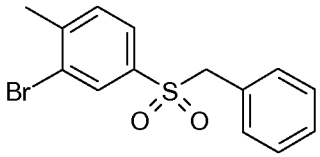
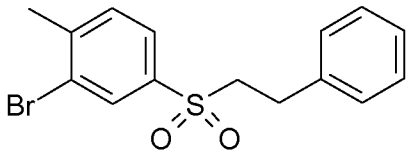
Step 3: 2-bromo-4-(isopropylsulfonyl)-1-methylbenzene



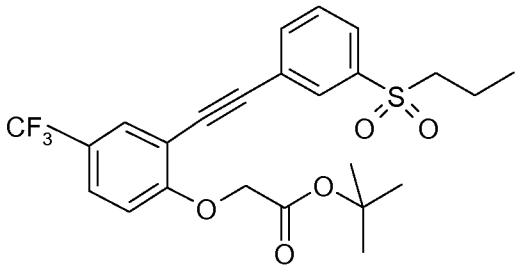
A cooled (0 °C) solution of 2-bromo-4-(isopropylthio)-1-methylbenzene (123 mg) in THF (10 ml) was treated with a solution of oxone (580 mg) in water (6 ml). The reaction mixture was stirred at RT for 16 hours.The reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over sodium sulfate and concentrated to give the title compound (120 mg, 92%).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.55 (dd, *J*= 8.4 Hz, *J*= 2.8 Hz, 1H), 7.18 (dd, *J*= 8.4 Hz, *J*= 5.8 Hz, 1H), 7.09-7.04 (m, 1H), 2.86-2.83 (m, 1H), 2.49 (s, 3H), 1.34 (d, *J*= 7.0 Hz, 3H), 1.13 (d, *J*= 6.8 Hz, 3H). MS (ESI$^+$): 294.3 $[M+NH4]^+$. HPLC (Condition A) Purity 93.0%; Rt 5.42 min.

The compounds in the table below were all prepared following the general method as outlined in Intermediate 64:

Int.	Structure	Chemical name	^{1}H NMR (400MHz) δ [ppm]
65		2-bromo-4-(ethylsulfonyl)-1-methylbenzene	8.07 (d, *J*= 1.7 Hz, 1H), 7.74 (dd, *J*= 7.9 Hz, *J*= 1.9 Hz, 1H), 7.44 (d, *J*= 7.9 Hz, 1H), 3.76 (q, *J*= 7.4 Hz, 2H), 2.50 (s, 3H), 1.29 (t, *J*= 7.4 Hz, 3H).
66		2-bromo-4-(isobutylsulfonyl)-1-methylbenzene	8.07 (d, *J*= 1.7 Hz, 1H), 7.54 (dd, *J*= 7.9 Hz, *J*= 1.8Hz, 1H), 7.42 (d, *J*= 7.9 Hz, 1H), 2.98 (d, *J*= 6.4 Hz, 2H), 2.49 (s, 3H), 2.28-2.21 (m, 1H), 1.08 (d, *J*= 6.7 Hz, 6H).
67		2-[(3-bromo-4-methylphenyl)sulfonyl]ethanol	8.03 (d, *J* = 1.8 Hz, 1H), 7.79 (dd, *J* = 8.0 Hz, *J* = 1.8 Hz, 1H), 7.61 (d, *J* = 8 Hz, 1H), 4.88 (t, *J* = 5.4 Hz, 1H), 3.67 (m, 2H), 3.49 (t, *J* = 6.0 Hz, 2H), 2.43 (s, 3H).
68		3-[(3-bromo-4-methylphenyl)sulfonyl]propan-1-ol	8.08 (d, *J*= 1.7 Hz, 1H), 7.75 (dd, *J*= 7.9 Hz, *J*= 1.8 Hz, 1H), 7.44 (d, *J*= 7.9 Hz, 1H), 3.12 (q, *J*= 5.5 Hz, 2H), 3.27-3.22 (m, 2H), 2.50 (s, 3H), 2.03-1.96 (m, 2H), 1.60 (bs, 1H).
69		4-(benzylsulfonyl)-2-bromo-1-methylbenzene	7.78 (d, *J*= 1.8 Hz, 1H), 7.43-7.40 (m, 2H), 7.36-7.28 (m, 3H), 7.13-7.10 (m, 2H), 4.31 (s, 2H), 2.46 (s, 3H).
70		2-bromo-1-methyl-4-[(2-phenylethyl)sulfonyl]benzene	δ 8.08 (d, *J*= 1.8 Hz, 1H), 7.75 (dd, *J*= 7.9 Hz, *J*= 1.8 Hz, 1H), 7.43 (d, *J*= 8.0 Hz, 1H), 7.30-7.20 (m, 2H), 7.14-7.11 (m, 2H), 3.39-3.35 (m, 2H), 3.08-3.04 (m, 2H), 2.50 (s, 3H).

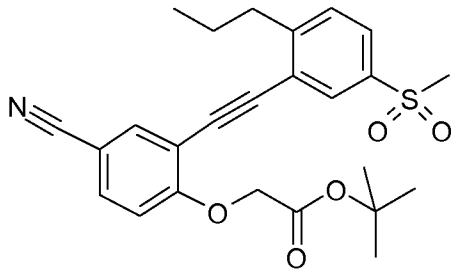
Intermediate 71: *tert*-butyl [2-{[3-(propylsulfonyl)phenyl]ethynyl}-4-(trifluoromethyl)phenoxy]acetate



Following the general method as outlined in Intermediate 20, starting from *tert*-butyl [2-bromo-4-(trifluoromethyl)phenoxy]acetate (Intermediate 35) and 1-ethynyl-3-(propane-1-sulfonyl)-benzene (Intermediate 42), the title compound was obtained as a colorless oil after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.05 (1H, m), 7.97-7.90 (3H, m), 7.79-7.72 (2H, m), 7.18 (1H, d, *J*= 8.8 Hz), 4.94 (2H, s), 3.40-3.34 (2H, m), 1.57 (2H, m), 1.45 (9H, s), 0.93 (3H, t, *J*= 7.5 Hz).

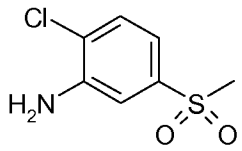
Intermediate 72: *tert*-butyl (4-cyano-2-{[5-(methylsulfonyl)-2-propylphenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 20, starting from (4-cyano-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 46) and 2-iodo-4-(methylsulfonyl)-1-propylbenzene (Intermediate 62), the title compound was obtained after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.08 (1H, d, *J*= 2.1 Hz), 8.02 (1H, d, *J*= 2.1 Hz), 7.89-7.86 (2H, m), 7.62 (1H, d, *J*= 8.1 Hz); 7.21 (1H, d, *J*= 8.8 Hz), 4.96 (2H, s), 3.27 (3H, s), 2.92 (2H, t, *J*= 7.5 Hz), 1.68 (2H, sext., *J*= 7.5 Hz), 1.43 (9H, s), 0.94 (3H, t, *J*= 7.5 Hz).

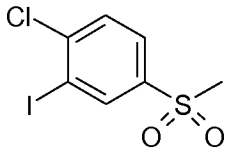
Intermediate 73: 2-chloro-5-(methylsulfonyl)aniline



Following the general method as outlined in Intermediate 61, starting from 2-chloro-5-methylsulphonylnitrobenzene, the title compound was obtained as a dark green sticky solid in quantitative yield.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.45 (d, *J*= 8.2 Hz, 1H), 7.30 (d, *J*= 2.1 Hz, 1H), 7.00 (dd, *J*= 2.1, *J*= 8.2 Hz, 1H), 5.94 (s, 2H), 3.14 (s, 3H). HPLC (Condition A) Rt 1.9 min.

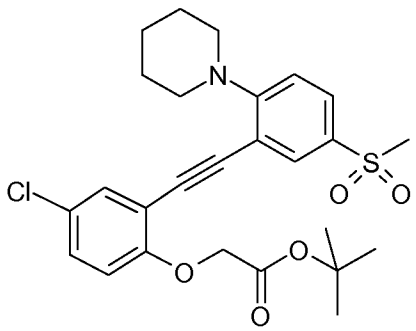
Intermediate 74: 1-chloro-2-iodo-4-(methylsulfonyl)benzene



Following the general method as outlined in Intermediate 58, starting from 2-chloro-5-(methylsulfonyl)aniline (Intermediate 73), the title compound was obtained as a white solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.39 (d, *J*= 2.1 Hz, 1H), 7.93 (dd, *J*= 2.1, *J*= 8.3 Hz, 1H), 7.85 (d, *J*= 8.3 Hz, 1H), 3.29 (s, 3H). HPLC (Condition A) Rt 3.3 min.

Intermediate 75: *tert*-butyl (4-chloro-2-{[5-(methylsulfonyl)-2-piperidin-1-ylphenyl]ethynyl}phenoxy)acetate

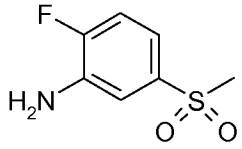


Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 1-chloro-2-iodo-4-(methylsulfonyl)benzene (Intermediate 74), the title compound was obtained as a yellow

sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.91 (d, *J*= 2.4 Hz, 1H), 7.76 (dd, *J*= 2.4, *J*= 8.8 Hz, 1H), 7.56 (d, *J*= 2.7 Hz, 1H), 7.42 (dd, *J*= 2.7, *J*= 9.0 Hz, 1. HPLC (Condition A) Rt 5.8 min.

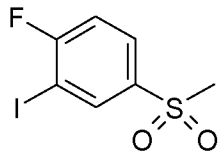
Intermediate 76: 2-fluoro-5-(methylsulfonyl)aniline



A mixture of 4-fluoro-3-nitrophenyl methyl sulfone (Acros; 1.00 g; 4.56 mmol) and PtO_2 (100 mg) in MeOH (150 ml) was placed in a PARR reactor and treated with a pressure of 20 atm of hydrogen for 3 hours. The reaction mixture was filtered through Celite and the filtrate was concentrated to dryness affording the title compound (964 mg) as a dark green oil.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.31-7.20 (2H, m), 7.03 (ddd, *J*= 8.4 Hz, *J*= 4.3 Hz, *J*= 2.4 Hz), 5.75 (s, 2H), 3.13 (s, 3H).

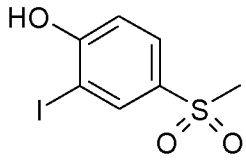
Intermediate 77: 1-fluoro-2-iodo-4-(methylsulfonyl)benzene



Following the general method as outlined in Intermediate 58, starting from 2-fluoro-5-(methylsulfonyl)aniline (Intermediate 76), the title compound was obtained as a white solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc. 2-Iodo-4-(methylsulfonyl)phenol was also isolated from the chromatography, and denominated as Intermediate 78.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.37 (dd, *J*= 5.8, *J*= 2.3 Hz, 1H), 8.00 (ddd, *J*= 2.3, *J*= 4.8, *J*= 8.6 Hz, 1H), 7.56 (dd, *J*= 0.35, *J*= 8.1 Hz, 1H), 3.30 (s, 3H)

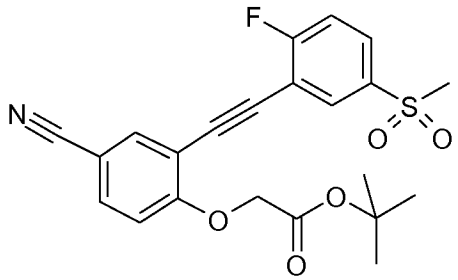
Intermediate 78: 2-iodo-4-(methylsulfonyl)phenol



The title compound was isolated as a yellow solid during the preparation of Intermediate 77.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 11.49 (s, 1H), 8.14 (d, *J*= 2.3 Hz, 1H), 7.74 (dd, *J*= 2.3, *J*= 8.5 Hz, 1H), 7.03 (d, *J*= 8.5 Hz, 1H), 3.16 (s, 3H)

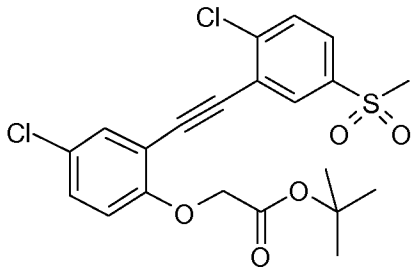
Intermediate 79: *tert*-butyl (4-cyano-2-{[2-fluoro-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate



A suspension of (4-cyano-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 46 ; 200 mg; 0.78 mmol), 1-fluoro-2-iodo-4-(methylsulfonyl)benzene (Intermediate 77 ; 233 mg; 0.78 mmol), 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) (34 mg; 0.05 mmol) and cuprous iodide (9 mg; 0.05 mmol) was degassed during 2 minutes under nitrogen then anhydrous THF (3 ml) and TEA (215 µl; 1.55 mmol) were added and the reaction mixture was stirred at 70°C for 16 hours. The solvents were removed under reduced pressure and the residue was purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc to give the title compound (260 mg, 78%) as a yellow sticky solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.20 (dd, *J*= 2.4, *J*= 6.5 Hz, 1H), 8.11 (d, *J*= 2.1 Hz, 1H), 8.02-8.07 (m, 1H), 7.91 (dd, *J*= 2.1, *J*= 9.0 Hz, 1H), 7.67 (t, *J*= 9.0 Hz, 1H), 7.19 (d, *J*= 9.0 Hz, 1H), 4.96 (s, 2H), 3.31 (s, 3H), 1.43 (s, 9H).

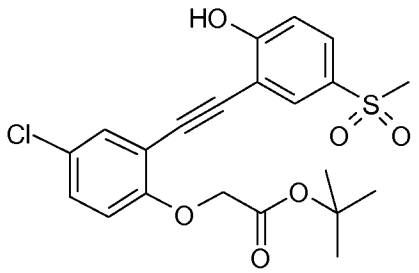
Intermediate 80: *tert*-butyl (4-chloro-2-{[2-chloro-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 79, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 1-chloro-2-iodo-4-(methylsulfonyl)benzene (Intermediate 74), the title compound was obtained after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.17 (d, *J*= 2.1 Hz, 1H), 7.95 (dd, *J*= 2.1, *J*= 8.5 Hz, 1H), 7.90 (d, *J*= 8.5 Hz, 1H), 7.64 (d, *J*= 2.7 Hz, 1H), 7.49 (dd, *J*= 2.7, *J*= 9.0 Hz, 1H), 7.04 (d, *J*= 9.0 Hz, 1H), 4.83 (s, 2H), 3.31 (s, 3H), 1.43 (s, 9H). HPLC (Condition A) Purity 99.2%; Rt 5.2 min.

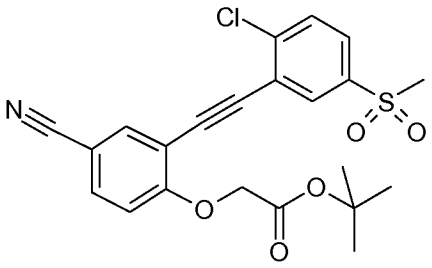
Intermediate 81: *tert*-butyl (4-chloro-2-{[2-hydroxy-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 79, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 2-iodo-4-(methylsulfonyl)phenol (Intermediate 78), the title compound was obtained after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.28 (m, 1H), 7.98 (d, *J*= 2.7 Hz, 1H), 7.91-7.94 (m, 3H), 7.49 (dd, *J*= 2.7, *J*= 9.0 Hz, 1H), 7.21 (d, *J*= 9.0 Hz, 1H), 4.94 (s, 2H), 3.27 (s, 3H), 1.50 (s, 9H). HPLC (Condition A) Purity 98.4%; Rt 5.12 min.

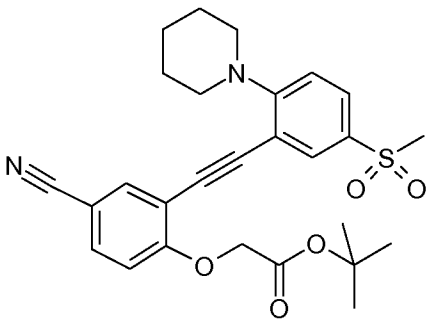
Intermediate 82: *tert*-butyl (2-{[2-chloro-5-(methylsulfonyl)phenyl]ethynyl}-4-cyanophenoxy)acetate



Following the general method as outlined in Intermediate 79, starting from (4-cyano-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 46) and 1-chloro-2-iodo-4-(methylsulfonyl)benzene (Intermediate 74), the title compound was obtained as a yellow solid in 74% yield after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.18 (d, *J*= 2.0 Hz, 1H), 8.11 (d, *J*= 2.0 Hz, 1H), 7.96 (dd, *J*= 2.0, *J*= 8.6 Hz, 1H), 7.89-7.93 (m, 2H), 7.21 (d, *J*= 8.6 Hz, 1H), 4.96 (s, 2H), 1.43 (s, 9H) (3 remaining protons, probably hidden under the signal of water). HPLC (Condition A) Rt 4.74 min.

Intermediate 83: *tert*-butyl (4-cyano-2-{[5-(methylsulfonyl)-2-piperidin-1-ylphenyl]ethynyl}phenoxy)acetate

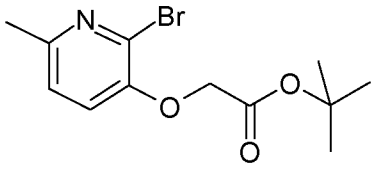


Following the general method as outlined in Intermediate 20, starting from (4-cyano-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 46) and 1-chloro-2-iodo-4-(methylsulfonyl)benzene (Intermediate 74), the title compound was obtained as a yellow sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.03 (d, *J*= 2.1 Hz, 1H), 7.93 (d, *J*= 2.4 Hz, 1H), 7.85 (dd, *J*= 2.1, *J*= 8.8Hz, 1H), 7.77 (dd, *J*= 2.4, *J*= 8.8 Hz, 1H), 7.18 (d, *J*= 8.8 Hz, 1H),

7.16 (d, *J*= 8.8 Hz, 1H), 4.95 (s, 2H), 3.34 (m, 4H), 3.19 (s, 3H), 1.67 (m, 4H), 1.58 (m, 2H), 1.42 (s, 9H). HPLC (Condition A) Rt 5.12 min.

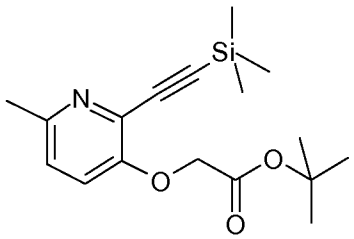
Intermediate 84: *tert*-Butyl [(2-bromo-6-methylpyridin-3-yl)oxy]acetate



Following the general method as outlined in Intermediate 1, starting from 2-Bromo-6-methylpyridin-3-ol (Activate Scientific), the title compound was obtained in 79% yield as a yellow liquid after purification by flash column chromatography (silica), eluting with chloroform and methanol (98:2).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.31 (1H, d), 7.21 (1H, d), 4.80 (2H, s), 2.36 (3H, s), 1.40 (9H, s). MS (ESI$^+$): 303.6. HPLC (Method D) Purity 97.0%; Rt 4.43 min.

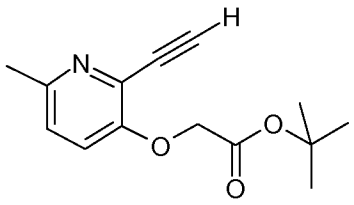
Intermediate 85: *tert*-Butyl {[2-(trimethylsilyl-1-ethynyl)-6-methylpyridin-3-yl]oxy}acetate



Following the general method as outlined in Intermediate 2, starting from *tert*-butyl [(2-bromo-6-methylpyridin-3-yl)oxy]acetate (Intermediate 84), the title compound was obtained as a brown oil after purification by flash column chromatography (silica), eluting with petroleum ether and ethyl acetate (98:2).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.26 (1H, d), 7.20 (1H, d), 4.73 (2H, s), 2.35 (3H, s), 1.41 (9H, s), 0.22 (9H, s).

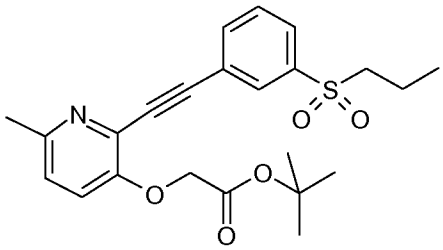
Intermediate 86: *tert*-Butyl [(2-ethynyl-6-methylpyridin-3-yl)oxy]acetate



Following the general method as outlined in Intermediate 2, starting from *tert*-butyl {[2-(trimethylsilyl-1-ethynyl)-6-methylpyridin-3-yl]oxy}acetate (Intermediate 85), the title compound was obtained in 91% yield as a brown oil after purification by flash column chromatography (silica), eluting with petroleum ether and ethyl acetate (98:2).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.28 (1H, d), 7.21 (1H, d), 4.78 (2H, s), 4.36 (1H, s), 2.35 (3H, s), 1.40 (9H, s). MS (ESI$^+$): 248.0. HPLC (Condition A) Purity 98.5%; Rt 3.03 min.

Intermediate 87: *tert*-butyl [(6-methyl-2-{[3-(propylsulfonyl)phenyl]ethynyl}pyridin-3-yl)oxy]acetate

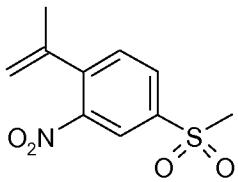


Following the general method as outlined in Intermediate 20, starting from (2-ethynyl-6-methyl-pyridin-3-yloxy)-acetic acid *tert*-butyl ester (Intermediate 86) and 1-bromo-3-(propane-1-sulfonyl)-benzene (Intermediate 5), the title compound was obtained as a yellow sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.02 (t, *J*= 1.5 Hz, 1H), 7.92-7.96 (m, 2H), 7.75 (t, *J*= 7.8 Hz, 1H), 7.37 (d, *J*= 8.7 Hz, 1H), 7.26 (d, *J*= 8.7 Hz, 1H), 4.83 (s, 2H), 3.35-3.40 (m, 2H), 2.42 (s, 3H), 1.56 (sext., *J*= 7.5 Hz, 2H), 1.43 (s, 9H), 0.93 (t, *J*= 7.5 Hz, 3H).

HPLC (Condition A) Purity 92.6%; Rt 3.93 min.

Intermediate 88: 1-isopropenyl-4-(methylsulfonyl)-2-nitrobenzene

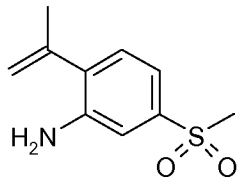


Following the general method as outlined in Intermediate 59, starting from 2-bromo-5-methylsulfonylnitrobenzene and isopropenylboronic acid pinacol ester, the title compound was obtained as a brown oil in quantitative yield after purification by flash

column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.44 (1H, d, *J*= 1.8 Hz) 8.20 (1H, dd, *J*= 8.1 Hz, *J*= 1.8 Hz), 7.78 (1H, d, *J*= 8.1 Hz), 5.30 (1H, t, *J*= 1.3 Hz), 5.30 (m, 1H), 5.00 (1H, s), 3.36 (3H, s), 2.08 (3H, s).

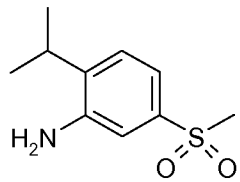
Intermediate 89: 2-isopropenyl-5-(methylsulfonyl)aniline



Following the general method as outlined in Intermediate 60, starting from 1-isopropenyl-4-(methylsulfonyl)-2-nitrobenzene (Intermediate 88), the title compound was obtained as an orange solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.18 (1H, d, *J*= 1.9 Hz), 7.13 (1H, d, *J*= 7.9 Hz), 7.00 (1H, dd, *J*= 7.9 Hz, *J*= 1.9 Hz), 5.37 (s, 2H), 5.29 (1H, m), 5.02 (1H, m), 3.10 (3H, s), 2.00 (3H, m).

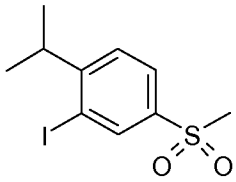
Intermediate 90: 2-isopropyl-5-(methylsulfonyl)aniline



Following the general method as outlined in Intermediate 61, starting from 2-isopropenyl-5-(methylsulfonyl)aniline (Intermediate 89), the title compound was obtained as a green solid in 81% yield after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.22 (1H, d, *J*= 8.0 Hz), 7.12 (1H, d, *J*= 2.0 Hz), 7.00 (1H dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 5.47 (2H, s), 3.07 (3H, s), 3.01 (1H, sept., *J*= 6.7 Hz), 1.15 (6H, d, *J*= 6.7 Hz)

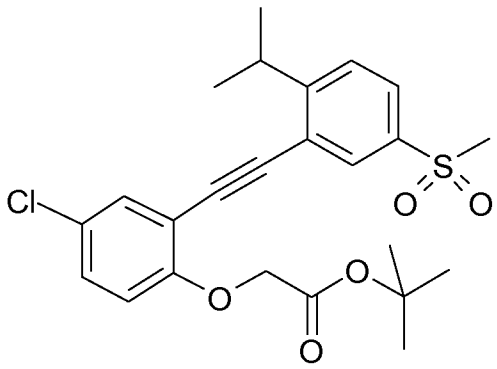
Intermediate 91: 2-iodo-1-isopropyl-4-(methylsulfonyl)benzene



Following the general method as outlined in Intermediate 58, starting from 2-isopropyl-5-(methylsulfonyl)aniline (Intermediate 90), the title compound was obtained as a white solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.28 (1H, d, *J*= 1.9 Hz), 7.90 (1H dd, *J*= 8.2 Hz, *J*= 1.9 Hz), 7.59 (1H d, *J*= 8.2 Hz), 3.25 (3H, s), 3.18 (1H, sept., *J*= 6.8 Hz), 1.21 (6H, d, *J*= 6.8 Hz)

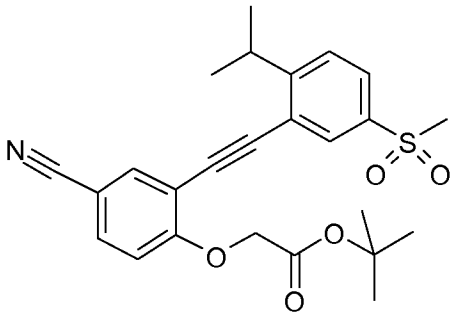
Intermediate 92: *tert*-butyl (4-chloro-2-{[2-isopropyl-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 79, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 2-iodo-1-isopropyl-4-(methylsulfonyl)benzene (Intermediate 91), the title compound was obtained as a brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.01 (1H, d, *J*= 2.0 Hz), 7.90 (1H, dd, *J*= 8.3 Hz, *J*= 2.0 Hz), 7.67 (1H, d, *J*= 8.3 Hz), 7.64 (1H, d, *J*= 2.7 Hz), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.06 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 3.65 (1H, sept., *J*= 6.9 Hz), 3.26 (3H, s), 1.43 (9H, s), 1.28 (6H, d, *J*= 6.9 Hz). HPLC (Condition A) Purity 92.4%; Rt 5.60 min.

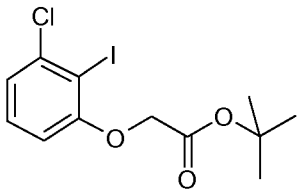
Intermediate 93: *tert*-butyl (4-cyano-2-{[2-isopropyl-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 79, starting from (4-cyano-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 46) and 2-iodo-1-isopropyl-4-(methylsulfonyl)benzene (Intermediate 91), the title compound was obtained as a brown solid in 74% yield after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.10 (1H, d, *J*= 2.1 Hz), 8.02 (1H, d, *J*= 2.1 Hz), 7.86-7.94 (2H, m), 7.67 (1H, d, *J*= 8.3 Hz), 7.22 (1H, d, *J*= 9.0 Hz)4.95 (2H, s), 3.65 (1H, sept., *J*= 7.0 Hz), 3.26 (3H, s), 1.43 (9H, s), 1.28 (6H, d, *J*= 7.0 Hz). HPLC (Condition A) Rt 5.16 min.

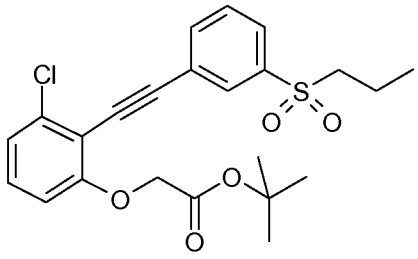
Intermediate 94: *tert*-butyl (3-chloro-2-iodophenoxy)acetate



Following the general method as outlined in Intermediate 1, starting from 3-chloro-2-iodophenol (prepared as described in *J. Org. Chem.*, **2005**, *70*, 6548-6551), the title compound was obtained as a white solid in 86% yield after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.34-7.30 (1H, m), 7.18-7.16 (1H, m), 6.80-6.77 (2H, d), 4.78 (2H, s), 1.40 (9H, s). MS (ESI$^+$): 310.8. HPLC (Condition A) Purity 98.9%; Rt 5.80 min.

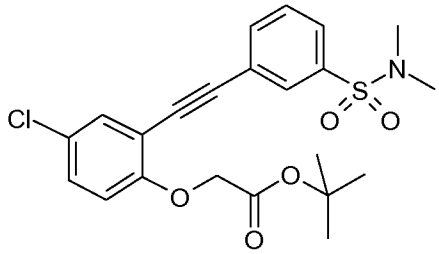
Intermediate 95: *tert*-butyl (3-chloro-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 79, starting from (3-chloro-2-iodo-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 94) and 1-ethynyl-3-(propane-1-sulfonyl)-benzene (Intermediate 42), the title compound was obtained a brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

MS (ESI^+): 466.1 $(M+NH_4)^+$.

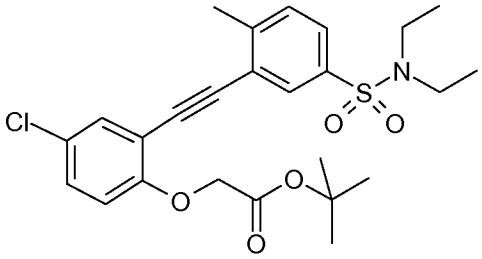
Intermediate 96: *tert*-butyl [4-chloro-2-({3-[(dimethylamino)sulfonyl]phenyl}ethynyl)phenoxy]acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and *N,N*-dimethyl 3-bromobenzenesulfonamide (Combiblocks), the title compound was obtained as a yellow oil after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^1H NMR (300MHz, DMSO-d_6) δ [ppm] 7.88-7.70 (4H, m), 7.66 (1H, d, *J*= 2.7 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.02 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 2.66 (6H, s), 1.44 (9H, s).

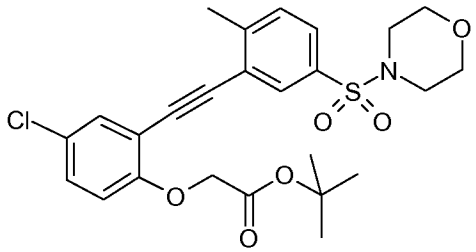
Intermediate 97: *tert*-butyl [4-chloro-2-({5-[(diethylamino)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and *N,N*-diethyl 3-bromobenzenesulfonamide (Combiblocks), the title compound was obtained as a yellow sticky solid in 72% yield after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.84 (1H, d, *J*= 2.0 Hz), 7.71 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.66 (1H, d, *J*= 2.7 Hz), 7.57 (1H, d, *J*= 8.0 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s), 3.18 (4H, q, *J*= 7.1 Hz), 2.55 (3H, s), 1.43 (9H, s), 1.05 (6H, t, *J*= 7.1 Hz). HPLC (Condition A) Purity 95.4%; Rt 6.23 min.

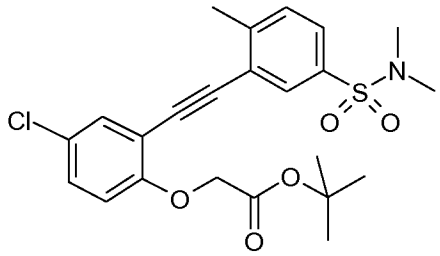
Intermediate 98: *tert*-butyl (4-chloro-2-{[2-methyl-5-(morpholin-4-ylsulfonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 1-(3-bromo-4-methylphenylsulfonyl)morpholine (Combiblocks), the title compound was obtained as a yellow sticky solid in 81% yield after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.80 (1H, d, *J*= 1.5 Hz), 7.62-7.69 (3H, m), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 3.64 (4H, m), 2.90 (4H, m), 2.59 (3H, s), 1.43 (9H, s). HPLC (Condition A) Purity 99.7%; Rt 5.73 min.

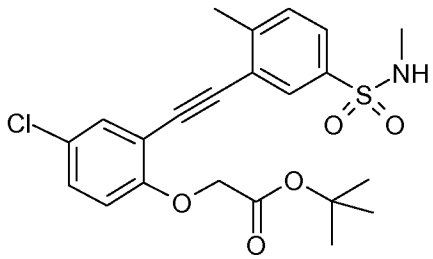
Intermediate 99: *tert*-butyl [4-chloro-2-({5-[(dimethylamino)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and *N,N*-dimethyl 3-bromo-4-methylbenzenesulfonamide (Combiblocks), the title compound was obtained as an orange sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.81 (1H, d, *J*= 1.9 Hz), 7.60-7.69 (3H, m), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s), 2.63 (6H, s), 2.57 (3H, s), 1.43 (9H, s). HPLC (Condition A) Purity 99.8%; Rt 5.84 min.

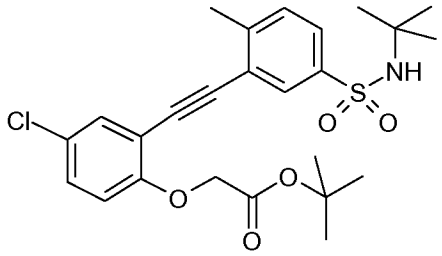
Intermediate 100: *tert*-butyl [4-chloro-2-({2-methyl-5-[(methylamino)sulfonyl]phenyl}ethynyl)phenoxy]acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 3-bromo-*N*,4-dimethylbenzenesulfonamide (Combiblocks), the title compound was obtained as an orange sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.85 (1H, d, *J*= 2.0 Hz), 7.69 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.64 (1H, d, *J*= 2.7 Hz), 7.57 (1H, d, *J*= 8.0 Hz), 7.48 (1H, bs), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.02 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 2.55 (3H, s), 2.42 (3H, s), 1.43 (9H, s). HPLC (Condition A) Purity 96.9%; Rt 5.19 min.

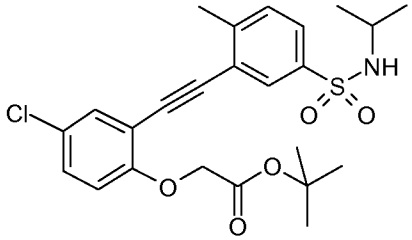
Intermediate 101: *tert*-butyl [2-({5-[(*tert*-butylamino)sulfonyl]-2-methylphenyl}ethynyl)-4-chlorophenoxy]acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and *N-tert*-butyl 3-bromo-4-methylbenzenesulfonamide (Combiblocks), the title compound was obtained as an orange sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.89 (1H, d, *J*= 1.9 Hz), 7.74 (1H, dd, *J*= 8.0 Hz, *J*= 1.9 Hz), 7.64 (1H, d, *J*= 2.7 Hz), 7.56 (1H, s), 7.53 (1H, d, *J*= 8.0 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 2.54 (3H, s), 1.42 (9H, s), 1.10 (9H, s). HPLC (Condition A) Purity 95.3%; Rt 6.05 min.

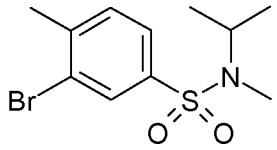
Intermediate 102: *tert*-butyl [4-chloro-2-({5-[(isopropylamino)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and *N*-isopropyl 3-bromo-4-methylbenzenesulfonamide (Combiblocks), the title compound was obtained as an orange sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.87 (1H, d, *J*= 2.0 Hz), 7.71 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.64 (1H, d, *J*= 2.7 Hz), 7.61 (1H, d, *J*= 6.5 Hz), 7.55 (1H, d, *J*= 8.0 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 3.26 (1H, m), 2.55 (3H, s), 1.43 (9H, s), 0.95 (6H, d, *J*= 6.5 Hz). HPLC (Condition A) Purity 94.7%; Rt 5.8 min.

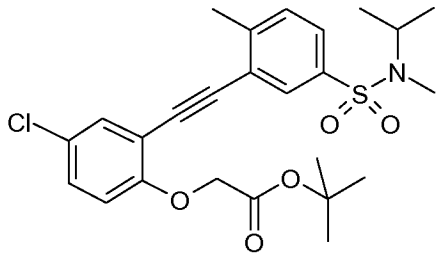
Intermediate 103: 3-bromo-*N*-isopropyl-*N*,4-dimethylbenzenesulfonamide



A solution of *N*-isopropyl 3-bromo-4-methylbenzenesulfonamide (Combiblocks; 200 mg; 0.68 mmol) in anhydrous DMF (4 mL) was treated with NaH (33 mg; 0.82 mmol) and stirred at RT for five minutes. The resulting mixture was treated with iodomethane (43 µl; 0.68 mmol) and the reaction mixture was stirred for 16 hours. The mixture was treated again with iodomethane (21 µl; 0.34 mmol) and the reaction mixture was stirred at RT for 24 hours. The mixture was quenched with an aqueous (5 N) solution of NaOH and extracted with EtOAc. The organic phase was washed with water and brine, dried over $MgSO_4$, concentrated and purified flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc affording the title compound as a colorless sticky solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.89 (1H, d, *J*= 1.9 Hz), 7.70 (1H, d, *J*= 8.0Hz, *J*= 1.9 Hz), 7.59 (1H, d, *J*= 8.0 Hz), 4.08 (1H, sept., *J*= 6.7 Hz), 2.64 (3H, s), 2.43 (3H, s), 0.90 (6H, d, *J*= 6.7 Hz). HPLC (Condition A) Purity 98.3%; Rt 4.4 min.

Intermediate 104: *tert*-butyl {4-chloro-2-[(5-{[isopropyl(methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetate

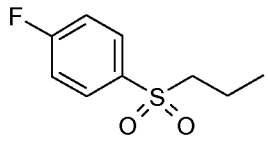


Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 3-bromo-*N*-isopropyl-*N*,4-dimethylbenzenesulfonamide (Intermediate 103), the title compound was obtained as a brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.84 (1H, d, *J*= 2.0 Hz), 7.71 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.66 (1H, d, *J*= 2.7 Hz), 7.57 (1H, d, *J*= 8.0 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s), 4.09 (1H, sept., *J*= 6.7 Hz), 2.66 (3H, s),

2.55 (3H, s), 1.43 (9H, s), 0.90 (6H, d, *J*= 6.7 Hz). HPLC (Condition A) Purity 96.7%; Rt 6.2 min.

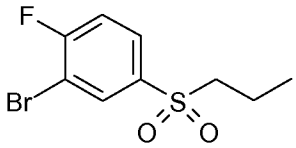
Intermediate 105: 1-fluoro-4-(propylsulfonyl)benzene



A cooled (0 °C) solution of 4-fluorothiophenol (Merck Kgaa; 2.00 g; 15.6 mmol) in MeOH (40 ml) was treated with a 5 N solution of NaOH in water (3.28 ml) and 1-iodopropane (1.67 ml; 17.2 mmol). The reaction mixture was stirred at RT for 1 hour, the mixture was concentrated under reduced pressure, the residue taken up in EtOAc and washed with brine, dried on $MgSO_4$, filtered and concentrated under reduced pressure. The intermediate thus obtained was dissolved in DCM (50 ml) and treated with 3-chloroperbenzoic acid (8.46 g; 34.33 mmol) and stirred at RT for 3 hours. The solvent was removed under reduced pressure, the residue taken up in EtOAc and washed with brine, dried on MgSO4, filtered and concentrated under reduced pressure to afford the title compound (2.75 g, 87%).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.99-7.94 (2H, m), 7.55-7.47 (2H, m), 3.30 (2H, m), 1.55 (2H, m), 0.92 (3H, t, *J*= 7.5 Hz).

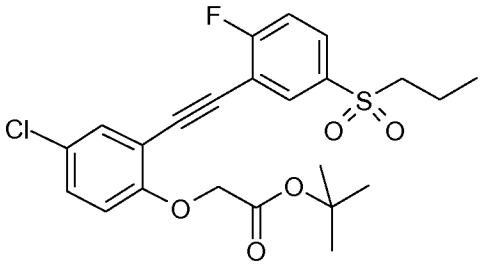
Intermediate 106: 2-bromo-1-fluoro-4-(propylsulfonyl)benzene



A suspension of 1-fluoro-4-(propylsulfonyl)benzene (Intermediate 105; 1.00 g; 4.94 mmol) in conc. sulfuric acid (3.97 ml; 74.2 mmol) was treated with *N*-bromosuccinimide (968 mg; 5.44 mmol) and stirred at RT for 6 hours. The reaction mixture was carefully poured on crushed ice, extracted with AcOEt and the organic phase was washed with a 0.1 N solution of NaOH in water twice, then with brine twice. The organic phase was dried on $MgSO_4$, filtered and concentrated under reduced pressure to give a residue, which was purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc to give the title compound.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.22 (1H, dd, *J*= 6.3 Hz, *J*= 2.3 Hz), 7.99 (1H, ddd, *J*= 8.6 Hz, *J*= 4.6 Hz, *J*= 2.3 Hz), 7.67 (1H, t, *J*= 8.6 Hz), 3.38 (2H, m), 1.56 (2H, m), 0.93 (3H, t, *J*= 7.5 Hz).

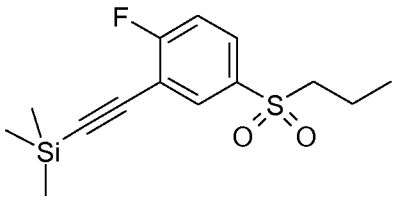
Intermediate 107: *tert*-butyl (4-chloro-2-{[2-fluoro-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate



A mixture of 2-bromo-1-fluoro-4-(propylsulfonyl)benzene (Intermediate 106; 541 mg; 1.93 mmol), *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (Intermediate 467 mg; 1.75 mmol), dichlorobis(triphenylphosphine)palladium(II) (49 mg; 0.07 mmol) and TEA (728 µL; 5.2 mmol) was heated at 60 °C for 18 hours. The reaction mixture was taken up in EtOAc, washed twice with a sat. NH_4Cl aqueous solution and once with brine. The organic phase was dried over $MgSO_4$, filtered and concentrated to dryness affording a crude, which was purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc. The title compound was obtained as a brown solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.14 (1H, dd, *J*= 6.5 Hz, *J*= 2.4 Hz), 7.99 (1H, ddd, *J*= 8.7 Hz, *J*= 4.6 Hz, *J*= 2.4 Hz), 7.69-7.63 (2H, m), 7.48 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 3.38 (2H, m), 1.58 (2H, m), 1.43 (9H, s), 0.93 (3H, t, *J*= 7.5 Hz).

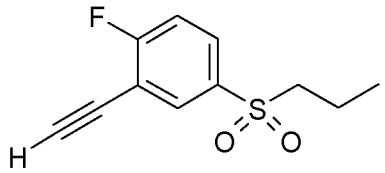
Intermediate 108: {[2-Fluoro-5-(propylsulfonyl)phenyl]ethynyl}trimethyl silane



Following the general method as outlined in Intermediate 2, starting from 2-bromo-1-fluoro-4-(propylsulfonyl) benzene (Intermediate 106) and trimethylsilylacetilene, the title compound was obtained as a brown liquid in 97% yield.

^{1}H NMR (300MHz, $CDCl_3$) δ [ppm] 8.03-8.01(dd, 1H, *J*= 2.3 Hz, 4.1 Hz), 7.85-7.81 (m, 1H), 7.24 (t, 1H, *J*= 9.3 Hz), 3.06 (t, 2H, *J*= 8 Hz), 1.77-1.69 (m, 2H), 1.02-0.99 (t, 3H, *J*= 7.5 Hz), 0.28-0.27 (s, 9H).

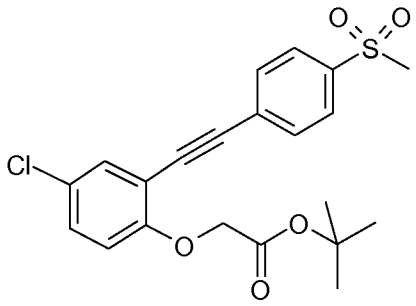
Intermediate 109: 2-Ethynyl-1-fluoro-4-(propylsulfonyl)benzene



Following the general method as outlined in Intermediate 3, starting from {[2-Fluoro-5-(propylsulfonyl)phenyl]ethynyl}trimethyl silane (Intermediate 107), the title compound was obtained as a brown liquid after purification by column chromatography (silica) eluting with petroleum ether and ethyl acetate.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.03 (dd, 1H, *J*= 2.3 Hz, *J*= 8.8 Hz), 7.98-7.94 (m, 1H), 7.60 (t, 1H, *J*= 8.0 Hz), 4.74 (s, 1H), 3.34 (t, 2H, *J*= 8.0 Hz), 1.56-1.49 (m, 2H), 0.90 (t, 3H, *J*= 7.4 Hz). MS (ESI^+): 227.0. HPLC (Condition A) Purity 98.2%; Rt 4.07 min.

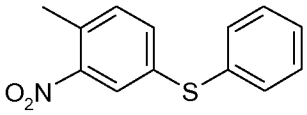
Intermediate 110: *tert*-butyl (4-chloro-2-{[4-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 4-bromophenyl methyl sulfone, the title compound was obtained as a brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.98 (2H, d, *J*= 8.6 Hz), 7.79 (2H, d, *J*= 8.6 Hz), 7.64 (1H, d, *J*= 2.7 Hz), 7.46 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.02 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 3.27 (3H, s), 1.43 (9H, s). HPLC (Condition A) Purity 98.9%; Rt 5.2 min.

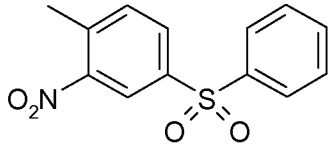
Intermediate 111: 1-methyl-2-nitro-4-(phenylthio)benzene



A mixture of 4-fluoro-2-nitrotoluene (ABCR; 120 µl; 0.97 mmol), thiophenol (120 µl; 1.16 mmol) and K_2CO_3 (267 mg; 1.93 mmol) in DMSO (3 ml) was placed in a microwave vial and submitted to microwave irradiation at 150 °C for 15 minutes. The reaction mixture was filtered, taken up in EtOAc and washed with water and brine. The organic phase was dried over $MgSO_4$, filtered, concentrated and purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc affording the title compound as a yellow solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.80 (1H, d, *J*= 1.4 Hz), 7.50-7.51 (2H, m), 7.43-7.45 (5H, m), 2.47 (3H, s). HPLC (Condition A) Purity 91.6%; Rt 5.2 min.

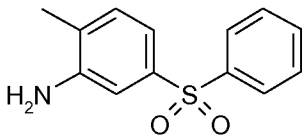
Intermediate 112: 1-methyl-2-nitro-4-(phenylsulfonyl)benzene



A solution of 1-methyl-2-nitro-4-(phenylthio)benzene (Intermediate 111; 745 mg; 3.04 mmol) in MeOH (11 ml) and water (11 ml) was treated with Oxone® (5.60 g; 9.11 mmol) and the reaction mixture was stirred at RT for 6 hours. Water was added and the reaction mixture was extracted 2 times with DCM. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated to dryness affording the title compound as a beige solid (690 mg, 82%).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.48 (1H, d, *J*= 2.0 Hz), 8.18 (1H, dd, *J*= 8.1 Hz, *J*= 2.0 Hz), 8.01-8.05 (2H, m), 7.62-7.77 (4H, m), 2.56 (3H, s). HPLC (Condition A) Purity 91.3%; Rt 3.9 min.

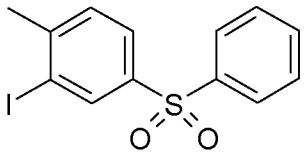
Intermediate 113: 2-methyl-5-(phenylsulfonyl)aniline



Following the general method as outlined in Intermediate 61 using MeOH and EtOAc as solvents, starting from 1-methyl-2-nitro-4-(phenylsulfonyl)benzene (Intermediate 112) and 4-bromophenyl methyl sulfone, the title compound was obtained as a beige solid in 94% yield.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.83-7.86 (2H, m), 7.56-7.63 (3H, m), 7.10-7.13 (2H, m), 6.97 (1H, dd, *J*= 7.8 Hz, *J*= 2.0 Hz), 5.42 (2H, s), 2.06 (3H, s). HPLC (Condition A) Rt 2.8 min.

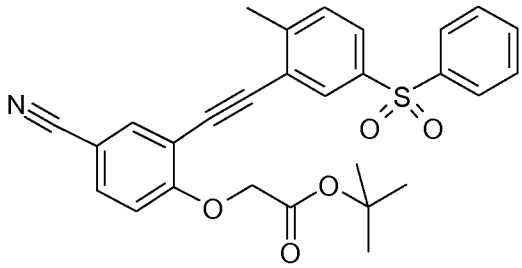
Intermediate 114: 2-iodo-1-methyl-4-(phenylsulfonyl)benzene



Following the general method as outlined in Intermediate 58, starting from 2-methyl-5-(phenylsulfonyl)aniline (Intermediate 113), the title compound was obtained as a white solid after purificatio by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc affording the title compound as a yellow solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.28 (1H, d, *J*= 2.0 Hz), 7.96-7.99 (2H, m), 7.88 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.54-7.73 (4H, m), 2.41 (3H, s).

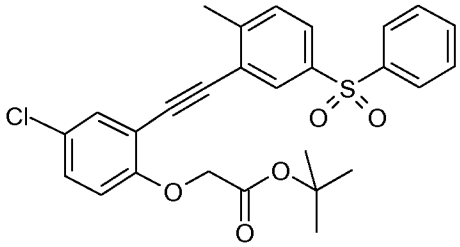
Intermediate 115: *tert*-butyl (4-cyano-2-{[2-methyl-5-(phenylsulfonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 79, starting from (4-cyano-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 46) and 2-iodo-1-methyl-4-(phenylsulfonyl)benzene (Intermediate 114), the title compound was obtained as a brown sticky solid in 89% yield.

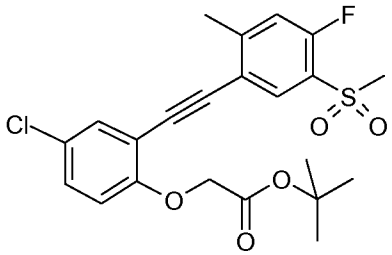
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.11 (1H, d, *J*= 2.0 Hz), 8.04 (1H, d, *J*= 2.0 Hz), 7.97-8.02 (2H, m), 7.86-7.92 (2H, m), 7.58-7.73 (4H, m), 7.19 (1H, d, *J*= 8.9 Hz), 4.94 (2H, s), 2.53 (3H, s), 1.43 (9H, s). HPLC (Condition A) Rt 5.5 min.

Intermediate 116: *tert*-butyl (4-chloro-2-{[2-methyl-5-(phenylsulfonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 2-iodo-1-methyl-4-(phenylsulfonyl)benzene (Intermediate 114), the title compound was obtained as a brown sticky solid in quantitative yield after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.97-8.03 (3H, m), 7.88 (1H, dd, *J*= 8.1 Hz, *J*= 2.0 Hz), 7.57-7.77 (5H, m), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s), 2.52 (3H, s), 1.43 (9H, s). HPLC (Condition A) Rt 6.1 min.

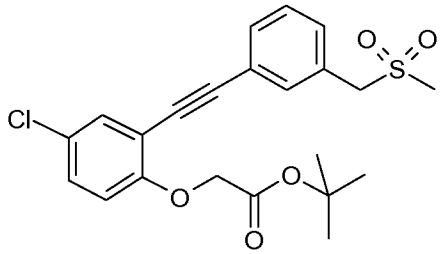
Intermediate 117: *tert*-butyl (4-chloro-2-{[4-fluoro-2-methyl-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 1-bromo-4-fluoro-5-methanesulfonyl-2-methyl-benzene (Ger. Offen. 2000; DE 19919349), the title compound was obtained as a brown oil after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.89 (1H, d, *J*= 7.2 Hz), 7.66 (1H, d, *J*= *J*= 2.6 Hz), 7.59 (1H, d, *J*= 11.1), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.6 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 3.34 (3H, s), 2.58 (3H, s), 1.43 (9H, s).

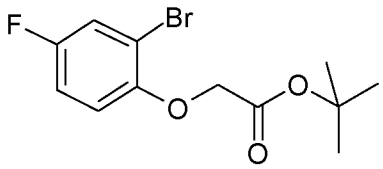
Intermediate 118: *tert*-butyl [4-chloro-2-({3-[(methylsulfonyl)methyl]phenyl}ethynyl)phenoxy]acetate



Following the general method as outlined in Intermediate 79, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 3-bromobenzylmethylsulfone (Fluorochem), the title compound was obtained after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.54-7.60 (3H, m), 7.40-7.51 (3H, m), 6.98 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 2.93 (2H, s), 1.43 (9H, s). HPLC (Condition A) Purity 99.8%; Rt 5.1 min.

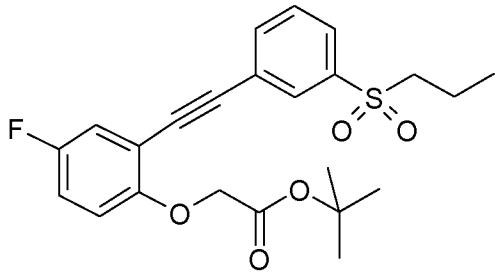
Intermediate 119: *tert*-butyl (2-bromo-4-fluorophenoxy)acetate



Following the general method as outlined in Intermediate 1, starting from 2-bromo-4-fluorophenol and *tert*-butyl bromoacetate, the title compound was obtained as a white solid in quantitative yield.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.56 (1H, dd, *J*= 8.2 Hz, *J*= 3.1 Hz), 7.21 (1H, ddd, *J*= 9.2 Hz, *J*= 8.2 Hz, *J*= 3.1 Hz), 7.02 (1H, dd, *J*= 9.2 Hz, *J*= 4.8 Hz), 4.77 (2H, s), 1.41 (9H, s). HPLC (Condition A) Purity 99.5%; Rt 4.9 min.

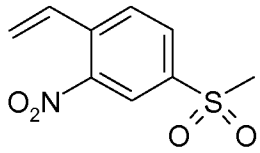
Intermediate 120: *tert*-butyl (4-fluoro-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 107, starting from *tert*-butyl (2-bromo-4-fluorophenoxy)acetate (Intermediate 119) and 1-ethynyl-3-(propane-1-sulfonyl)-benzene (Intermediate 42), the title compound was obtained as a yellow sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.01 (1H, t, *J*= 1.5 Hz), 7.87-7.94 (2H, m), 7.73 (1H, t, *J*= 7.8 Hz), 7.45 (1H, dd, *J*= 8.7 Hz, *J*= 3.1 Hz), 7.26 (1H, m), 7.00 (1H, dd, *J*= 9.4 Hz, *J*= 4.5 Hz), 4.79 (2H, s), 3.36 (2H, m), 1.57 (2H, sext., *J*= 7.5 Hz), 1.43 (9H, s), 0.93 (3H, t, *J*= 7.5 Hz). HPLC (Condition A) Purity 91.0%; Rt 5.4 min.

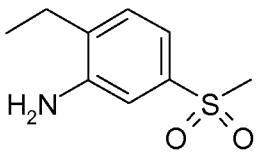
Intermediate 121: 4-(methylsulfonyl)-2-nitro-1-vinylbenzene



Following the general method as outlined in Intermediate 20, starting from 2-bromo-5-methylsulfonylnitrobenzene and vinylboronic acid pinacol ester, the title compound was obtained as a brown oil in quantitative yield.

HPLC (Condition A): Rt 3.04 min.

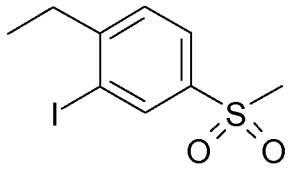
Intermediate 122: 2-ethyl-5-(methylsulfonyl)aniline



A solution of 4-(methylsulfonyl)-2-nitro-1-vinylbenzene (Intermediate 121; 3.60 g; 15.8 mmol) in AcOH (100 mL) was treated with a solution of iron (15.9 g; 285 mmol) in AcOH (20 ml) and the reaction mixture was stirred at 60 °C for 1h. EtOAc was added and the solution was filtered, the solvents removed under reduced pressure. The residue was

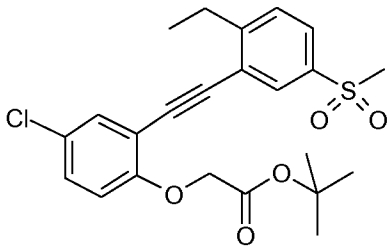
taken up in EtOAc, washed with a sat. $NaHCO_3$ solution in water, then with brine. The organic layer was dried, filtered and concentrated to give the title compound.
MS (ESI^-): 194.1

Intermediate 123: 1-ethyl-2-iodo-4-(methylsulfonyl)benzene



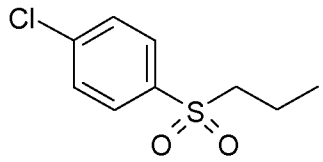
Following the general method as outlined in 58, starting from 2-ethyl-5-(methylsulfonyl)aniline (Intermediate 122), the title compound was obtained as a pink solid.
^1H NMR (300MHz, DMSO-d_6) δ [ppm] 8.27 (1H, d, *J*= 2.0 Hz), 7.88 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.58 (1H, d, *J*= 2.0 Hz), 3.25 (3H, s), 2.77 (2H, q, *J*= 7.5 Hz), 1.17 (3H, t, *J*= 7.5 Hz). HPLC (Condition A) Purity 96.6%; Rt 3.8 min.

Intermediate 124: *tert*-butyl (4-chloro-2-{[2-ethyl-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 1-ethyl-2-iodo-4-(methylsulfonyl)benzene (Intermediate 123), the title compound was obtained as an orange oil after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.
^1H NMR (300MHz, DMSO-d_6) δ [ppm] 8.01 (1H, d, *J*= 2.0 Hz), 7.88 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.65-7.61 (2H, m), 7.45 (1H, dd, *J*= 8.7 Hz, *J*= 3.1 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 3.26 (3H, s), 2.96 (2H, q, *J*= 7.5 Hz), 1.26 (3H, t, *J*= 7.5 Hz). MS (ESI^-): 447.1. HPLC (Condition A) Purity 93.5%; Rt 5.6 min.

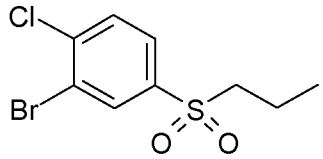
Intermediate 125: 1-chloro-4-(propylsulfonyl)benzene



Following the general method as outlined in Intermediate 105, starting from 4-chlorothiophenol (Aldrich) and 1-iodopropane, the title compound was obtained as an oil which solidified upon standing in 82% yield after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.93-7.88 (2H, m), 7.76-7.72 (2H, m), 3.31 (2H, m), 1.57 (2H, m), 1.55 (9H, s), 0.91 (3H, t, *J*= 7.4 Hz).

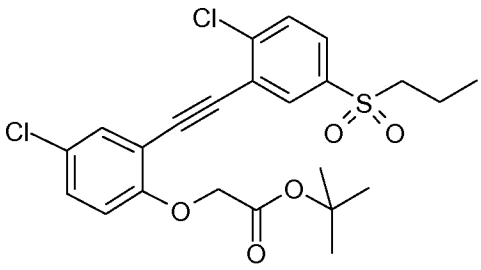
Intermediate 126: 2-bromo-1-chloro-4-(propylsulfonyl)benzene



Following the general method as outlined in Intermediate 106, starting from 1-chloro-4-(propylsulfonyl)benzene (Intermediate 125), the title compound was obtained as an oil which solidified upon standing in 86% yield.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.22 (1H, d, *J*= 1.8 Hz), 7.95-7.87 (2H, m), 3.39 (2H, m), 1.57 (2H, m), 0.93 (3H, m).

Intermediate 127: *tert*-butyl (4-chloro-2-{[2-chloro-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate

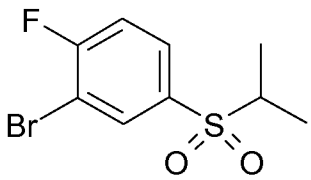


Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 2-bromo-1-chloro-4-(propylsulfonyl)benzene (Intermediate 126), the title compound was obtained as a

colorless oil after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.13 (1H, t, *J*= 1.3 Hz), 7.90 (2H, d, *J*= 1.3 Hz), 7.65 (1H, d, *J*= 2.7 Hz), 7.49 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.05 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 3.40 (2H, m), 1.57 (2H, m), 1.43 (9H, s), 0.93 (3H, t, *J*= 7.4 Hz).

Intermediate 128: 2-bromo-1-fluoro-4-(isopropylsulfonyl)benzene



Step 1: 1-fluoro-4-(isopropylthio)benzene

A cooled (0 °C) solution of *p*-thiocresol (5.0 mL; 46.8 mmol) in MeOH (100 ml) was treated with a 5 N solution of NaOH in water (9.8 ml; 49 mmol) and 2-iodopropane (5.2 ml; 52 mmol). The reaction mixture was stirred at RT for 4.5 hour, the mixture was concentrated under reduced pressure, the residue taken up in EtOAc and washed with brine, dried on $MgSO_4$, filtered and concentrated under reduced pressure to afford the title compound as a colorless oil (6.56 g, 82%).

Step 2: 1-fluoro-4-(isopropylsulfonyl)benzene

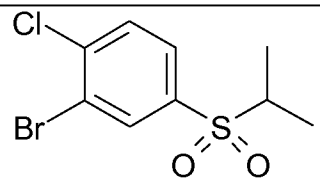
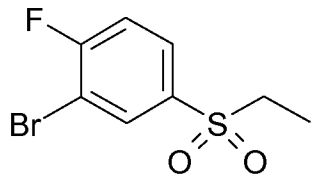
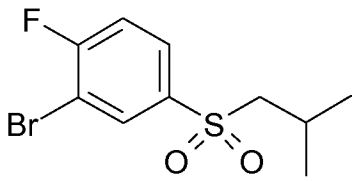
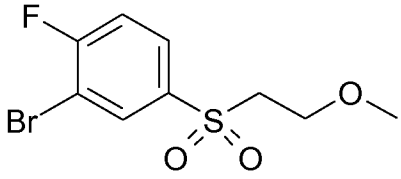
1-Fluoro-4-(isopropylthio)benzene (6.56 g; 38.5 mmol) was dissolved in DCM (150 ml) and treated with 3-chloroperbenzoic acid (20.90 g; 84.77 mmol) and stirred at RT for 3 hours. The solvent was removed under reduced pressure, the residue taken up in EtOAc and washed with brine, dried on $MgSO_4$, filtered and concentrated under reduced pressure to afford the title compound as a white solid (6.88 g, 88%).

Step 3: 2-bromo-1-fluoro-4-(isopropylsulfonyl)benzene

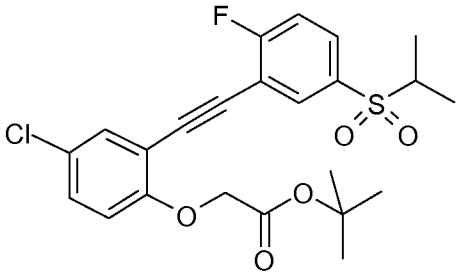
Following the general method as outlined in Intermediate 106, starting from 1-fluoro-4-(isopropylsulfonyl)benzene, the title compound was obtained as an oil which solidifies upon standing in 89% yield.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.17 (1H, dd, *J*= 6.4 Hz, *J*= 2.2 Hz), 7.93 (1H, ddd, *J*= 8.7 Hz, *J*= 4.8 Hz, *J*= 2.3 Hz), 7.68 (1H, d, *J*= 8.7 Hz), 3.55 (2H, septet, *J*= 6.8 Hz), 1.43 (9H, s), 1.17 (6H, d, *J*= 6.8 Hz).

The compounds in the table below were all prepared following the general method as outlined in Intermediate 128:

Int.	Structure	Chemical name	^{1}H NMR (DMSO-d_6; 400MHz) δ [ppm]
129		2-bromo-1-chloro-4-(isopropylsulfonyl)benzene	8.18 (1H, d, *J*= 2.1 Hz), 7.95 (1H, d, *J*= 8.4 Hz), 7.86 (1H, dd, *J*= 8.4 Hz, *J*= 2.1 Hz), 3.58 (2H, septet, *J*= 6.8 Hz), 1.17 (6H, d, *J*= 6.8 Hz).
130		2-bromo-4-(ethylsulfonyl)-1-fluorobenzene	8.21-8.19 (1H, dd, J=2.2Hz, J=6.4Hz), 7.96-7.92 (1H, m), 7.69-7.64 (1H, t, J=8.64Hz), 3.41-3.35 (2H, dd), 1.11-1.07 (3H, t).
131		2-bromo-1-fluoro-4-(isobutylsulfonyl)benzene	8.24-8.22 (1H, dd, J=2.2Hz, J=6.4Hz), 7.98-7.95 (1H, m), 7.68-7.64 (1H, t, J=8.64Hz), 3.32-3.30 (2H, d), 2.02 (1H, t), 0.97 (6H, t).
132		2-bromo-1-fluoro-4-[(2-methoxyethyl)sulfonyl]benzene	8.21-8.19 (1H, dd, J=2.2Hz, J=6.4Hz), 7.95-7.91 (1H, m), 7.64 (1H, t, J=8.7Hz), 3.70-3.67 (2H, m), 3.63-3.59 (1H, m), 3.07 (3H, s).

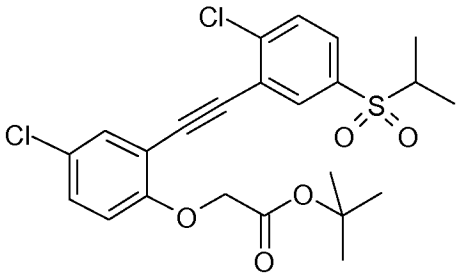
Intermediate 133: *tert*-butyl (4-chloro-2-{[2-fluoro-5-(isopropylsulfonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 2-bromo-1-fluoro-4-(isopropylsulfonyl)benzene (Intermediate 128), the title compound was obtained as a white solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.09 (1H, dd, *J*= 6.5 Hz, *J*= 2.4 Hz), 7.99 (1H, ddd, *J*= 8.7 Hz, *J*= 4.8 Hz, *J*= 2.4 Hz), 7.70-7.64 (2H, m), 7.48 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 3.55 (2H, septet, *J*= 6.8 Hz), 1.43 (9H, s), 1.19 (6H, d, *J*= 6.8 Hz).

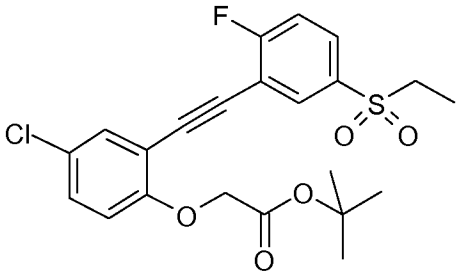
Intermediate 134: *tert*-butyl (4-chloro-2-{[2-chloro-5-(isopropylsulfonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 2-bromo-1-chloro-4-(isopropylsulfonyl)benzene (Intermediate 129), the title compound was obtained as a white solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.09 (1H, d, *J*= 1.9 Hz), 7.93-7.85 (2H, m), 7.66 (1H, d, *J*= 2.7 Hz), 7.48 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.05 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 3.55 (2H, septet, *J*= 6.8 Hz), 1.43 (9H, s), 1.19 (6H, d, *J*= 6.8 Hz).

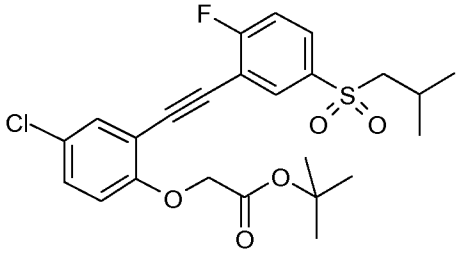
Intermediate 135: *tert*-butyl (4-chloro-2-{[5-(ethylsulfonyl)-2-fluorophenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 2-bromo-4-ethanesulfonyl-1-fluoro-benzene (Intermediate 130), the title compound was obtained as a colorless oil in 86% yield after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.13 (dd, *J*= 6.4, 2.3 Hz, 1H), 7.85 (ddd, *J*= 7.1, 4.6, 2.4 Hz, 1H), 7.48 (d, *J*= 2.6 Hz, 1H), 7.27 (m, 2H), 6.71 (d, *J*= 8.9 Hz, 1H), 4.60 (s, 2H), 3.13 (t, *J*= 7.5 Hz, 2H), 1.46 (s, 9H), 1.28 (t, *J*= 7.4 Hz, 3H), (, H). HPLC (Condition A) Purity 95.8%; Rt 5.8 min.

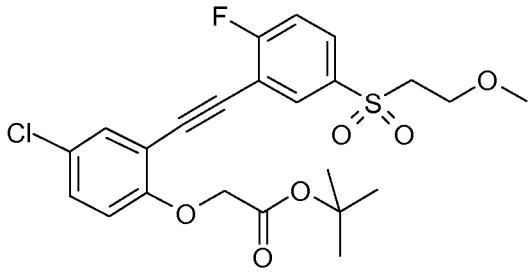
Intermediate 136: *tert*-butyl (4-chloro-2-{[2-fluoro-5-(isobutylsulfonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 2-Bromo-1-fluoro-4-(2-methyl-propane-1-sulfonyl)-benzene (Intermediate 131), the title compound was obtained as a colorless oil in 99% yield after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.12 (dd, *J*= 6.4, 2.6 Hz, 1H), 7.85 (ddd, *J*= 7.1, 4.8, 2.4 Hz, 1H), 7.48 (d, *J*= 2.6 Hz, 1H), 7.27 (m, 2H), 6.72 (d, *J*= 9.1 Hz, 1H), 4.61 (s, 2H), 2.99 (d, *J*= 6.4 Hz, 2H), 2.24 (septet, *J*= 6.8 Hz, 1H), 1.47 (s, 9H), 1.06 (d, *J*= 6.9 Hz, 6H). HPLC (Condition A) Purity 100.0%; Rt 6.3 min.

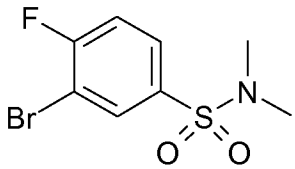
Intermediate 137: *tert*-butyl [4-chloro-2-({2-fluoro-5-[(2-methoxyethyl)sulfonyl]phenyl}ethynyl)phenoxy]acetate



Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 2-Bromo-1-fluoro-4-(2-methoxy-ethanesulfonyl)-benzene (Intermediate 132), the title compound was obtained as a colorless oil in 80% yield after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.12 (dd, *J*= 6.4, 2.4 Hz, 1H), 7.84 (ddd, *J*= 7.1,4.7,2.4 Hz, 1H), 7.48 (d, *J*= 2.6 Hz, 1H), 7.25 (m, 2H), 6.71 (d, *J*= 8.9 Hz, 1H), 4.60 (s, 2H), 3.73 (t, *J*= 6.1 Hz, 2H), 3.36 (t, *J*= 6.2 Hz, 2H), 3.21 (t, 3H), 1.46 (s, 9H). 1H NMR (DMSO-d6) δ . HPLC (Condition A) Purity 99.0%; Rt 5.8 min.

Intermediate 138: 3-bromo-4-fluoro-*N,N*-dimethylbenzenesulfonamide



Step 1: 4-fluoro-*N,N*-dimethylbenzenesulfonamide

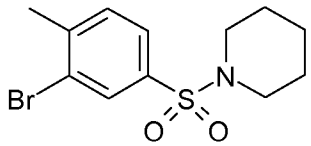
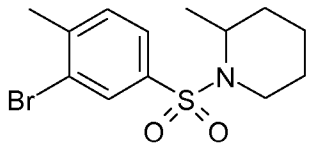
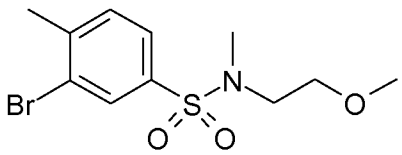
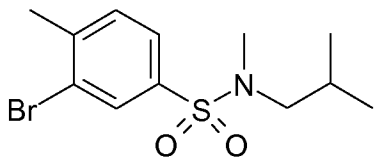
A cooled (0 °C) solution of 4-fluorobenzenesulfonyl chloride (2.00 g; 10.3 mmol) in THF (40 ml) is treated with a 2 M solution of dimethylamine in THF (11.3 ml; 22.6 mmol) and stirred at 0 °C for 30 minutes. The solvents were removed under reduced pressure, the residue taken up in EtOAc, the organic phase was washed with a saturated solution of NH_4Cl twice and with water. The organic phase was dried on $MgSO_4$, filtered and the solvent removed under reduced pressure to afford the title compound (1.80 g, 86%).

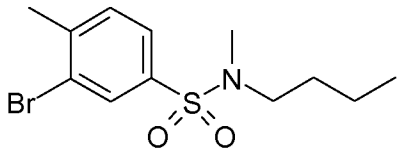
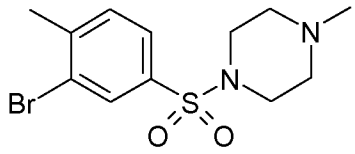
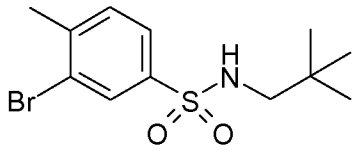
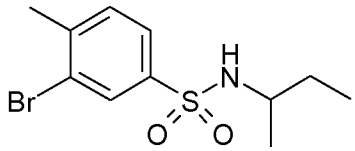
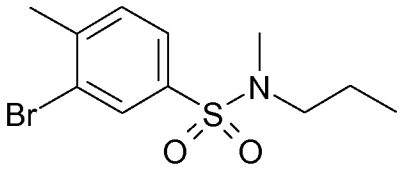
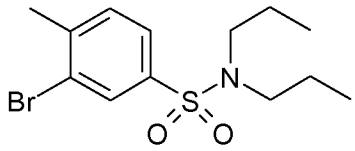
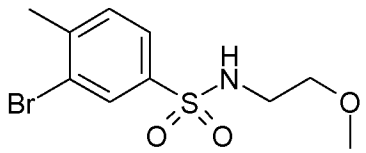
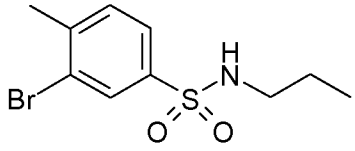
Step 2: 3-bromo-4-fluoro-*N,N*-dimethylbenzenesulfonamide

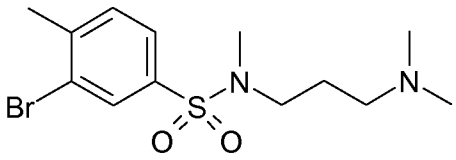
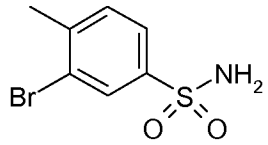
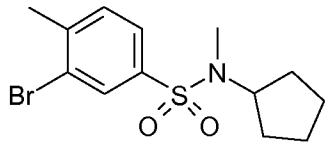
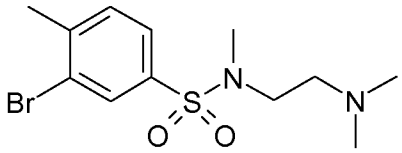
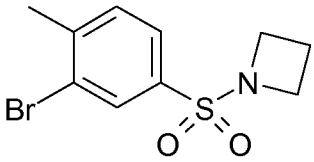
A solution of 4-fluoro-*N,N*-dimethylbenzenesulfonamide (1.80 g; 8.86 mmol) in conc. sulfuric acid (7 ml; 130 mmol) was treated with *N*-bromosuccinimide (1 730 mg; 9.74 mmol) and stirred at RT for 3 h. The reaction mixture was carefully poured on crushed ice, extracted with AcOEt and the organic phase was washed with a 0.1 N solution of NaOH in water twice, then with brine twice. The organic phase was dried on $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound as a white solid (2.04 g, 82%).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.04 (1H, dd, *J*= 6.5 Hz, *J*= 2.2 Hz), 7.83 (1H, ddd, *J*= 8.7 Hz, *J*= 4.6 Hz, *J*= 2.3 Hz), 7.66 (1H, t, *J*= 8.7 Hz), 2.65 (6H, s).

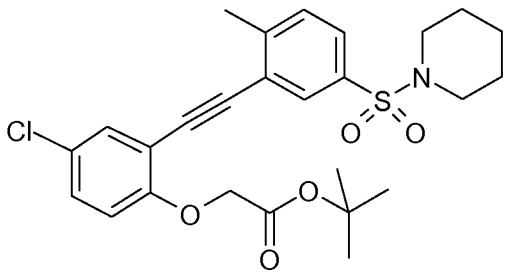
The compounds in the table below were all prepared following the general method as outlined in Intermediate 138:

Int.	Structure	Chemical name	^{1}H NMR ($CDCl_3$, 400MHz), δ [ppm]
139		1-[(3-bromo-4-methylphenyl)sulfonyl]piperidine	7.84 (1H, s), 7.64-7.63 (2H, m), 2.89 (1H, t, *J*= 5.5 Hz), 2.44 (3H, s), 1.54 (4H, m), 1.37 (2H, m).
140		1-[(3-bromo-4-methylphenyl)sulfonyl]-2-methylpiperidine	7.98 (s, 1H), 7.66-7.64 (d, 1H, *J*= 8Hz), 7.35-7.33 (d, 1H, *J*= 8Hz), 4.25-4.24 (s, 1H), 3.73-3.70 (m, 1H), 3.0-2.9 (t, 1H), 2.46 (s, 3H), 1.62-1.37 (m, 7H), 1.10-1.08 (bs, 3H)
141		3-bromo-*N*-(2-methoxyethyl)-*N*,4-dimethylbenzene sulfonamide	7.97-7.96 (s, 1H), 7.63-7.61 (d, 1H, *J*= 9.8 Hz), 7.38-7.36 (d, 1H, *J*= 8.0 Hz) 3.56-3.53 (t, 2H), 3.33 (s, 3H), 3.26-3.23 (t, 2H), 2.85 (s, 3H), 2.47 (s, 3H)
142		3-bromo-*N*-isobutyl-*N*,4-dimethylbenzene sulfonamide	7.95-7.94 (s,1H), 7.62-7.60 (d, 1H, *J*= 8.0 Hz), 7.39-7.37(d, 1H, *J*= 8 Hz), 2.77-2.75(d, 2H, *J*= 7.5 Hz), 2.72 (s, 3H), 2.47 (s, 3H), 1.90-1.83 (m, 1H), 0.96-0.94 (d, 6H, *J*= 6.6 Hz)

143		3-bromo-*N*-butyl-*N*,4-dimethylbenzene sulfonamide	7.94 (s, 1H), 7.60 (d, 1H, *J*= 9.6 Hz), 7.37 (d, 1H, *J*= 8.0 Hz), 3.02-2.99 (t, 2H), 2.72 (s, 3H), 2.47(s, 3H) 1.55-1.48 (m, 2H), 1.38-1.33 (m, 2H), 0.95-0.91 (t, 3H)
144		1-[(3-bromo-4-methylphenyl)sulfonyl]-4-methylpiperazine	7.91-7.87 (s, 1H), 7.59-7.57(d, 1H, *J*= 9.7 Hz), 7.40-7.38 (d, 1H, *J*= 7.9 Hz), 3.04 (bs, 4H), 2.50-2.47 (m, 7H), 2.28 (s, 3H)
145		3-bromo-*N*-(2,2-dimethylpropyl)-4-methylbenzenesulfonamide	8.03-8.02 (s, 1H), 7.69 (d, 1H, *J*= 9.8 Hz),7.37 (d, 1H, *J*= 8.0 Hz), 4.65-4.61(bs, 1H), 2.69 (d, 2H, *J*= 6.8Hz), 0.89 (s, 9H).
146		3-bromo-*N*-(*sec*-butyl)-4-methylbenzenesulfonamide	8.05 (s, 1H) 7.71 (d, 1H, *J*= 9.8 Hz); 7.36 (s, 1H); 4.75 (bs,1H) 3.29-3.22(m, 1H); 2.46 (s, 3H),1.45-1.38 (m, 2H); 1.04 (d, 3H,*J*= 6.5); 0.83-0.79(t, 3H).
147		3-bromo-*N*,4-dimethyl-*N*-propylbenzenesulfonamide	7.94 (s, 1H), 7.60 (d, 1H, *J*= 9.8 Hz), 7.37 (d, 1H, *J*= 8.0 Hz), 2.98-2.95 (t, 2H), 2.73 (s, 3H), 2.4 (s, 3H), 1.59-1.53 (m, 2H), 0.94-0.91 (t, 3H)
148		3-bromo-4-methyl-*N*,*N*-dipropylbenzenesulfonamide	7.97 (s, 1H), 7.63 (d, 1H, *J*= 9.8 Hz), 7.35 (d, 1H, *J*= 8.0 Hz), 3.09-3.06 (t, 4H), 2.4 (s, 3H), 1.59-1.53 (m, 4H), 0.9-0.8 (t, 6H)
149		3-bromo-*N*-(2-methoxyethyl)-4-methylbenzenesulfonamide	8.02 (s, 1H), 7.7 (d, 1H, *J*= 9.8 Hz), 7.37 (d, 1H, *J*= 8.0 Hz), 4.9 (bs, 1H), 3.43-3.41 (t, 2H), 3.29 (s, 3H), 3.15-3.11 (t, 2H), 2.47(s, 3H)
150		3-bromo-4-methyl-*N*-propylbenzenesulfonamide	8.04 (s, 1H), 7.70 (d, 1H, *J*= 9.8 Hz), 7.38 (d, 1H, *J*= 8.0 Hz), 4.53-4.50 (m, 1H), 2.96-2.91 (m, 2H), 2.47 (s, 3H), 1.54-1.48 (m, 2H), 0.91-0.87 (m, 3H)

151		3-bromo-*N*-[3-(dimethylamino)propyl]-*N*,4-dimethylbenzene sulfonamide	7.92 (s, 1H), 7.62 (d, 1H, *J*= 9.8 Hz), 7.41 (d, 1H, *J*= 8.0 Hz), 3.16-3.10 (m, 4H), 2.8 (s, 3H), 2.78 (s, 6H), 2.48 (s, 3H), 2.19-2.15 (m, 2H)
152		3-bromo-4-methylbenzenesulfonamide	7.96 (s, 1H), 7.70 (d, 1H, *J*= 8.0 Hz), 7.54 (d, 1H, *J*= 8.0Hz), 7.44 (s, 2H), 2.40 (s, 3H)
153		3-bromo-*N*-cyclopentyl-*N*,4-dimethylbenzene sulfonamide	7.96 (s, 1H), 7.63 (d, 1H, *J*= 9.8Hz), 7.36 (d, 1H, *J*= 7.8 Hz), 4.39-4.30 (m, 1H), 2.72 (s, 3H), 2.47 (s, 3H).
154		bromo-*N*-[2-(dimethylamino)ethyl]-*N*,4-dimethylbenzene sulfonamide	7.98 (s, 1H), 7.62 (d, 1H, *J*= 9.8 Hz), 7.38 (d, 1H, *J*= 8 Hz), 3.15-3.12 (t, 2H), 2.8 (s, 3H), 2.51-2.47 (t, 2H), 2.26 (s, 6H)
155		1-[(3-bromo-4-methylphenyl)sulfonyl]azetidine	8.02 (s, 1H), 7.68 (d, 1H, *J*= 9.7 Hz), 7.44 (d, 1H, *J*= 7.9 Hz), 3.82-3.78 (t, 4H), 2.51 (s, 3H), 2.15-2.07(m, 2H)

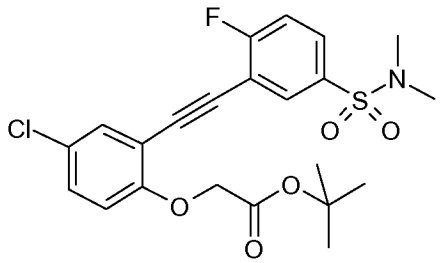
Intermediate 156: *tert*-butyl (4-chloro-2-{[2-methyl-5-(piperidin-1-ylsulfonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 1-[(3-bromo-4-methylphenyl)sulfonyl]piperidine (Intermediate 139), the title compound was obtained as a yellow solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.78 (1H, d, *J*= 1.8 Hz), 7.67-7.59 (3H, m), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s), 2.91 (4H, m), 2.57 (3H, s); 1.55 (4H, m), 1.43 (9H, s), 1.40 (2H, m).

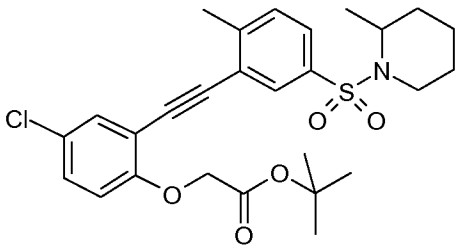
Intermediate 157: *tert*-butyl [4-chloro-2-({5-[(dimethylamino)sulfonyl]-2-fluorophenyl}ethynyl)phenoxy]acetate



Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 3-bromo-4-fluoro-*N,N*-dimethylbenzenesulfonamide (Intermediate 138), the title compound was obtained as a colorless oil after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.99 (1H, dd, *J*= 6.5 Hz, *J*= 2.4 Hz), 7.85 (1H, ddd, *J*= 8.7 Hz, *J*= 4.8 Hz, *J*= 2.4 Hz), 7.67-7.61 (2H, m), 7.48 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 2.67 (6H, s).

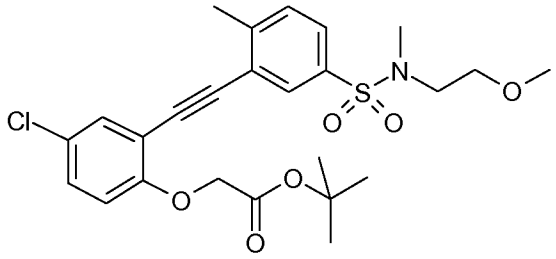
Intermediate 158: *tert*-butyl [4-chloro-2-({2-methyl-5-[(2-methylpiperidin-1-yl)sulfonyl]phenyl}ethynyl)phenoxy]acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 1-(3-bromo-4-methyl-benzenesulfonyl)-2-methyl-piperidine (Intermediate 140), the title compound was obtained as a yellow sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.85 (1H, d, *J*= 2.0 Hz), 7.72 (1H, dd, *J*= 8.1 Hz, *J*= 2.0 Hz), 7.66 (1H, d, *J*= 2.7 Hz), 7.56 (1H, d, *J*= 8.1 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s), 4.14 (1H, m), 3.63 (1H, m), 2.98 (1H, dt, *J*= 13.0 Hz, *J*= 2.5 Hz), 2.55 (3H, s), 1.40-1.56 (14H, m), 1.21 (1H, m), 1.00 (3H, d, *J*= 6.9 Hz). HPLC (Condition A) Purity 99.6%; Rt 6.4 min.

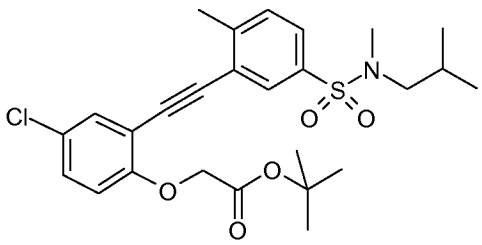
Intermediate 159: *tert*-butyl {4-chloro-2-[(5-{[(2-methoxyethyl)(methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 3-bromo-*N*-(2-methoxy-ethyl)-4,*N*-dimethyl-benzenesulfonamide (Intermediate 141), the title compound was obtained as a yellow sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.84 (1H, d, *J*= 1.9 Hz), 7.70 (1H, dd, *J*= 8.1 Hz, *J*= 1.9 Hz), 7.66 (1H, d, *J*= 2.7 Hz), 7.58 (1H, d, *J*= 8.1 Hz), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s), 3.45 (2H, t, *J*= 5.3 Hz), 3.22 (3H, s), 3.17 (2H, t, *J*= 5.3 Hz), 2.73 (3H, s), 2.56 (3H, s), 1.43 (9H, s). HPLC (Condition A) Purity 97.1%; Rt 5.8 min.

Intermediate 160: *tert*-butyl {4-chloro-2-[(5-{[isobutyl(methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetate

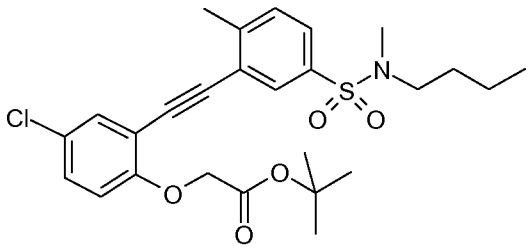


Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 3-bromo-*N*-isobutyl-

4,*N*,dimethyl-benzenesulfonamide (Intermediate 142), the title compound was obtained as a yellow sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.81 (1H, d, *J*= 2.0 Hz), 7.68 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.67 (1H, d, *J*= 2.7 Hz), 7.59 (1H, d, *J*= 8.0 Hz), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s), 2.71 (2H, d, *J*= 7.4 Hz), 2.66 (3H, s), 2.56 (3H, s), 1.84 (1H, m), 1.43 (9H, s), 0.87 (6H, d, *J*= 6.6 Hz). HPLC (Condition A) Purity 100.0%; Rt 6.4 min.

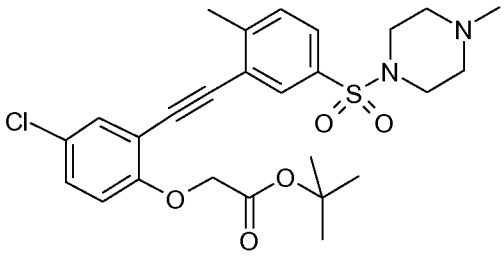
Intermediate 161: *tert*-butyl {2-[(5-{[butyl(methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]-4-chlorophenoxy}acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 3-bromo-*N*-butyl-4,*N*,dimethyl-benzenesulfonamide (Intermediate 143), the title compound was obtained as a yellow sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.82 (1H, d, *J*= 1.9 Hz), 7.69 (1H, dd, *J*= 8.1 Hz, *J*= 1.9 Hz), 7.66 (1H, d, *J*= 2.7 Hz), 7.59 (1H, d, *J*= 8.1 Hz), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s), 2.95 (2H, t, *J*= 7.0 Hz), 2.66 (3H, s), 2.56 (3H, s), 1.45 (2H, m), 1.43 (9H, s), 1.28 (2H, m), 0.88 (3H, t, *J*= 7.3 Hz). HPLC (Condition A) Purity 95.6%; Rt 6.4 min.

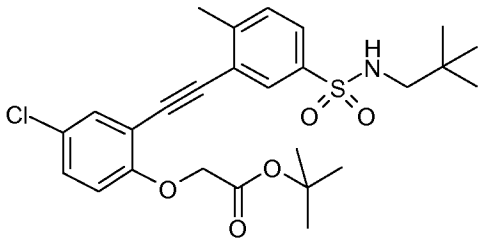
Intermediate 162: *tert*-butyl [4-chloro-2-({2-methyl-5-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}ethynyl)phenoxy]acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 1-(3-bromo-4-methyl-benzenesulfonyl)-4-methyl-piperazine (Intermediate 144), the title compound was obtained after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.79 (1H, d, *J*= 1.6 Hz), 7.63-7.67 (3H, m), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s), 2.91 (4H, m), 2.58 (3H, s), 2.36 (4H,m), 2.13 (3H, s), 1.43 (9H, s). HPLC (Condition A) Purity 94.4%; Rt 4.2 min.

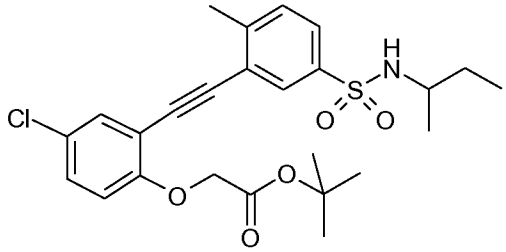
Intermediate 163: *tert*-butyl {4-chloro-2-[(5-{[(2,2-dimethylpropyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 3-bromo-*N*-(2,2-dimethyl-propyl)-4-methyl-benzenesulfonamide (Intermediate 145), the title compound was obtained after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.87 (1H, d, *J*= 2.0 Hz), 7.70 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.64 (1H, d, *J*= 2.7 Hz), 7.53-7.61 (2H, m), 7.44 (1H, dd, *J*= 9.0 Hz; *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 2.54 (3H, s), 1.42 (9H, s), 0.83 (9H, s) (3 remaining protons, probably hidden under the signal of DMSO). HPLC (Condition A) Purity 94.0%; Rt 5.7 min.

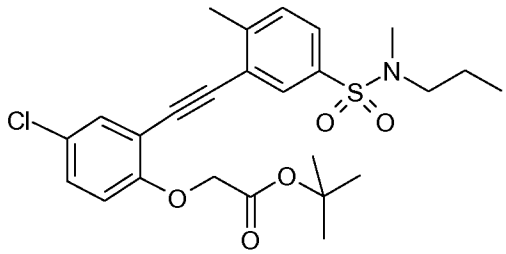
Intermediate 164: *tert*-butyl [2-({5-[(*sec*-butylamino)sulfonyl]-2-methylphenyl}ethynyl)-4-chlorophenoxy]acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 3-bromo-*N*-*sec*-butyl-4-methyl-benzenesulfonamide (Intermediate 146), the title compound was obtained as a brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.87 (1H, d, *J*= 2.0 Hz), 7.71 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.65 (1H, d, *J*= 2.7 Hz), 7.53-7.57 (2H, m), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 3.05 (1H, m), 2.54 (3H, s), 1.42 (9H, s), 1.30 (2H, quint., *J*= 7.0 Hz), 0.87 (3H, d, *J*= 6.6 Hz), 0.72 (3H, t, *J*= 7.0 Hz). HPLC (Condition A) Purity 92.2%; Rt 5.7 min.

Intermediate 165: *tert*-butyl {4-chloro-2-[(2-methyl-5-{[methyl(propyl)amino]sulfonyl}phenyl)ethynyl]phenoxy}acetate

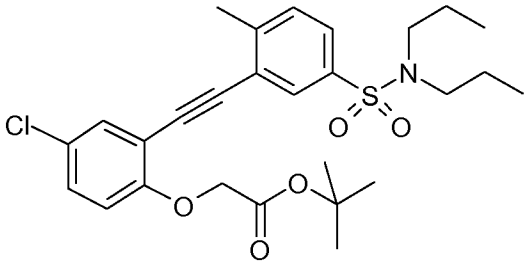


Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 3-bromo-4,*N*-dimethyl-*N*,propyl-benzenesulfonamide (Intermediate 147), the title compound was obtained as a yellow sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.82 (1H, d, *J*= 2.0 Hz), 7.69(1H, dd, *J*= 8.1 Hz, *J*= 2.0 Hz), 7.66 (1H, d, *J*= 2.7 Hz), 7.59 (1H, d, *J*= 8.1 Hz), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s), 2.92 (2H, t, *J*= 7.2 Hz), 2.67 (3H, s), 2.56

(3H, s), 1.48 (2H, sext., *J*= 7.2 Hz), 1.43 (9H, s), 0.85 (3H, t, *J*= 7.2 Hz). HPLC (Condition A) Purity 98.4%; Rt 5.9 min.

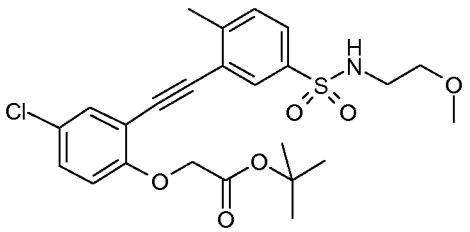
Intermediate 166: *tert*-butyl [4-chloro-2-({5-[(dipropylamino)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 3-bromo-4-methyl-*N,N*-dipropyl-benzenesulfonamide (Intermediate 148), the title compound was obtained as a yellow sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.84 (1H, d, *J*= 2.0 Hz), 7.72 (1H, dd, *J*= 8.1 Hz, *J*= 2.0 Hz), 7.66 (1H, d, *J*= 2.7 Hz), 7.56 (1H, d, *J*= 8.1 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s), 3.04 (4H, m), 2.55 (3H, s), 1.46 (4H, m), 1.43 (9H, s), 0.82 (6H, t, *J*= 7.4 Hz). HPLC (Condition A) Purity 97.8%; Rt 6.3 min.

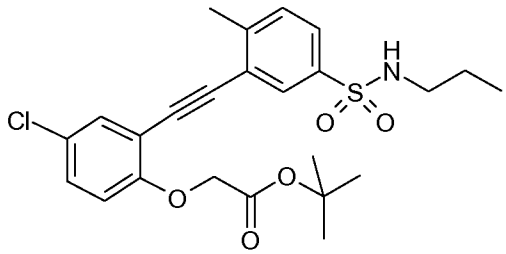
Intermediate 167: *tert*-butyl {4-chloro-2-[(5-{[(2-methoxyethyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 3-bromo-*N*-(2-methoxy-ethyl)-4-methyl-benzenesulfonamide (Intermediate 149), the title compound was obtained as a orange sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.87 (1H, d, *J*= 2.0 Hz), 7.77 (1H, t, *J*= 5.8 Hz), 7.70 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.64 (1H, d, *J*= 2.7 Hz), 7.55 (1H, d, *J*= 8.0 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 3.30 (2H, t, *J*= 5.8 Hz), 3.16 (3H, s), 2.91 (2H, q, *J*= 5.8 Hz), 2.55 (3H, s), 1.42 (9H, s). HPLC (Condition A) Purity 97.2%; Rt 5.4 min.

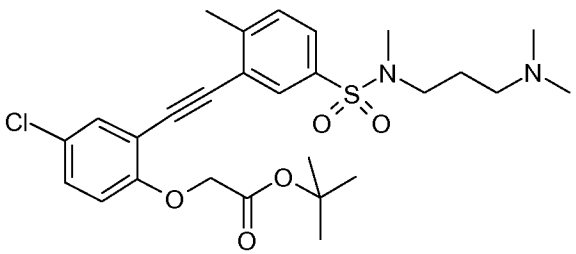
Intermediate 168: *tert*-butyl [4-chloro-2-({2-methyl-5-[(propylamino)sulfonyl]phenyl}ethynyl)phenoxy]acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 3-bromo-4-methyl-*N*-propyl-benzenesulfonamide (Intermediate 150), the title compound was obtained as a yellowb sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.85 (1H, d, *J*= 2.0 Hz), 7.69 (1H, dd, *J*= 8.1 Hz, *J*= 2.0 Hz), 7.64 (1H, d, *J*= 2.7 Hz), 7.61 (1H, bs), 7.56 (1H, d, *J*= 8.1 Hz), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 2.70 (2H, t, *J*= 6.9 Hz), 2.55 (3H, s), 1.43 (9H, s), 1.37 (2H, m), 0.79 (3H, t, *J*= 7.3 Hz). HPLC (Condition A) Purity 95.4%; Rt 5.8 min.

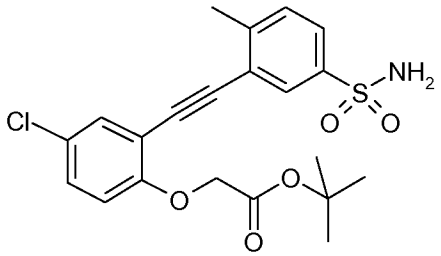
Intermediate 169: *tert*-butyl {4-chloro-2-[(5-{[[3-(dimethylamino)propyl](methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 3-bromo-*N*-(3-dimethylamino-propyl)-4,*N*-dimethyl-benzenesulfonamide (Intermediate 151), the title compound was obtained after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.84 (1H, d, *J*= 2.0 Hz), 7.71 (1H, dd, *J*= 8.1 Hz, *J*= 2.0 Hz), 7.65 (1H, d, *J*= 2.7 Hz), 7.61 (1H, d, *J*= 8.1 Hz), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 3.00-3.05 (4H, m), 2.73 (6H, s), 2.70 (3H, s), 2.57 (3H, s), 1.84-1.93 (2H, m), 1.43 (9H, s). HPLC (Condition A) Purity 98.5%; Rt 5.0 min.

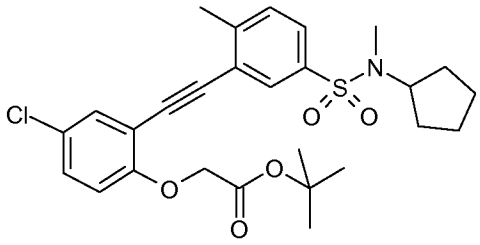
Intermediate 170: *tert*-butyl (2-{[5-(aminosulfonyl)-2-methylphenyl]ethynyl}-4-chlorophenoxy)acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 3-bromo-4-methylbenzenesulfonamide (Intermediate 152), the title compound was obtained as a brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.90 (1H, d, *J*= 2.0 Hz), 7.73 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.63 (1H, d, *J*= 2.7 Hz), 7.53 (1H, d, *J*= 8.0 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.40 (2H, bs), 7.02 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 2.54 (3H, s), 1.43 (9H, s). HPLC (Condition A) Purity 93.1%; Rt 5.0 min.

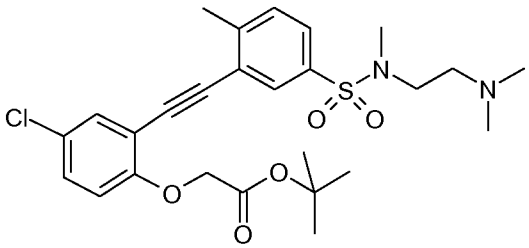
Intermediate 171: *tert*-butyl {4-chloro-2-[(5-{[cyclopentyl(methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 3-bromo-*N*-cyclopentyl-4,*N*-dimethyl-benzenesulfonamide (Intermediate 153), the title compound was obtained as a orange sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.84 (1H, d, *J*= 2.0 Hz), 7.71 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.66 (1H, d, *J*= 2.7 Hz), 7.57(1H, d, *J*= 8.0 Hz), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s), 4.25 (1H, quint., *J*= 7.7 Hz), 2.66 (3H, s), 2.56 (3H, s), 1.31-1.53 (17H, m). HPLC (Condition A) Purity 87.7%; Rt 6.1 min.

Intermediate 172: *tert*-butyl {4-chloro-2-[(5-{[[2-(dimethylamino)ethyl](methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetate

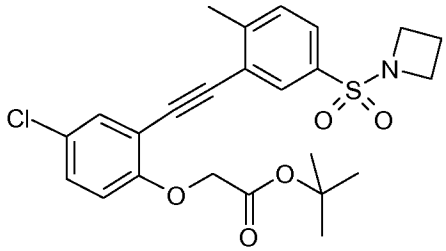


Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 3-bromo-*N*-(2-dimethylamino-ethyl)-4,*N*-dimethyl-benzenesulfonamide (Intermediate 154), the title compound was obtained as a yellow sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.85 (1H, d, *J*= 2.0 Hz), 7.71 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.663 (1H, d, *J*= 2.7 Hz), 7.58 (1H, d, *J*= 8.0 Hz), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s), 3.07 (2H, t, *J*= 6.6 Hz), 2.72 (3H, s), 2.56

(3H, s), 2.37 (2H, t, *J*= 6.6 Hz), 2.13 (6H, s), 1.43 (9H, s). HPLC (Condition A) Purity 95.2%; Rt 4.2 min.

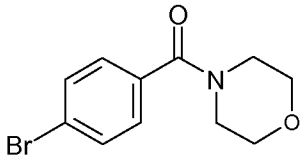
Intermediate 173: *tert*-butyl (2-{[5-(azetidin-1-ylsulfonyl)-2-methylphenyl]ethynyl}-4-chlorophenoxy)acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 1-(3-bromo-4-methyl-benzenesulfonyl)-azetidine (Intermediate 155), the title compound was obtained as a yellow sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.85 (1H, d, *J*= 2.0 Hz), 7.73 (1H, dd, *J*= 8.0 Hz, *J*= 2.0Hz), 7.65-7.68 (2H, m), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 3.69 (4H, t, *J*= 7.7 Hz), 2.60 (3H, s), 2.01 (2H, quint., *J*= 7.7 Hz), 1.43 (9H, s). HPLC (Condition A) Purity 96.9%; Rt 5.6 min.

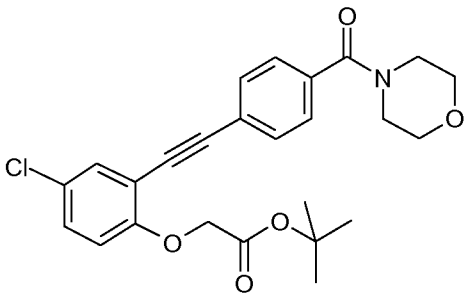
Intermediate 174: 4-(4-bromobenzoyl)morpholine



A cooled (0 °C) solution of 4-bromobenzoyl chloride (250 mg; 1.14 mmol) in THF (5 ml) was treated with a 2 M solution of morpholine in THF (219 µl; 2.51 mmol). The reaction mixture was allowed to warm to RT and stirred for 2 days, diluted with EtOAc and washed with a saturated NH_4Cl solution in water. The organic phase was dried over $MgSO_4$, filtered and concentrated to dryness affording the title compound as a pink solid (307 mg, quantitative yield).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.65 (2H, d, *J*= 8.5 Hz), 7.37 (2H, d, *J*= 8.5 Hz), 3.59 (6H, bs), 3.33 (2H, bs). HPLC (Condition A) Purity 94.2%; Rt 2.6 min.

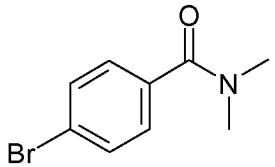
Intermediate 175: *tert*-butyl (4-chloro-2-{[4-(morpholin-4-ylcarbonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 4-(4-bromobenzoyl)morpholine (Intermediate 174), the title compound was obtained as a brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.59-7.62 (3H, m), 7.41-7.49 (3H, m), 7.00 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s), 3.60 (6H, bs), 1.43 (9H, s) (2 remaining protons, probably hidden under the signal of water). HPLC (Condition A) Purity 98.4%; Rt 5.0 min.

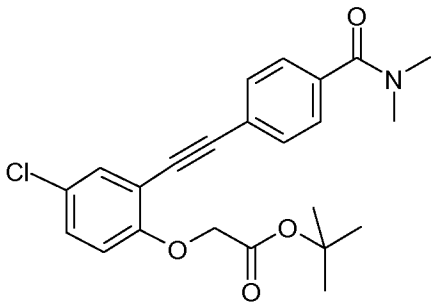
Intermediate 176: 4-bromo-*N*,*N*-dimethylbenzamide



Following the general method as outlined in Intermediate 174, starting from 4-bromobenzoyl chloride and dimethylamine, the title compound was obtained as a pink solid in 93% yield.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.63 (2H, d, *J*= 8.5 Hz), 7.36 (2H, d, *J*= 8.5 Hz), 2.97 (3H, s), 2.89 (3H, s). HPLC (Condition A) Purity 91.3%; Rt 2.7 min.

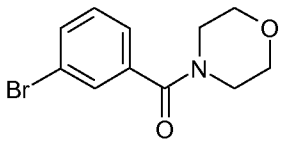
Intermediate 177: *tert*-butyl [4-chloro-2-({4-[(dimethylamino)carbonyl]phenyl}ethynyl)phenoxy]acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 4-bromo-*N,N*-dimethylbenzamide (Intermediate 176), the title compound was obtained as a brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.57-7.60 (3H, m), 7.41-7.47 (3H, m), 6.99 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s), 2.99 (3H, s), 2.91 (3H, s), 1.43 (9H, s). HPLC (Condition A) Purity 99.5%; Rt 5.0 min.

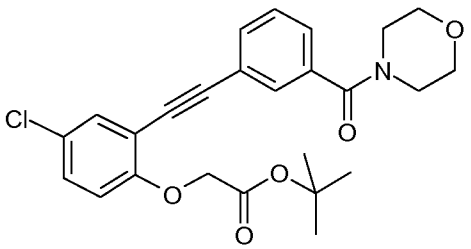
Intermediate 178: 4-(3-bromobenzoyl)morpholine



Following the general method as outlined in Intermediate 174, starting from 3-bromobenzoyl chloride and morpholine, the title compound was obtained as a colorless sticky solid in 71% yield.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.66 (1H, m), 7.61 (1H, m), 7.41 (2H, m), 3.60 (6H, bs), 3.32 (2H, bs). HPLC (Condition A) Purity 96.4%; Rt 2.6 min.

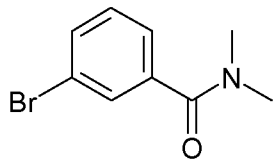
Intermediate 179: *tert*-butyl (4-chloro-2-{[3-(morpholin-4-ylcarbonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 4-(3-bromobenzoyl)morpholine (Intermediate 178), the title compound was obtained as a brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.40-7.63 (6H, m), 7.00 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s), 3.61 (6H, bs), 1.43 (9H, s) (2 remaining protons, probably hidden under the signal of water). HPLC (Condition A) Purity 96.6%; Rt 4.8 min.

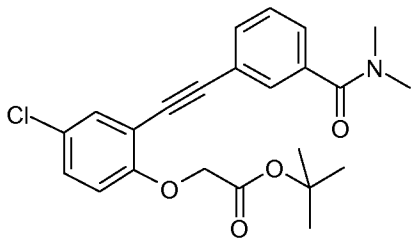
Intermediate 180: 3-bromo-*N,N*-dimethylbenzamide



Following the general method as outlined in Intermediate 174, starting from 3-bromobenzoyl chloride and dimethylamine, the title compound was obtained as a orange sticky solid in 85% yield.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.64 (1H, m), 7.58 (1H, m), 7.36-7.43 (2H, m), 2.97 (3H, s), 2.88 (3H, s). HPLC (Condition A) Purity 98.2%; Rt 2.6 min.

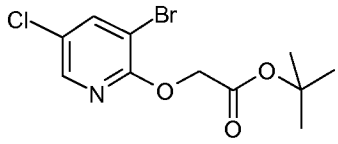
Intermediate 181: *tert*-butyl [4-chloro-2-({3-[(dimethylamino)carbonyl]phenyl}ethynyl)phenoxy]acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 3-bromo-*N,N*-dimethylbenzamide (Intermediate 180), the title compound was obtained as a brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.37-7.61 (6H, m), 6.99 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s), 2.99 (3H, s), 2.92 (3H, s), 1.43 (9H, s). HPLC (Condition A) Purity 99.0%; Rt 5.5 min.

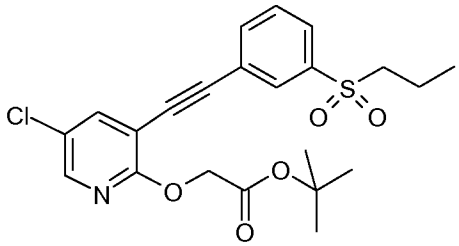
Intermediate 182: *tert*-butyl [(3-bromo-5-chloropyridin-2-yl)oxy]acetate



A solution of 2-*tert*-butyl glycolate (437 mg; 3.31 mmol) in anhydrous THF (5 mL) was treated with NaH (159 mg; 3.97 mmol) and stirred at RT for 10 minutes before treating with a solution of 3-bromo-2,5-dichloropyridine (Matrix; 500 mg; 2.20 mmol) in anhydrous THF (5 mL). The resulting reaction mixture was stirred for 22 hours. The reaction mixture was treated with a solution of 2-*tert*-butyl glycolate (437 mg; 3.31 mmol) in THF (2 ml), then with NaH (159 mg; 3.97 mmol) and the reaction mixture was stirred for 16 h. The reaction was quenched with tBuOH, the sovent removed under reduced pressure affording a brown solid, which was purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc, affording the title compound as a yellow sticky solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.33 (1H, d, *J*= 2.3 Hz), 8.21 (1H, d, *J*= 2.3 Hz), 4.86 (2H, s), 1.38 (9H, s). HPLC (Condition A) Rt 5.1 min.

Intermediate 183: *tert*-butyl [(5-chloro-3-{[3-(propylsulfonyl)phenyl]ethynyl}pyridin-2-yl)oxy]acetate

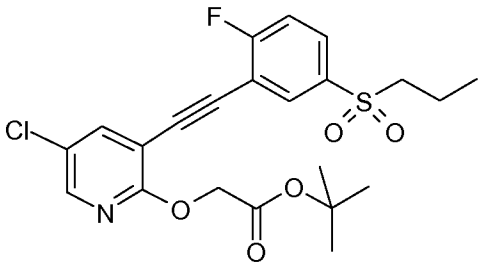


A mixture of *tert*-butyl [(3-bromo-5-chloropyridin-2-yl)oxy]acetate (Intermediate 182 ; 160 mg; 0.50 mmol), 1-ethynyl-3-(propane-1-sulfonyl)-benzene (Intermediate 42; 155 mg; 0.74 mmol), bis(triphenylphosphine)palladium (II) chloride (10 mg; 0.01 mmol) and triphenylphosphine (26 mg; 0.10 mmol) is treated with cuprous iodide (3 mg; 0.01 mmol) and TEA (1.10 ml) and heated at 90 °C in a sealed vessel for 15 hours. The mixture was

diluted with EtOAc and washed with a saturated NH_4Cl solution and brine. The organic phase was dried over $MgSO_4$, concentrated to dryness under reduced pressure affording a sticky solid, which was purified by column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc, affording the title compound as a yellow sticky solid

^1H NMR (300MHz, DMSO-d_6) δ [ppm] 8.26 (1H, d, *J*= 2.6 Hz), 8.24 (1H, d, *J*= 2.6 Hz), 8.04 (1H, t, *J*= 1.5 Hz), 7.96 (1H, dt, *J*= 7.8 Hz, *J*= 1.5 Hz), 7.92 (1H, dt, *J*= 7.8 Hz, *J*= 1.5 Hz), 7.75 (1H, t, *J*= 7.8 Hz), 4.89 (2H, s), 3.37 (2H, m), 1.56 (2H, sext., *J*= 7.6 Hz), 1.40 (9H, s), 0.92 (3H, t, *J*= 7.6 Hz). HPLC (Condition A) Purity 98.4%; Rt 5.6 min.

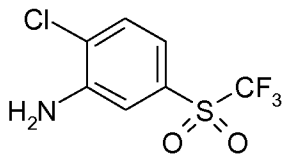
Intermediate 184: *tert*-butyl [(5-chloro-3-{[2-fluoro-5-(propylsulfonyl)phenyl]ethynyl}pyridin-2-yl)oxy]acetate



Following the general method as outlined in Intermediate 182, starting from *tert*-butyl [(3-bromo-5-chloropyridin-2-yl)oxy]acetate (Intermediate 183) and 2-ethynyl-1-fluoro-4-(propane-1-sulfonyl)-benzene (Intermediate 109), the title compound was obtained as a yellow sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^1H NMR (300MHz, DMSO-d_6) δ [ppm] 8.29 (1H, d, *J*= 2.5 Hz), 8.254 (1H, d, *J*= 2.5 Hz), 8.15 (1H, dd, *J*= 6.4 Hz, *J*= 2.2 Hz), 8.02 (1H, m), 7.68 (1H, t, *J*= 9.0 Hz), 4.89 (2H, s), 3.397 (2H, m), 1.57 (2H, sext., *J*= 7.4 Hz), 1.40 (9H, s), 0.93 (3H, t, *J*= 7.4 Hz). HPLC (Condition A) Purity 97.0%; Rt 5.4 min.

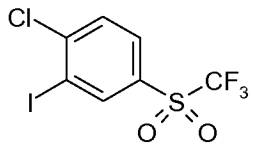
Intermediate 185: 2-chloro-5-[(trifluoromethyl)sulfonyl]aniline



Following the general method as outlined in Intermediate 76, starting from 1-chloro-2-nitro-4-[(trifluoromethyl)sulfonyl]benzene (MDA), the title compound was obtained as a brown solid in quantitative yield.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.65 (1H, d, *J*= 8.3 Hz), 7.47 (1H, d, *J*= 2.2 Hz), 7.16 (1H, dd, *J*= 8.3 Hz, *J*= 2.2 Hz), 6.29 (2H, s). HPLC (Condition A) Purity 92.2%; Rt 3.9 min.

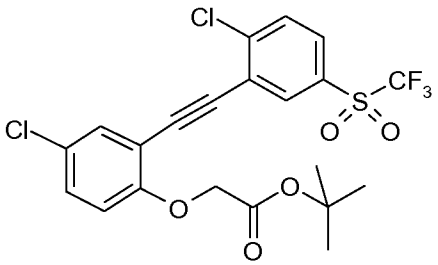
Intermediate 186: 1-chloro-2-iodo-4-[(trifluoromethyl)sulfonyl]benzene



Following the general method as outlined in Intermediate 58, starting from 2-chloro-5-[(trifluoromethyl)sulfonyl]aniline (Intermediate 185), the title compound was obtained as a beige solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.53 (1H, d, *J*= 2.2 Hz), 8.15 (1H, dd, *J*= 8.5 Hz, *J*= 2.2 Hz), 8.03 (1H, d, *J*= 8.5 Hz). HPLC (Condition A) Rt 5.0 min.

Intermediate 187: *tert*-butyl [4-chloro-2-({2-chloro-5-[(trifluoromethyl)sulfonyl]phenyl}ethynyl)phenoxy]acetate

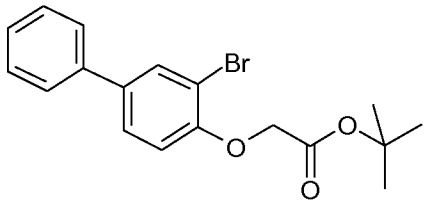


Following the general method as outlined in Intermediate 79, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 1-chloro-2-iodo-4-[(trifluoromethyl)sulfonyl]benzene (Intermediate 186), the title compound was obtained as a white solid in 72% yield after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.39 (1H, d, *J*= 2.2 Hz), 8.16 (1H, dd, *J*= 8.6 Hz, *J*= 2.2 Hz), 8.08 (1H, d, *J*= 8.6 Hz), 7.70 (1H, d, *J*= 2.7 Hz), 7.50 (1H, dd, *J*= 9.0 Hz, *J*=

2.0 Hz), 7.06 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 1.43 (9H, s). HPLC (Condition A) Purity 100.0%; Rt 6.1 min.

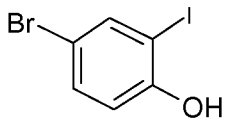
Intermediate 188: *tert*-butyl [(3-bromobiphenyl-4-yl)oxy]acetate



Following the general method as outlined in Intermediate 1, starting from 3-bromo[1,1'-biphenyl]-4-ol and *tert*-butyl bromoacetate (Matrix), the title compound was obtained as a colorless sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.88 (1H, d, *J*= 2.3 Hz), 7.61-7.66 (3H, m), 7.41-7.47 (2H, m), 7.34 (1H, m), 7.06 (1H, d, *J*= 8.7 Hz), 4.83 (2H, s), 1.44 (9H, s). HPLC (Condition A) Purity 94.2%; Rt 5.6 min.

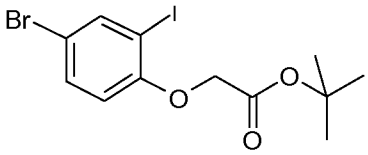
Intermediate 189: 4-Bromo-2-iodophenol



A solution of 4-bromophenol (35.0 g, 145 mmol) in acetic acid (250 ml) was treated with *N*-iodosuccinimide (32.5 g, 145 mmol) at RT. The reaction mixture was stirred at RT for 18 h. The reaction mixture was filtered to remove the solid and the filtrate was concentrated under reduced pressure. The crude material was purified by column chromatography (silica) eluting with 1% methanol in chloroform to afford the title compound as a brown liquid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 10.59 (1H, s), 7.78 (1H, s), 7.35 (1H, d), 6.82 (1H, d). MS (ESI$^+$): 296.6. HPLC (Method D) Purity 99.3 %; Rt 3.81 min.

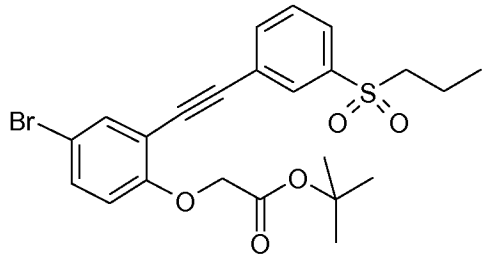
Intermediate 190: *tert*-Butyl (4-bromo-2-iodophenoxy)acetate



Following the general method as outlined in Intermediate 1, starting from 4-bromo-2-iodophenol (Interemdiate 189), the title compound was obtained as a brown oil after purification by flash column chromatography (silica), eluting with 2% methanol in chloroform.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.92 (1H, t), 7.51 (1H, p), 6.83 (1H, d), 4.76 (2H, s), 1.40 (9H, s). MS (ESI$^+$): 355.0. HPLC (Condition A) Purity 96.7%; Rt 6.03 min.

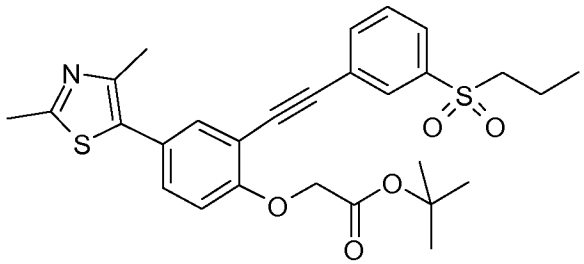
Intermediate 191: *tert*-butyl (4-bromo-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 20, starting from (4-bromo-2-iodo-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 190) and 1-ethynyl-3-(propane-1-sulfonyl)-benzene (Intermediate 42), the title compound was obtained as a yellow sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.02 (1H, t, *J*= 1.6 Hz), 7.84-7.94 (2H, m), 7.77 (1H, d, *J*= 2.5 Hz), 7.73 (1H, t, *J*= 7.8 Hz), 7.57 (1H, dd, *J*= 9.0 Hz, *J*= 2.5 Hz), 6.96 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 3.36 (2H, m); 1.57 (2H, sext., *J*= 7.6 Hz), 1.73 (9H, s), 0.92 (3H, t, *J*= 7.6 Hz). HPLC (Condition A) Purity 100.0%; Rt 5.4 min.

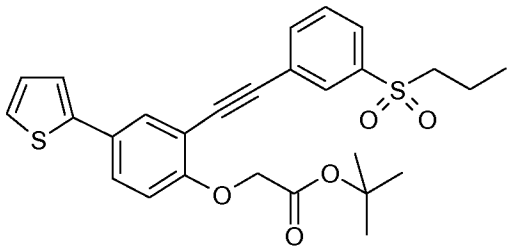
Intermediate 192: *tert*-butyl (4-(2,4-dimethyl-1,3-thiazol-5-yl)-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate



A solution of *tert*-butyl (4-bromo-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 191; 100 mg; 0.20 mmol), 2,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-

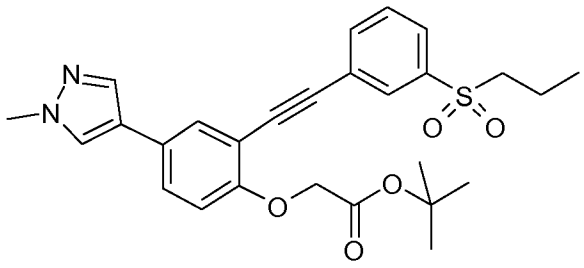
dioxaborolan-2-yl)-1,3-thiazole (73 mg; 0.30 mmol) was placed in a microwave vial and treated with caesium fluoride (93 mg; 0.61 mmol) and bis(triphenylphosphine)palladium(II) chloride (14 mg; 0.02 mmol). The tube was sealed and degased with N_2 before adding dioxane (2 ml) and water (1 ml). The resulting reaction mixture was irradiated in a microwave reactor at 120 °C for 10 minutes. The reaction mixture was taken up in EtOAc and washed with water and brine. The organic phase was dried over $MgSO_4$, filtered, concentrated and purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc affording the title compound as a brown sticky solid (78 mg, 73%).
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.02 (1H, t, *J*= 1.5 Hz), 7.89-7.93 (2H, m), 7.73 (1H, t, *J*= 7.8 Hz), 7.60 (1H, d, *J*= 2.4 Hz), 7.46 (1H, dd, *J*= 8.8 Hz), 7.05 (1H, d, *J*= 7.8 Hz), 4.86 (2H, s), 3.36 (2H, m), 2.62 (3H, s), 2.36 (3H, s), 1.57 (2H, sext., *J*= 7.5 Hz), 1.45 (9H, s), 0.93 (3H, t, *J*= 7.5 Hz). HPLC (Condition A) Purity 97.7%; Rt 4.5 min.

Intermediate 193: *tert*-butyl [2-{[3-(propylsulfonyl)phenyl]ethynyl}-4-(2-thienyl)phenoxy]acetate



Following the general method as outlined in Intermediate 192, starting from *tert*-butyl (4-bromo-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 191) and 2-(4,4,5,5-tetramethyl-1,3,2- dioxaborolan-2-yl)thiophene, the title compound was obtained as a yellow sticky solid in 99% yield after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.04 (1H, t, *J*= 1.5 Hz), 7.90-7.94 (2H, m), 7.85 (1H, d, *J*= 2.4 Hz), 7.74 (1H, t, *J*= 7.8 Hz), 7.67 (1H, dd, *J*= 8.8 Hz, *J*= 2.4 Hz), 7.50-7.53 (2H, m), 7.13 (1H, dd, *J*= 8.8 Hz), 7.03 (1H, d, *J*= 8.8 Hz), 4.84 (2H, s), 3.37 (2H, m), 1.58 (2H, sext., *J*= 7.5 Hz), 1.45 (9H, s), 0.93 (3H, t, *J*= 7.5 Hz). HPLC (Condition A) Purity 99.2%; Rt 5.8 min.

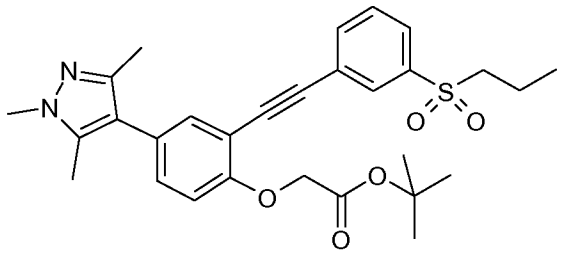
Intermediate 194: *tert*-butyl (4-(1-methyl-1*H*-pyrazol-4-yl)-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 192, starting from *tert*-butyl (4-bromo-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 191) and 1-methyl-1*H*-pyrazole-4-boronic acid, pinacol ester, the title compound was obtained as a yellow sticky solid in 79% yield after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.13 (1H, s), 8.01 (1H, t, *J*= 1.5 Hz), 7.90 (2H, m), 7.86 (1H, s), 7.77 (1H, d, *J*= 2.4 Hz), 7.73 (1H, t, *J*= 7.8 Hz), 7.58 (1H, dd, *J*= 8.7 Hz, *J*= 2.4 Hz), 6.96 (1H, d, *J*= 8.7 Hz), 4.80 (2H, s), 3.85 (3H, s), 3.37 (2H, m), 1.57 (2H, sext., *J*= 7.5 Hz), 1.44 (9H, s), 0.93 (3H, t, *J*= 7.5 Hz). HPLC (Condition A) Purity 98.9%; Rt 4.7 min.

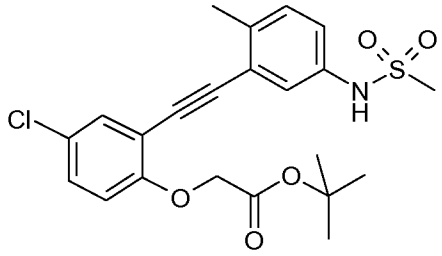
Intermediate 195: *tert*-butyl [2-{[3-(propylsulfonyl)phenyl]ethynyl}-4-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)phenoxy]acetate



Following the general method as outlined in Intermediate 192, starting from *tert*-butyl (4-bromo-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 191) and 1,3,5-trimethyl-1*H*-pyrazole-4-boronic acid, pinacol ester, the title compound was obtained as a black sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.01 (1H, t, *J*= 1.5 Hz), 7.80-7.92 (2H, m), 7.72 (1H, t, *J*= 7.8 Hz), 7.39 (1H, d, *J*= 2.2 Hz), 7.26 (1H, dd, *J*= 8.6 Hz, *J*= 2.2 Hz), 7.00 (1H, d, *J*= 8.6 Hz), 4.82 (2H, s), 3.69 (3H, s), 3.37 (2H, m), 2.20 (3H, s), 2.11 (3H, s), 1.57 (2H, sext., *J*= 7.5 Hz), 1.45 (9H, s), 0.93 (3H, t, *J*= 7.5 Hz). HPLC (Condition A) Purity 99.2%; Rt 4.4 min.

Intermediate 196: *tert*-butyl [4-chloro-2-({2-methyl-5-[(methylsulfonyl)amino]phenyl}ethynyl)phenoxy]acetate



Step 1: *N*-(3-bromo-4-methylphenyl)methanesulfonamide

A cooled (0 °C) solution of 3-bromo-4-methylaniline (ABCR; 1.00 g; 5.37 mmol) in pyridine (20 ml) was treated with methanesulfonyl chloride (500 µl; 6.45 mmol). The reaction mixture was allowed to warm to RT and stirred for 1 hour, then EtOAc was added and the organic layer was washed with a 1N aqueous solution of HCl. The organic layer was dried over $MgSO_4$, filtered and concentrated to dryness to give the title compound as a brown solid (1.42 g, quantitative).

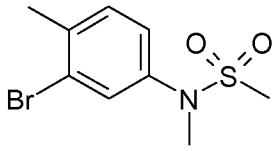
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 9.81 (1H, s), 7.40 (1H, d, *J*= 2.1 Hz), 7.31 (1H, d, *J*= 8.3 Hz), 7.13 (1H, d, *J*= 8.3 Hz, *J*= 2.1 Hz), 2.99 (3H, s), 2.29 (3H, s)

Step 2: *tert*-butyl [4-chloro-2-({2-methyl-5-[(methylsulfonyl)amino]phenyl}ethynyl)phenoxy]acetate

Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and *N*-(3-bromo-4-methylphenyl)methanesulfonamide, the title compound was obtained after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

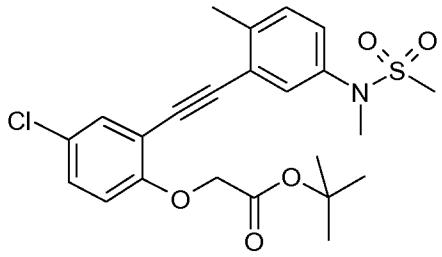
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 9.73 (1H, bs), 7.59 (1H, d, *J*= 2.7 Hz), 7.41 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.28-7.31 (2H, m), 7.16 (1H, dd, *J*= 8.2 Hz, *J*= 2.3 Hz), 7.00 (1H, d, *J*= 9.0 Hz), 4.80 (2H, s), 2.97 (3H, s), 2.41 (3H, s), 1.42 (9H, s). HPLC (Condition A) Rt 5.3 min.

Intermediate 197: *N*-(3-bromo-4-methylphenyl)-*N*-methylmethanesulfonamide



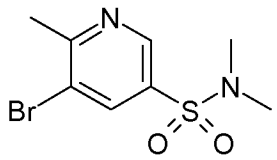
A solution of *N*-(3-bromo-4-methylphenyl)methanesulfonamide (Intermediate 196, step 1; 710 mg; 2.69 mmol) in anhydrous DMF (14 mL) was treated with NaH (129 mg; 3.23 mmol) followed after 5 minutes by treatment with iodomethane (200 µl; 3.23 mmol). The reaction mixture was stirred for 16 hours, then quenched with a 5 N solution of NaOH in water. The reaction mixture was stirred for few minutes and extracted with EtOAc. The organic phase was washed with water and brine, dried over $MgSO_4$ and concentrated to dryness affording the title compound as a brown sticky solid (730 mg, 98%).
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.63 (1H, d, *J*= 2.1 Hz), 7.39 (1H, d, *J*= 8.3 Hz), 7.33 (1H, dd, *J*= 8.3 Hz, *J*= 2.1 Hz), 3.22 (3H, s), 2.95 (3H, s), 2.33 (3H, s). HPLC (Condition A) Purity 98.9%; Rt 3.8 min.

Intermediate 198: *tert*-butyl [4-chloro-2-({2-methyl-5-[methyl(methylsulfonyl)amino]phenyl}ethynyl)phenoxy]acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and *N*-(3-bromo-4-methylphenyl)-*N*-methylmethanesulfonamide (Intermediate 197), the title compound was obtained after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.59 (1H, d, *J*= 2.7 Hz), 7.52 (1H, t, *J*= 1.2 Hz), 7.42 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.36 (2H, m), 7.01 (1H, d, *J*= 9.0 Hz), 4.80 (2H, s), 3.24 (3H, s), 2.95 (3H, s), 2.46 (3H, s), 1.43 (9H, s). HPLC (Condition A) Purity 94.9%; Rt 5.6 min.

Intermediate 199: 5-bromo-*N*,*N*,6-trimethylpyridine-3-sulfonamide



Step 1: 5-bromo-6-chloropyridine-3-sulfonyl chloride

A cooled (0 °C) solution of 6-amino-5-bromopyridine-3-sulfonic acid (12.65 g; 50.00 mmol) in HCl (60 ml; 5 N solution in water) was treated carefully with a solution of sodium nitrite (3.80 g; 55.0 mmol) in water (15 ml) and stirred at 0 °C for 1 hour. The solvents were evaporated and the residue was dried under high vacuum for 2 days, then treated with phosphorus pentachloride (15.00 g; 72 mmol) and phosphorus oxide chloride (0.50 ml; 5.5 mmol). The solid mixture was heated at 125 °C to give a refluxing solution. After heating at 75 °C for 3 hours, the solution was cooled and carefully poured on crushed ice. EtOAc was added and the phases separated. The organic phase was washed with brine, dried on $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound as a brown oil (14.91 g, quantitative yield), which was used without purification.

Step 2: 5-bromo-6-chloro-*N,N*-dimethylpyridine-3-sulfonamide

A cooled (0 °C) solution of 5-bromo-6-chloropyridine-3-sulfonyl chloride (2.00 g; 6.87 mmol) in DCM (20 mL) was treated first with triethylamine (1.06 ml; 7.56 mmol) then with a 5.6 M solution of dimethylamine in EtOH (1.35 ml; 7.56 mmol). The reaction was stirred at 0°C for 1.5 hours then brine was added and the phases separated. The organic phase was washed with brine, dried on $MgSO_4$, filtered and concentrated under reduced pressure to give a residue which was purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc to give the title compound as a colorless oil.

Step 3: diethyl {3-bromo-5-[(dimethylamino)sulfonyl]pyridin-2-yl}malonate

A solution of 5-bromo-6-chloro-*N,N*-dimethylpyridine-3-sulfonamide (400 mg; 1.34 mmol) and diethyl malonate (204 µl; 1.34 mmol) in anhydrous THF (2 ml) was added to a suspension of sodium hydride (53 mg; 1.34 mmol) in anhydrous THF (2 ml). The resulting mixture was stirred for 48 hours, then quenched by careful addition of a saturated solution of NH_4Cl in water. EtOAc was added and the phases separated. The organic phase was washed with brine, dried on $MgSO_4$, filtered and concentrated under

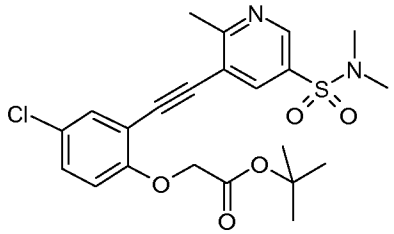
reduced pressure to give a residue which was purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc to give the title compound as a colorless oil.

Step 4: 5-bromo-*N,N*,6-trimethylpyridine-3-sulfonamide

Diethyl {3-bromo-5-[(dimethylamino)sulfonyl]pyridin-2-yl}malonate (222 mg; 0.52 mmol) was treated with a 5 N solution of HCl in water (11 ml) and the resulting solution was refluxed for 6 h. The solvent was removed under reduced pressure, and the solid residue was carefully quenched with a saturated Na_2CO_3 solution in water. The resulting suspension was extracted with AcOEt. The organic phase was washed with brine, dried on $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound as a white solid (125 mg; 86% yield).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.78 (1H, d, *J*= 2.0 Hz), 8.31 (1H, d, *J*= 2.0 Hz), 2.70 (3H, s), 2.69 (6H, s).

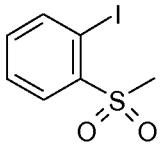
Intermediate 200: *tert*-butyl [4-chloro-2-({5-[(dimethylamino)sulfonyl]-2-methylpyridin-3-yl}ethynyl)phenoxy]acetate



Following the general method as outlined in Intermediate 79, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and *N*-(4-bromophenyl)-4-(trifluoromethyl)benzamide (Intermediate 199), the title compound was obtained after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.77 (1H, d, *J*= 2.2 Hz), 8.18 (1H, d, *J*= 2.2 Hz), 7.70 (1H, d, *J*= 2.7 Hz), 7.48 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.08 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 2.79 (3H, s), 2.69 (6H, s), 1.44 (9H, s).

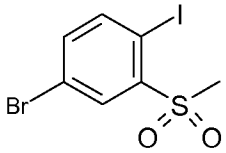
Intermediate 201: 1-iodo-2-(methylsulfonyl)benzene



A cooled (0 °C) solution of 2-iodothioanisole (2.00 g; 8.00 mmol) in DCM (40 ml) was treated carefully with 3-chloroperbenzoic acid (3.94 g; 17.59 mmol) and the reaction mixture was stirred at RT for 20 hours. DCM was added and the reaction mixture was washed twice with NaOH 0.1N and twice with brine. The organic phase was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc to give the title compound as a white solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.20 (1H, dd, *J*= 7.8 Hz, *J*= 1.5 Hz), 8.09 (1H, dd, *J*= 7.8 Hz, *J*= 1.5 Hz), 7.67 (1H, dt, *J*= 7.8 Hz, *J*= 1.5 Hz), 7.40 (1H, dt, *J*= 7.8 Hz, *J*= 1.5 Hz), 3.33 (3H, s). HPLC (Condition A) Rt 2.6 min.

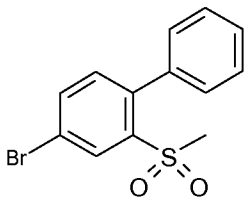
Intermediate 202: 4-bromo-1-iodo-2-(methylsulfonyl)benzene



A suspension of 1-iodo-2-(methylsulfonyl)benzene (Intermediate 201; 1.45 g; 5.14 mmol) in conc. H_2SO_4 (4 mL) was treated with *N*-bromosuccinimide (1.01 g; 5.65 mmol) and the resulting mixture was stirred for 4 h. The reaction mixture was carefully poured on crushed ice and extracted with EtOAc. The organic phase was washed twice with NaOH 0.1 N and brine, dried over $MgSO_4$, filtered and concentrated to dryness affording the title compound as a white solid (1.6 g, 86%).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.11 (1H, d, *J*= 8.3 Hz), 8.10 (1H, d, *J*= 2.4 Hz), 7.63 (1H, dd, *J*= 8.3 Hz, *J*= 2.4 Hz), 3.38 (3H, s). HPLC (Condition A) Purity 90.1%; Rt 3.5 min.

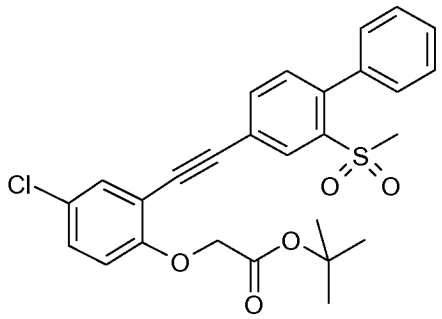
Intermediate 203: 4-bromo-2-(methylsulfonyl)biphenyl



A solution of 4-bromo-1-iodo-2-(methylsulfonyl)benzene (Intermediate 202 ; 200 mg; 0.55 mmol), phenylboronic acid (68 mg; 0.55 mmol;) was placed in a microwave vial and treated with caesium fluoride (252 mg; 1.66 mmol) and bis(triphenylphosphine)palladium(II) chloride (39 mg; 0.06 mmol). The tube was sealed and degased with N_2 before adding dioxane (3 ml) and water (1.5 ml). The resulting reaction mixture was irradiated in a microwave reactor at 110 °C for 20 minutes. The reaction mixture was taken up in EtOAc and washed with water and brine. The organic phase was dried over $MgSO_4$, filtered, concentrated and purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc affording the title compound as an orange sticky solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.17 (1H, dd, *J*= 2.2 Hz), 7.98 (1H, dd, *J*= 8.2 Hz, *J*= 2.2 Hz), 7.36-7.47 (6H, m), 2.86 (3H, s). HPLC (Condition A) Purity 90.7%; Rt 4.2 min.

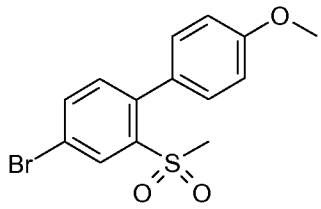
Intermediate 204: *tert*-butyl (4-chloro-2-{[2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 4-bromo-2-(methylsulfonyl)biphenyl (Intermediate 203), the title compound was obtained as a brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.43 (1H, d, *J*= 1.7 Hz), 7.82 (1H, dd, *J*= 7.9 Hz, *J*= 1.7 Hz), 7.53 (1H, d, *J*= 2.6 Hz), 7.46-7.49 (5H, m), 7.39 (1H, d, *J*= 7.9 Hz), 7.28 (1H, dd, *J*= 8.8 Hz, *J*= 2.6 Hz), 6.75 (1H, d, *J*= 8.8 Hz), 4.66 (2H, s), 2.66 (3H, s), 1.51 (9H, s). HPLC (Condition A) Purity 91.9%; Rt 5.8 min.

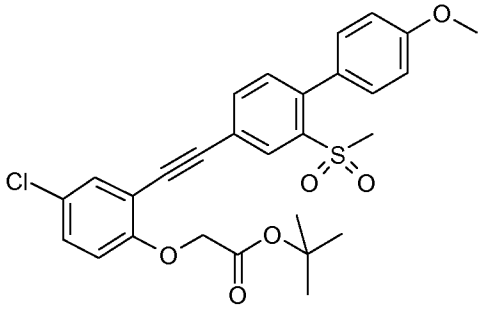
Intermediate 205: 4-bromo-4'-methoxy-2-(methylsulfonyl)biphenyl



Following the general method as outlined in Intermediate 203, starting from 4-bromo-1-iodo-2-(methylsulfonyl)benzene (Intermediate 202) and 4-methoxyphenylboronic acid, the title compound was obtained as a brown solid in 73% yield after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.14 (1H, dd, *J*= 2.1 Hz), 7.95 (1H, dd, *J*= 8.1 Hz, *J*= 2.1 Hz), 7.32-7.36 (3H, m), 7.02 (2H, d, *J*= 8.8 Hz), 3.81 (3H, s), 2.83 (3H, s). HPLC (Condition A) Rt 4.1 min.

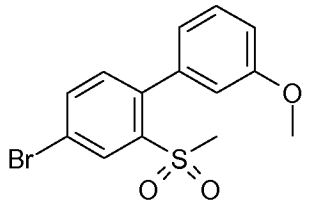
Intermediate 206: *tert*-butyl (4-chloro-2-{[4'-methoxy-2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 4-bromo-4'-methoxy-2-(methylsulfonyl)biphenyl (Intermediate 205), the title compound was obtained as a brown sticky solid in 72% yield after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.17 (1H, d, *J*= 1.7 Hz), 7.87 (1H, dd, *J*= 7.9 Hz, *J*= 1.9 Hz), 7.68 (1H, d, *J*= 2.7 Hz), 7.44-7.48 (2H, m), 7.38 (2H, d, *J*= 8.7 Hz), 7.00-7.05 (3H, m), 4.84 (2H, s), 3.82 (3H, s), 2.84 (3H, s), 1.44 (9H, s). HPLC (Condition A) Rt 5.8 min.

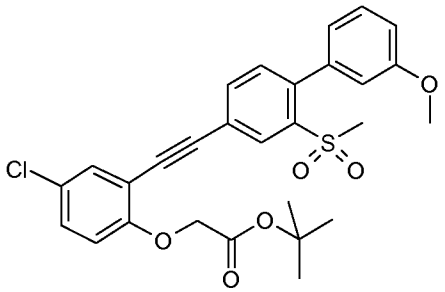
Intermediate 207: 4-bromo-3'-methoxy-2-(methylsulfonyl)biphenyl



Following the general method as outlined in Intermediate 203, starting from 4-bromo-1-iodo-2-(methylsulfonyl)benzene (Intermediate 202) and 3-methoxyphenylboronic acid, the title compound was obtained as a brown sticky solid in 74% yield after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.16 (1H, dd, *J*= 2.1 Hz), 7.97 (1H, dd, *J*= 8.1 Hz, *J*= 2.1 Hz), 7.34-7.40 (2H, m), 6.95-7.05 (3H, m), 3.77 (3H, s), 2.88 (3H, s). HPLC (Condition A) Rt 4.3 min.

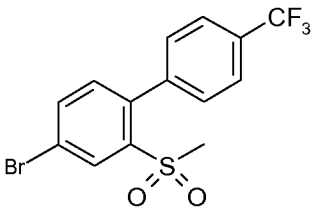
Intermediate 208: *tert*-butyl (4-chloro-2-{[3'-methoxy-2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 4-bromo-3'-methoxy-2-(methylsulfonyl)biphenyl (Intermediate 207), the title compound was obtained as a brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.17 (1H, d, *J*= 1.7 Hz), 7.87 (1H, dd, *J*= 7.9 Hz, *J*= 1.9 Hz), 7.68 (1H, d, *J*= 2.7 Hz), 7.44-7.48 (2H, m), 7.38 (2H, d, *J*= 8.7 Hz), 7.00-7.05 (3H, m), 4.84 (2H, s), 3.82 (3H, s), 2.84 (3H, s), 1.44 (9H, s). HPLC (Condition A) Rt 6.3 min.

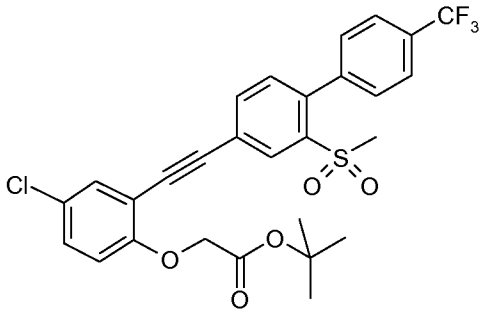
Intermediate 209: 4-bromo-2-(methylsulfonyl)-4'-(trifluoromethyl)biphenyl



Following the general method as outlined in Intermediate 203, starting from 4-bromo-1-iodo-2-(methylsulfonyl)benzene (Intermediate 202) and 4-trifluorophenylboronic acid, the title compound was obtained as a brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.20 (1H, dd, *J*= 2.1 Hz), 8.02 (1H, dd, *J*= 8.1 Hz, *J*= 2.1 Hz), 7.81 (2H, d, *J*= 8.1 Hz), 7.62 (2H, d, *J*= 8.1 Hz), 7.40 (1H, d, *J*= 8.1 Hz), 3.02 (3H, s). HPLC (Condition A) Rt 5.3 min.

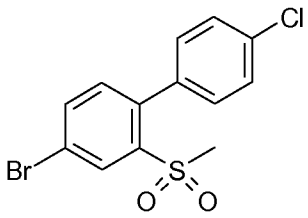
Intermediate 210: *tert*-butyl (4-chloro-2-{[2-(methylsulfonyl)-4'-(trifluoromethyl)biphenyl-4-yl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 4-bromo-2-(methylsulfonyl)-4'-(trifluoromethyl)biphenyl (Intermediate 209), the title compound was obtained as a brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.21 (1H, d, *J*= 1.7 Hz), 7.92 (1H, dd, *J*= 8.0 Hz, *J*= 1.7 Hz), 7.83 (1H, d, *J*= 8.0 Hz), 7.69 (1H, d, *J*= 2.7 Hz), 7.67 (2H, d, *J*= 8.0 Hz), 7.51 (2H, d, *J*= 8.0 Hz), 7.47 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 3.02 (3H, s), 1.44 (9H, s). HPLC (Condition A) Purity 92.2%; Rt 6.6 min.

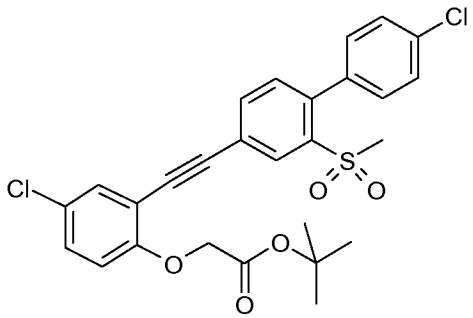
Intermediate 211: 4-bromo-4'-chloro-2-(methylsulfonyl)biphenyl



Following the general method as outlined in Intermediate 203, starting from 4-bromo-1-iodo-2-(methylsulfonyl)benzene (Intermediate 202) and 4-chlorophenylboronic acid, the title compound was obtained as a beige solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.17 (1H, dd, *J*= 2.1 Hz), 7.99 (1H, dd, *J*= 8.2 Hz, *J*= 2.1 Hz), 7.52 (2H, d, *J*= 8.6 Hz), 7.42 (2H, d, *J*= 8.6 Hz), 7.37 (1H, d, *J*= 8.2 Hz), 2.96 (3H, s). HPLC (Condition A) Rt 4.6 min.

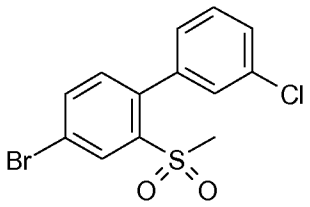
Intermediate 212: *tert*-butyl (4-chloro-2-{[4'-chloro-2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 4-bromo-4'-chloro-2-(methylsulfonyl)biphenyl (Intermediate 211), the title compound was obtained as a brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.19 (1H, d, *J*= 1.8 Hz), 7.90 (1H, dd, *J*= 8.0 Hz, *J*= 1.8 Hz), 7.68 (1H, d, *J*= 2.7 Hz), 7.54 (2H, d, *J*= 8.6 Hz), 7.44-7.50 (4H, m), 7.01 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 2.97 (3H, s), 1.44 (9H, s). HPLC (Condition A) Rt 5.8 min.

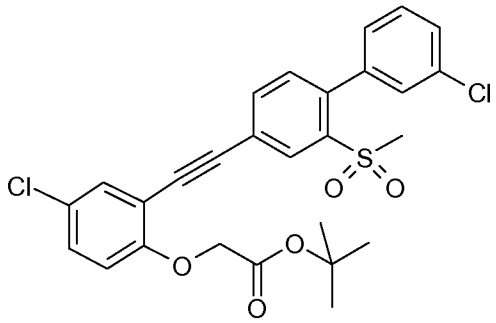
Intermediate 213: 4-bromo-3'-chloro-2-(methylsulfonyl)biphenyl



Following the general method as outlined in Intermediate 203, starting from 4-bromo-1-iodo-2-(methylsulfonyl)benzene (Intermediate 202) and 3-chlorophenylboronic acid, the title compound was obtained as a brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.18 (1H, dd, *J*= 2.0 Hz), 7.99 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.45-7.55 (3H, m), 7.34-7.40 (2H, m), 2.98 (3H, s). HPLC (Condition A) Purity 90.6%; Rt 4.6 min.

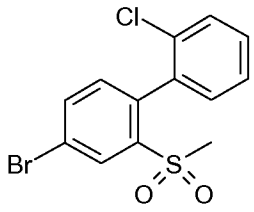
Intermediate 214: *tert*-butyl (4-chloro-2-{[3'-chloro-2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 4-bromo-3'-chloro-2-(methylsulfonyl)biphenyl (Intermediate 213), the title compound was obtained as a brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.19 (1H, d, *J*= 1.7 Hz), 7.90 (1H, dd, *J*= 8.0 Hz, *J*= 1.7 Hz), 7.68 (1H, d, *J*= 2.7 Hz), 7.44-7.568 (5H, m), 7.40 (1H, dt, *J*= 7.0 Hz, *J*= 1.7 Hz), 7.01 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 2.98 (3H, s), 1.44 (9H, s). HPLC (Condition A) Purity 93.7%; Rt 6.1 min.

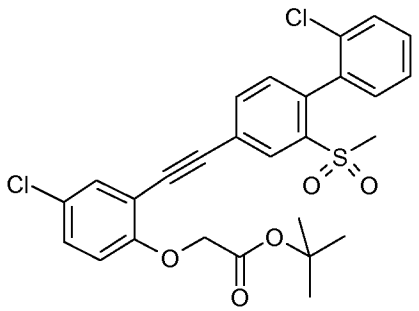
Intermediate 215: 4-bromo-2'-chloro-2-(methylsulfonyl)biphenyl



Following the general method as outlined in Intermediate 203, starting from 4-bromo-1-iodo-2-(methylsulfonyl)benzene (Intermediate 202) and 2-chlorophenylboronic acid, the title compound was obtained as a brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.20 (1H, dd, *J*= 2.2 Hz), 8.01 (1H, dd, *J*= 8.2 Hz, *J*= 2.2 Hz), 7.56 (1H, m), 7.38-7.50 (3H, m), 7.34 (1H, d, *J*= 8.2 Hz), 3.04 (3H, s). HPLC (Condition A) Purity 98.4%; Rt 4.4 min.

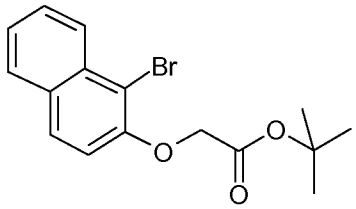
Intermediate 216: *tert*-butyl (4-chloro-2-{[2'-chloro-2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 4-bromo-2'-chloro-2-(methylsulfonyl)biphenyl (Intermediate 215), the title compound was obtained as a brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.20 (1H, d, *J*= 1.6 Hz), 7.92 (1H, dd, *J*= 7.9 Hz, *J*= 1.6 Hz), 7.68 (1H, d, *J*= 2.7 Hz), 7.57 (1H, m), 7.40-7.51 (5H, m), 7.02 (1H, d, *J*= 9.0 Hz), 4.85 (2H, s), 3.04 (3H, s), 1.44 (9H, s). HPLC (Condition A) Purity 96.5%; Rt 5.9 min.

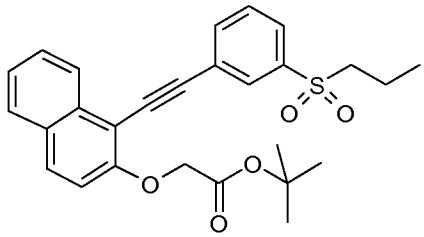
Intermediate 217: *tert*-Butyl [(1-bromo-2-naphthyl)oxy]acetate



Following the general method as outlined in Intermediate 1, starting from 1-bromo-2-naphthol, the title compound was obtained as an off-white solid in 98% yield after purification by flash column chromatography (silica), eluting with petroleum ether and EtOAc (95:5).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.10 (1H, d), 7.94 (2H, m), 7.61(1H, m), 7.45 (1H, m), 7.38 (1H, d), 4.94 (2H,s), 1.42(9H,S). MS (ESI$^+$): 279.0. HPLC (Condition A) Purity 98.0%; Rt 5.85 min.

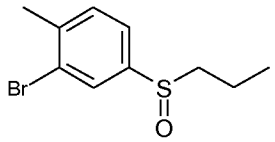
Intermediate 218: *tert*-butyl [(1-{[3-(propylsulfonyl)phenyl]ethynyl}-2-naphthyl)oxy]acetate



A mixture of (1-bromo-naphthalen-2-yloxy)-acetic acid *tert*-butyl ester (Intermediate 217; 500 mg; 1.48 mmol), 1-ethynyl-3-(propane-1-sulfonyl)-benzene (618 mg; 2.97 mmol) and PPh3 (39 mg; 0.15 mmol) in water (4.40 ml) and Acetone (5.6 ml) was treated with palladium(II) chloride (13 mg; 0.07 mmol) and piperidine (295 µl; 2.97 mmol) and heated at 60 °C for 2 days. The reaction mixture was extracted with EtOAc, the organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc to give the title compound as a yellow sticky solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.29 (1H, d, *J*= 8.2 Hz), 8.12 (1H, t, *J*= 1.5 Hz), 8.01-8.04 (2H, m), 7.92-7.96 (2H, m), 7.76 (1H, t, *J*= 7.7 Hz), 7.66 (1H, ddd, *J*= 8.2 Hz, *J*= 7.0 Hz, *J*= 1.5 Hz), 7.48 (1H, ddd, *J*= 8.2 Hz, *J*= 7.0 Hz, *J*= 1.5 Hz), 7.36 (1H, d, *J*= 9.2 Hz), 4.99 (2H, s), 3.40 (2H, m), 1.60 (2H, sext., *J*= 7.5 Hz), 1.44 (9H, s), 0.94 (3H, t, *J*= 7.5 Hz). HPLC (Condition A) Purity 94.7%; Rt 5.4 min.

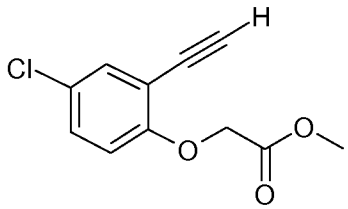
Intermediate 219: 2-bromo-1-methyl-4-(propylsulfinyl)benzene



A solution of 3-bromo-4-methyl-benzenethiol (1.27 g; 6.25 mmol) in anhydrous DMF (12.5 ml) was treated with sodium hydride (300 mg; 7.5 mmol). Then reaction mixture was stirred at RT for 15 minutes, then the treated with 1-iodopropane (0.73 ml; 7.5 mmol). The reaction was stirred for 24 hours, before being quenched by dropwise addition of water. EtOAc was added and the layers separated. The organic layer was washed with brine, dried on MgSO4, filtered and concentrated under reduced pressure. The residue was dissolved in MeOH (13 mL), cooled to 0 °C and treated with a 0.5 M solution of sodium (meta)periodate in water (12.5 ml; 6.24 mmol). After stirring for 24 hours at RT, EtOAc and water were added and the phases separated and the organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc to give the title compound as a yellow sticky solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.28 (1H, s), 8.00 (2H, m), 3.40-3.15 (2H, m), 2.91 (3H, s), 2.28-1.96 (2H, m), 1.48 (3H, t, *J*= 7.4 Hz).

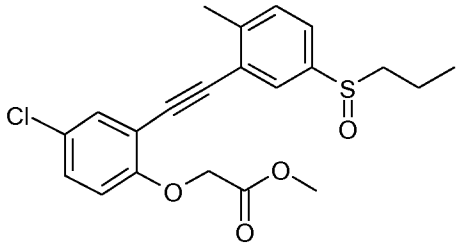
Intermediate 220: methyl (4-chloro-2-ethynylphenoxy)acetate



A solution of (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3; 500 mg; 1.87 mmol) in MeOH (10 ml) was treated with an 1.25 N solution of HCl in methanol (1.5 ml). The solution was heated at 60 °C for 24 hours. The solvents were removed under reduced pressure to give the title compound as an oil which solidifies upon standing (445 mg, quantitative yield).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.47 (1H, d, *J*= 2.7 Hz), 7.38 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 6.98 (1H, d, *J*= 9.0 Hz), 4.91 (2H, s), 4.40 (1H, s), 3.68 (3H, s).

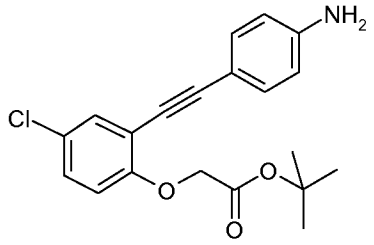
Intermediate 221: methyl (4-chloro-2-{[2-methyl-5-(propylsulfinyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 107, starting from methyl (4-chloro-2-ethynylphenoxy)acetate (Intermediate 220) and 2-bromo-1-methyl-4-(propylsulfinyl)benzene (Intermediate 219), the title compound was obtained as a yellow oil after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.75 (1H, d, *J*= 1.6 Hz), 7.63-7.52 (3H, m), 7.43 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.08 (1H, d, *J*= 9.0 Hz), 4.96 (2H, s), 3.72 (3H, s), 2.94 (1H, m), 2.78 (1H, m), 2.54 (3H, s), 1.64 (1H, m), 1.47 (1H, m), 0.97 (3H, t, *J*= 7.4 Hz).

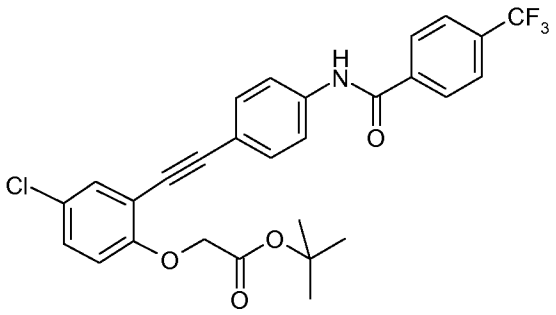
Intermediate 222: *tert*-butyl {2-[(4-aminophenyl)ethynyl]-4-chlorophenoxy}acetate



A mixture of (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3 ; 800 mg; 3.00 mmol), 4-iodoaniline (788 mg; 3.60 mmol) and dichlorobis(triphenylphosphine)palladium(II) (526 mg; 0.75 mmol) in anhydrous THF (20 mL) was treated with cuprous iodide (29 mg; 0.15 mmol), then the mixture was degassed with N_2 for 10 minutes, then treated with triethylamine (5.0 ml; 36 mmol). The mixture was stirred for 18 hours at RT, then EtOAc and water were added, the phases separated and the organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc to give the title compound.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.44 (1H, d, *J*= 2.6 Hz), 7.38 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.18 (2H, d, *J*= 8.5 Hz), 6.92 (1H, d, *J*= 9.0 Hz), 6.56 (2H, d, *J*= 8.5 Hz), 5.60 (2H, bs), 4.77 (2H, s), 1.44 (9H, s).

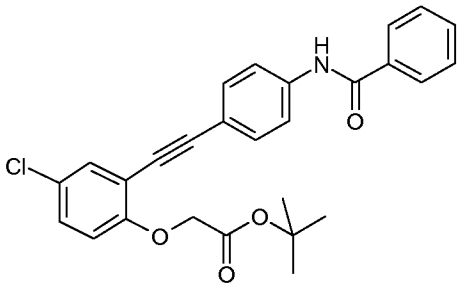
Intermediate 223: *tert*-butyl {4-chloro-2-[(4-{[4-(trifluoromethyl)benzoyl]amino}phenyl)ethynyl]phenoxy}acetate



A solution of *tert*-butyl {2-[(4-aminophenyl)ethynyl]-4-chlorophenoxy}acetate (Intermediate 222; 72 mg ; 0.20 mmol) and triethylamine (83 µl; 0.60 mmol) in DCM (2 ml) was treated with 4-(trifluoromethyl)-benzoyl chloride (30 µl; 0.20 mmol). After stirring at RT for 1 hour, the reaction was quenched with a saturated aqueous ammonia solution (1 mL). EtOAc and a saturated NH_4Cl solution in water were added, the phases separated and the organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc to give the title compound.

MS (ESI$^+$): 547.2 $[M+NH_4]^+$. HPLC (Condition A): Rt 5.88 min (HPLC purity >99%).

Intermediate 224: *tert*-butyl (2-{[4-(benzoylamino)phenyl]ethynyl}-4-chlorophenoxy)acetate

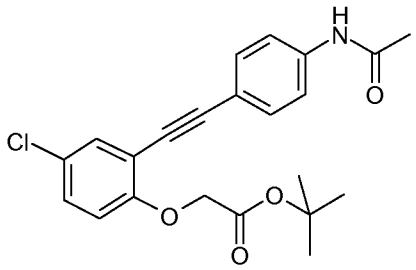


Following the general method as outlined in Intermediate 223, starting from *tert*-butyl {2-[(4-aminophenyl)ethynyl]-4-chlorophenoxy}acetate (Intermediate 222) and benzoyl

chloride, the title compound was obtained after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

MS (ESI^+): 479.2 $[M+NH_4]^+$. HPLC (Condition A): Rt 5.48 min (HPLC purity 99.1%).

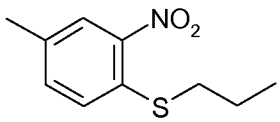
Intermediate 225: *tert*-butyl (2-{[4-(acetylamino)phenyl]ethynyl}-4-chlorophenoxy)acetate



Following the general method as outlined in Intermediate 223, starting from *tert*-butyl {2-[(4-aminophenyl)ethynyl]-4-chlorophenoxy}acetate (Intermediate 222) and acetyl chloride, the title compound was obtained in 91% yield after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^1H NMR (300MHz, DMSO-d_6) δ [ppm] 10.15 (1H, s), 7.64 (2H, d, *J*= 8.7 Hz), 7.54 (1H, d, *J*= 2.7 Hz), 7.47 (2H, d, *J*= 8.7 Hz), 7.38 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 6.96 (1H, d, *J*= 9.0 Hz), 4.80 (2H, s), 2.07 (3H, s), 1.44 (9H, s).

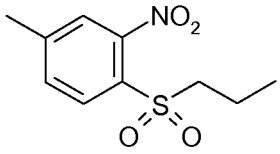
Intermediate 226: 4-Methyl-2-nitro-1-(propylthio)benzene



A solution of 4-chloro-3-nitro-toluene (25 g, 145 mmol) in anhydrous DMF (200 ml) was treated with K_2CO_3 (40.29 g, 291 mmol) and 1-propane thiol (12.2 g, 160 mmol). The reaction mixture was heated to70 °C for 12 h. The reaction mixture was filtered, the filtrate was concentrated under reduced pressure, diluted water and extracted with ethyl acetate (200 ml). The organic layer was washed with brine, dried over sodium sulphate and evaporated under reduced pressure, to give a crude which was purified by column chromatography (silica) using petroleum ether/ethyl acetate as eluent to afford the title compound (28 g, 91%) as a pale yellow solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.01 (s, 1H), 7.37-7.35(d, 2H, *J*= 10Hz), 7.29-7.27(dd, 1H, *J*= 9.6Hz), 2.96-2.89 (m, 2H), 2.40(s, 3H), 1.81-1.17(m, 2H), 1.11(s, 1H).

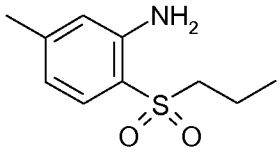
Intermediate 227: 4-Methyl-2-nitro-1-(propylsulfonyl) benzene



A cooled (0 °C) solution of 4-methyl-2-nitro-1-(propylthio) benzene (Intermediate 226; 15 g, 70 mmol) in anhydrous DCM (200 ml) was treated with a solution of 3-chloroperbenzoic acid (60%) (51.0 g, 177 ,mol) in DCM (300 ml). The reaction mixture was stirred at 0 °C for 3 h, then at RT for 16 h. The reaction mixture was filtered and the filtrate was extracted with ethyl acetate. The organic layer was washed with 1N NaOH (200 ml), water (200 ml), brine and dried over sodium sulphate and evaporated under reduced pressure. The crude product was purified by column chromatography (silica) using petroleum ether / ethyl acetate as eluent to afford the title compound as a pale yellow liquid.

^{1}H NMR (300MHz, $CDCl_3$) δ [ppm] 8.01-7.99 (dd, 1H), 7.62(s, 1H), 7.56-7.54 (dd, 1H), 3.53-3.49 (m, 2H), 2.53 (s, 3H), 1.89-1.80 (m, 2H), 1.09 (s, 3H)

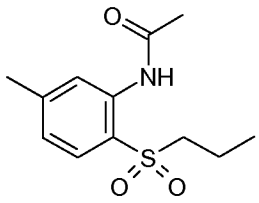
Intermediate 228: 5-Methyl-2-(propylsulfonyl) aniline



A solution of 4-methyl-2-nitro-1-(propylsulfonyl) benzene(Intermediate 227; 11 g, 45 mmol) in methanol (150 ml) was treated with Pd/C (1.1 g) and the reaction mixture was stirred under 3 Kg/cm^2 pressure of hydrogen at RT for 5 h. The catalyst was filtered through celite and the solvent was removed under reduced pressure to afford the title compound (9 g, 94 %) as pale yellow liquid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.35-7.33 (dd, 1H), 6.65(s, 1H), 6.51-6.49 (dd, 1H), 5.94 (brs, 2H), 3.13-3.10 (m, 2H), 2.20 (s, 3H), 1.55-1.49 (m, 2H), 0.90-0.85 (t, 3H). MS (ESI$^+$): 214.2. HPLC (Method D) Purity 99.8%; Rt 3.34 min.

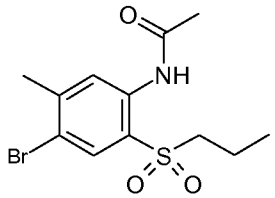
Intermediate 229: *N*-[5-Methyl-2-(propylsulfonyl)phenyl]acetamide



A solution of 5-methyl-2-(propylsulfonyl) aniline (Intermediate 228; 6.0 g, 28 mmol) in DCM (100 ml) was added *N*-methyl morpholine(4.3 g, 42.1 mmol) and Acetyl chloride (2.4 g, 31 mmol). The reaction mixture was stirred at RT for 12 h. The reaction mixture was diluted with water (200 ml), the organic layer was washed with brine solution and dried over sodium sulphate and evaporated. The crude product was purified by column chromatography (silica) using petroleum ether/ethyl acetate as eluent to afford the title compound (5.0 g, 70%) as a white solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 9.53 (brs, 1H), 7.84(s, 1H), 7.72-7.70(dd, 1H, *J*= 8.12Hz), 7.21-7.19 (dd, 1H, *J*= 7.96Hz), 3.28-3.24(m, 2H), 2.36 (s, 3H), 2.10 (s, 3H), 1.54-1.48(m, 2H), 0.9-0.86(t, 3H, *J*= 14.84Hz). MS (ESI$^+$): 256. HPLC (Condition A) Purity 99.1%; Rt 3.36 min.

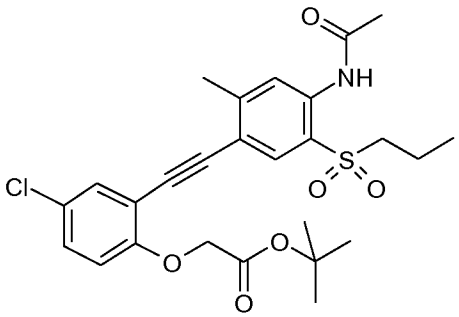
Intermediate 230: *N*-[4-Bromo-5-methyl-2-(propylsulfonyl)phenyl]acetamide



A mixture of *N*-[5-methyl-2-(propylsulfonyl)phenyl]acetamide (Intermediate 229; 5.0 g, 20 mmol) in conc.sulphuric acid (25 ml) was treated in portions with *N*-bromosuccinamide(3.8 g, 22 mmol). Reaction mixture was stirred at RT for 18 hrs, carefully quenched on ice and extracted to DCM (100 ml). The organic layer was washed with water and brine, dried over sodium sulphate and concentrated. The crude product was purified by column chromatography (silica) eluting with petroleum ether/ethyl acetate to afford the title compound as a white solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 9.54 (brs, 1H), 7.98(s, 1H), 7.91(s, 1H), 3.37-3.33(m, 2H), 2.40 (s, 3H), 2.10 (s, 3H), 1.59-1.5(m, 2H), 0.92-0.89(t, 3H, *J*= 14.76Hz). MS (ESI$^+$): 334. HPLC (Condition A) Purity 97%; Rt 4.35 min.

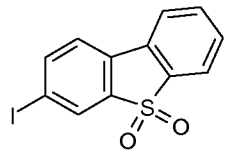
Intermediate 231: *tert*-butyl (2-{[4-(acetylamino)-2-methyl-5-(propylsulfonyl)phenyl]ethynyl}-4-chlorophenoxy)acetate



Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and *N*-[4-Bromo-5-methyl-2-(propane-1-sulfonyl)-phenyl]-acetamide (Intermediate 230), the title compound was obtained as a brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 9.62 (1H, s), 8.11 (1H, s), 7.89 (1H, s), 7.64 (1H, d, *J*= 2.7 Hz), 7.43 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.02 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s), 3.38 (2H, m), 2.54 (3H, s), 2.15 (3H, s), 1.57 (2H, sext., *J*= 7.5 Hz), 1.43 (9H, s), 0.92 (3H, t, *J*= 7.5 Hz). HPLC (Condition A) Purity 100.0%; Rt 6.1 min.

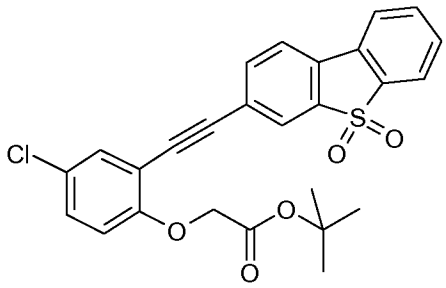
Intermediate 232: 3-iododibenzo[b,d]thiophene 5,5-dioxide



Following the general method as outlined in Intermediate 58, starting from 5,5-dioxidodibenzo[b,d]thien-3-ylamine (Zerenex), the title compound was obtained as a beige solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.40 (1H, d, *J*= 1.5 Hz), 8.21 (1H, d, *J*= 7.6 hz), 8.18 (1H, dd, *J*= 8.3 Hz, *J*= 1.5 Hz), 7.97-8.01 (2H, m), 7.81 (1H, dt, *J*= 7.6 Hz, *J*= 1.0 Hz), 7.69 (1H, dt, *J*= 7.6 Hz, *J*= 1.0 Hz). HPLC (Condition A) Purity 91.5%; Rt 4.1 min.

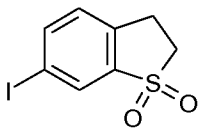
Intermediate 233: *tert*-butyl {4-chloro-2-[(5,5-dioxidodibenzo[b,d]thien-3-yl)ethynyl]phenoxy}acetate



Following the general method as outlined in Intermediate 79, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) 3-iododibenzo[b,d]thiophene 5,5-dioxide (Intermediate 232), the title compound was obtained as a pink solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.28 (1H, d, *J*= 8.0 Hz), 8.25 (1H, d, *J*= 7.6 Hz), 8.18 (1H, d, *J*= 1.5 Hz), 8.02 (1H, d, *J*= 7.6 Hz), 7.94 (1H, dd, *J*= 8.0 Hz, *J*= 1.5 Hz), 7.84 (1H, dt, *J*= 7.6 Hz, *J*= 1.0 Hz), 7.65 (1H, dt, *J*= 7.6 Hz, *J*= 1.0 Hz), 7.47 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.02 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 1.44 (9H, s). HPLC (Condition A) Purity 99.0%; Rt 5.7 min.

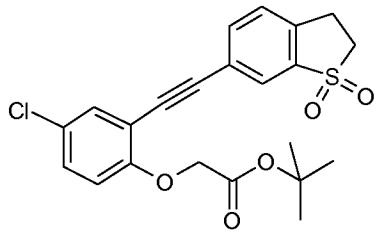
Intermediate 234: 6-iodo-2,3-dihydro-1-benzothiophene 1,1-dioxide



Following the general method as outlined in Intermediate 58, starting from 1,1-dioxido-2,3-dihydro-1-benzothien-6-ylamine (Intermediate 233), the title compound was obtained as a beige solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.08 (1H, d, *J*= 1.5 Hz), 7.99 (1H, dd, *J*= 8.1 Hz, *J*= 1.5 Hz), 7.36 (1H, d, *J*= 8.1 Hz), 3.60 (2H, t, *J*= 6.9 Hz), 3.29 (2H, t, *J*= 6.9 Hz). HPLC (Condition A) Purity 98.2%; Rt 2.9 min.

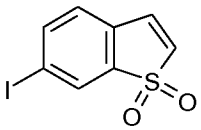
Intermediate 235: *tert*-butyl {4-chloro-2-[(1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetate



Following the general method as outlined in Intermediate 20, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 6-iodo-2,3-dihydro-1-benzothiophene 1,1-dioxide (Intermediate 234), the title compound was obtained as a beige solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.90 (1H, d, *J*= 1.5 Hz), 7.79 (1H, dd, *J*= 8.0 Hz, *J*= 1.5 Hz), 7.61-7.64 (2H, m), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.00 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 3.64 (2H, m), 3.40 (2H, t, *J*= 6.8 Hz), 1.43 (9H, s). HPLC (Condition A) Purity 96.6%; Rt 5.1 min.

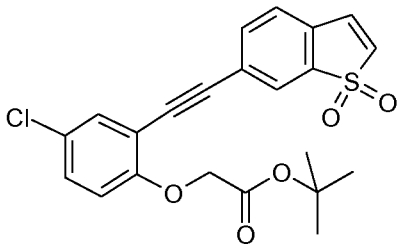
Intermediate 236: 6-iodo-1-benzothiophene 1,1-dioxide



Following the general method as outlined in Intermediate 58, starting from 6-amino-1,1-dioxobenzo[β]thiophene, the title compound was obtained as a beige solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.25 (1H, m), 8.07 (1H, dd, *J*= 7.9 Hz, *J*= 1.6 Hz), 7.601 (1H, dd, *J*= 6.9 Hz, *J*= 1.0 Hz), 7.38 (1H, d, *J*= 7.9 Hz), 7.34 (1H, d, *J*= 6.9 Hz). HPLC (Condition A) Purity 97.4%; Rt 3.0 min.

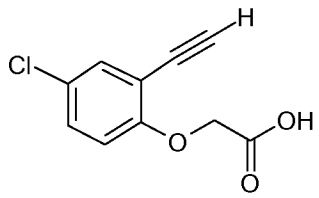
Intermediate 237: *tert*-butyl {4-chloro-2-[(1,1-dioxido-1-benzothien-6-yl)ethynyl]phenoxy}acetate



Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 6-iodo-1-benzothiophene 1,1-dioxide (Intermediate 236), the title compound was obtained as a yellow solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.03 (1H, m), 7.82 (1H, dd, *J*= 7.8 Hz, *J*= 1.5 Hz), 7.63-7.70 (3H, m), 7.49 (1H, d, *J*= 6.7 Hz), 7.46 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.01 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 1.44 (9H, s). HPLC (Condition A) Purity 97.6%; Rt 5.7 min.

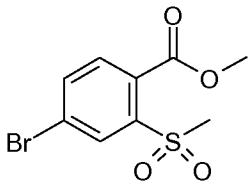
Intermediate 238: (4-chloro-2-ethynylphenoxy)acetic acid



A solution of (4-chloro-2-ethynyl-phenoxy)-acetic acid tert-butyl ester (Intermediate 3; 500 mg; 1.87 mmol) in DCM (2.5 ml) was treated with a 4 N solution of HCl in dioxane (14 ml; 56 mmol) and stirred overnight. The solvents were removed under reduced pressure, to give the title compound.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.0 (1H, bs), 7.34-7.24 (2H, m), 6.82 (1H, d, *J*= 9.0 Hz), 4.66 (2H, s), 4.25 (1H, s).

Intermediate 239: methyl 4-bromo-2-(methylsulfonyl)benzoate

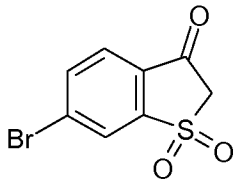


A suspension of 4-bromo-2-(methylsulphonyl)benzoic acid (5.00 g; 17.9 mmol) in MeOH (100 ml) was treated with conc. sulphuric acid and the resulting mixture was heated at

reflux for 5 days. The mixture was concentrated under reduced pressure, the residue was dissolved in EtOAc then washed with water, twice with $NaHCO_3$ (sat) then with brine, dried on $MgSO_4$, filtered and concentrated to give the title compound as a yellow solid (4.00 g, 72%).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.14 (1H, d, *J*= 1.9 Hz), 8.08 (1H, d, *J*= 1.9 Hz, 8.1Hz), 7.73 (1H, d, *J*= 8.1 Hz), 3.86 (3H, s), 3.42 (3H, s). HPLC (Condition A): Rt 3.54 min (HPLC purity 95.5%).

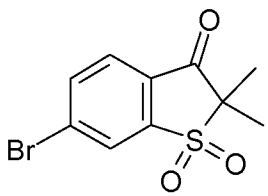
Intermediate 240: 6-bromo-1-benzothiophen-3(2H)-one 1,1-dioxide



A solution of methyl 4-bromo-2-(methylsulfonyl)benzoate (Intermediate 239; 4.00 g; 13.6 mmol) in anhydrous THF (60 ml) was treated with NaH (595 mg; 13.6 mmol) and stirred at RT for 1.5 h. The reaction was quenched with water. AcOEt and a 1N solution of HCl in water were added and the phases were separated. The organic phase was washed with brine, dried on $MgSO_4$, filtered and concentrated to give the title compound as a yellow solid (3.63 g).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.55 (1H, d, *J*= 1.7 Hz), 8.15 (1H, d, *J*= 1.7 Hz, 8.2Hz), 7.93 (1H, d, *J*= 8.2 Hz), 4.62 (2H, s). MS (ESI$^-$): 261.0. HPLC (Condition A): Rt 2.56 min.

Intermediate 241: 6-bromo-2,2-dimethyl-1-benzothiophen-3(2H)-one 1,1-dioxide

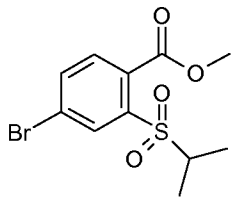


A solution of 6-bromo-1-benzothiophen-3(2*H*)-one 1,1-dioxide (Intermediate 240; 1.00 g; 3.83 mmol) in anhydrous DMF (4 mL) was treated with sodium hydride (337 mg; 8.43 mmol) and stirred for 1 h. The resulting mixture was treated with iodomethane (715 µl; 11.5 mmol) and stirred for 15 min. The reaction was quenched with water, then partitioned between AcOEt and brine. The organic phase was washed with brine, dried on $MgSO_4$, filtered and concentrated to give a residue wich was purified by flash column

chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc. The title compound was obtained as an orange oil. Methyl 4-bromo-2-(isopropylsulfonyl)benzoate was also isolated and and denominated as Intermediate 242.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.64-858 (1H, m), 8.22-8.12 (1H,m), 8.0-7.94 (1H, m), 1.50 (6H, s). HPLC (Condition A): Rt 3.65 min (HPLC purity 100%).

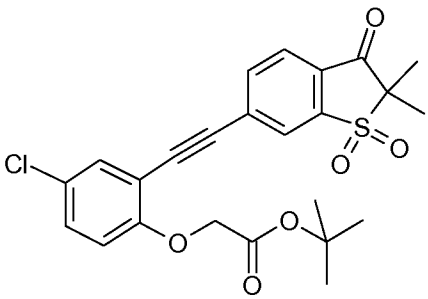
Intermediate 242: Methyl 4-bromo-2-(isopropylsulfonyl)benzoate



The title compound was isolated by column chromatography during the synthesis of Intermediate 241.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.12-8.04 (2H, m), 7.74 (1H, d, *J*= 8Hz), 3.85 (3H, s), 3.81 (1H, m), 1.24 (3H, s), 1.22 (3H, s). MS (ESI$^+$): 321.0. HPLC (Condition A): Rt 3.78 min.

Intermediate 243: *tert*-butyl {4-chloro-2-[(2,2-dimethyl-1,1-dioxido-3-oxo-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetate

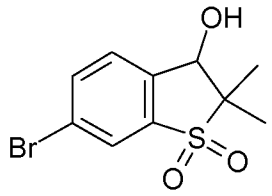


Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 6-bromo-2,2-dimethyl-1-benzothiophen-3(2*H*)-one 1,1-dioxide (Intermediate 241), the title compound was obtained in 91% yield after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.42-8.40 (1H, m), 8.11 (1H, dd, *J*= 0.6 Hz, 8.1Hz), 8.05 (1H, m, *J*= 1.3 Hz, 8.1 Hz), 7.71 (1H, d, *J*= 2.7 Hz), 7.51 (1H, dd, *J*= 2.7 Hz,

9 Hz) 7.05 (1H, d, *J*= 9. Hz), 4.85 (2H, s), 1.52 (6H, s), 1.44 (9H, s). MS (ESI^+): 492 $[M+NH4]^+$. HPLC (Condition A): Rt 5.73 min (purity 99%).

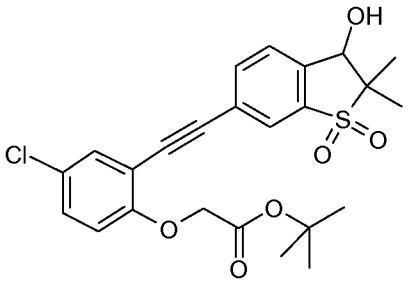
Intermediate 244: 6-bromo-2,2-dimethyl-2,3-dihydro-1-benzothiophene-3-ol 1,1-dioxide



A cooled (0 °C) solution of 6-bromo-2,2-dimethyl-1-benzothiophen-3(2*H*)-one 1,1-dioxide (Intermediate 241; 652 mg; 2.25 mmol) in MeOH (15 ml) and DCM (7 ml) was treated with $NaBH_4$ (43 mg; 1.13 mmol) portionwise. The resulting solution was stirred at RT for 1.5 h, before being cooled to 0 °C and carefully quenched with water. The mixture was concentrated under reduced pressure, water was added to the residue and the aqueous phase was extracted three times with DCM. The combined organic phases were washed with brine, dried with $MgSO_4$, filtered and concentrated to dryness to give the title compound as a white solid (637 mg, 97%).

^1H NMR (300MHz, DMSO-d_6) δ [ppm] 8.12 (1H, d, *J*= 1.8 Hz), 7.99 (1H, dd, *J*= 1.8 Hz, 8.1 Hz), 7.65 (1H, d, *J*= 8.1 Hz), 6.62 (1H, s), 4.95 (1H, s), 1.47 (3H, s), 1.19 (3H, s). MS (ESI^+):308.0 $[M+NH_4]^+$. HPLC (Condition A): Rt 3.30 min (purity 97%).

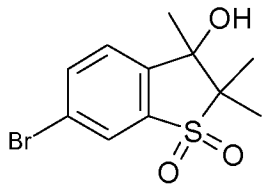
Intermediate 245: *tert*-butyl {4-chloro-2-[(3-hydroxy-2,2-dimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetate



Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 6-bromo-2,2-dimethyl-2,3-dihydro-1-benzothiophene-3-ol 1,1-dioxide (Intermediate 244), the title compound was obtained after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.94 (1H, m), 7.86 (1H, dd, *J*= 1.4 Hz, 7.9 Hz), 7.69 (1H, m), 7.63 (1H, d, *J*= 2.7 Hz) 7.05 (1H, dd, *J*= 7.9 Hz, 2.7 Hz), 7.00 (1H, d, *J*= 8.9 Hz), 4.96 (1H, s), 4.82 (2H, s), 1.43 (9H, s), 1.39 (3H, s) 1.13 (3H, s) . MS (ESI$^+$): 594 $[M+NH_4]^+$. HPLC (Condition A): Rt 5.09 min (HPLC purity 95%).

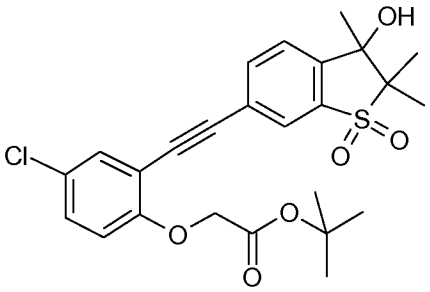
Intermediate 246: 6-bromo-2,2,3-trimethyl-2,3-dihydro-1-benzothiophene-3-ol 1,1-dioxide



A cooled (0 °C) solution of 6-bromo-2,2-dimethyl-1-benzothiophen-3(2*H*)-one 1,1-dioxide (Intermediate 241; 750 mg; 2.59 mmol) in anhydrous Et_2O (22.5 ml) was treated carefully with a 3 M solution of methylmagnesium bromide in Et_2O (2.6 ml; 7.8 mmol). The white solution was stirred at RT for 1.5 before being quenched with a saturated solution of NH_4Cl in water. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with water and brine, dried over anhydrous magnesium sulfate and concentrated to dryness to afford the title compound as a white solid (767 mg, 97%).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.02 (1H, d, *J*= 1.9 Hz), 7.93 (1H, dd, *J*= 1.9 Hz, 8.1Hz), 7.64 (1H, d, *J*= 8.1 Hz), 6.11 (1H, s), 1.45 (3H, s), 1.32 (3H, s), 1.19 (3H, s). MS (ESI$^-$): 305.1. HPLC (Condition A): Rt 3.07 min (HPLC purity 99.1%).

Intermediate 247: *tert*-butyl {4-chloro-2-[(3-hydroxy-2,2,3-trimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetate

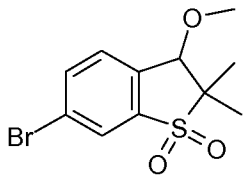


Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 6-bromo-2,2,3-trimethyl-2,3-dihydro-1-benzothiophene-3-ol 1,1-dioxide (Intermediate 246), the title

compound was obtained as a white foam after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.92 (1H, m), 7.87 (1H, dd, *J*= 1.6 Hz, 8 Hz), 7.75 (1H, d, *J*= 8 Hz), 7.65 (1H, d, *J*= 2.7 Hz) 7.44 (1H, dd, *J*= 9 Hz, 2.7 Hz), 7.01 (1H, d, *J*= 9 Hz), 6.13 (1H, brs), 4.82 (2H, s), 1.47 (3H, s), 1.43 (9H, s) 1.34 (3H, s), 1.20 (3H, s). MS (ESI$^+$): 508.4 $[M+NH_4]^+$. HPLC (Condition A): Rt 5.20 min.

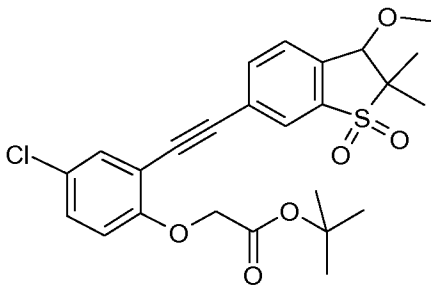
Intermediate 248: 6-bromo-2,2-dimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-3-yl methyl ether



A cooled (o °C) suspension of NaH (20.61 mg; 0.52 mmol; 1.00 eq.) in dry DMF was carefully treated with solution of 6-bromo-2,2-dimethyl-2,3-dihydro-1-benzothiophene-3-ol 1,1-dioxide (Intermediate 244 ; 150 mg; 0.52 mmol) in anhydrous DMF. The reaction mixture was stirred at RT for 4 min then treated with a 3 M solution of iodomethane (240 µl; 0.72 mmol). The mixture was stirred at RT for 2.5h, then quenched with water. EtOAc was added, the phases were separated and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous magnesium sulfate and concentrated to dryness to afford a residue, which was purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc. The title compound was obtained as a white solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.11 (1H, d, *J*= 1.8 Hz), 7.94 (1H, dd, *J*= 1.8 Hz, 8 Hz), 7.65 (1H, d, *J*= 8 Hz), 4.69 (1H, s), 3.52 (3H, s), 1.40 (3H, s) 1.27 (3H, s) . HPLC (Condition A): Rt 3.64 min.

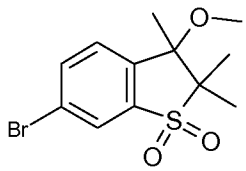
Intermediate 249: *tert*-butyl {4-chloro-2-[(3-methoxy-2,2-dimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetate



Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 6-bromo-2,2-dimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-3-yl methyl ether (Intermediate 248), the title compound was obtained after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.98 (1H, m), 7.87 (1H, dd, *J*= 1.6 Hz, 8 Hz), 7.76 (1H, d, *J*= 8 Hz), 7.63 (1H, d, *J*= 2.7 Hz) 7.45 (1H, dd, *J*= 9 Hz, 2.7 Hz), 7.00 (1H, d, *J*= 9 Hz), 4.81 (2H, s), 4.76 (1H, s), 3.56 (3H, s), 1.43 (9H, s) 1.39 (6H, s). MS (ESI$^+$): 508.4 $[M+NH_4]^+$. HPLC (Condition A): Rt 5.61 min.

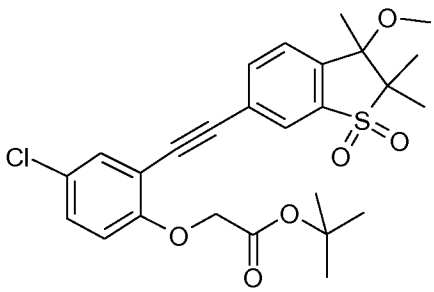
Intermediate 250: 6-bromo-2,2,3-trimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-3-yl methyl ether



Following the general method as outlined in Intermediate 248, starting from 6-bromo-2,2,3-trimethyl-2,3-dihydro-1-benzothiophene-3-ol 1,1-dioxide (Intermediate 246), the title compound was obtained.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.10 (1H, d, *J*= 1.9 Hz), 7.95 (1H, dd, *J*= 1.9 Hz, 8.1 Hz), 7.72 (1H, d, *J*= 8.1 Hz), 3.95 (3H, s), 1.53 (3H, s) 1.35 (3H, s), 1.24 (3H, s) . HPLC (Condition A): Rt 3.64 min.

Intermediate 251: *tert*-butyl {4-chloro-2-[(3-methoxy-2,2,3-trimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetate

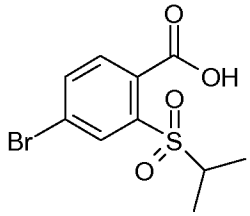


Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 6-bromo-2,2,3-trimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-3-yl methyl ether (Intermediate 250), the title compound was obtained after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.98 (1H, m), 7.88 (1H, dd, *J*= 1.5 Hz, 8 Hz), 7.83 (1H, d, *J*= 8 Hz), 7.64 (1H, d, *J*= 2.7 Hz) 7.45 (1H, dd, *J*= 9 Hz, 2.7 Hz), 7.01 (1H, d, *J*= 9 Hz), 4.82 (2H, s), 3.06 (3H, s), 1.56 (3H, s), 1.43 (9H, s) 1.36 (3H, s), 1.25 (3H, s).

HPLC (Condition A): Rt 5.65 min (HPLC purity 97%).

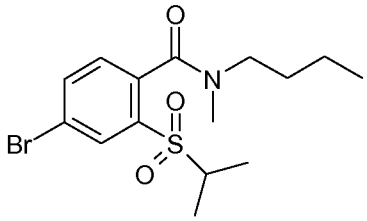
Intermediate 252: 4-bromo-2-(isopropylsulfonyl)benzoic acid



A solution of methyl 4-bromo-2-(isopropylsulfonyl)benzoate (Intermediate 242; 516 mg; 1.61 mmol) in THF (10 ml) was treated with a 5 N solution of NaOH in water (4 mL) and the reaction mixture was heated at 60°C for 1 day. The reaction mixture was acidified with aqueous HCl and the reaction mixture was extracted 3 times with EtOAc.The combined organic phases were dried over MgSO4, filtered and concentrated to dryness affording the title compound as a pale yellow solid (386 mg; 78%).

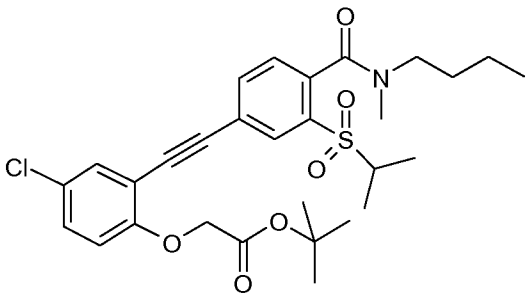
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 12.50 (1H, bs), 8.05 (1H, dd, *J*= 8.1 Hz, *J*= 2.0 Hz), 8.01 (1H, d, *J*= 2.0 Hz), 7.73 (1H, dd, *J*= 8.1 Hz), 3.96 (1H, sext., *J*= 6.9 Hz), 1.22 (6H, d, *J*= 6.9 Hz). HPLC (Condition A) Purity 97.8%; Rt 3.1 min.

Intermediate 253: 4-bromo-*N*-butyl-2-(isopropylsulfonyl)-*N*-methylbenzamide



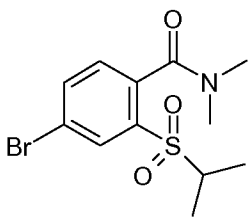
A solution of 4-bromo-2-(isopropylsulfonyl)benzoic acid (Intermediate 242; 260 mg; 0.85 mmol), *N*-methylbuthylamine (200 µl; 1.69 mmol) and TEA (352 µl; 2.54 mmol) in DMF (10 ml) was treated with polymer-supported Mukaiyama reagent (1.35 g; 1.69 mmol) and the reaction mixture was stirred for 18 hours. The reaction mixture was filtered and the polymer was washed with DCM. The filtrate was washed twice with a sat. $NaHCO_3$ solution and twice with brine. The organic phase was dried over $MgSO_4$, filtered and concentrated to dryness to afford the title compound as a pink solid.
MS (ESI^+): 378.0. HPLC (Condition A) Purity 90.6%; Rt 4.2 min.

Intermediate 254: *tert*-butyl (2-{[4-{[butyl(methyl)amino]carbonyl}-3-(isopropylsulfonyl)phenyl]ethynyl}-4-chlorophenoxy)acetate



Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 4-bromo-*N*-butyl-2-(isopropylsulfonyl)-*N*-methylbenzamide (Intermediate 253), the title compound was obtained.
MS (ESI^+): 562.0. HPLC (Condition A) Purity 94.4%; Rt 5.9 min.

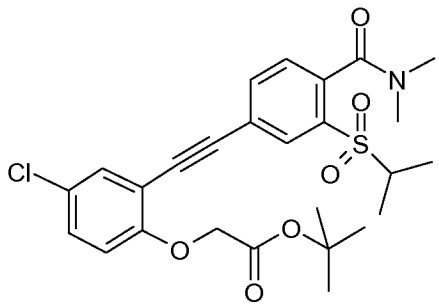
Intermediate 255: 4-bromo-2-(isopropylsulfonyl)-*N*,*N*-dimethylbenzamide



Following the general method as outlined in Intermediate 253, starting from 4-bromo-2-(isopropylsulfonyl)benzoic acid (Intermediate 242) and dimethylamine, the title compound was obtained as a pink solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.04 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.99 (1H, d, *J*= 2.0 Hz), 7.48 (1H, d, *J*= 8.0 Hz), 3.71 (1H, sept., *J*= 7.0 Hz), 2.96 (3H, s), 2.71 (3H, s), 1.27 (3H, m), 1.04 (3H, m). HPLC (Condition A) Purity 99.4%; Rt 3.0 min.

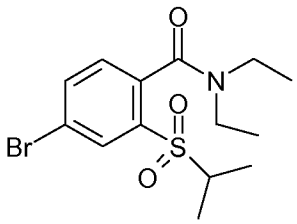
Intermediate 256: *tert*-butyl (4-chloro-2-{[4-[(dimethylamino)carbonyl]-3-(isopropylsulfonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 4-bromo-2-(isopropylsulfonyl)-*N,N*-dimethylbenzamide (Intermediate 255), the title compound was obtained as brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.99 (1H, d, *J*= 1.7 Hz), 7.93 (1H, dd, *J*= 8.0 Hz, *J*= 1.7 Hz), 7.68 (1H, d, *J*= 2.7 Hz), 7.57 (1H, d, *J*= 8.0 Hz), 7.46 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.01 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 3.72 (1H, sept., *J*= 6.8 Hz), 2.98 (3H, s), 2.73 (3H, s), 1.43 (9H, s), 1.28 (3H, m), 1.05 (3H, m). HPLC (Condition A) Rt 5.2 min.

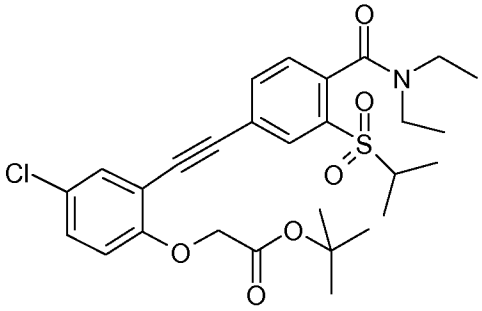
Intermediate 257: 4-bromo-*N,N*-diethyl-2-(isopropylsulfonyl)benzamide



Following the general method as outlined in Intermediate 253, starting from 4-bromo-2-(isopropylsulfonyl)benzoic acid (Intermediate 242) and diethylamine, the title compound was obtained as a pink solid in 81% yield.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.02 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.98 (1H, d, *J*= 2.0 Hz), 7.48 (1H, d, *J*= 8.0 Hz), 3.74 (1H, sept., *J*= 6.9 Hz), 3.57 (1H, m), 3.25 (1H, m), 2.92-3.09 (2H, m), 1.28 (3H, d, *J*= 6.9 Hz), 1.12 (3H, t, *J*= 7.1 Hz), 1.03 (3H, d, *J*= 6.9 Hz), 1.01 (3H, t, *J*= 7.1 Hz). HPLC (Condition A) Purity 95.1%; Rt 4.2 min.

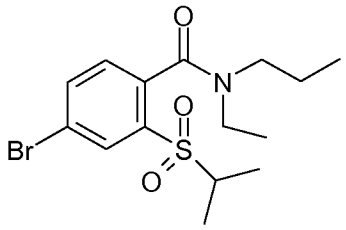
Intermediate 258: *tert*-butyl (4-chloro-2-{[4-[(diethylamino)carbonyl]-3-(isopropylsulfonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 4-bromo-*N,N*-diethyl-2-(isopropylsulfonyl)benzamide (Intermediate 257), the title compound was obtained as a brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.99 (1H, d, *J*= 1.7 Hz), 7.92 (1H, dd, *J*= 7.9 Hz, *J*= 1.7 Hz), 7.68 (1H, d, *J*= 2.7 Hz), 7.58 (1H, d, *J*= 7.9 Hz), 7.46 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.02 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 3.75 (1H, sept., *J*= 6.9 Hz), 3.57 (1H, m), 3.28 (1H, m), 3.01 (2H, m), 1.43 (9H, s), 1.29 (3H, d, *J*= 6.9 Hz), 1.14 (3H, t, *J*= 7.0 Hz), 1.05 (3H, d, *J*= 6.9 Hz), 1.03 (3H, t, *J*= 7.0 Hz). HPLC (Condition A) Purity 97.6%; Rt 5.6 min.

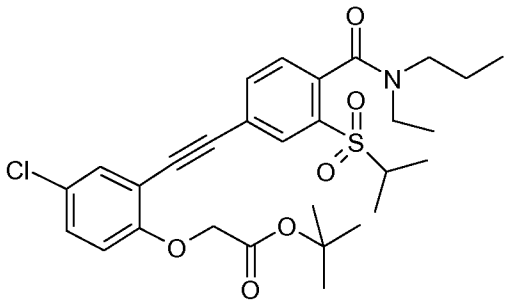
Intermediate 259: 4-bromo-*N*-ethyl-2-(isopropylsulfonyl)-*N*-propylbenzamide



Following the general method as outlined in Intermediate 253, starting from 4-bromo-2-(isopropylsulfonyl)benzoic acid (Intermediate 242) and *N*-ethyl-*N*-propylamine, the title compound was obtained as a pink solid in 80% yield.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.03 (1H, m), 7.99 (1H, m), 7.47 (0.5H, d, *J*= 8.0 Hz), 7.45 (0.5H, d, *J*= 8.0 Hz), 3.72 (1H, m), 3.60 (0.5H, m), 3.38-3.47 (0.5H, m), 3.19-3.30 (1H, m), 2.97-3.11 (1H, m), 2.91-2.97 (0.5H, m), 2.77-2.85 (0.5H, m), 1.42-1.64 (2H, m), 1.27 (3H, d, *J*= 7.0 Hz), 1.12 (1.5 H, t, *J*= 7.0 Hz), 0.98-1.04 (4.5H, m), 0.91 (1.5H, t, *J*= 7.5 Hz), 0.67 (1.5 H, t, *J*= 7.5 Hz). HPLC (Condition A) Purity 95.0%; Rt 4.2 min.

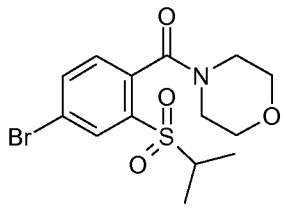
Intermediate 260: *tert*-butyl (4-chloro-2-{[4-{[ethyl(propyl)amino]carbonyl}-3-(isopropylsulfonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 4-bromo-*N*-ethyl-2-(isopropylsulfonyl)-*N*-propylbenzamide (Intermediate 259), the title compound was obtained as a brown sticky solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.99 (1H, m), 7.92 (1H, dd, *J*= 7.9 Hz, *J*= 1.6 Hz), 7.68 (1H, d, *J*= 2.7 Hz), 7.57 (1H, m), 7.46 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.02 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 3.74 (1H, m), 3.60 (0.5H, m), 3.38-3.47 (0.5H, m), 3.21-3.30 (1H, m), 2.76-3.13 (2H, m), 1.50-1.65 (2H, m), 1.43 (9H, s), 1.29 (3H, d, *J*= 7.0 Hz), 1.15 (1.5 H, t, *J*= 7.0 Hz), 1.00-1.06 (4.5H, m), 0.93 (1.5H, t, *J*= 7.4 Hz), 0.69 (1.5 H, t, *J*= 7.4 Hz). HPLC (Condition A) Purity 93.6%; Rt 5.9 min.

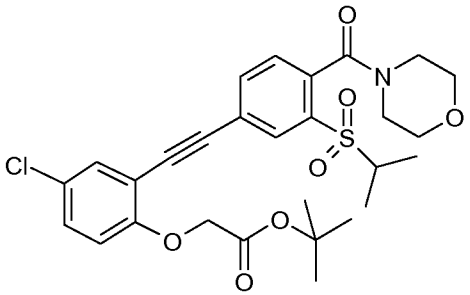
Intermediate 261: 4-[4-bromo-2-(isopropylsulfonyl)benzoyl]morpholine



Following the general method as outlined in Intermediate 253, starting from 4-bromo-2-(isopropylsulfonyl)benzoic acid (Intermediate 242) and morpholine, the title compound was obtained as a pink solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.04 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 8.01 (1H, d, *J*= 2.0 Hz), 7.52 (1H, d, *J*= 8.0 Hz), 3.46-3.76 (7H, m), 2.98-3.18 (2H, m), 1.28 (3H, d, *J*= 6.8 Hz), 1.05 (3H, d, *J*= 6.8 Hz). HPLC (Condition A) Purity 98.4%; Rt 3.0 min.

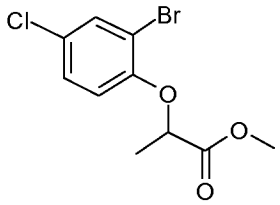
Intermediate 262: *tert*-butyl (4-chloro-2-{[3-(isopropylsulfonyl)-4-(morpholin-4-ylcarbonyl)phenyl]ethynyl}phenoxy)acetate



Following the general method as outlined in Intermediate 107, starting from (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3) and 4-[4-bromo-2-(isopropylsulfonyl)benzoyl]morpholine (Intermediate 261), the title compound was obtained.

HPLC (Condition A) Rt 3.5 min.

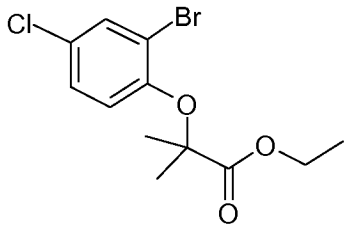
Intermediate 263: methyl 2-(2-bromo-4-chlorophenoxy)propanoate



A mixture of 2-bromo-4-chlorophenol (250 mg; 1.21 mmol) and methyl-2-bromopropionate (VWR; 135 µL, 1.21 mmol) in DME (5 mL) was treated with K_2CO_3 (250 mg, 1.81 mmol) and refluxed for 18 hours. The reaction mixture was filtered, the filtrate was concentrated and purified by flash column chromatography (silica), eluting with heptane containing increasing amounts of EtOAc. The title compound was obtained as a yellow liquid (306 mg; 87%).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.71 (1H, d, *J*= 2.6 Hz), 7.38 (1H, dd, *J*= 9.0 Hz, *J*= 2.6 Hz), 6.99 (1H, d, *J*= 9.0 Hz), 5.10 (1H, q, *J*= 6.8 Hz), 3.68 (3H, s), 1.54 (3H, d, *J*= 6.8 Hz). HPLC (Condition A) Purity 98.8%; Rt 4.6 min.

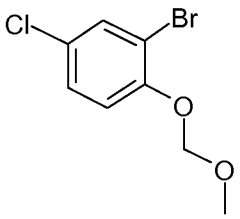
Intermediate 264: ethyl 2-(2-bromo-4-chlorophenoxy)-2-methylpropanoate



A mixture of 2-bromo-4-chlorophenol (250 mg; 1.21 mmol) and ethyl-2-bromoisobutyrate (450 µl; 3.0 mmol) in DMF (5 mL) was treated with K_2CO_3 (250 mg, 1.81 mmol) and heated at 120 °C for 4.5 hours. Water was added and the reaction mixture was extracted 3 times with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered, concentrated and purified by flash column chromatography (silica), eluting with heptane containing increasing amounts of EtOAc. The title compound was obtained as a yellow sticky solid (320 mg; 83%).

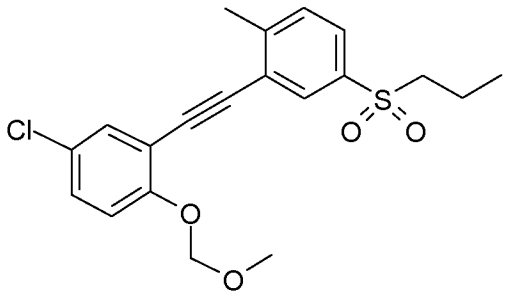
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.73 (1H, d, *J*= 2.6 hz), 7.37 (1H, dd, *J*= 9.0 Hz, *J*= 2.6 Hz), 6.85 (1H, d, *J*= 9.0 Hz), 4.18 (2H, q, *J*= 7.1 Hz), 1.55 (6H, s), 1.17 (3H, t, *J*= 7.1 Hz). HPLC (Condition A) Purity 99.4%; Rt 5.3 min.

Intermediate 265: 2-bromo-4-chloro-1-(methoxymethoxy)benzene



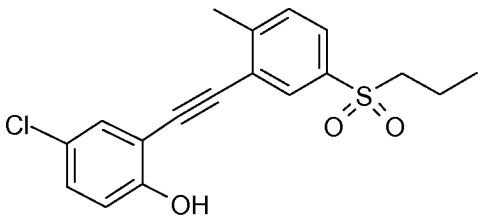
A solution of 2-bromo-4-chlorophenol (3.00 g; 14.5 mmol) in DCM (20 ml) was treated with chloromethyl methyl ether (1.3 ml; 17 mmol) DIEA (3.3 ml; 19 mmol) for 18 hours. The solvents were evaporated, the residue was taken up in EtOAc, washed with sat. NH4Cl solution and brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to afford the title compound as a colorless oil (3.27 g, 90%).
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.70 (1H, d, *J*= 2.6 Hz), 7.41 (1H, dd, *J*= 9.0 Hz, *J*= 2.6 Hz), 7.23 (1H, d, *J*= 9.0 Hz), 5.29 (2H, s), 3.40 (3H, s).

Intermediate 266: 3-{[5-chloro-2-(methoxymethoxy)phenyl]ethynyl}-4-methylphenyl propyl sulfone



Following the general method as outlined in Intermediate 183, starting from 2-bromo-4-chloro-1-(methoxymethoxy)benzene (Intermediate 265) and 2-ethynyl-1-methyl-4-(propane-1-sulfonyl)-benzene (Intermediate 40), the title compound was obtained as a white solid in 70% yield after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.94 (1H, d, *J*= 2.0 Hz), 7.80 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.67 (1H, d, *J*= 2.7 Hz), 7.63 (1H, d, *J*= 8.0 Hz), 7.47 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.24 (1H, d, *J*= 9.0 Hz), 5.34 (2H, s), 3.43 (3H, s), 3.31 (2H, m), 2.58 (3H, s), 1.55 (2H, sext., *J*= 7.5 Hz), 0.92 (3H, t, *J*= 7.5 Hz). HPLC (Condition A) Purity 100.0%; Rt 5.3 min.

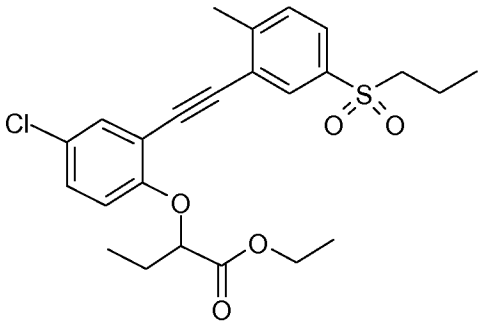
Intermediate 267: 4-chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenol



3-{[5-Chloro-2-(methoxymethoxy)phenyl]ethynyl}-4-methylphenyl propyl sulfone (Intermediate 266; 1.09 g; 2.77 mmol) was treated with a 4 N solution hydrogen chloride in 1,4-dioxane (21 ml) and stirred at RT for 7 hours. The reaction mixture was concentrated to dryness under reduced pressure to afford the title compound as a beige solid (884 mg; 91%).

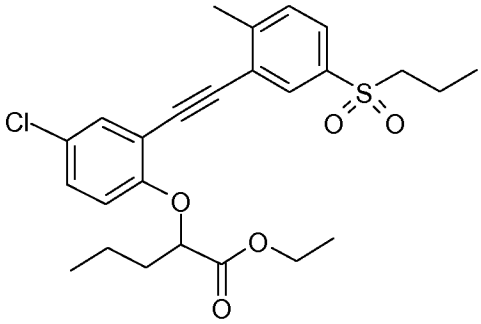
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 10.48 (1H, s), 7.94 (1H, d, *J*= 2.0 Hz), 7.78 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.61 (1H, d, *J*= 8.0 Hz), 7.51 (1H, d, *J*= 2.7 Hz), 7.30 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 6.94 (1H, d, *J*= 9.0 Hz), 3.32 (2H, m), 2.57 (3H, s), 1.55 (2H, sext., *J*= 7.5 Hz), 0.91 (3H, t, *J*= 7.5 Hz). HPLC (Condition A) Purity 99.8%; Rt 4.8 min.

Intermediate 268: ethyl 2-(4-chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)butanoate



A mixture of 4-chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenol (Intermediate 267; 110 mg; 0.32 mmol) and ethyl 2-bromobutyrate (50 µl; 0.35 mmol) in DME (2 mL) was treated with K_2CO_3 (250 mg, 1.81 mmol) and refluxed for 18 hours. Water was added and the reaction mixture was extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered, concentrated and purified by flash column chromatography (silica), eluting with heptane containing increasing amounts of EtOAc. The title compound was obtained as a colorless sticky solid which was not further purified before use.
HPLC (Condition A) Rt 5.2 min.

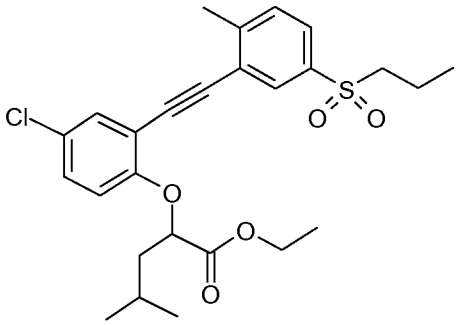
Intermediate 269: ethyl 2-(4-chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)pentanoate



Following the general method as outlined in Intermediate 268, starting from 4-chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenol (Intermediate 267) and ethyl 2-bromovalerate, the title compound was obtained as a colorless sticky solid.

MS (ESI$^+$): 494.3 $(M+NH_4)^+$. HPLC (Condition A) Rt 5.7 min.

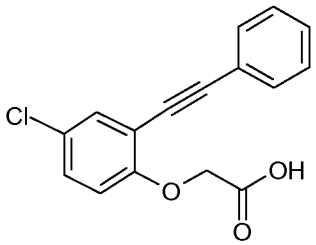
Intermediate 270: ethyl 2-(4-chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)-4-methylpentanoate



Following the general method as outlined in Intermediate 268, starting from 4-chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenol (Intermediate 267) and 2-bromo-4-methyl-pentanoic acid ethyl ester, the title compound was obtained as a colorless sticky solid in 81% yield.

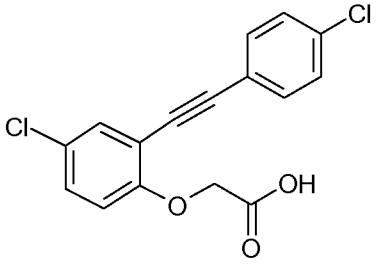
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.93 (1H, d, *J*= 2.0 Hz), 7.80 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.67 (1H, d, *J*= 2.7 Hz), 7.62 (1H, d, *J*= 8.0 Hz), 7.43 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 6.98 (1H, d, *J*= 9.0 Hz), 5.00 (1H, dd, *J*= 8.7 Hz, *J*= 4.0 Hz), 4.16 (2H, m), 3.30 (2H, m), 2.58 (3H, s), 1.84-1.95 (2H, m), 1.70-1.79 (1H, m), 1.54 (2H, sext., *J*= 7.5 Hz), 1.17 (3H, t, *J*= 7.0 Hz), 0.89-0.96 (9H, s). HPLC (Condition A) Rt 6.2 min.

Example 1: [4-chloro-2-(phenylethynyl)phenoxy]acetic acid



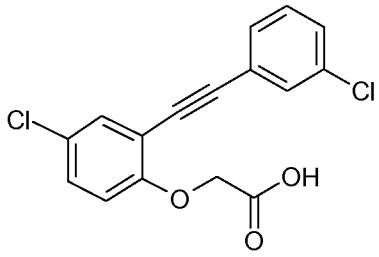
A solution of *tert*-butyl (2-bromo-4-chlorophenoxy)acetate (350 mg; 1.09 mmol) and phenylacetylene (Aldrich; 122 mg; 1.20 mmol) in degassed, anhydrous ACN (2.80 mL) was treated with dichlorobis(triphenylphosphine)palladium(II) (38 mg; 0.05 mmol), copper(I) iodide (10 mg; 0.05 mmol) and triethylamine (0.45 mL; 3.26 mmol). The reaction mixture was heated at 50 °C under stirring for 16 hours. The solvent was evaporated, the residue dissolved in DCM (4 mL) and TFA (1 mL) was added. After stirring for 45 minutes, the solvents were removed under vacuum and the crude product purified by preparative HPLC. The title compound was obtained as a brown solid. ^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.17 (1 H, s), 7.57-7.52 (3 H, m), 7.46-7.38 (4 H, m), 6.99 (1 H, d, *J*= 9.0 Hz), 4.82 (2 H, s). MS (ESI$^-$): 285.1. HPLC (Condition A): Rt 4.61 min (HPLC purity 98.3%).

Example 2: {4-chloro-2-[(4-chlorophenyl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 1, starting from *tert*-butyl (2-bromo-4-chlorophenoxy)acetate (Intermediate 1) and 4-chlorophenylacetylene (Apollo), the title compound was obtained as a beige solid after purification by preparative HPLC ^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.17 (1 H, bs), 7.59-7.48 (5 H, m), 7.42 (1 H, dd, *J*= 9.0, 2.7 Hz), 7.00 (1 H, d, *J*= 9.0 Hz), 4.83 (2 H, s). MS (ESI$^-$): 319.0. HPLC (Condition A): Rt 4.79 min (HPLC purity 98.7%).

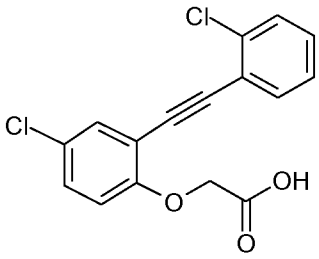
Example 3: {4-chloro-2-[(3-chlorophenyl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 1, starting from *tert*-butyl (2-bromo-4-chlorophenoxy)acetate (Intermediate 1) and 3-chloro-1-ethynylbenzene (Aldrich), the title compound was obtained as a brown solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.19 (1H, s), 7.62 (1H, m), 7.58 (1H, d, *J*= 2.7 Hz), 7.45-7.54 (3H, m), 7.42 (1H, dd, *J*= 9.1, *J*= 2.7 Hz), 7.01 (d, *J*= 9.1 Hz, 1H), 4.83 (2H, s). MS (ESI$^-$): 319.0. HPLC (Condition A): Rt 4.91 min (HPLC purity 100%).

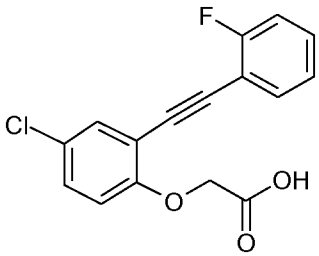
Example 4: {4-chloro-2-[(2-chlorophenyl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 1, starting from *tert*-butyl (2-bromo-4-chlorophenoxy)acetate (Intermediate 1) and 1-chlorophenylacetylene (ABCR), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.21 (1H, s), 7.66 (1H, dd, *J*= 7.3, *J*= 2.5 Hz), 7.60 (1H, dd, *J*= 7.3, *J*= 1.5 Hz), 7.55 (1H, d, *J*= 2.5 Hz), 7.37-7.48 (3H, m), 7.02 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s). MS (ESI$^-$): 319.0. HPLC (Condition A): Rt 4.54 min (HPLC purity 99.8%).

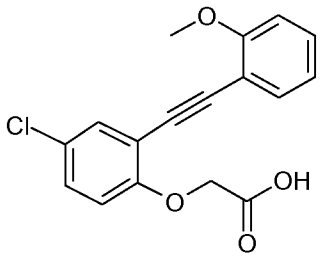
Example 5: {4-chloro-2-[(2-fluorophenyl)ethynyl]phenoxy}acetic acid



A solution of *tert*-butyl (2-bromo-4-chlorophenoxy)acetate (Intermediate 1; 350 mg; 1.09 mmol) and 1-fluorophenylacetylene (Aldrich, 135 µL; 1.20 mmol) in degassed, anhydrous CH_3CN (2.80 mL) was treated with dichlorobis(triphenylphosphine)palladium(II) (38 mg; 0.05 mmol), copper(I) iodide (10 mg; 0.05 mmol) and triethylamine (0.45 mL; 3.26 mmol). The reaction mixture was heated at 50 °C under stirring for 16 hours. The solvent was evaporated and the residue purified by column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc. The purified ester intermediate was dissolved in DCM (6 mL) and an HCl solution (4 N in dioxane, 2.7 mL) was added. After stirring for 16 hours, the solvents were removed under vacuum and the crude product purified by preparative HPLC. The title compound was obtained as a light brown solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.63 (1 H, td, *J*= 7.5, 1.8 Hz), 7.57 (1 H, d, *J*= 2.6 Hz), 7.55-7.23 (4 H, m), 7.01 (1 H, d, *J*= 9.0 Hz), 4.83 (2 H, s). MS (ESI$^-$): 303.1. HPLC (Condition A): Rt 4.42 min (HPLC purity 98.3%).

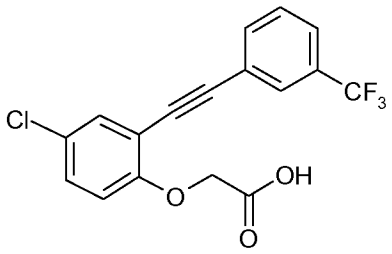
Example 6: {4-chloro-2-[(2-methoxyphenyl)ethynyl]phenoxy}acetic acid



A solution of (2-bromo-4-chlorophenoxy)acetic acid (200 mg; 0.75 mmol, Intermediate 4) and 2-ethynylanisole (Aldrich, 107 µL; 0.83 mmol) in anhydrous, degassed ACN (2 mL) was treated with dichlorobis(triphenylphosphine)palladium(II) (38 mg; 0.05 mmol) followed after 5 minutes by copper iodide (10 mg; 0.05 mmol) and triethylamine (0.45 mL; 3.3 mmol). The reaction mixture was heated at 50 °C under stirring for 16 hours. The solvents were removed under vacuum, the residue was then taken up in EtOAc and washed with HCl (1N aqueous solution), the organic phase was washed with water (750 mL) then with brine (750 mL), dried over $MgSO_4$, filtered and concentrated under vacuum to give a brown oily residue which was purified by preparative HPLC to afford the title compound as a brown oil.

MS (ESI$^-$): 315.1. HPLC (Condition A): Rt 4.27 min (HPLC purity 100%).

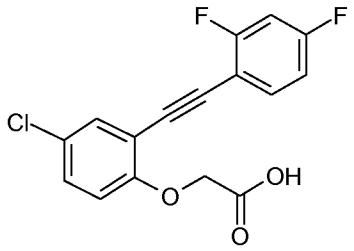
Example 7: (4-chloro-2-{[3-(trifluoromethyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 6, starting from (2-bromo-4-chlorophenoxy)acetic acid (Intermediate 4) and 3-ethynyl-□,□,□-trifluorotoluene (Aldrich), using degassed, anhydrous DMF as solvent, the title compound was obtained as a brown sticky solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.16 (1H, bs), 7.91 (1 H, s), 7.85 (1 H, d, *J*= 7.8 Hz), 7.80 (1 H, d, *J*= 7.8 Hz), 7.69 (1 H, t, *J*= 7.8 Hz), 7.63 (1 H, d, *J*= 2.7 Hz), 7.44 (1 H, dd, *J*= 9.0, 2.7 Hz), 7.02 (1 H, d, *J*= 9.0 Hz), 4.84 (2 H, s). MS (ESI$^-$): 353.1. HPLC (Condition A): Rt 5.12 min (HPLC purity 96.1%).

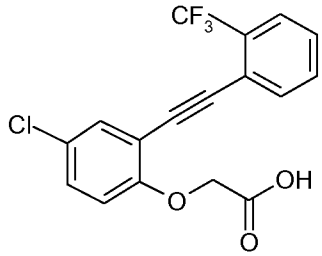
Example 8: {4-chloro-2-[(2,4-difluorophenyl)ethynyl]phenoxy}acetic acid



A solution of *tert*-butyl (2-bromo-4-chlorophenoxy)acetate (350 mg; 1.09 mmol) and 1-ethynyl-2,4-difluorobenzene (Aldrich, 165 mg; 1.20 mmol) in degassed, anhydrous CH_3CN (2.80 mL) was treated with dichlorobis(triphenylphosphine)palladium(II) (38 mg; 0.05 mmol), copper(I) iodide (10 mg; 0.05 mmol) and triethylamine (0.45 mL; 3.26 mmol). The reaction mixture was heated at 50 °C under stirring for 16 hours. The solvent was evaporated and the residue dissolved in DCM (1 mL) and an HCl solution (4 N in dioxane, 2.7 mL) was added. After stirring for 16 hours, the solvents were removed under vacuum and the crude product purified by preparative HPLC. The title compound was obtained as an off-white solid.

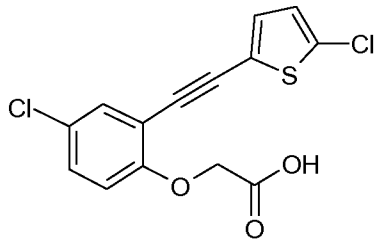
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.17 (1 H, s), 7.70 (1 H, td, *J*= 8.5, 6.5 Hz), 7.57 (1 H, d, *J*= 2.7 Hz), 7.49-7.40 (2 H, m), 7.24-7.16 (1 H, m), 7.01 (1 H, d, *J*= 9.0 Hz), 4.83 (2 H, s). MS (ESI$^-$): 321.1. HPLC (Condition A): Rt 4.50 min (HPLC purity 100%).

Example 9: (4-chloro-2-{[2-(trifluoromethyl)phenyl]ethynyl}phenoxy)acetic acid



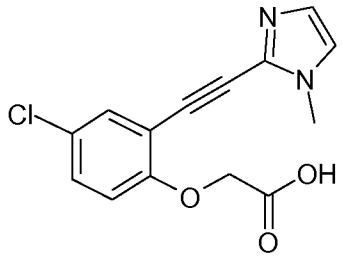
Following the general method as outlined in Example 8, starting from *tert*-butyl (2-bromo-4-chlorophenoxy)acetate (Intermediate 1) and 2-ethynyl-□,□,□-trifluorotoluene (Aldrich), the title compound was obtained as a beige solid after purification by preparative HPLC. ^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.2 (1H, bs), 7.86-7.69 (3 H, m), 7.63 (1 H, t, *J*= 7.5 Hz), 7.49-7.42 (2 H, m), 7.03 (1 H, d, *J*= 8.8 Hz), 4.82 (2 H, s). MS (ESI$^-$): 353.1. HPLC (Condition A): Rt 4.75 min (HPLC purity 95.9%).

Example 10: {4-chloro-2-[(5-chloro-2-thienyl)ethynyl]phenoxy}acetic acid



A mixture of 2-bromo-5-chlorothiophene (Aldrich, 163 mg; 0.82 mmol), *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (Intermediate 3, 200 mg; 0.75 mmol), dichlorobis(triphenylphosphine)palladium(II) (33 mg; 0.04 mmol), copper(I) iodide (8.6 mg; 0.04 mmol) was degassed during two minutes under nitrogen then THF (3 mL) and triethylamine (208 µL; 1.50 mmol) were added and reaction mixture was stirred at 60 °C for 16 hours. The solvent was evaporated and the residue was treated with an HCl solution (4 N in dioxane, 3.7 mL). After stirring for 16 hours, the solvents were removed under vacuum and the crude product purified by preparative HPLC. The title compound was obtained as a brown sticky solid.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.2 (1H, bs), 7.57 (1 H, d, *J*= 2.7 Hz), 7.43 (1 H, dd, *J*= 9.0, 2.7 Hz), 7.31 (1 H, d, *J*= 4.0 Hz), 7.19 (1 H, d, *J*= 4.0 Hz), 7.00 (1 H, d, *J*= 9.0 Hz), 4.82 (2 H, s). MS (ESI$^+$): 325.0. HPLC (Condition A): Rt 5.35 min (HPLC purity 96.4%).

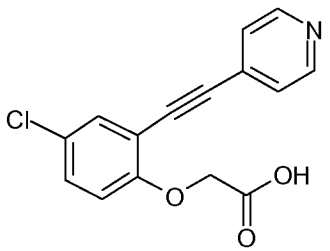
Example 11: {4-chloro-2-[(1-methyl-1H-imidazol-2-yl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 10, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (Intermediate 3) and 2-bromo-1-methyl-1*H*-imidazole (Aldrich), the title compound was obtained as an off-white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.2 (1H, bs), 7.73 (1 H, d, *J*= 2.7 Hz), 7.68 (1 H, d, *J*= 1.6 Hz), 7.55 (1 H, dd, *J*= 9.0, 2.7 Hz), 7.49 (1 H, H, d, *J*= 1.6 Hz), 7.12 (1 H, d, *J*= 9.0 Hz), 4.89 (2 H, s), 3.92-3.89 (3 H, s). MS (ESI$^+$): 291.1. HPLC (Condition A): Rt 2.16 min (HPLC purity 98.2%).

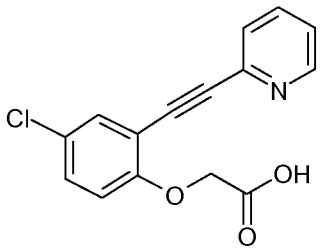
Example 12: [4-chloro-2-(pyridin-4-ylethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 10, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (Intermediate 3) and 4-bromopyridine hydrochloride (Fluka), the title compound was obtained as a yellow solid after purification by precipitation in dioxane.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.2 (1H, bs), 8.66-8.62 (2 H, m), 7.64 (1 H, d, *J*= 2.7 Hz), 7.53-7.44 (3 H, m), 7.04 (1 H, d, *J*= 9.0 Hz), 4.86 (2 H, s). MS (ESI$^+$): 288.0. HPLC (Condition A): Rt 2.37 min (HPLC purity 97.5%).

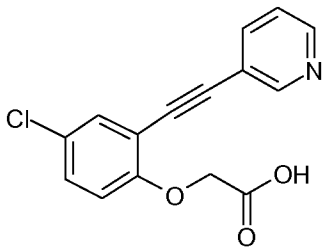
Example 13: [4-chloro-2-(pyridin-2-ylethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 10, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (Intermediate 3) and 2-bromopyridine (Acros), the title compound was obtained as a beige powder after purification by precipitation in acetonitrile.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.18 (1 H, s), 8.62 (1 H, ddd, *J*= 4.9, 1.8, 1.0 Hz), 7.87 (1 H, td, *J*= 7.7, 1.8 Hz), 7.66-7.61 (2 H, m), 7.48-7.39 (2 H, m), 7.02 (1 H, d, *J*= 9.0 Hz), 4.86 (2 H, s). MS (ESI$^+$): 288.1. HPLC (Condition A): Rt 2.53 min (HPLC purity 98.4%).

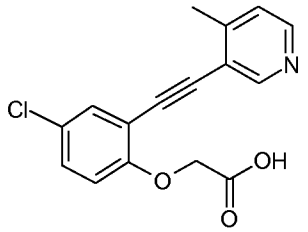
Example 14: [4-chloro-2-(pyridin-3-ylethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 10, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (Intermediate 3) and 3-bromopyridine (Fluka), the title compound was obtained as an off-white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.17 (1 H, s), 8.75 (1 H, d, *J*= 2.1 Hz), 8.61 (1 H, dd, *J*= 4.9, 1.8 Hz), 7.97 (1 H, dt, *J*= 7.9, 1.8 Hz), 7.61 (1 H, d, *J*= 2.7 Hz), 7.52-7.42 (2 H, m), 7.02 (1 H, d, *J*= 9.0 Hz), 4.85 (2 H, s). MS (ESI$^+$): 288.0. HPLC (Condition A): Rt 2.56 min (HPLC purity 98.1%).

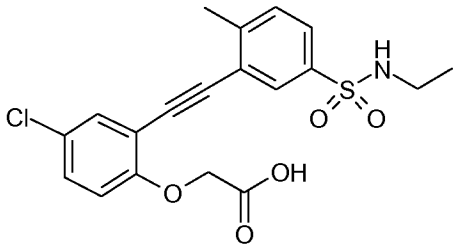
Example 15: {4-chloro-2-[(4-methylpyridin-3-yl)ethynyl]phenoxy}acetic acid



A solution of *tert*-butyl {4-chloro-2-[(4-methylpyridin-3-yl)ethynyl]phenoxy}acetate (Intermediate 19, 138 mg; 0.39 mmol) in DCM (1.4 mL) was treated with an HCl solution (4 N in dioxane, 2.7 mL). After stirring for 20 hours, the solvents were removed under vacuum to afford the title compound as a beige solid (107 mg, 82%).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.91 (1 H, s), 8.68 (1 H, s), 7.86-7.72 (1 H, m), 7.65 (1 H, d, *J*= 2.7 Hz), 7.49 (1 H, dd, *J*= 9.0, 2.7 Hz), 7.08 (1 H, d, *J*= 9.0 Hz), 4.86 (2 H, s), 2.64 (3 H, s). MS (ESI$^+$): 302.2. HPLC (Condition A): Rt 2.53 min (HPLC purity 99.6%).

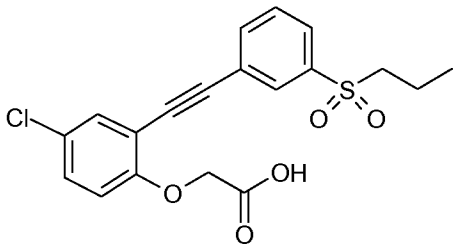
Example 16: [4-chloro-2-({5-[(ethylamino)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 10, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (Intermediate 3) and *N*-ethyl 3-bromo-4-methylbenzenesulfonamide (Combi-Blocks), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.15 (1H, s), 7.85 (1H, d, *J*= 2.0 Hz), 7.69 (1H, dd, *J*= 8.0, *J*= 2.0 Hz), 7.63 (1H, d, *J*= 2.7 Hz), 7.54-7.60 (2H, m), 7.44 (1H, dd, *J*= 9.0, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 2.78 (2H, qd, *J*= 7.1, *J*= 5.7 Hz), 2.55 (3H, s), 0.97 (3H, t, *J*= 7.1 Hz). MS (ESI$^+$): 408.2. HPLC (Condition A): Rt 4.31 min (HPLC purity 99.6%).

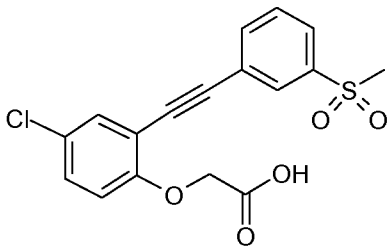
Example 17: (4-chloro-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl {4-chloro-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 20), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.17 (1H, s), 8.01 (1H, t, *J*= 1.6 Hz), 7.88-7.94 (2H, m), 7.73 (1H, t, *J*= 7.6 Hz), 7.64 (1H, d, *J*= 2.7 Hz), 7.44 (1H, dd, *J*= 9.0, *J*= 2.7 Hz), 7.02 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 3.34-3.39 (2H, m), 1.57 (2H, sext., *J*= 7.6 Hz), 0.93 (3H, t, *J*= 7.6 Hz). MS (ESI$^-$): 391.3. HPLC (Condition A): Rt 4.27 min (HPLC purity 99.8%).

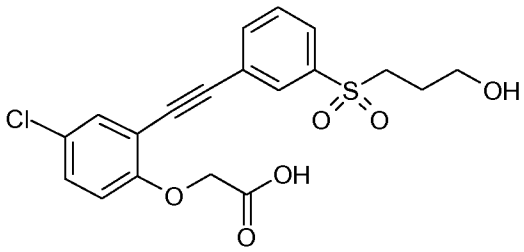
Example 18: (4-chloro-2-{[3-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 10, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (Intermediate 3) and 3-bromophenylmethylsulfone (Asymchem), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.21 (1H, s), 8.06 (1H, t, *J*= 1.6 Hz), 7.96 (1H, dt, *J*= 7.8, *J*= 1.6 Hz), 7.88 (1H, dt, *J*= 7.8, *J*= 1.6 Hz), 7.72 (1H, t, *J*= 7.8Hz), 7.63 (1H, d, *J*= 2.6 Hz), 7.44 (1H, dd, *J*= 9.0, *J*= 2.6 Hz), 7.01 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 3.29 (1H, s). MS (ESI$^-$): 363.2. HPLC (Condition A): Rt 3.81 min (HPLC purity 99.2%).

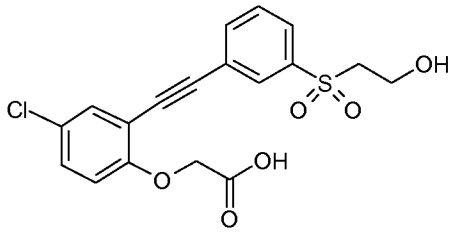
Example 19: [4-chloro-2-({3-[(3-hydroxypropyl)sulfonyl]phenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 10, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (Intermediate 3) and 3-(3-bromo-benzenesulfonyl)-propan-1-ol (Intermediate 6), the title compound was obtained as a brown solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.21 (1H, s), 8.01 (1H, t, *J*= 1.6 Hz), 7.92 (2H, m), 7.74 (1H, t, *J*= 7.8 Hz), 7.65 (1H, d, *J*= 2.6 Hz), 7.44 (1H, dd, *J*= 9.0, *J*= 2.6 Hz), 7.01 (1H, d, *J*= 9.0 Hz); 4.85 (2H, s), 4.66 (1H, s), 3.36-3.43 (4H, m), 1.68 (2H, m). MS (ESI$^+$): 409.2. HPLC (Condition A): Rt 3.60 min (HPLC purity 93.7%).

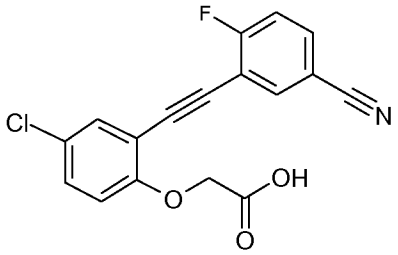
Example 20: [4-chloro-2-({3-[(2-hydroxyethyl)sulfonyl]phenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 10, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (Intermediate 3) and 2-(3-bromo-benzenesulfonyl)-ethanol (Intermediate 7), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.28 (1H, s), 8.00 (1H, t, *J*= 1.6 Hz), 7.90 (1H, dt, *J*= 7.8, *J*= 1.6 Hz), 7.85 (1H, dt, *J*= 7.8, *J*= 1.6 Hz), 7.68 (1H, t, *J*= 7.8 Hz), 7.61 (1H, d, *J*= 2.7 Hz), 7.41 (1H, dd, 9.0, *J*= 2.7 Hz), 6.99 (1H, d, *J*= 9.0 Hz), 4.85 (1H, bs), 4.83 (2H, s), 3.67 (2H, t, *J*= 6.1 Hz), 3.51 (2H, t, *J*= 6.1 Hz). MS (ESI$^-$): 393.2. HPLC (Condition A): Rt 3.46 min (HPLC purity 97.9%).

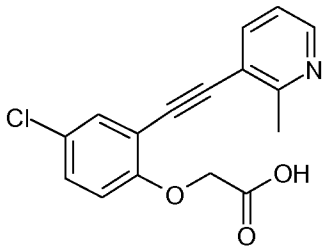
Example 21: {4-chloro-2-[(5-cyano-2-fluorophenyl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl {4-chloro-2-[(5-cyano-2-fluorophenyl)ethynyl]phenoxy}acetate (Intermediate 21), the title compound was obtained as a white solid (119 mg, 99%).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.20 (1H, s), 8.22 (1H, dd, *J*= 6.6, *J*= 2.2 Hz), 7.99-8.04 (1H, m), 7.58-7.65 (2H, m), 7.47 (1H, dd, *J*= 9.0, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.85 (2H, s). MS (ESI$^-$): 328.1. HPLC (Condition A): Rt 4.26 min (HPLC purity 97.1%).

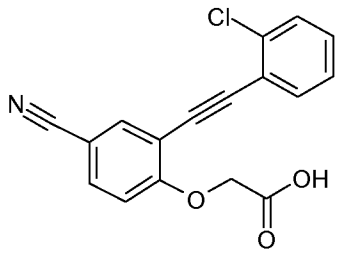
Example 22: {4-chloro-2-[(2-methylpyridin-3-yl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl{4-chloro-2-[(2-methylpyridin-3-yl)ethynyl]phenoxy}acetate (Intermediate 22), the title compound was obtained as a dark brown solid (37.6 quant).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.32 (1H, s), 8.65 (1H, d, *J*= 5.1 Hz), 8.29 (1H, d, *J*= 7.9 Hz), 7.65-7.70 (2H, m), 7.48 (1H, dd, *J*= 9.0, *J*= 2.8 Hz), 7.07 (1H, d, *J*= 9.0 Hz), 4.85 (2H, s), 2.81 (3H, s). MS (ESI$^+$): 302.1. HPLC (Condition A): Rt 2.56 min (HPLC purity 93.4%).

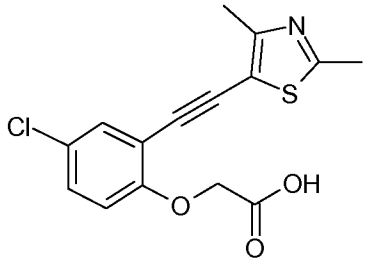
Example 23: {2-[(2-chlorophenyl)ethynyl]-4-cyanophenoxy}acetic acid



Following the general method as outlined in Example 8, starting from *tert*-butyl (2-bromo-4-cyanophenoxy)acetate (Intermediate 8) and 2-bromochlorobenzene (Aldrich), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.3 (1H, bs), 8.02 (1 H, d, *J*= 2.2 Hz), 7.87 (1 H, dd, *J*= 8.8, 2.2 Hz), 7.68 (1 H, dd, *J*= 7.3, 2.1 Hz), 7.61 (1 H, dd, *J*= 7.7, 1.6 Hz), 7.51-7.39 (2 H, m), 7.19 (1 H, d, *J*= 8.8 Hz), 4.95 (2 H, s). MS (ESI$^-$): 310.1. HPLC (Condition A): Rt 4.19 min (HPLC purity 98.0%).

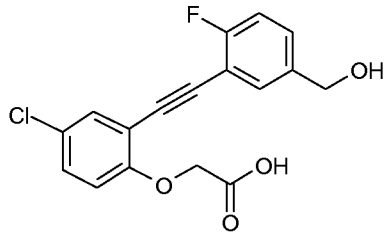
Example 24: {4-chloro-2-[(2,4-dimethyl-1,3-thiazol-5-yl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 8, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (Intermediate 3) and 5-bromo-2,4-dimethyl-1,3-thiazole (Acros), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.2 (1H, bs), 7.57 (1 H, d, *J*= 2.7 Hz), 7.41 (1 H, dd, *J*= 9.0, 2.7 Hz), 7.01 (1 H, d, *J*= 9.0 Hz), 4.80 (2 H, s), 2.64 (3 H, s), 2.45 (3 H, s). MS (ESI$^+$): 322.1. HPLC (Condition A): Rt 3.85 min (HPLC purity 94.7%).

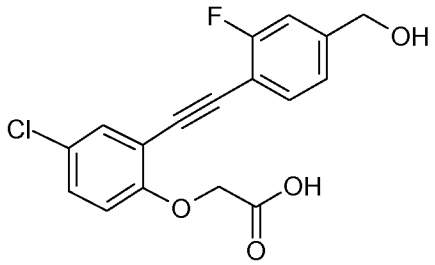
Example 25: (4-chloro-2-{[2-fluoro-5-(hydroxymethyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl(4-chloro-2-{[2-fluoro-5-(hydroxymethyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 23), the title compound was obtained as a beige solid after purification by preparative HPLC.

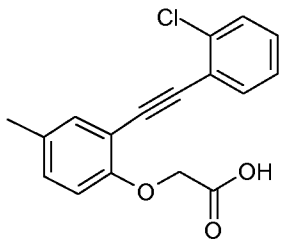
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.2 (1H, s), 7.55 (1H, d, *J*= 2.6 Hz), 7.54 (1H, dd, *J*= 5.1, *J*= 2.2 Hz), 7.42 (1H, dd, *J*= 9.0, *J*= 2.6 Hz), 7.40 (1H, ddd, *J*= 8.7, *J*= 5.1, *J*= 2.2 Hz), 7.29 (1H, t, *J*= 5.7 Hz), 6.99 (1H, d, *J*= 9.0 Hz), 5.31 (1H, bs), 4.81 (2H, s), 4.50 (2H, s). MS (ESI$^-$): 333.2. HPLC (Condition A): Rt 3.83 min (HPLC purity 99.2%).

Example 26: (4-chloro-2-{[2-fluoro-4-(hydroxymethyl)phenyl]ethynyl}phenoxy)acetic acid



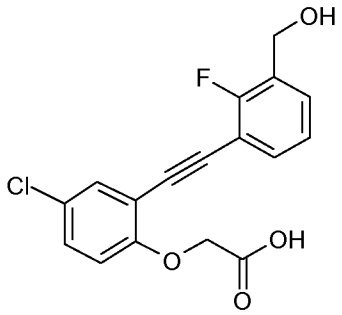
Following the general method as outlined in Example 15, starting from *tert*-butyl(4-chloro-2-{[2-fluoro-4-(hydroxymethyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 24), the title compound was obtained as a white solid after purification by preparative HPLC. ^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.2 (1H, s), 7.57 (1H, d, *J*= 7.8 Hz), 7.54 (1H, d, *J*= 2.6 Hz), 7.42 (1H, dd, *J*= 9.0, *J*= 2.6 Hz), 7.24 (1H, d, *J*= 10.7 Hz), 7.20 (1H, d, *J*= 7.8 Hz), 6.98 (1H, d, *J*= 9.0 Hz), 5.43 (1H, s), 4.80 (2H, s), 4.55 (2H, s). MS (ESI$^-$): 333.2. HPLC (Condition A): Rt 3.73 min (HPLC purity 99.7%).

Example 27: {2-[(2-chlorophenyl)ethynyl]-4-methylphenoxy}acetic acid



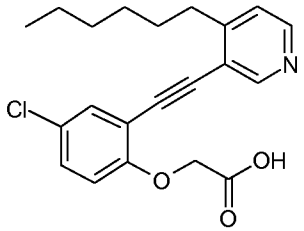
Following the general method as outlined in Example 8, starting from *tert*-butyl (2-bromo-4-methylphenoxy)acetate (Intermediate 10) and 2'-chlorophenyl acetylene (ABCR), the title compound was obtained as a brown solid after purification by preparative HPLC. MS (ESI$^-$): 299.1. HPLC (Condition B): Rt 1.31 min (HPLC purity 97.5%).

Example 28: (4-chloro-2-{[2-fluoro-3-(hydroxymethyl)phenyl]ethynyl}phenoxy)acetic acid



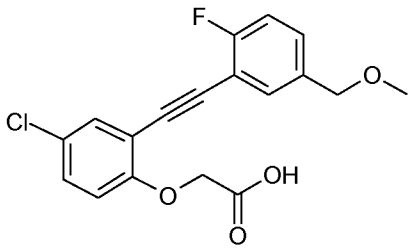
Following the general method as outlined in Example 15, starting from *tert*-butyl(4-chloro-2-{[2-fluoro-3-(hydroxymethyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 25), the title compound was obtained as a white solid after purification by preparative HPLC.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.47-7.54 (3H, m), 7.41 (1H, dd, *J*= 9.0, *J*= 2.7 Hz), 7.25 (1H, t, *J*= 7.6 Hz), 6.97 (1H, d, *J*= 9.0 Hz), 5.37 (1H, bs), 4.75 (2H, s), 4.58 (2H, s). MS (ESI$^-$): 333.1. HPLC (Condition A): Rt 3.70 min (HPLC purity 98.8%).

Example 29: {4-chloro-2-[(4-hexylpyridin-3-yl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 8, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (Intermediate 3) and 3-bromo-4-hexylpyridine (Intermediate 13), the title compound was obtained as a beige solid after purification by preparative HPLC.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.2 (1H, bs), 8.64 (1H, s), 8.46 (1H, d, *J*= 5.1 Hz), 7.56 (1H, d, *J*= 2.7 Hz), 7.44 (1H, d, *J*= 9.0, *J*= 2.7 Hz), 7.36 (1H, d, *J*= 5.1 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s), 2.83 (2H, m), 1.62 (2H, m), 1.27 (6H, m), 0.82 (3H, t, *J*= 7.2 Hz). MS (ESI$^+$): 372.3. HPLC (Condition A): Rt 3.85 min (HPLC purity 96.7%).

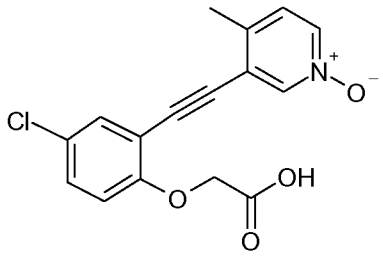
Example 30: (4-chloro-2-{[2-fluoro-5-(methoxymethyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl(4-chloro-2-{[2-fluoro-5-(methoxymethyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 26), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.2 (1H, bs), 7.56-7.59 (2H, m), 7.41-7.47 (2H, m), 7.34 (1H, m), 7.01 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 4.43 (2H, s), 3.32 (3H, s). MS (ESI$^-$): 347.2. HPLC (Condition A): Rt 4.37 min (HPLC purity 96.0%).

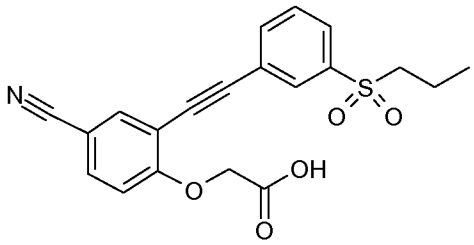
Example 31: {4-chloro-2-[(4-methyl-1-oxidopyridin-3-yl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl{4-chloro-2-[(4-methyl-1-oxidopyridin-3-yl)ethynyl]phenoxy}acetate (Intermediate 27), the title compound was obtained as a white solid after precipitation from the reaction mixture.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.57 (1 H, d, *J*= 2.0 Hz), 8.37 (1 H, dd, *J*= 6.6, 2.0 Hz), 7.64 (1 H, d, *J*= 2.7 Hz), 7.56 (1 H, d, *J*= 6.6 Hz), 7.49 (1 H, dd, *J*= 9.0, 2.7 Hz), 7.08 (1 H, d, *J*= 9.0 Hz), 4.85 (2 H, s), 2.50 (3H, s). MS (ESI$^+$): 318.1. HPLC (Condition A): Rt 2.96 min (HPLC purity 97.7%).

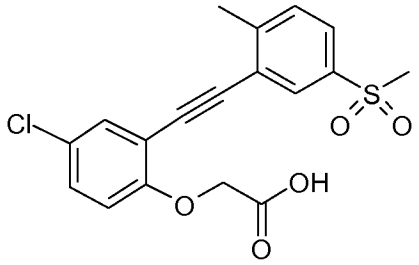
Example 32: (4-cyano-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-cyano-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 28), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.3 (1 H, bs), 8.10 (1 H, d, *J*= 2.2 Hz), 8.03 (1 H, t, *J*= 1.7 Hz), 7.96-7.85 (3 H, m), 7.75 (1 H, t, *J*= 7.8 Hz), 7.19 (1 H, d, *J*= 8.9 Hz), 4.96 (2 H, s), 3.41-3.33 (2 H, m), 1.62-1.51 (2 H, m), 0.97-0.89 (3 H, t, *J*= 7.4). MS (ESI$^-$): 382.3. HPLC (Condition A): Rt 3.75 min (HPLC purity 99.5%).

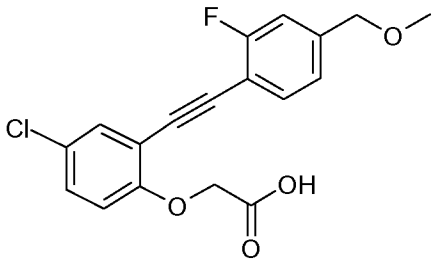
Example 33: (4-chloro-2-{[2-methyl-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[2-methyl-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 29), the title compound was obtained as a light brown solid (150.2 mg, 91%).

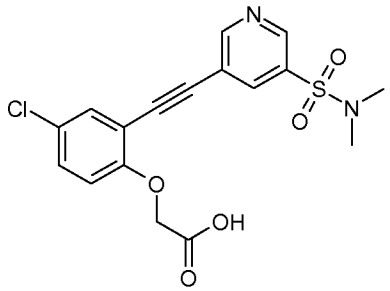
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.2 (1 H, bs), 8.00 (1 H, d, *J*= 2.0 Hz), 7.84 (1 H, dd, *J*= 8.0, 2.0 Hz), 7.65 (1 H, d, *J*= 2.7 Hz), 7.62 (1 H, d, *J*= 8.0 Hz), 7.45 (1 H, dd, *J*= 9.0, 2.7 Hz), 7.05 (1 H, d, *J*= 9.0 Hz), 4.85 (2 H, s), 3.25 (3 H, s), 2.58 (3 H, s). MS (ESI$^-$): 377.2. HPLC (Condition A): Rt 4.00 min (HPLC purity 93.4%).

Example 34: (4-chloro-2-{[2-fluoro-4-(methoxymethyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[2-fluoro-4-(methoxymethyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 30), the title compound was obtained as a beige solid after purification by preparative HPLC. ^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.25 (1H, s), 7.62 (1H, t, *J*= 7.6 Hz), 7.58 (1H, d, *J*= 2.7 Hz), 7.44 (1H, dd, *J*= 9.0, *J*= 2.7 Hz), 7.29 (1H, d, *J*= 10.5 Hz), 7.24 (1H, m), 7.02 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 4.49 (2H, s), 3.3 (3H). MS (ESI$^+$): 347.2. HPLC (Condition A): Rt 4.40 min (HPLC purity 99.9%).

Example 35: [4-chloro-2-({5-[(dimethylamino)sulfonyl]pyridin-3-yl}ethynyl)phenoxy]acetic acid



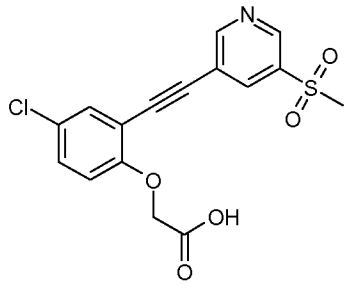
Step 1: *tert*-butyl [4-chloro-2-({5-[(dimethylamino)sulfonyl]pyridin-3-yl}ethynyl)phenoxy]acetate

A solution of *tert*-butyl(4-chloro-2-ethynyl phenoxy) acetate (Intermediate 3; 250 mg, 0.93 mmol), 5-bromo-pyridine-3-sulfonic acid dimethylamide (Intermediate 32; 270 mg, 1.03 mmol) and triethylamine (0.25 ml, 1.86 mmol) in anhydrous THF was degassed for 20 min with argon, then treated with 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) (45 mg) and cuprous iodide (11 mg) and heated to 65 °C for 5 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (silica), eluting with petroleum ether and ethylacetate (85:15) to give the tert-butyl ester intermediate as a brown sticky solid.

Step 2: [4-chloro-2-({5-[(dimethylamino)sulfonyl]pyridin-3-yl}ethynyl)phenoxy]acetic acid

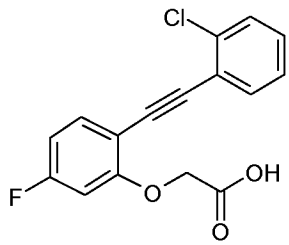
Following the general method as outlined in Example 15, starting from *tert*-butyl [4-chloro-2-({5-[(dimethylamino)sulfonyl]pyridin-3-yl}ethynyl)phenoxy]acetate, the title compound was obtained as a white solid after precipitation from the reaction mixture.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.17 (bs, 1H), 9.01 (d, *J*= 1.9 Hz, 1H), 8.91 (d, *J*= 2.1 Hz, 1H), 8.26 (d, *J*= 2.1 Hz, 1H), 7.67 (d, *J*= 2.6 Hz, 1H), 7.47 (dd, *J*= 8.9 Hz, *J*= 2.6 Hz, 1H), 7.04 (d, *J*= 9.0 Hz, 1H), 4.85 (s, 2H), 2.70 (s, 6H). MS (ESI$^+$): 393.0. HPLC (Condition A): Rt 4.40 min (HPLC purity 98.2%).

Example 36: (4-chloro-2-{[5-(methylsulfonyl)pyridin-3-yl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 35, starting from *tert*-butyl(4-chloro-2-ethynyl phenoxy) acetate (Intermediate 3) and 5-bromo-3-methylsulfonylpyridine (Combiblocks), the title compound was obtained as a white solid after purification by flash column chromatography (silica).
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 9.06-9.04 (m, 2H) 8.45 (t, *J*= 2.0 Hz, 1H), 7.66 (d, *J*= 2.7 Hz, 1H), 7.47 (dd, *J*= 9.0 Hz, *J*= 2.7 Hz, 1H), 7.04 (d, *J*= 9.0 Hz, 1H), 4.85 (s, 2H) 3.39 (s, 3H). MS (ESI$^+$): 363.9. HPLC (Condition A): Rt 3.93 min (HPLC purity 98.9%).

Example 37: {2-[(2-chlorophenyl)ethynyl]-5-fluorophenoxy}acetic acid



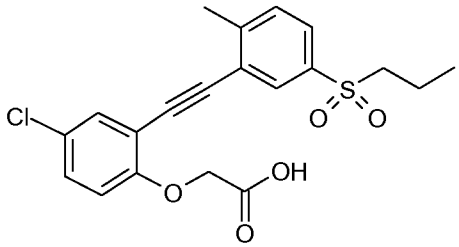
A solution of *tert*-butyl (2-bromo-5-fluorophenoxy)acetate (Intermediate 35; 305 mg; 1.00 mmol) and 2'-chlorophenyl acetylene (137 mg; 1.00 mmol) in piperidine (300 µl; 3.00 mmol) was treated with dichlorobis(triphenylphosphine)palladium(II) (28 mg; 0.04 mmol)

and heated at 70 °C. The reaction mixture was taken up in EtOAc, washed twice with citric acid (0.5 M aqueous solution) and once with brine. The organic phase was dried over $MgSO_4$, filtered and concentrated to dryness affording a crude, which was purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc. The partially purified intermediate was dissolved in a solution of HCl in dioxane (4N, 3 mL). After stirring for 16 hours, the solvents were removed under vacuum and the crude product purified by preparative HPLC. The title compound was obtained as a red oil.

MS (ESI^-): 303.2. HPLC (Condition A): Rt 4.48 min.

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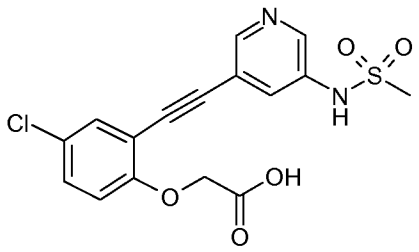
Example 38: (4-chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 38), the title compound was obtained as a white solid in 82% yield after recrystallization from acetonitrile.

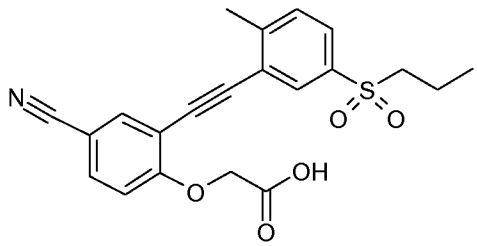
^1H NMR (300MHz, DMSO-d_6) δ [ppm] 13.17 (1H, bs), 7.95 (1H, t, *J*= 2.0 Hz), 7.80 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.65 (1H, d, *J*= 2.7 Hz), 7.62 (1H, d, *J*= 8.0 Hz), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 3.32 (2H, m), 2.58 (3H, s), 1.55 (2H, sext., *J*= 7.5 Hz), 0.92 (3H, t, *J*= 7.5 Hz). MS (ESI^-): 405.2. HPLC (Condition A): Rt 4.61 min (HPLC purity 98.6%).

Example 39: [4-chloro-2-({5-[(methylsulfonyl)amino]pyridin-3-yl}ethynyl)phenoxy]acetic acid



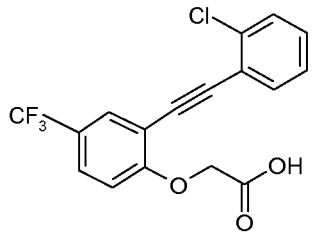
Following the general method as outlined in Example 35, starting from *tert*-butyl(4-chloro-2-ethynyl phenoxy) acetate (Intermediate 3) and *N*-(5-bromopyridin-3-yl)methanesulfonamide (prepared according to the method described in WO2008141065), the title compound was obtained as a beige solid after purification.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 10.24 (s, 1H), 8.47 (d, *J*= 1.6 Hz, 1H), 8.43-8.40 (m, 1H), 7.70 (d, *J*= 2.3 Hz, 1H), 7.63 (d, *J*= 2.6 Hz, 1H), 7.44 (dd, *J*= 8.9 Hz, *J*= 2.6 Hz, 1H), 7.00 (d, *J*= 9.0 Hz, 1H), 4.84 (s, 2H), 3.12 (s, 3H). MS (ESI$^+$): 381.0. HPLC (Condition A): Rt 3.66 min (HPLC purity 95.4%).

Example 40: (4-cyano-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 37, starting from 2-bromo-1-methyl-4-(propylsulfonyl)benzene (Intermediate 37) and *tert*-butyl (4-cyano-2-ethynylphenoxy)acetate (Intermediate 46), the title compound was obtained as a white solid after purification by preparative HPLC.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm]13.2 (1H, bs), 8.11 (1H, d, *J*= 2.0 Hz), 7.95 (1H, d, *J*= 2.0 Hz), 7.87 (1H, dd, *J*= 8.8 Hz, *J*= 2.0 Hz), 7.81 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.61 (1H, d, *J*= 8.0 Hz), 7.21 (1H, d, *J*= 8.8 Hz), 4.96 (2H, s), 3.32 (2H, m), 2.59 (3H, s), 1.55 (2H, m), 0.94 (3H, t, *J*= 7.5 Hz). MS (ESI$^-$): 396.3. HPLC (Condition A): Rt 4.04 min (HPLC purity 99.7%).

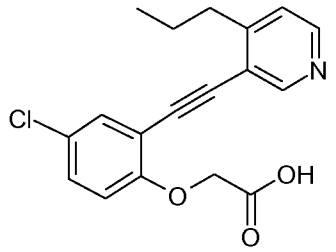
Example 41: [2-[(2-chlorophenyl)ethynyl]-4-(trifluoromethyl)phenoxy]acetic acid



Following the general method as outlined in Example 37, starting from *tert*-butyl [2-bromo-4-(trifluoromethyl)phenoxy]acetate (Intermediate 47) and 2'-chlorophenyl acetylene (ABCR), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm]13.2 (1H, bs), 7.84 (1H, d, *J*= 2.0 Hz), 7.77 (1H, dd, *J*= 9.0 Hz, *J*= 2.0 Hz), 7.07 (1H, m), 7.61 (1H, m), 7.50-7.39 (2H, m), 7.20 (1H, d, *J*= 8.8 Hz), 4.94 (2H, s). MS (ESI$^-$): 353.2. HPLC (Condition A): Rt 4.80 min (HPLC purity 98.3%).

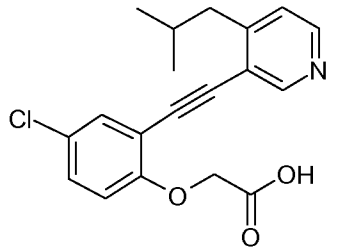
Example 42: {4-chloro-2-[(4-propylpyridin-3-yl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl {4-chloro-2-[(4-propylpyridin-3-yl)ethynyl]phenoxy}acetate (Intermediate 50), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.66 (s, 1H), 8.48 (d, *J*= 5.1 Hz, 1H), 7.59 (d, *J*= 2.7 Hz, 1H), 7.45 (dd, *J*= 2.7, *J*= 9.0 Hz, 1H), 7.38 (d, *J*= 5.1 Hz, 1H), 7.05 (d, *J*= 9.0 Hz, 1H), 4.82 (s, 2H), 2.83 (t, *J*= 7.5 Hz, 2H), 1.69 (sext. *J*= 7.5 Hz, 2H), 0.94 (t, *J*= 7.5 Hz, 3H). MS (ESI$^-$): 328.2. HPLC (Condition A): Rt 3.06 min (HPLC purity 97.2%).

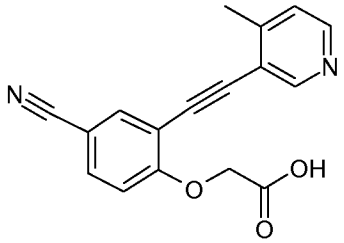
Example 43: {4-chloro-2-[(4-isobutylpyridin-3-yl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl {4-chloro-2-[(4-isobutylpyridin-3-yl)ethynyl]phenoxy}acetate (Intermediate 53), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.68 (s, 1H), 8.48 (d, *J*= 5.1 Hz, 1H), 7.58 (d, *J*= 2.7 Hz, 1H), 7.45 (dd, *J*= 2.7, *J*= 9.0 Hz, 1H), 7.34 (d, *J*= 5.1 Hz, 1H), 7.05 (d, *J*= 9.0 Hz, 1H), 4.83 (s, 2H), 2.74 (d, *J*= 6.8 Hz, 2H), 2.05 (sept., *J*= 6.8 Hz, 1H), 0.91 (d, *J*= 6.8 Hz, 6H). MS (ESI$^-$): 342.2. HPLC (Condition A): Rt 3.84 min (HPLC purity 99.7).

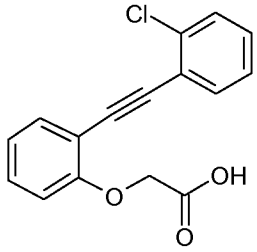
Example 44: {4-cyano-2-[(4-methylpyridin-3-yl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl {4-cyano-2-[(4-methylpyridin-3-yl)ethynyl]phenoxy}acetate (Intermediate 54), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.26 (bs, 1H), 8.71 (s, 1H), 8.51 (d, *J*= 5.1 Hz, 1H), 8.09 (d, *J*= 2.1 Hz, 1H), 7.89 (dd, *J*= 2.1, *J*= 8.8 Hz, 1H), 7.48 (d, *J*= 5.1 Hz, 1H), 7.23 (d, *J*= 8.8 Hz, 1H), 4.98 (s, 2H), 2.54 (s, 3H). MS (ESI$^-$): 291.2 (Condition A): Rt 1.99 (HPLC purity 98.0%).

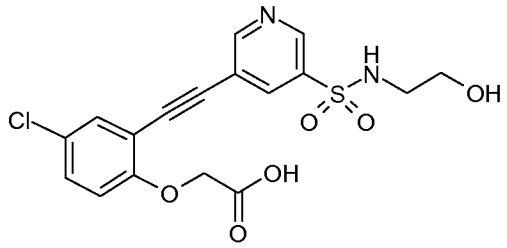
Example 45: {2-[(2-chlorophenyl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl {2-[(2-chlorophenyl)ethynyl]phenoxy}acetate (Intermediate 56), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.14 (bs, 1H), 7.67 (m, 1H), 7.61 (m, 1H), 7.53 (d, *J*= 1.6, *J*= 7.5 Hz, 1H), 7.48-7.37 (m, 3H), 7.06-6.97 (m, 2H), 4.82 (s, 2H). MS (ESI$^-$): 285.1. HPLC (Condition A): Rt 4.18 min (HPLC purity 98.8%).

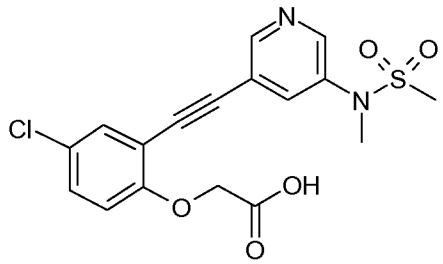
Example 46: {4-chloro-2-[(5-{[(2-hydroxyethyl)amino]sulfonyl}pyridin-3-yl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 37, starting from *tert*-butyl(4-chloro-2-ethynyl phenoxy) acetate (Intermediate 3) and 5-bromo-*N*-(2-hydroxyethyl)pyridine-3-sulfonamide (Intermediate 31), the title compound was obtained as an off-white solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.95 (d, *J*= 2.2 Hz, 1H), 8.91 (d, *J*= 2.0 Hz, 1H), 8.31 (d, *J*= 1.8 Hz, 1H), 8.02 (bs, 1H), 7.64 (d, *J*= 2.6 Hz, 1H), 7.44 (dd, *J*= 9.0 Hz, *J*= 2.6 Hz, 1H), 6.98 (d, *J*= 9.0 Hz, 1H), 4.71 (s, 2H), 3.39-3.36 (m, 2H), 2.99 (bs, 1H), 2.90-2.88 (m, 2H). MS (ESI$^+$): 410.8. HPLC (Condition A): Rt 3.73 min (HPLC purity 93.5%).

Example 47: [4-chloro-2-({5-[methyl(methylsulfonyl)amino]pyridin-3-yl}ethynyl)phenoxy]acetic acid

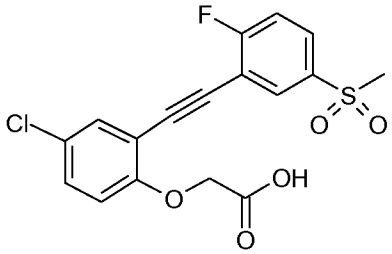


Following the general method as outlined in Example 37, starting from *tert*-butyl(4-chloro-2-ethynyl phenoxy) acetate (Intermediate 3) and *N*-(5-bromopyridin-3-yl)-*N*-

methylmethanesulfonamide (Intermediate 33), the title compound was obtained as an off-white solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.64-8.62 (m, 2H), 8.03 (t, *J*= 6.9 Hz, 1H), 7.61 (d, *J*= 2.6 Hz, 1H), 7.44 (dd, *J*= 8.9 Hz, *J*= 2.6 Hz, 1H), 7.01 (d, *J*= 9.0 Hz, 1H), 4.83 (s, 2H), 3.32 (s, 3H), 3.05 (s, 3H). MS (ESI$^+$): 395.0. HPLC (Condition A): Rt 4.93 min (HPLC purity 99.0%).

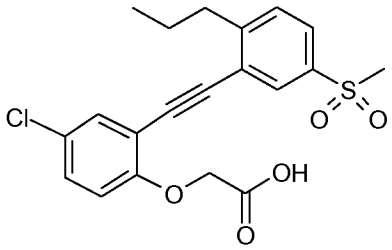
Example 48: (4-chloro-2-{[2-fluoro-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



A mixture of (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (Intermediate 3, 164 mg; 0.61 mmol), 1-fluoro-2-iodo-4-(methylsulfonyl)benzene (Intermediate 58, 184 mg; 0.61 mmol), 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(ii) (27 mg; 0.04 mmol) and cuprous iodide (7 mg; 0.04 mmol) was degassed during two minutes under nitrogen then anhydrous THF (3 mL) and triethylamine (170 µL; 1.23 mmol) were added and reaction mixture was stirred at 60 °C for 60 hours. The solvent was evaporated and the residue was treated with an HCl solution (4 N in dioxane, 3.7 mL). After stirring for 16 hours, the solvents were removed under vacuum and the crude product purified by preparative HPLC. The title compound was obtained as a brown solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.25 (bs, 1H), 8.18 (dd, *J*= 2.4, *J*= 6.5 Hz, 1H), 8.03 (m, 1H), 7.69-7.63 (m, 2H), 7.47 (dd, *J*= 2.7,*J*= 9.0 Hz, 1H), 7.03 (d, *J*= 9.0 Hz, 1H), 4.85 (s, 2H), 3.31 (s, 3H). MS (ESI$^-$): 381.2. HPLC (Condition A): Rt 3.89 min (HPLC purity 96.7%).

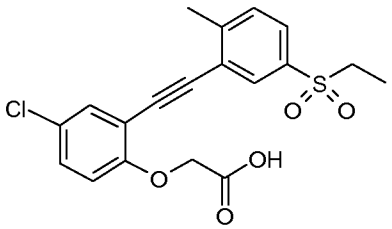
Example 49: (4-chloro-2-{[5-(methylsulfonyl)-2-propylphenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[5-(methylsulfonyl)-2-propylphenyl]ethynyl}phenoxy)acetate (Intermediate 63), the title compound was obtained as a white solid in 87% yield after slurrying in diethyl ether.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.18 (1H, bs), 8.01 (1H, d, *J*= 1.5 Hz), 7.86 (1H, dd, *J*= 8.0 Hz, *J*= 1.5 Hz), 7.62-7.59 (2H, m), 7.45 (1H, dd, *J*= 8.8 Hz, *J*= 2.0 Hz), 7.05 (1H, d, *J*= 8.8 Hz), 4.85 (2H, s), 3.26 (3H, s), 2.91 (2H, t, *J*= 7.5 Hz), 1.68 (2H, sextet, *J*= 7.5 Hz), 0.94 (3H, t, *J*= 7.5 Hz). MS (ESI$^-$): 405.3. HPLC (Condition A): Rt 4.60 min (HPLC purity 98.8%).

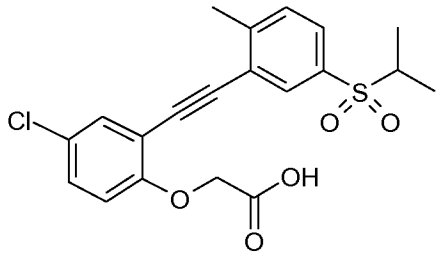
Example 50: (4-chloro-2-{[5-(ethylsulfonyl)-2-methylphenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 37, starting from *tert*-butyl(4-chloro-2-ethynyl phenoxy) acetate (Intermediate 3) and 2-bromo-4-(ethylsulfonyl)-1-methylbenzene (Intermediate 65), the title compound was obtained as a brown oil.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.93 (s, 1H), 7.92-7.76 (m, 1H), 7.62-7.58 (m, 2H), 7.38 (dd, *J*= 9.0 Hz, *J*= 2.4 Hz, 1H), 6.91 (d, *J*= 9.0 Hz, 1H), 4.53 (s, 2H), 3.34 (m, 2H), 2.57 (s, 3H), 1.08 (t, *J*= 7.3 Hz, 3H). MS (ESI$^+$): 392.8. HPLC (Condition A): Rt 4.77 min (HPLC purity 96.0%).

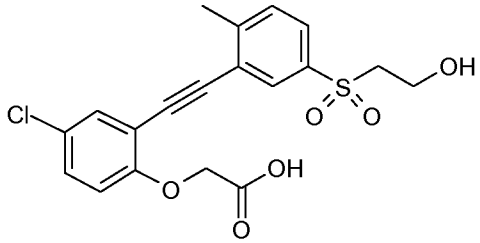
Example 51: (4-chloro-2-{[5-(isopropylsulfonyl)-2-methylphenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 37, starting from *tert*-butyl(4-chloro-2-ethynyl phenoxy) acetate (Intermediate 3) and 2-bromo-4-(isopropylsulfonyl)-1-methylbenzene (Intermediate 64), the title compound was obtained as a yellow solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.15 (s, 1H), 7.89 (d, *J*= 1.8 Hz, 1H), 7.60 (dd, *J*= 8.0 Hz, *J*= 1.8 Hz, 1H), 7.65-7.61 (m, 2H), 7.43 (dd, *J*= 9.0 Hz, *J*= 2.6 Hz, 1H), 7.03 (d, *J*= 9.0 Hz, 1H), 4.83 (s, 2H), 3.46 (septet, *J*= 6.8 Hz, 1H), 2.57 (s, 3H), 1.12 (d, *J*= 6.8 Hz, 6H). MS (ESI$^-$): 407.0. HPLC (Condition A): Rt 4.98 min (HPLC purity 92.3%).

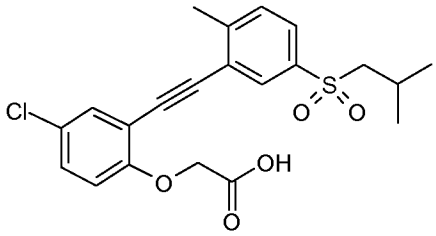
Example 52: [4-chloro-2-({5-[(2-hydroxyethyl)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 37, starting from *tert*-butyl(4-chloro-2-ethynyl phenoxy) acetate (Intermediate 3) and 2-[(3-bromo-4-methylphenyl)sulfonyl]ethanol (Intermediate 67), the title compound was obtained as a yellow solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.15 (s, 1H), 7.94 (d, *J*= 2.0 Hz, 1H), 7.79 (dd, *J*= 8.0 Hz, *J*= 2.0 Hz, 1H), 7.64 (d, *J*= 2.6 Hz, 1H), 7.59 (d, *J*= 8.0 Hz, 1H), 7.43 (dd, *J*= 9.0 Hz, *J*= 2.6 Hz, 1H), 7.03 (d, *J*= 9.0 Hz, 1H), 4.83 (s, 2H), 3.67 (m, 2H), 3.48 (t, *J*= 6.0 Hz, 2H), 2.56 (s, 3H). MS (ESI$^+$): 408.8. HPLC (Condition A): Rt 4.17 min (HPLC purity 96.4%).

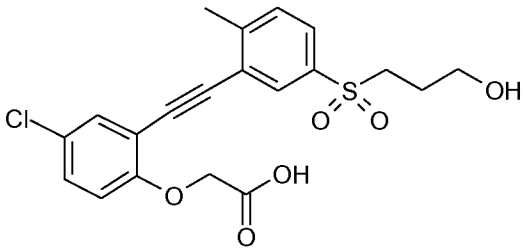
Example 53: (4-chloro-2-{[5-(isobutylsulfonyl)-2-methylphenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 37, starting from *tert*-butyl(4-chloro-2-ethynyl phenoxy) acetate (Intermediate 3) and 2-bromo-4-(isobutylsulfonyl)-1-methylbenzene (Intermediate 66), the title compound was obtained as a yellow solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.95 (s, 1H), 7.80 (d, *J*= 8.0 Hz, 1H), 7.63-7.60 (m, 2H), 7.43 (dd, *J*= 9.0 Hz, *J*= 2.6 Hz, 1H), 7.01 (d, *J*= 9.0 Hz, 1H), 4.79 (s, 2H), 3.25 (d, *J*= 6.4 Hz, 2H), 2.57 (s, 3H), 2.03-1.96 (m, 1H), 0.96 (d, *J*= 6.7 Hz, 6H). MS (ESI$^+$): 420.0. HPLC (Condition A): Rt 5.33 min (HPLC purity 97.6%).

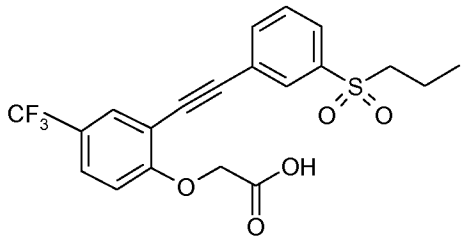
Example 54: [4-chloro-2-({5-[(3-hydroxypropyl)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 37, starting from *tert*-butyl(4-chloro-2-ethynyl phenoxy) acetate (Intermediate 3) and 3-[(3-bromo-4-methylphenyl)sulfonyl]propan-1-ol (Intermediate 68), the title compound was obtained as a yellow solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.93 (d, *J*= 2.0 Hz, 1H), 7.79 (dd, *J*= 8.0 Hz, *J*= 2.0 Hz, 1H), 7.64-7.61 (m, 2H), 7.43 (dd, *J*= 9.0 Hz, *J*= 2.6 Hz, 1H), 7.02 (d, *J*= 9.0 Hz, 1H), 4.80 (s, 2H), 3.39 (t, *J*= 6.2 Hz, 2H), 3.35-3.31 (m, 2H), 2.57 (s, 3H), 1.65 (d, *J*= 7.9 Hz, 2H). MS (ESI$^-$): 422.0. HPLC (Condition A): Rt 4.27 min (HPLC purity 97.2%).

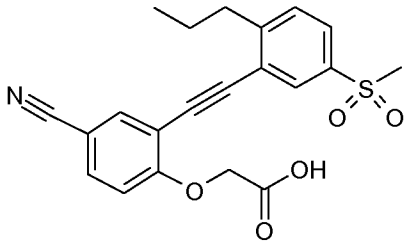
Example 55: [2-{[3-(propylsulfonyl)phenyl]ethynyl}-4-(trifluoromethyl)phenoxy]acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [2-{[3-(propylsulfonyl)phenyl]ethynyl}-4-(trifluoromethyl)phenoxy]acetate (Intermediate 71), the title compound was obtained as a yellow solid after slurrying in diethyl ether.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.2 (1H, bs), 8.05 (1H, m), 7.96-7.91 (3H, m), 7.78-7.71 (2H, m), 7.20 (1H, d, *J*= 8.8 Hz), 4.97 (2H, s), 3.40-3.34 (2H, m), 1.57 (2H, m), 0.93 (3H, t, *J*= 7.5 Hz). MS (ESI$^-$): 425.2. HPLC (Condition A): Rt 4.45 min (HPLC purity 96.2%).

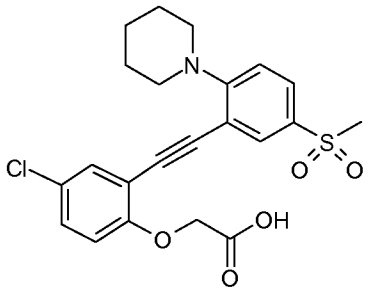
Example 56: (4-cyano-2-{[5-(methylsulfonyl)-2-propylphenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-cyano-2-{[5-(methylsulfonyl)-2-propylphenyl]ethynyl}phenoxy)acetate (Intermediate 72), the title compound was obtained as a pink solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.31 (s, 1H), 8.08 (d, *J*= 2.1 Hz, 1H), 8.02 (d, *J*= 2.1 Hz, 1H), 7.85-7.89 (m, 2H), 7.61 (d, *J*= 8.1 Hz, 1H); 7.21 (d, *J*= 8.8 Hz, 1H), 4.97 (s, 2H), 3.26 (s, 3H), 2.92 (t, *J*= 7.5 Hz, 2H), 1.69 (sext., *J*= 7.5 Hz, 2H), 0.94 (t, *J*= 7.5 Hz, 3H). MS (ESI$^-$): 396.2. HPLC (Condition A): Rt 3.94 min (HPLC purity 97.9%).

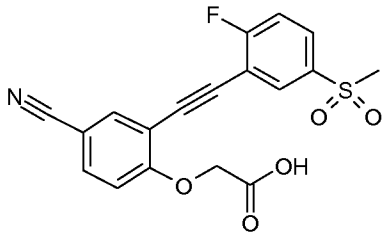
Example 57: (4-chloro-2-{[5-(methylsulfonyl)-2-piperidin-1-ylphenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[5-(methylsulfonyl)-2-piperidin-1-ylphenyl]ethynyl}phenoxy)acetate (Intermediate 75), the title compound was obtained as a white solid after filtration from the reaction mixutre.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.91 (d, *J*= 2.4 Hz, 1H), 7.76 (dd, *J*= 2.4, *J*= 8.8 Hz, 1H), 7.56 (d, *J*= 2.7 Hz, 1H), 7.41 (dd, *J*= 2.7, *J*= 9.0 Hz, 1H), 7.14 (d, *J*= 8.8 Hz, 1H), 7.01 (d, *J*= 9.0 Hz, 1H), 4.83 (s, 2H), 3.35 (m, 4H), 3.18 (s, 3H), 1.68 (m, 4H), 1.59 (m, 2H). MS (ESI$^-$): 446.3. HPLC (Condition A): Rt 4.48 min (HPLC purity 98.0%).

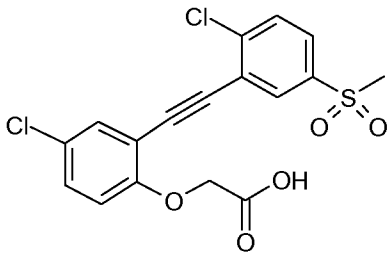
Example 58: (4-cyano-2-{[2-fluoro-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-cyano-2-{[2-fluoro-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 79), the title compound was obtained as a grey solid after purification by preparative HPLC.

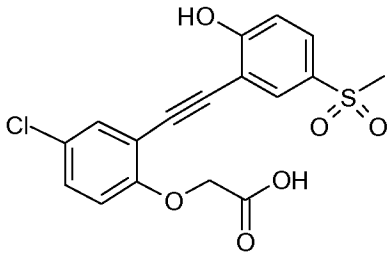
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.30 (bs, 1H), 8.18 (dd, *J*= 2.2, *J*= 6.5 Hz, 1H), 8.09 (d, *J*= 2.2 Hz, 1H), 8.04 (m, 1H), 7.89 (dd, *J*= 2.2, *J*= 8.8 Hz, 1H), 7.66 (t, *J*= 9.0 Hz, 1H), 7.20 (d, *J*= 8.8 Hz, 1H), 4.97 (s, 2H), 3.31 (s, 1H). MS (ESI$^-$): 372.2. HPLC (Condition A): Rt 3.41 min (HPLC purity 94.1%).

Example 59: (4-chloro-2-{[2-chloro-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



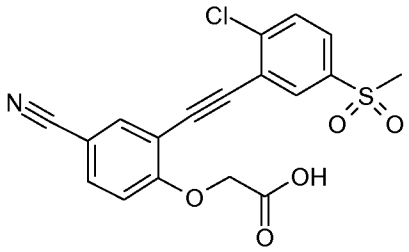
Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[2-chloro-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 80), the title compound was obtained as a beige solid after purification by preparative HPLC.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.17 (s, 1H), 8.17 (d, *J*= 2.0 Hz, 1H), 7.94 (dd, *J*= 2.0, *J*= 8.4, 1H), 7.90 (d, *J*= 8.4 Hz, 1H), 7.64 (d, *J*= 2.7 Hz, 1H), 7.47 (dd, *J*= 2.7, *J*= 9.0 Hz, 1H), 7.05 (d, *J*= 9.0 Hz, 1H), 4.85 (s, 2H) (3 remaining protons, probably hidden under the signal of water). MS (ESI$^-$): 397.2. HPLC (Condition A): Rt 4.10 min (HPLC purity 96.8%).

Example 60: (4-chloro-2-{[2-hydroxy-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



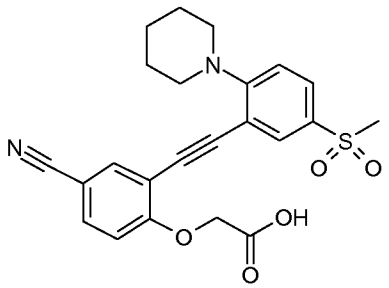
Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[2-hydroxy-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 81), the title compound was obtained as a beige solid after precipitation from the reaction mixture.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.30 (bs, 1H), 8.27 (t, *J*= 1.1 Hz, 1H), 7.97 (d, *J*= 2.7 Hz, 1H), 7.94-7.91 (m, 3H), 7.48 (dd, *J*= 2.7, *J*= 9.0 Hz, 1H), 7.20 (d, *J*= 9.0 Hz, 1H), 4.96 (s, 2H), 3.26 (s, 3H). MS (ESI$^-$): 379.1. HPLC (Condition A): Rt 3.96 min (HPLC purity 100%).

Example 61: (2-{[2-chloro-5-(methylsulfonyl)phenyl]ethynyl}-4-cyanophenoxy)acetic acid



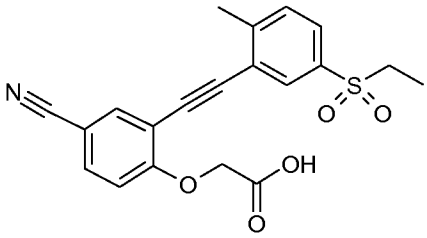
Following the general method as outlined in Example 15, starting from *tert*-butyl (2-{[2-chloro-5-(methylsulfonyl)phenyl]ethynyl}-4-cyanophenoxy)acetate (Intermediate 82), the title compound was obtained as a beige solid after purification by preparative HPLC.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.28 (bs, 1H), 8.18 (d, *J*= 2.1 Hz, 1H), 8.10 (d, *J*= 2.1 Hz, 1H), 7.96 (dd, *J*= 2.1, *J*= 8.6 Hz, 1H), 7.88-7.92 (m, 2H), 7.22 (d, *J*= 8.6 Hz, 1H), 4.98 (sm 2H) (3 remaining protons, probably hidden under the signal of water). MS (ESI$^-$): 388.1. HPLC (Condition A): Rt 3.66 min (HPLC purity 97.7%).

Example 62: (4-cyano-2-{[5-(methylsulfonyl)-2-piperidin-1-ylphenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-cyano-2-{[5-(methylsulfonyl)-2-piperidin-1-ylphenyl]ethynyl}phenoxy)acetate (Intermediate 83), the title compound was obtained as a beige solid after purification by preparative HPLC followed by trituration in diethyl ether.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.01 (d, *J*= 2.1 Hz, 1H), 7.92 (d, *J*= 2.3 Hz, 1H), 7.83 (dd, *J*= 2.1, *J*= 8.7 Hz, 1H), 7.76 (dd, *J*= 2.3, *J*= 8.7 Hz, 1H), 7.16 (2d, *J*= 8.7 Hz, 2H), 4.89 (s, 2H), 3.18 (s, 3H), 1.67 (m, 4H), 1.58 (m, 2H) (4 remaining protons, probably hidden under the signal of water). MS (ESI$^-$): 437.2. HPLC (Condition A): Rt 4.11 min (HPLC purity 95.2%).

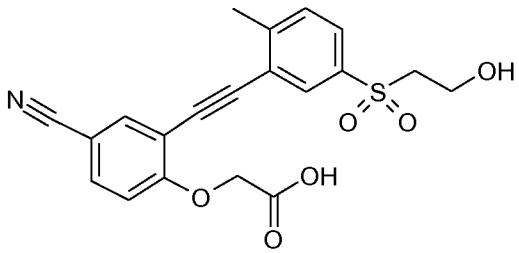
Example 63: (4-cyano-2-{[5-(ethylsulfonyl)-2-methylphenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 37, starting from *tert*-butyl(4-cyano-2-ethynyl phenoxy) acetate (Intermediate 46) and 2-ethynyl-1-methyl-4-(propylsulfonyl) benzene (Intermediate 40), the title compound was obtained as a yellow solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.26 (bs, 1H), 8.10 (s, 1H), 7.94 (d, *J*= 1.8 Hz, 1H), 7.87 (dd, *J*= 8.0 Hz, *J*= 1.9 Hz, 1H), 7.80 (dd, *J*= 8.1 Hz, *J*= 2.0 Hz, 1H), 7.63 (d, *J*= 8.1 Hz, 1H), 7.20 (d, *J*= 8.0 Hz, 1H), 4.96 (s, 2H), 3.33 (q, *J*= 7.4 Hz, 2H), 1.07 (t, *J*= 7.4 Hz, 3H). MS (ESI$^+$): 383.8. HPLC (Condition A): Rt 4.15 min.

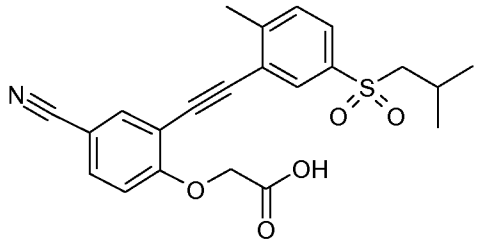
Example 64: [4-cyano-2-({5-[(2-hydroxyethyl)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 37, starting from *tert*-butyl(4-cyano-2-ethynyl phenoxy) acetate (Intermediate 46) and 2-[(3-bromo-4-methylphenyl)sulfonyl]ethanol (Intermediate 67), the title compound was obtained as a yellow solid.

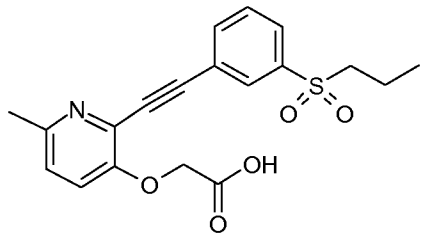
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.36 (bs, 1H), 8.10 (d, *J*= 2.0 Hz, 1H), 7.95 (d, *J*= 1.8 Hz, 1H), 7.87-7.79 (m, 2H), 7.60 (d, *J*= 8.1 Hz, 1H), 7.19 (d, *J*= 8.8 Hz, 1H), 4.94 (s, 2H) , 3.67 (t, *J*= 6.2 Hz, 2H), 3.48 (d, *J*= 6.8 Hz, 2H), 2.57 (s, 3H). MS (ESI$^+$): 400.0. HPLC (Condition A): Rt 3.56 min (HPLC purity 97.7%).

Example 65: (4-cyano-2-{[5-(isobutylsulfonyl)-2-methylphenyl]ethynyl}phenoxy)acetic acid



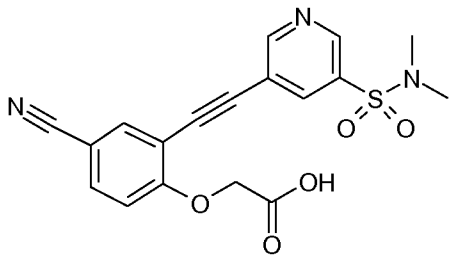
Following the general method as outlined in Example 37, starting from *tert*-butyl(4-cyano-2-ethynyl phenoxy) acetate (Intermediate 46) and 2-bromo-4-(isobutylsulfonyl)-1-methylbenzene (Intermediate 66), the title compound was obtained as a yellow solid.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.10 (d, *J*= 1.9 Hz, 1H), 7.96 (s, 1H), 7.87-7.81 (m, 2H), 7.62 (d, *J*= 8.2 Hz, 1H), 7.20 (d, *J*= 8.6 Hz, 1H), 4.95 (s, 2H) , 3.25 (d, *J*= 6.4 Hz, 2H), 2.57 (s, 3H), 2.03-1.98 (m, 1H), 0.96 (d, *J*= 6.7 Hz, 6H). MS (ESI$^-$): 412.0. HPLC (Condition A): Rt 4.74 min (HPLC purity 98.8%).

Example 66: [(6-methyl-2-{[3-(propylsulfonyl)phenyl]ethynyl}pyridin-3-yl)oxy]acetic acid



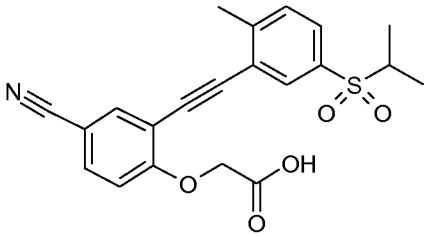
Following the general method as outlined in Example 15, starting from *tert*-butyl [(6-methyl-2-{[3-(propylsulfonyl)phenyl]ethynyl}pyridin-3-yl)oxy]acetate (Intermediate 87), the title compound was obtained as a beige solid after purification by preparative HPLC followed by precipitation from DMSO/acetonitrile.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.30 (bs, 1H), 8.18 (dd, *J*= 2.2, *J*= 6.5 Hz, 1H), 8.09 (d, *J*= 2.2 Hz, 1H), 8.04 (m, 1H), 7.89 (dd, *J*= 2.2, *J*= 8.8 Hz, 1H), 7.66 (t, *J*= 9.0 Hz, 1H), 7.20 (d, *J*= 8.8 Hz, 1H), 4.97 (s, 2H), 3.31 (s, 1H). HPLC (Condition A): Rt 2.38 min (HPLC purity 96.9%).

Example 67: [4-cyano-2-({5-[(dimethylamino)sulfonyl]pyridin-3-yl}ethynyl)phenoxy]acetic acid



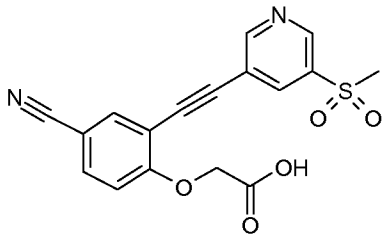
Following the general method as outlined in Example 37, starting from *tert*-butyl(4-cyano-2-ethynyl phenoxy) acetate (Intermediate 46) and 5-bromo-pyridine-3-sulfonic acid dimethylamide (Intermediate 32), the title compound was obtained as a yellow solid. ^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.30 (s, 1H), 9.03 (d, *J*= 1.8 Hz, 1H), 8.93 (d, *J*= 2.1 Hz, 1H), 8.28 (t, *J*= 1.9 Hz, 1H), 8.12 (d, *J*= 2.1 Hz, 1H), 7.89 (dd, *J*= 8.8 Hz, *J*= 2.0 Hz, 1H), 7.21 (d, *J*= 8.8 Hz, 1H), 4.97 (s, 2H), 2.70 (s, 6H). MS (ESI$^-$): 386.0. HPLC (Condition A): Rt 3.75 min (HPLC purity 93.2%).

Example 68: (4-cyano-2-{[5-(isopropylsulfonyl)-2-methylphenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 37, starting from *tert*-butyl(4-cyano-2-ethynyl phenoxy) acetate (Intermediate 46) and 2-bromo-4-(isopropylsulfonyl)-1-methylbenzene (Intermediate 64), the title compound was obtained as a yellow solid. ^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.26 (bs, 1H), 8.11 (d, *J*= 2.1 Hz, 1H), 7.90-7.78 (m, 2H), 7.77 (t, *J*= 1.8 Hz, 1H), 7.63 (d, *J*= 8.24 Hz, 1H), 7.20 (d, *J*= 8.8 Hz, 1H), 4.96 (s, 2H), 3.50-3.42 (m, 1H), 2.66 (s, 3H), 1.16 (d, *J*= 6.8 Hz, 6H). MS (ESI$^+$): 398.0. HPLC (Condition A): Rt 4.35 min (HPLC purity 98.5%).

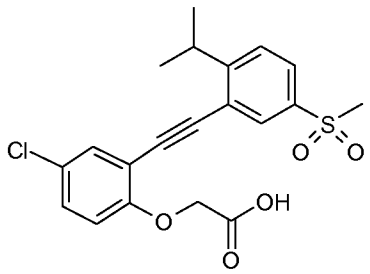
Example 69: (4-cyano-2-{[5-(methylsulfonyl)pyridin-3-yl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 37, starting from *tert*-butyl (4-cyano-2-ethynyl phenoxy) acetate (Intermediate 46) and 5-bromo-3-methylsulfonylpyridine (Combiblocks), the title compound was obtained as a yellow solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 9.07-9.05 (m, 2H), 8.46 (t, *J*= 2.1 Hz, 1H), 8.11 (d, *J*= 2.0 Hz, 1H), 7.90 (dd, *J*= 8.8 Hz, *J*= 2.1 Hz, 1H), 7.21 (d, *J*= 2.1 Hz, 1H), 4.98 (s, 2H), 3.39 (s, 3H). MS (ESI$^+$): 357.0. HPLC (Condition A): Rt 3.27 min (HPLC purity 93.9%).

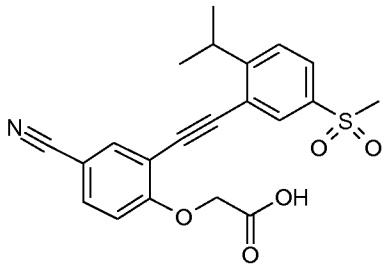
Example 70: (4-chloro-2-{[2-isopropyl-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[2-isopropyl-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 92), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.18 (1H, bs), 8.01 (1H, d, *J*= 2.0 Hz), 7.90 (1H, dd, *J*= 8.3 Hz, *J*= 2.0 Hz), 7.67 (1H, d, *J*= 8.3 Hz), 7.63 (1H, d, *J*= 2.7 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.05 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 3.65 (1H, sept., *J*= 6.9 Hz), 3.26 (3H, s), 1.28 (6H, d, *J*= 6.9 Hz). MS (ESI$^-$): 405.2. HPLC (Condition A): Rt 4.43 min (HPLC purity 99.8%).

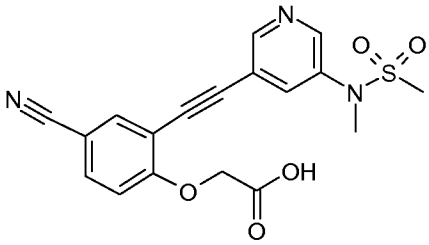
Example 71: (4-cyano-2-{[2-isopropyl-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-cyano-2-{[2-isopropyl-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 94), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.31 (1H, bs), 8.10 (1H, d, *J*= 2.1 hz), 8.01 (1H, d, *J*= 2.0 Hz), 7.91 (1H, dd, *J*= 8.3 Hz, *J*= 2.0 Hz), 7.87 (1H, dd, *J*= 8.7 Hz, *J*= 2.1 Hz), 7.68 (1H, d, *J*= 8.3 Hz), 7.21 (1H, d, *J*= 8.7 Hz), 4.95 (2H, s), 3.65 (1H, sept., *J*= 6.9 Hz), 3.26 (3H, s), 1.28 (6H, d, *J*= 6.9 Hz). MS (ESI$^-$): 396.3. HPLC (Condition A): Rt 3.93 min (HPLC purity 97.3%).

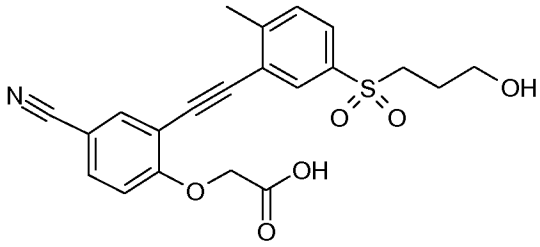
Example 72: [4-cyano-2-({5-[methyl(methylsulfonyl)amino]pyridin-3-yl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 35, starting from *tert*-butyl(4-cyano-2-ethynyl phenoxy) acetate (Intermediate 46) and *N*-(5-bromopyridin-3-yl)-*N*-methylmethanesulfonamide (Intermediate 33), the title compound was obtained as an off-white solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.64-8.62 (m, 2H), 8.06 (d, *J*= 1.8 Hz, 1H), 7.99 (d, *J*= 2.0 Hz, 1H), 7.81 (d, *J*= 8.9 Hz, 1H), 6.97 (d, *J*= 8.9 Hz, 1H), 4.48 (s, 2H), 3.33 (s, 3H), 3.05 (s, 3H). MS (ESI$^+$): 385.0. HPLC (Condition A): Rt 3.35 min (HPLC purity 95.6%).

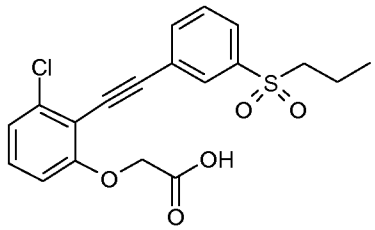
Example 73: [4-cyano-2-({5-[(3-hydroxypropyl)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 37, starting from *tert*-butyl(4-cyano-2-ethynyl phenoxy) acetate (Intermediate 46) and 3-[(3-bromo-4-methylphenyl)sulfonyl]propan-1-ol (Intermediate 68), the title compound was obtained as an off-white solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.02 (d, *J*= 1.8 Hz, 1H), 7.93 (d, *J*= 1.6 Hz, 1H), 7.80-7.78 (m, 2H), 7.62 (d, *J*= 8.0 Hz, 1H), 6.97 (d, *J*= 8.8 Hz, 1H), 4.46 (s, 2H), 4.10 (s, 1H), 3.41-3.36 (m, 2H), 3.16-3.15 (m, 2H), 1.69-1.62 (m, 2H). MS (ESI$^-$): 414.0. HPLC (Condition A): Rt 3.67 min (HPLC purity 95.4%).

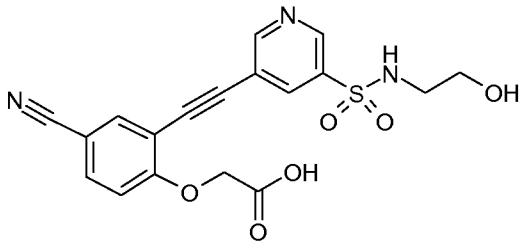
Example 74: (3-chloro-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (3-chloro-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 95), the title compound was obtained as a dark brown sticky solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.28 (1H, bs), 7.97-7.89 (3H, m), 7.74 (1H, t, *J*= 7.8 Hz), 7.39 (1H, t, *J*= 8.3 Hz), 7.20 (1H, d, 7.8 Hz), 6.99 (1H, d, *J*= 8.3 Hz), 4.86 (2H, s), 3.38 (2H, m), 1.56 (2H, sext., *J*= 7.5 Hz), 0.93 (3H, t, *J*= 7.5 Hz). MS (ESI$^-$): 391.1. HPLC (Condition A): Rt 4.29 min (HPLC purity 98.8%).

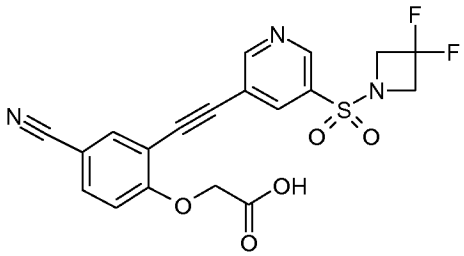
Example 75: {4-cyano-2-[(5-{[(2-hydroxyethyl)amino]sulfonyl}pyridin-3-yl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 37, starting from *tert*-butyl (4-cyano-2-ethynyl phenoxy) acetate (Intermediate 46) and 5-bromo-*N*-(2-hydroxyethyl)pyridine-3-sulfonamide (Intermediate 31), the title compound was obtained as a yellow solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.30 (bs, 1H), 8.95 (dd, *J*= 11.7 Hz, *J*= 1.9 Hz, 1H), 8.29 (t, *J*= 2.0 Hz, 1H), 8.11 (d, *J*= 2.1 Hz, 1H), 7.98 (d, *J*= 5.8 Hz, 1H), 7.89 (dd, *J*= 8.7 Hz, *J*= 2.1 Hz, 1H), 7.20 (d, *J*= 8.8 Hz, 1H), 5.02 (s, 2H), 3.39-3.33 (m, 2H), 2.91-2.87 (m, 2H). MS (ESI$^+$): 401.9. HPLC (Condition A): Rt 3.05 min (HPLC purity 91.6%).

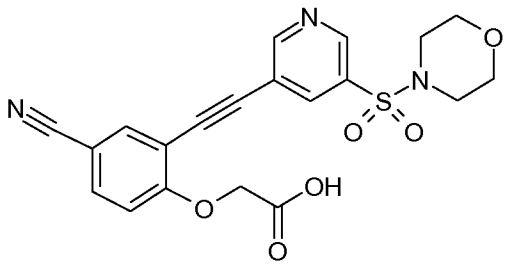
Example 76: [4-cyano-2-({5-[(3,3-difluoroazetidin-1-yl)sulfonyl]pyridin-3-yl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 35, starting from *tert*-butyl (4-cyano-2-ethynyl phenoxy) acetate (Intermediate 46) and 3-bromo-5-[(3,3-difluoroazetidin-1-yl)sulfonyl]pyridine (Intermediate 34), the title compound was obtained as an off-white solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 9.10-9.08 (m, 2H), 8.47 (s, 1H), 8.10 (s, 1H), 7.89 (d, *J*= 8.7 Hz, 1H), 7.18 (d, *J*= 8.7 Hz, 1H), 4.91 (s, 2H), 4.45 (t, *J*= 13.7 Hz, 4H). MS (ESI$^+$): 435.8. HPLC (Condition A): Rt 4.19 min (HPLC purity 95.3%).

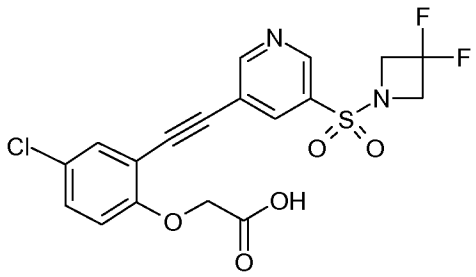
Example 77: (4-cyano-2-{[5-(morpholin-4-ylsulfonyl)pyridin-3-yl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 35, starting from *tert*-butyl(4-cyano-2-ethynyl phenoxy) acetate (Intermediate 46) and 4-[(5-bromopyridin-3-yl)sulfonyl]morpholine (Apollo), the title compound was obtained as an off-white solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 9.05 (d, *J*= 1.6 Hz, 1H), 8.90 (d, *J*= 2.0 Hz, 1H), 8.25 (dd, *J*= 2.0 Hz, *J*= 1.6 Hz, 1H), 8.04 (d, *J*= 2.0 Hz, 1H), 7.82 (dd, *J*= 9.0 Hz, *J*= 2.0 Hz, 1H), 6.97 (d, *J*= 9.0 Hz, 1H), 4.47 (s, 2H), 3.65-3.57 (m, 4H), 3.01-2.99 (m, 4H). MS (ESI$^-$): 427.8. HPLC (Condition A): Rt 3.77 min (HPLC purity 98.4%).

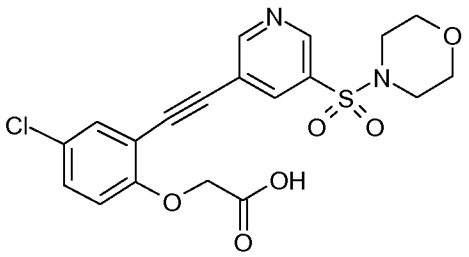
Example 78: [4-chloro-2-({5-[(3,3-difluoroazetidin-1-yl)sulfonyl]pyridin-3-yl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 35, starting from *tert*-butyl(4-chloro-2-ethynyl phenoxy) acetate (Intermediate 3) and 3-bromo-5-[(3,3-difluoroazetidin-1-yl)sulfonyl]pyridine (Intermediate 34), the title compound was obtained as an off-white solid.

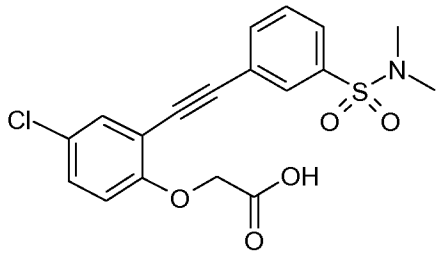
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 9.09-9.07 (m, 2H), 8.45 (t, *J*= 1.8 Hz, 1H), 7.67 (d, *J*= 2.6 Hz, 1H), 7.48 (dd, *J*= 9.0 Hz, *J*= 2.6 Hz, 1H), 7.04 (d, *J*= 9.0 Hz, 1H), 4.86 (s, 2H), 4.44 (t, *J*= 12.7 Hz, 4H). MS (ESI$^+$): 442.8. HPLC (Condition A): Rt 4.77 min (HPLC purity 98.0%).

Example 79: (4-chloro-2-{[5-(morpholin-4-ylsulfonyl)pyridin-3-yl]ethynyl}phenoxy)acetic acid



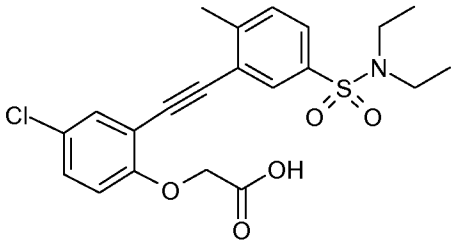
Following the general method as outlined in Example 35, starting from *tert*-butyl(4-chloro-2-ethynyl phenoxy) acetate (Intermediate 3) and 4-[(5-bromopyridin-3-yl)sulfonyl]morpholine (Apollo), the title compound was obtained as an off-white solid.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 9.04 (d, *J*= 2.0 Hz, 1H), 8.90 (d, *J*= 2.0 Hz, 1H), 8.25 (t, *J*= 2.0 Hz, 1H), 7.67 (d, *J*= 2.6 Hz, 1H), 7.47 (dd, *J*= 9.0 Hz, *J*= 2.6 Hz, 1H), 7.04 (d, *J*= 9.0 Hz, 1H), 4.85 (s, 2H), 3.64 (t, *J*= 4.7 Hz, 4H), 3.00 (t, *J*= 4.7 Hz, 4H). MS (ESI$^+$): 435.0. HPLC (Condition A): Rt 4.36 min (HPLC purity 98.4%).

Example 80: [4-chloro-2-({3-[(dimethylamino)sulfonyl]phenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [4-chloro-2-({3-[(dimethylamino)sulfonyl]phenyl}ethynyl)phenoxy]acetate (Intermediate 96), the title compound was obtained as an off-white solid in 93% yield.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.16 (1H, bs), 7.89-7.60 (4H, m), 7.66 (1H, d, *J*= 2.7 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.85 (2H, s), 2.66 (6H, s). MS (ESI$^-$): 392.1. HPLC (Condition A): Rt 4.40 min (HPLC purity 96.5%).

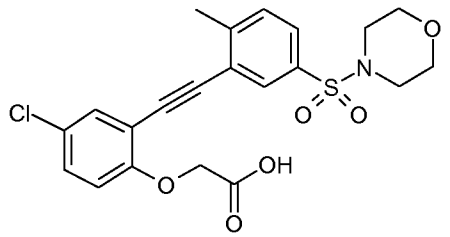
Example 81: [4-chloro-2-({5-[(diethylamino)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [4-chloro-2-({5-[(diethylamino)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetate (Intermediate 97), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.16 (1H, bs), 7.84 (1H, d, *J*= 2.0 Hz), 7.71 (1H, dd, *J*= 8.1 Hz, *J*= 2.0 Hz), 7.66 (1H, d, *J*= 2.7 Hz), 7.57 (1H, d, *J*= 8.1 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 3.17 (4H, q, *J*= 7.1 Hz), 2.56 (3H, s), 1.05 (6H, t, *J*= 7.1 Hz). MS (ESI$^-$): 434.1. HPLC (Condition A): Rt 4.80 min (HPLC purity 99.2%).

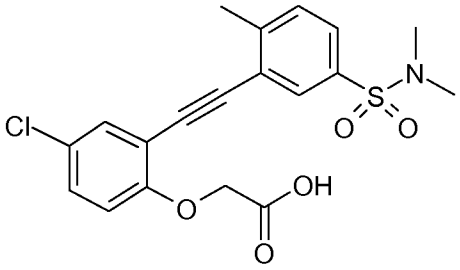
Example 82: (4-chloro-2-{[2-methyl-5-(morpholin-4-ylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[2-methyl-5-(morpholin-4-ylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 98), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.16 (1H, bs), 7.79 (1H, d, *J*= 1.5 Hz), 7.68-7.61 (3H, m), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 3.64 (4H, m), 2.89 (4H, m), 2.59 (3H, s). MS (ESI$^-$): 448.1. HPLC (Condition A): Rt 4.46 min (HPLC purity 98.9%).

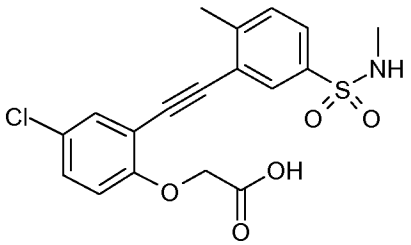
Example 83: [4-chloro-2-({5-[(dimethylamino)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [4-chloro-2-({5-[(dimethylamino)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetate (Intermediate 99), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.15 (1H, bs), 7.80 (1H, d, *J*= 1.8 Hz), 7.69-7.60 (3H, m), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 2.63 (6H, s), 2.58 (3H, s). MS (ESI$^-$): 406.1. HPLC (Condition A): Rt 4.55 min (HPLC purity 97.1%).

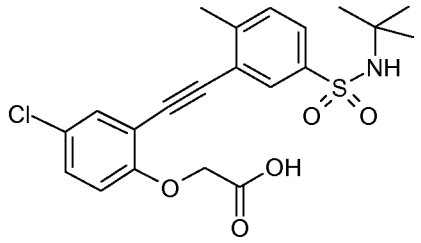
Example 84: [4-chloro-2-({2-methyl-5-[(methylamino)sulfonyl]phenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [4-chloro-2-({2-methyl-5-[(methylamino)sulfonyl]phenyl}ethynyl)phenoxy]acetate (Intermediate 100), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.19 (1H, bs), 7.85 (1H, d, *J*= 2.0 Hz), 7.68 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.64 (1H, d, *J*= 2.7 Hz), 7.57 (1H, d, *J*= 8.0 Hz), 7.50 (1H, q, *J*= 5.0 Hz), 7.45 (1H, dd, *J*= 9.0 Hz, *J*=2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 2.55 (3H, s), 2.41 (3H, d, *J*= 5.0 Hz). MS (ESI$^-$): 392.1. HPLC (Condition A): Rt 4.05 min (HPLC purity 99.3%).

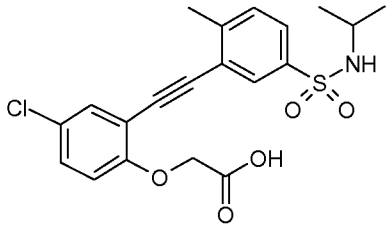
Example 85: [2-({5-[(*tert*-butylamino)sulfonyl]-2-methylphenyl}ethynyl)-4-chlorophenoxy]acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [2-({5-[(*tert*-butylamino)sulfonyl]-2-methylphenyl}ethynyl)-4-chlorophenoxy]acetate (Intermediate 101), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.17 (1H, bs), 7.90 (1H, d, *J*= 2.0 Hz), 7.74 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.64 (1H, d, *J*= 2.7 Hz), 7.57 (1H, s), 7.53 (1H, d, *J*= 8.0 Hz), 7.43 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 2.54 (3H, s); 1.10 (9H, s). MS (ESI$^-$): 434.2. HPLC (Condition A): Rt 4.86 min (HPLC purity 96.7%).

Example 86: [4-chloro-2-({5-[(isopropylamino)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetic acid

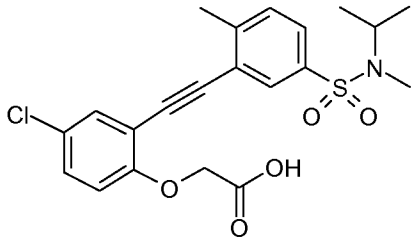


Following the general method as outlined in Example 15, starting from *tert*-butyl [4-chloro-2-({5-[(isopropylamino)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetate (Intermediate 102), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.17 (1H, bs), 7.87 (1H, d, *J*= 2.0 Hz), 7.71 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.64 (1H, d, *J*= 2.7 Hz), 7.61 (1H, d, *J*= 7.0 Hz), 7.54 (1H, d, *J*= 8.0 Hz), 7.43 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 3.25 (1H, m), 2.55 (3H, s), 0.95 (6H, d, *J*= 6.6 Hz). MS (ESI$^-$): 420.2. HPLC (Condition A): Rt 4.64 min (HPLC purity 98.4%).

HPLC (max plot) 98.4%; Rt 4.64min.

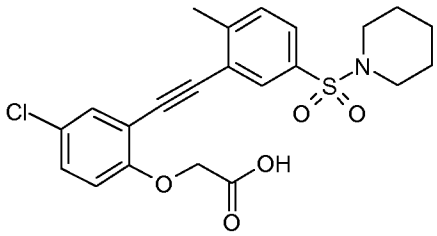
Example 87: {4-chloro-2-[(5-{[isopropyl(methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl {4-chloro-2-[(5-{[isopropyl(methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetate (Intermediate 104), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.16 (1H, bs), 7.83 (1H, d, *J*= 2.0 Hz), 7.71 (1H, dd, *J*= 8.1 Hz, *J*= 2.0 Hz), 7.66 (1H, d, *J*= 2.7 Hz), 7.57 (1H, d, *J*= 8.1 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 4.09 (1H, septet., *J*= 6.7 Hz), 2.66 (3H, s); 2.56 (3H, s), 0.91 (6H, d, *J*= 6.7 Hz). MS (ESI$^-$): 434.1. HPLC (Condition A): Rt 4.99 min (HPLC purity 98.6%).

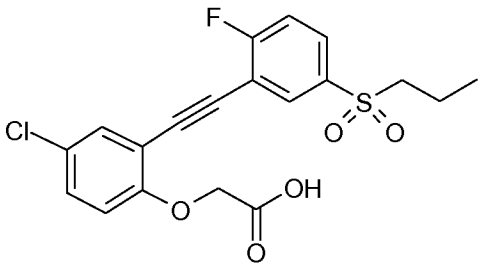
Example 88: (4-chloro-2-{[2-methyl-5-(piperidin-1-ylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[2-methyl-5-(piperidin-1-ylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 156), the title compound was obtained as an off-white solid in 89% yield.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.06 (1H, bs), 7.68 (1H, d, *J*= 1.8 Hz), 7.59-7.50 (3H, m), 7.35 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 6.96 (1H, d, *J*= 9.0 Hz), 4.75 (2H, s), 2.81 (4H, m), 2.49 (3H, s); 1.46 (4H, m), 1.28 (2H, m). MS (ESI$^-$): 446.1. HPLC (Condition A): Rt 4.88 min (HPLC purity 96.8%).

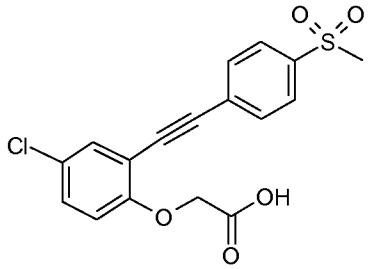
Example 89: (4-chloro-2-{[2-fluoro-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[2-fluoro-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 107), the title compound was obtained as a beige solid in 97% yield.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.18 (1H, bs), 8.13 (1H, dd, *J*= 6.5 Hz, *J*= 2.4 Hz), 7.95 (1H, ddd, *J*= 8.7 Hz, *J*= 4.6 Hz, *J*= 2.4 Hz), 7.68-7.62 (2H, m), 7.47 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.86 (2H, s), 3.38 (2H, m), 1.58 (2H, m), 0.93 (3H, t, *J*= 7.5 Hz). MS (ESI$^-$): 409.1. HPLC (Condition A): Rt 4.48 min (HPLC purity 96.1%).

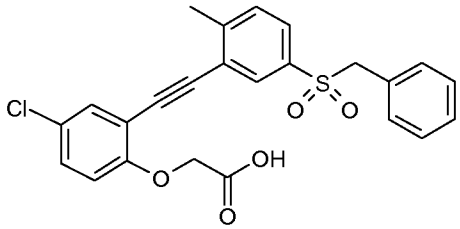
Example 90: (4-chloro-2-{[4-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[4-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 110), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.20 (1H, bs), 77.98 (2H, d, *J*= 8.5 Hz), 7.80 (2H, d, *J*= 8.5 Hz), 7.63 (1H, d, *J*= 2.7 Hz), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.02 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 3.27 (3H, s). MS (ESI$^-$): 363.0. HPLC (Condition A): Rt 3.91 min (HPLC purity 100%).

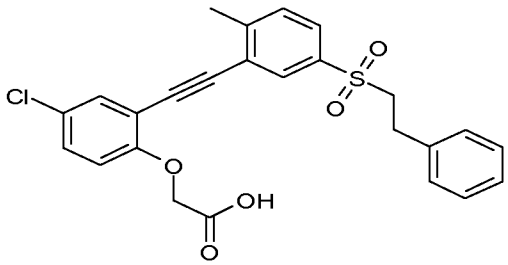
Example 91: (2-{[5-(benzylsulfonyl)-2-methylphenyl]ethynyl}-4-chlorophenoxy)acetic acid



Following the general method as outlined in Example 37, starting from *tert*-butyl(4-chloro-2-ethynyl phenoxy) acetate (Intermediate 3) and 4-(benzylsulfonyl)-2-bromo-1-methylbenzene (Intermediate 69), the title compound was obtained as a yellow solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.15 (bs, 1H), 7.80 (s, 1H), 7.62 (d, *J*= 2.6 Hz, 1H), 7.54-7.53 (m, 2H), 7.45 (s, 1H), 7.31-7.30 (m, 3H), 7.18 (d, *J*= 5.0 Hz, 2H), 7.03 (d, *J*= 9.2 Hz, 1H), 4.83 (s, 2H), 4.71 (s, 2H), 2.55 (s, 3H). MS (ESI$^+$): 455.0. HPLC (Condition A): Rt 5.29 min (HPLC purity 97.2%).

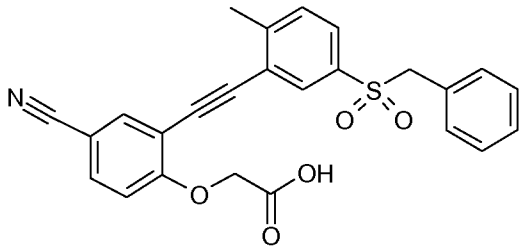
Example 92: [4-chloro-2-({2-methyl-5-[(2-phenylethyl)sulfonyl]phenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 37, starting from *tert*-butyl(4-chloro-2-ethynyl phenoxy) acetate (Intermediate 3) and 2-bromo-1-methyl-4-[(2-phenylethyl)sulfonyl]benzene (Intermediate 70), the title compound was obtained as a yellow solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.16 (s, 1H), 7.97 (s, 1H), 7.82 (d, *J*= 8.0 Hz, 1H), 7.61 (t, *J*= 9.1 Hz, 1H), 7.44 (d, *J*= 8.4 Hz, 1H), 7.24-7.17 (m, 5H), 7.04 (d, *J*= 9.0 Hz, 1H), 4.84 (s, 2H), 3.68 (t, *J*= 8.0 Hz, 2H), 2.88 (t, *J*= 8.0 Hz, 2H), 2.57 (s, 3H). MS (ESI$^+$): 467.0. HPLC (Condition A): Rt 5.53 min (HPLC purity 97.0%).

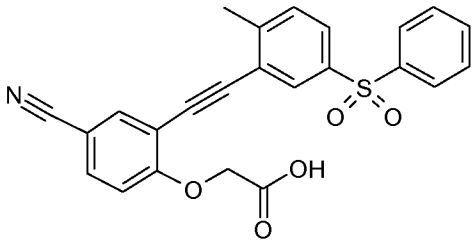
Example 93: (2-{[5-(benzylsulfonyl)-2-methylphenyl]ethynyl}-4-cyanophenoxy)acetic acid



Following the general method as outlined in Example 37, starting from *tert*-butyl (4-cyano-2-ethynyl phenoxy) acetate (Intermediate 46) and 4-(benzylsulfonyl)-2-bromo-1-methylbenzene (Intermediate 69), the title compound was obtained as a yellow solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.36 (bs, 1H), 8.08 (d, *J*= 2.0 Hz, 1H), 7.86 (dd, *J*= 8.7 Hz, *J*= 2.1 Hz, 1H), 7.81 (d, *J*= 1.6 Hz, 1H), 7.58-7.52 (m, 2H), 7.31-7.28 (m, 3H), 7.20-7.16 (m, 3H), 4.94 (s, 2H), 4.71 (s, 2H), 2.55 (s, 3H). MS (ESI$^+$): 446.0. HPLC (Condition A): Rt 4.77 min (HPLC purity 98.9%).

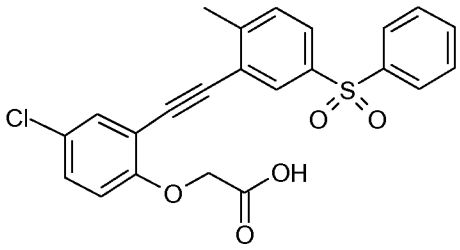
Example 94: (4-cyano-2-{[2-methyl-5-(phenylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-cyano-2-{[2-methyl-5-(phenylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 115), the title compound was obtained as a brown solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.36 (1H, bs), 8.10 (1H, d, *J*= 2.1 Hz), 7.97-8.02 (3H, m), 7.84-7.90 (2H, m), 7.57-7.73 (4H, m), 7.19 (1H, d, *J*= 8.9 Hz), 4.93 (2H, s), 2.53 (3H, s). MS (ESI$^-$): 430.2. HPLC (Condition A): Rt 4.24 min (HPLC purity 99.6%).

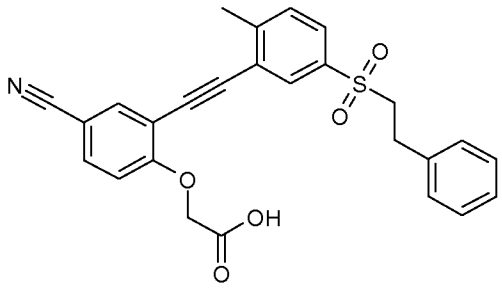
Example 95: (4-chloro-2-{[2-methyl-5-(phenylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[2-methyl-5-(phenylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 116), the title compound was obtained as a brown solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.26 (1H, bs), 7.97-8.02 (3H, m), 7.87 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.56-7.73 (5H, m), 7.43 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.79 (2H, s), 2.52 (3H, s). MS (ESI$^-$): 439.2. HPLC (Condition A): Rt 4.90 min (HPLC purity 98.4%).

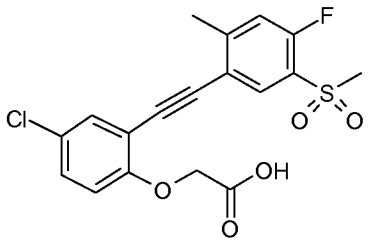
Example: 96[4-cyano-2-({2-methyl-5-[(2-phenylethyl)sulfonyl]phenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 37, starting from *tert*-butyl(4-cyano-2-ethynyl phenoxy) acetate (Intermediate 46) and 2-bromo-1-methyl-4-[(2-phenylethyl)sulfonyl]benzene (Intermediate 70), the title compound was obtained as a yellow solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.05 (s, 1H), 7.97 (s, 1H) 7.83 (d, *J*= 6.6 Hz, 2H), 7.60 (d, *J*= 8.2 Hz, 1H), 7.26-7.17 (m, 5H), 7.08 (d, *J*= 9.0 Hz, 1H), 4.71 (s, 2H), 3.69 (d, *J*= 7.9 Hz, 2H), 2.88 (d, *J*= 7.9 Hz, 2H), 2.57 (s, 3H). MS (ESI$^+$): 460.0. HPLC (Condition A): Rt 5.03 min (HPLC purity 98.3%).

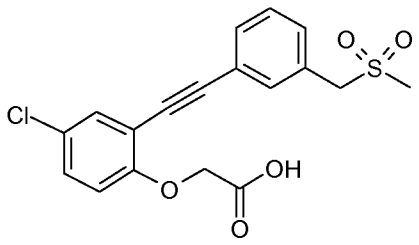
Example 97: (4-chloro-2-{[4-fluoro-2-methyl-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[4-fluoro-2-methyl-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 117), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.17 (1H, bs), 7.89 (1H, d, *J*= 7.2 Hz), 7.66 (1H, d, *J*= *J*= 2.6 Hz), 7.59 (1H, d, *J*= 11.1), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.6 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 3.34 (3H, s), 2.58 (3H, s). MS (ESI$^-$):395.0. HPLC (Condition A): Rt 4.28 min (HPLC purity 97.4%).

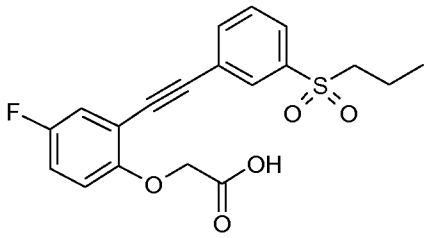
Example 98: [4-chloro-2-({3-[(methylsulfonyl)methyl]phenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [4-chloro-2-({3-[(methylsulfonyl)methyl]phenyl}ethynyl)phenoxy]acetate (Intermediate 118), the title compound was obtained as a beige solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.16 (1H, bs), 7.55-7.59 (3H,m), 7.46-7.48 (2H, m), 7.41 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.00 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 4.54 (2H, s), 2.93 (3H, s). MS (ESI$^-$): 377.0. HPLC (Condition A): Rt 3.82 min (HPLC purity 94.8%).

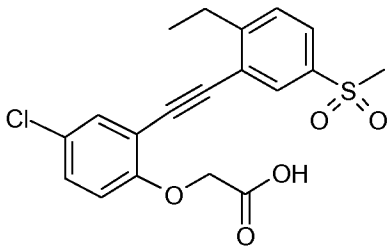
Example 99: (4-fluoro-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-fluoro-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 119), the title compound was obtained as an orange sticky solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.12 (1H, bs), 8.00 (1H, t, *J*= 1.5 hz), 7.91 (2H, m), 7.73 (1H, t, *J*= 7.8 Hz), 7.45 (1H, dd, *J*= 8.7 Hz, *J*= 3.1 Hz), 7.26 (1H, m), 7.00 (1H, dd, *J*= 9.3 Hz, *J*= 4.4 Hz), 4.82 (2H, s), 3.37 (2H, m), 1.57 (2H, sext., *J*= 7.5 Hz), 0.92 (3H, t, *J*= 7.5 Hz). MS (ESI$^-$): 375.1. HPLC (Condition A): Rt 3.95 min (HPLC purity 95.4%).

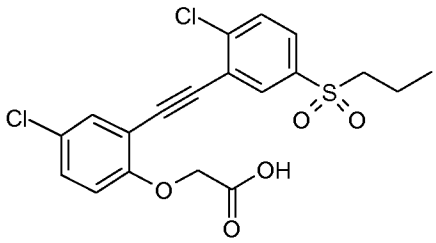
Example 100: (4-chloro-2-{[2-ethyl-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[2-ethyl-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 124), the title compound was obtained as a pale pink solid after precipitation from pentane.

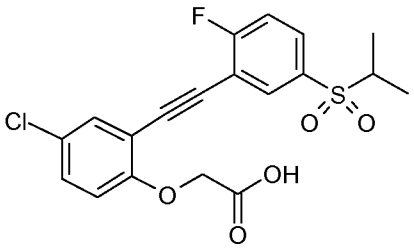
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.16 (1H, bs), 8.00 (1H, d, *J*= 2.0 Hz), 7.88 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.65-7.61 (2H, m), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.06 (1H, d, *J*= 9.0 Hz), 4.85 (2H, s), 3.26 (3H, s), 2.96 (2H, q, *J*= 7.5 Hz), 1.26 (3H, t, *J*= 7.5 Hz). MS (ESI$^-$): 392.9. HPLC (Condition A): Rt 4.39 min (HPLC purity 97.7%).

Example 101: (4-chloro-2-{[2-chloro-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



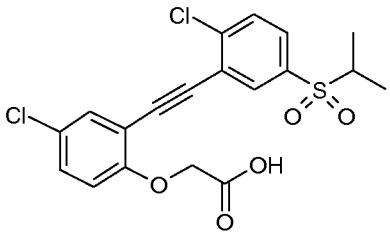
Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[2-chloro-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 127), the title compound was obtained as a white solid after purification by preparative HPLC.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.20 (1H, bs), 8.12 (1H, t, *J*= 1.3 Hz), 7.90 (2H, d, *J*= 1.3 Hz), 7.65 (1H, d, *J*= 2.7 Hz), 7.48 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.05 (1H, d, *J*= 9.0 Hz), 4.85 (2H, s), 3.40 (2H, m), 1.58 (2H, m), 0.93 (3H, t, *J*= 7.5 Hz). MS (ESI$^-$): 425.0. HPLC (Condition A): Rt 4.51 min (HPLC purity 100%).

Example 102: (4-chloro-2-{[2-fluoro-5-(isopropylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[2-fluoro-5-(isopropylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 133), the title compound was obtained as a white solid after purification by preparative HPLC.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.20 (1H, bs), 8.08 (1H, dd, *J*= 6.5 Hz, *J*= 2.4 Hz), 7.95 (1H, ddd, *J*= 8.7 Hz, *J*= 4.6 Hz, *J*= 2.4 Hz), 7.70-7.64 (2H, m), 7.47 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.85 (2H, s), 3.55 (2H, septet, *J*= 6.8 Hz), 1.18 (6H, d, *J*= 6.8 Hz). MS (ESI$^-$): 409.0. HPLC (Condition A): Rt 4.34 min (HPLC purity 98.3%).

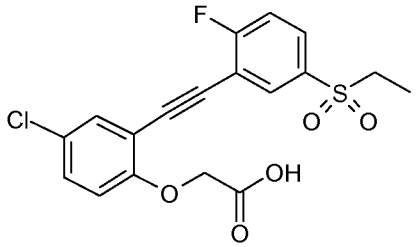
Example 103: (4-chloro-2-{[2-chloro-5-(isopropylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[2-chloro-5-(isopropylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 134), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.19 (1H, bs), 8.07 (1H, d, *J*= 1.9 Hz), 7.93-7.85 (2H, m), 7.66 (1H, d, *J*= 2.7 Hz), 7.48 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.05 (1H, d, *J*= 9.0 Hz), 4.85 (2H, s), 3.57 (2H, septet, *J*= 6.8 Hz), 1.19 (6H, d, *J*= 6.8 Hz). MS (ESI$^-$): 424.9. HPLC (Condition A): Rt 4.57 min (HPLC purity 99.6%).

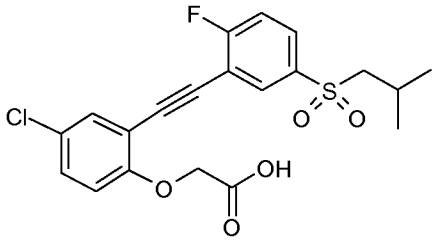
Example 104: (4-chloro-2-{[5-(ethylsulfonyl)-2-fluorophenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [4-chloro-2-({2-fluoro-5-[(2-methoxyethyl)sulfonyl]phenyl}ethynyl)phenoxy]acetate (Intermediate 135), the title compound was obtained as a white solid after precipitation from DCM/pentane.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.18 (brs, 1H), 8.11 (dd, *J*= 2.3, *J*= 6.6 Hz, 1H), 7.98 (ddd, *J*= 2.3, *J*= 4.9, *J*= 7.3 Hz, 1H), 7.63 (m, 2H), 7.45 (dd, *J*= 2.6, *J*= 9.1 Hz, 1H), 7.02 (d, *J*= 9.5 Hz, 1H), 4.84 (d, 2H), 3.39 (q, *J*= 7.5 Hz, 2H), 1.11 (t, *J*= 7.2 Hz, 3H). m.p. = 165-169 ° C. MS (ESI$^-$): 395.1. HPLC (Condition A): Rt 4.22 min (HPLC purity 96.7%).

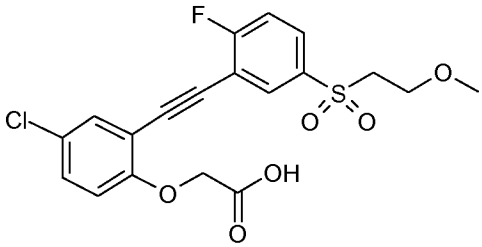
Example 105: (4-chloro-2-{[2-fluoro-5-(isobutylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [4-chloro-2-({2-fluoro-5-[(2-methoxyethyl)sulfonyl]phenyl}ethynyl)phenoxy]acetate (Intermediate 136), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.2 (brs, 1H), 8.14 (dd, *J*= 2.3, *J*= 6.4 Hz, 1H), 8.00 (ddd, *J*= 2.5, *J*= 4.8, *J*= 7.5 Hz, 1H), 7.63 (m, 2H), 7.46 (dd, *J*= 2.7, *J*= 9.1 Hz, 1H), 7.02 (d, *J*= 9.1 Hz, 1H), 4.84 (s, 2H), 3.30 (m, 2H), 2.02 (septet, *J*= 6.6 Hz, 1H), 0.98 (d, 6H). m.p. = 141-143 ° C. MS (ESI$^-$): 423.2. HPLC (Condition A): Rt 5.18 min (HPLC purity 100%).

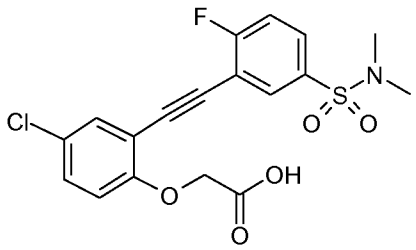
Example 106: [4-chloro-2-({2-fluoro-5-[(2-methoxyethyl)sulfonyl]phenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [4-chloro-2-({2-fluoro-5-[(2-methoxyethyl)sulfonyl]phenyl}ethynyl)phenoxy]acetate (Intermediate 137), the title compound was obtained as a white solid after purification by preparative HPLC followed by crystallization from DCM/hexane.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.2 (brs, 1H), 8.11 (dd, 1H), 7.96 (ddd, *J*= 2.5, *J*= 4.9, *J*= 7.4 Hz, 1H), 7.63 (m, 2H), 7.46 (dd, *J*= 2.7, *J*= 9.01 Hz, 1H), 7.02 (d, *J*= 9.1 Hz, 1H), 4.84 (s, 2H), 3.65 (m, 4H), 3.08 (s, 3H). m.p. = 125-128 ° C. MS (ESI$^-$): 425.2. HPLC (Condition A): Rt 4.62 min (HPLC purity 100%).

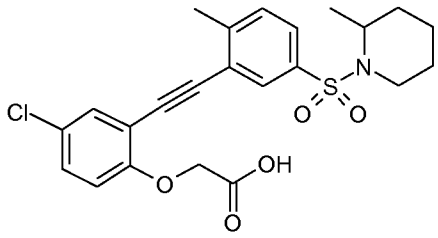
Example 107: [4-chloro-2-({5-[(dimethylamino)sulfonyl]-2-fluorophenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [4-chloro-2-({5-[(dimethylamino)sulfonyl]-2-fluorophenyl}ethynyl)phenoxy]acetate (Intermediate 157), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.18 (1H, bs), 7.97 (1H, dd, *J*= 6.5 Hz, *J*= 2.4 Hz), 7.86 (1H, ddd, *J*= 8.7 Hz, *J*= 4.6 Hz, *J*= 2.4 Hz), 7.67-7.61 (2H, m), 7.47 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.85 (2H, s), 2.66 (6H, s). MS (ESI$^-$): 410.0. HPLC (Condition A): Rt 4.27 min (HPLC purity 99.7%).

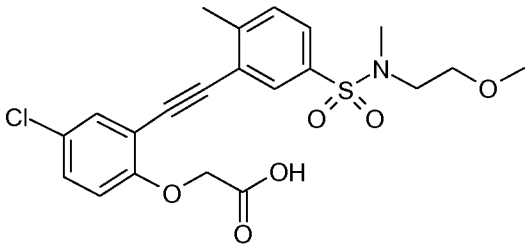
Example 108: [4-chloro-2-({2-methyl-5-[(2-methylpiperidin-1-yl)sulfonyl]phenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [4-chloro-2-({2-methyl-5-[(2-methylpiperidin-1-yl)sulfonyl]phenyl}ethynyl)phenoxy]acetate (Intermediate 158), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.17 (1H, bs), 7.84 (1H, d, *J*= 2.0 Hz), 7.71 (1H, dd, *J*= 8.1 Hz, *J*= 2.0 Hz), 7.66 (1H, d, *J*= 2.7 Hz), 7.56 (1H, d, *J*= 8.1 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 4.13 (1H, m), 3.63 (1H, m), 2.98 (1H, dt, *J*= 13.0 Hz, *J*= 2.0 Hz), 2.55 (3H, s), 1.40-4.56 (5H, m), 1.20 (1H, m), 1.00 (3H, d, *J*= 6.9 Hz). MS (ESI$^-$): 460.1. HPLC (Condition A): Rt 5.19 min (HPLC purity 99.6%).

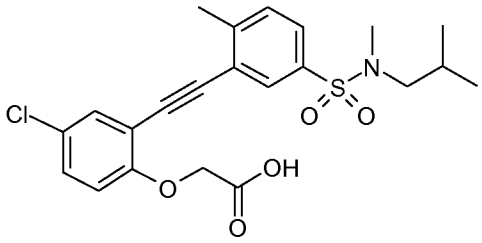
Example 109: {4-chloro-2-[(5-{[(2-methoxyethyl)(methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl {4-chloro-2-[(5-{[(2-methoxyethyl)(methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetate (Intermediate 159), the title compound was obtained as a pink solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.17 (1H, bs), 7.83 (1H, d, *J*= 2.0 Hz), 7.70 (1H, dd, *J*= 8.1 Hz, *J*= 2.0 Hz), 7.66 (1H, d, *J*= 2.7 Hz), 7.58 (1H, d, *J*= 8.1 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 3.45 (2H, t, *J*= 5.5 Hz), 3.22 (3H, s), 3.17 (2H, t, *J*= 5.5 Hz), 2.73 (3H, s), 2.56 (3H, s). MS (ESI$^-$): 450.1. HPLC (Condition A): Rt 4.39 min (HPLC purity 100%).

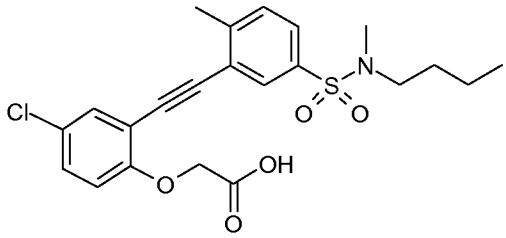
Example 110: {4-chloro-2-[(5-{[isobutyl(methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl {4-chloro-2-[(5-{[isobutyl(methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetate (Intermediate 160), the title compound was obtained as a beige solid in 77% yield after tituration in pentane/diethyl ether.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.14 (1H, bs), 7.81 (1H, d, *J*= 2.0 Hz), 7.69 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.66 (1H, d, *J*= 2.7 Hz), 7.58 (1H, d, *J*= 8.0 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 2.71 (2H, d, *J*= 7.4 Hz), 2.66 (3H, s), 2.56 (3H, s), 1.83 (1H, m), 0.87 (6H, d, *J*= 6.7 Hz). MS (ESI$^-$): 448.1. HPLC (Condition A): Rt 5.03 min (HPLC purity 92.2%).

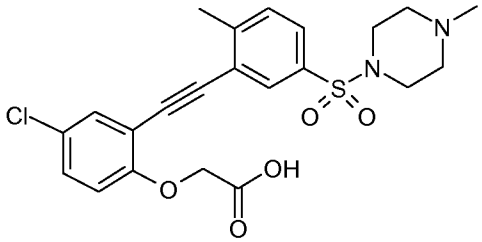
Example 111: {2-[(5-{[butyl(methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]-4-chlorophenoxy}acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl {2-[(5-{[butyl(methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]-4-chlorophenoxy}acetate (Intermediate 161), the title compound was obtained as a beige solid in 96% yield after trituration in diethyl ether / pentane.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.15 (1H, bs), 7.81 (1H, d, *J*= 2.0 Hz), 7.68 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.66 (1H, d, *J*= 2.7 Hz), 7.58 (1H, d, *J*= 8.0 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 2.95 (2H, t, *J*= 7.0 Hz), 2.66 (3H, s), 2.56 (3H, s), 1.45 (2H, m), 1.27 (2H, m), 0.88 (3H, d, *J*= 7.3 Hz). MS (ESI$^-$): 448.1. HPLC (Condition A): Rt 5.06 min (HPLC purity 94.6%).

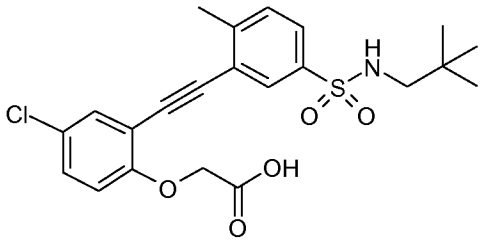
Example 112: [4-chloro-2-({2-methyl-5-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [4-chloro-2-({2-methyl-5-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}ethynyl)phenoxy]acetate (Intermediate 162), the title compound was obtained as a white solid after filtration from the reaction mixture.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.84 (1H, d, *J*= 1.7 Hz), 7.65-7.73 (3H, m), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.05 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 3.79 (2H, bs), 3.36 (4H, bs), 3.19 (2H, bs), 2.74 (3H, s), 2.60 (3H, s). MS (ESI$^-$): 461.0. HPLC (Condition A): Rt 3.31 min (HPLC purity 99.7%).

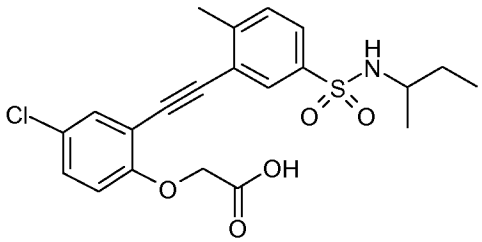
Example 113: {4-chloro-2-[(5-{[(2,2-dimethylpropyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl {4-chloro-2-[(5-{[(2,2-dimethylpropyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetate (Intermediate 163), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.14 (1H, bs), 7.88 (1H, d, *J*= 1.9 Hz), 7.70 (1H, dd, *J*= 8.0 Hz, *J*= 1.9 Hz), 7.63 (1H, d, *J*= 2.7 Hz), 7.53-7.61 (2H, m), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 2.54 (3H, s), 0.83 (9H, s) + 2H under the signal of DMSO. MS (ESI$^-$): 448.0. HPLC (Condition A): Rt 5.14 min (HPLC purity 98.6%).

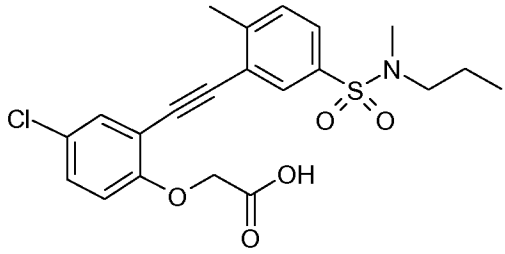
Example 114: [2-({5-[(*sec*-butylamino)sulfonyl]-2-methylphenyl}ethynyl)-4-chlorophenoxy]acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [2-({5-[(*sec*-butylamino)sulfonyl]-2-methylphenyl}ethynyl)-4-chlorophenoxy]acetate (Intermediate 164), the title compound was obtained as a white solid after purification by preparative HPLC.

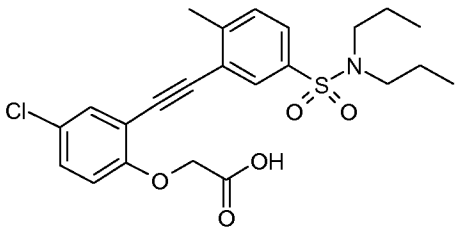
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.18 (1H, bs), 7.87 (1H, d, *J*= 2.0 Hz), 7.71 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.65 (1H, d, *J*= 2.7 Hz), 7.53-7.58 (2H, m), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 3.07 (1H, m), 2.55 (3H, s), 1.31 (2H, quint., *J*= 7.2 Hz), 0.88 (3H, d, *J*= 6.7 Hz), 0.72 (3H, t, *J*= 7.2 Hz). MS (ESI$^-$): 434.2. HPLC (Condition A): Rt 4.82 min (HPLC purity 99.3%).

Example 115: {4-chloro-2-[(2-methyl-5-{[methyl(propyl)amino]sulfonyl}phenyl)ethynyl]phenoxy}acetic acid



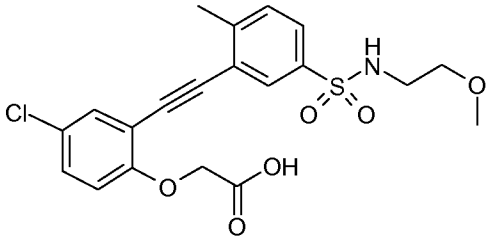
Following the general method as outlined in Example 15, starting from *tert*-butyl {4-chloro-2-[(2-methyl-5-{[methyl(propyl)amino]sulfonyl}phenyl)ethynyl]phenoxy}acetate (Intermediate 165), the title compound was obtained in 80% yield as a beige solid.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.14 (1H, bs), 7.81 (1H, d, *J*= 2.0 Hz), 7.69 (1H, d, J0 8.0 Hz, *J*= 2.0 Hz), 7.67 (1H, d, *J*= 2.7 Hz), 7.59 (1H, d, *J*= 8.0 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 2.92 (2H, m), 2.67 (3H, s), 2.57 (3H, s), 1.49 (2H, sext., *J*= 7.3 Hz), 0.85 (3H, t, *J*= 7.3 Hz). MS (ESI$^-$): 434.2. HPLC (Condition A): Rt 4.82 min (HPLC purity 97.6%).

Example 116: [4-chloro-2-({5-[(dipropylamino)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [4-chloro-2-({5-[(dipropylamino)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetate (Intermediate 166), the title compound was obtained as a grey solid after purification by preparative HPLC.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.17 (1H, bs), 7.83 (1H, d, *J*= 2.0 Hz), 7.71(1H, d, *J*= 8.1 Hz, *J*= 2.0 Hz), 7.66 (1H, d, *J*= 2.7 Hz), 7.56 (1H, d, *J*= 8.1 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 3.04 (4H, m), 2.55 (3H, s), 1.47 (4H, sext., *J*= 7. Hz), 0.82 (6H, t, *J*= 7.3 Hz). MS (ESI$^-$): 462.1. HPLC (Condition A): Rt 5.22 min (HPLC purity 100%).

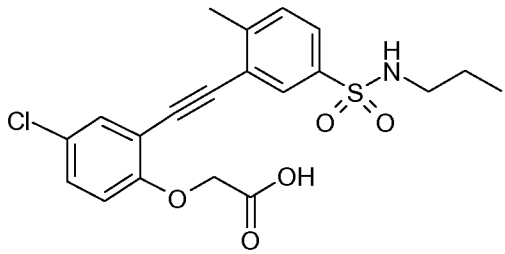
Example 117: {4-chloro-2-[(5-{[(2-methoxyethyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl {4-chloro-2-[(5-{[(2-methoxyethyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetate (Intermediate 167), the title compound was obtained as a white solid in 99% yield after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.17 (1H, bs), 7.87 (1H, d, *J*= 2.0 Hz), 7.77 (1H, t, *J*= 5.9 Hz), 7.70 (1H, dd, *J*= 8.1 Hz, *J*= 2.0 Hz), 7.63 (1H, d, *J*= 2.7 Hz), 7.55 (1H, d, *J*= 8.1 Hz), 7.44 (1H, d, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 3.30 (2H, t, *J*= 5.7 Hz), 3.16 (3H, s), 2.91 (2H, q, *J*= 5.7 Hz), 2.55 (3H, s). MS (ESI$^-$): 436.0.

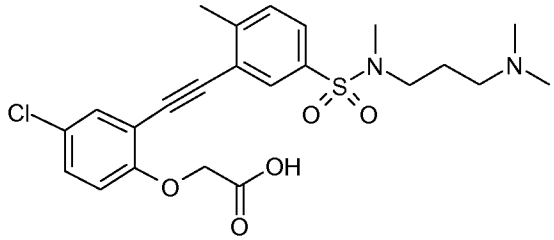
Example 118: [4-chloro-2-({2-methyl-5-[(propylamino)sulfonyl]phenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [4-chloro-2-({2-methyl-5-[(propylamino)sulfonyl]phenyl}ethynyl)phenoxy]acetate (Intermediate 168), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.17 (1H, bs), 7.85 (1H, t, *J*= 2.0 Hz), 7.69 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.64 (1H, d, *J*= 2.7 Hz), 7.61 (1H, t, *J*= 5.8 Hz), 7.56 (1H, d, *J*= 8.0 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 2.69 (2H, m), 2.55 (3H, s), 1.37 (2H, sext., *J*= 7.3 Hz), 0.79 (3H, t, *J*= 7.3 Hz). MS (ESI$^-$): 420.0. HPLC (Condition A): Rt 4.68 min (HPLC purity 98.8%).

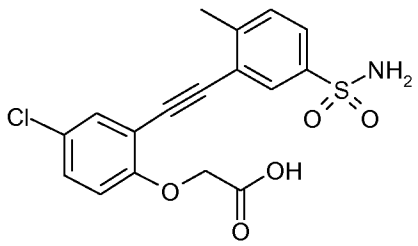
Example 119: {4-chloro-2-[(5-{[[3-(dimethylamino)propyl](methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl {4-chloro-2-[(5-{[[3-(dimethylamino)propyl](methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetate (Intermediate 169), the title compound was obtained as a white solid in quantitative yield.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.83 (1H, d, *J*= 1.9 Hz), 7.71 (1H, dd, *J*= 8.0 Hz, *J*= 1.9 Hz), 7.65 (1H, d, *J*= 2.7 Hz), 7.61 (1H, d, *J*= 8.0 Hz), 7.45 (1H, dd, = 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 3.04 (4H, m), 2.75 (6H, s), 2.70 (3H, s), 2.57 (3H, s), 1.89 (2H, m). MS (ESI$^-$): 477.2. HPLC (Condition A): Rt 3.57 min (HPLC purity 98.8%).

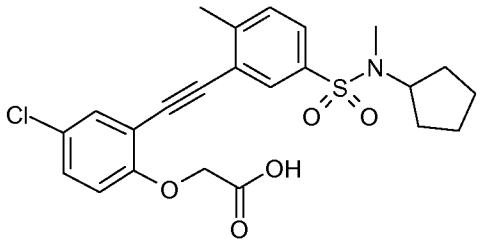
Example 120: (2-{[5-(aminosulfonyl)-2-methylphenyl]ethynyl}-4-chlorophenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (2-{[5-(aminosulfonyl)-2-methylphenyl]ethynyl}-4-chlorophenoxy)acetate (Intermediate 170), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.18 (1H, bs), 7.91 (1H, s), 7.72 (1H, d, *J*= 8.0 Hz), 7.63 (1H, d, *J*= 2.7 Hz), 7.53 (1H, d, *J*= 8.0 Hz), 7.44 (1H,d, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.40 (2H, bs), 7.04 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 2.54 (3H, s). MS (ESI$^-$): 378.0. HPLC (Condition A): Rt 3.69 min (HPLC purity 99.2%).

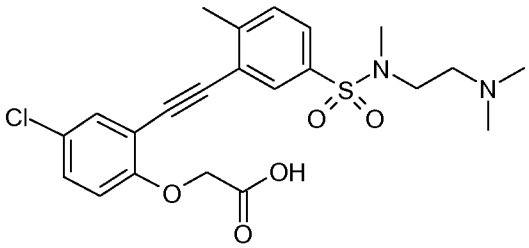
Example 121: {4-chloro-2-[(5-{[cyclopentyl(methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl {4-chloro-2-[(5-{[cyclopentyl(methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetate (Intermediate 171), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.17 (1H, bs), 7.83 (1H, t, *J*= 2.0 Hz), 7.71 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.66 (1H, d, *J*= 2.7 Hz), 7.57 (1H, d, *J*= 8.0 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 4.25 (1H, quint., *J*= 7.7 Hz), 2.65 (3H, s), 2.56 (3H, s), 1.30-1.53 (8H, m). MS (ESI$^-$): 460.2. HPLC (Condition A): Rt 5.27 min (HPLC purity 97.9%).

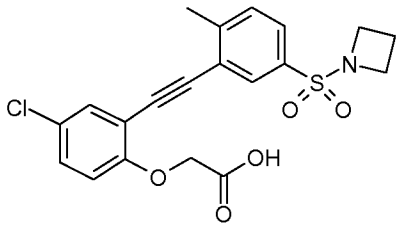
Example 122: {4-chloro-2-[(5-{[[2-(dimethylamino)ethyl](methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 15, starting *tert*-butyl {4-chloro-2-[(5-{[[2-(dimethylamino)ethyl](methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetate (Intermediate 172), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.95 (1H, t, *J*= 2.0 Hz), 7.69 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.58-7.61 (2H, m), 7.42 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.05 (1H, d, *J*= 9.0 Hz), 4.54 (2H, s), 3.23 (2H, m), 2.83 (2H, m), 2.69 (3H, s), 2.56 (3H, s), 2.43 (6H, s). MS (ESI$^-$): 463.0. HPLC (Condition A): Rt 3.47 min (HPLC purity 99.1%).

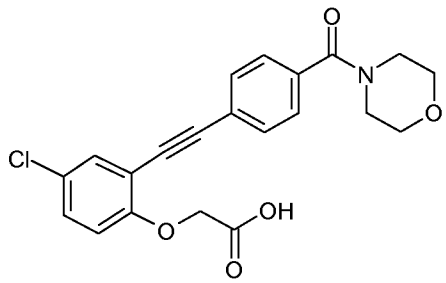
Example 123: (2-{[5-(azetidin-1-ylsulfonyl)-2-methylphenyl]ethynyl}-4-chlorophenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (2-{[5-(azetidin-1-ylsulfonyl)-2-methylphenyl]ethynyl}-4-chlorophenoxy)acetate (Intermediate 173), the title compound was obtained in 70% yield as a pink solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.15 (1H, bs), 7.84 (1H, d, *J*= 2.0 Hz), 7.73 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.65-7.68 (2H, m), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.05 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 3.69 (4H, t, *J*= 7.7 Hz), 2.60 (3H, s), 2.01 (2H, quint., *J*= 7.7 Hz). MS (ESI$^-$): 418.0. HPLC (Condition A): Rt 4.54 min (HPLC purity 98.8%).

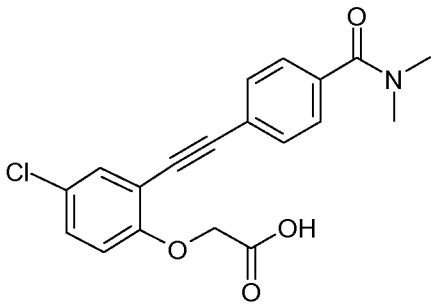
Example 124: (4-chloro-2-{[4-(morpholin-4-ylcarbonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[4-(morpholin-4-ylcarbonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 175), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.09 (1H, bs), 7.61 (2H, d, *J*= 8.2 Hz), 7.58 (1H, d, *J*= 2.7 Hz), 7.47 (2H, d, *J*= 8.2 Hz), 7.42 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 6.99 (1H, d, *J*= 9.0 Hz), 4.80 (2H, s), 3.60 (6H, bs) (2 remaining protons, probably hidden under the signal of water). MS (ESI$^-$): 398.1. HPLC (Condition A): Rt 3.75 (HPLC purity 96.2%).

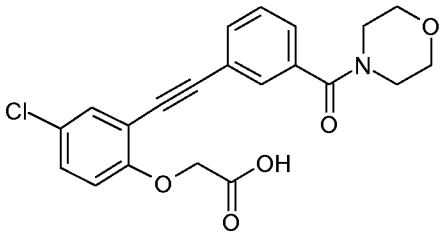
Example 125: [4-chloro-2-({4-[(dimethylamino)carbonyl]phenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [4-chloro-2-({4-[(dimethylamino)carbonyl]phenyl}ethynyl)phenoxy]acetate (Intermediate 177), the title compound was obtained in 84% yield as a beige solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.15 (1H, bs), 7.58-7.61 (3H, m), 7.40-7.47 (3H, m), 7.01 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 2.99 (3H, s), 2.92 (3H, s). MS (ESI$^-$): 356.1. HPLC (Condition A): Rt 4.21 min (HPLC purity 95.8%).

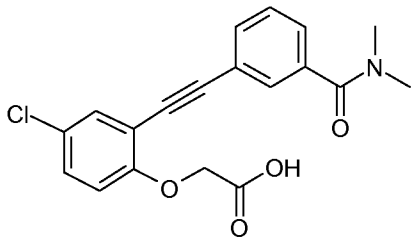
Example 126: (4-chloro-2-{[3-(morpholin-4-ylcarbonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[3-(morpholin-4-ylcarbonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 179), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.20 (1H, bs), 7.40-7.64 (6H, m), 7.00 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s), 3.61 (6H, bs) (2 remaining protons, probably hidden under the signal of water). MS (ESI$^-$): 398.1. HPLC (Condition A): Rt 3.73 min (HPLC purity 97.3%).

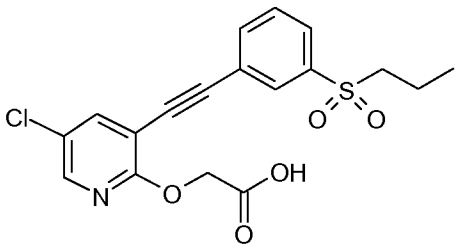
Example 127: [4-chloro-2-({3-[(dimethylamino)carbonyl]phenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [4-chloro-2-({3-[(dimethylamino)carbonyl]phenyl}ethynyl)phenoxy]acetate (Intermediate 181), the title compound was obtained as a white solid after purification preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.17 (1H, bs), 7.39-7.62 (6H, m), 6.99 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 2.99 (3H, s), 2.92 (3H, s). MS (ESI$^-$): 356.0. HPLC (Condition A): Rt 3.78 min (HPLC purity 100%).

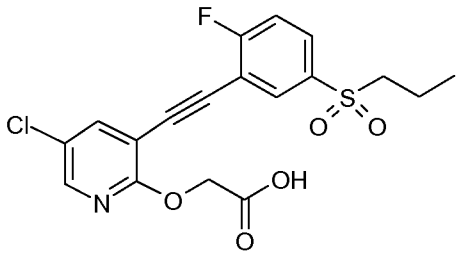
Example 128: [(5-chloro-3-{[3-(propylsulfonyl)phenyl]ethynyl}pyridin-2-yl)oxy]acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [(5-chloro-3-{[3-(propylsulfonyl)phenyl]ethynyl}pyridin-2-yl)oxy]acetate (Intermediate 183), the title compound was obtained as a beige solid .

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.02 (1H, bs), 8.27 (1H, d, *J*= 2.6 Hz), 8.22 (1H, d, *J*= 2.6 Hz), 8.04 (1H, t, *J*= 1.5 Hz), 7.90-7.98 (2H, m), 7.75 (1H, t, *J*= 7.8 Hz), 4.93 (2H, s), 3.38 (2H, m), 1.57 (2H, sext., *J*= 7.5 Hz), 0.93 (3H, t, *J*= 7.5 Hz). MS (ESI$^-$): 392.0. HPLC (Condition A): Rt 4.07 min (HPLC purity 91.7%).

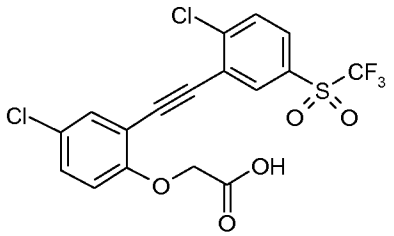
Example 129: [(5-chloro-3-{[2-fluoro-5-(propylsulfonyl)phenyl]ethynyl}pyridin-2-yl)oxy]acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [(5-chloro-3-{[2-fluoro-5-(propylsulfonyl)phenyl]ethynyl}pyridin-2-yl)oxy]acetate (Intermediate 184), the title compound was obtained in 80% yield as a beige solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.04 (1H, bs), 8.30 (1H, d, *J*= 2.5 Hz), 8.24 (1H, d, *J*= 2.5 Hz), 8.15 (1H, dd, *J*= 6.6 Hz, *J*= 2.0 Hz), 8.02 (1H, m), 7.68 (1H, t, *J*= 9.0 Hz), 4.94 (2H, s), 3.39 (2H, m), 1.57 (2H, sext., *J*= 7.5 Hz), 0.93 (3H, t, *J*= 7.5 Hz). MS (ESI$^-$): 410.1. HPLC (Condition A): Rt 4.20 min (HPLC purity 97.9%).

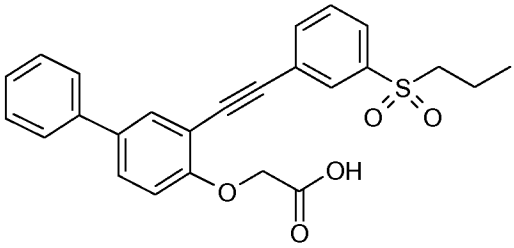
Example 130: [4-chloro-2-({2-chloro-5-[(trifluoromethyl)sulfonyl]phenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [4-chloro-2-({2-chloro-5-[(trifluoromethyl)sulfonyl]phenyl}ethynyl)phenoxy]acetate (Intermediate 187), the title compound was obtained as a white solid in 75% yield after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.19 (1H, bs), 8.36 (1H, d, *J*= 2.2 Hz), 8.15 (1H, dd, *J*= 8.6 Hz, *J*= 2.2 Hz), 8.08 (1H, d, *J*= 8.6 Hz), 7.70 (1H, d, *J*= 2.7 Hz), 7.50 (1H, d, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.06 (1H, d, *J*= 9.0 Hz), 4.85 (2H, s). MS (ESI$^-$): 450.8. HPLC (Condition A): Rt 5.01 min (HPLC purity 100%).

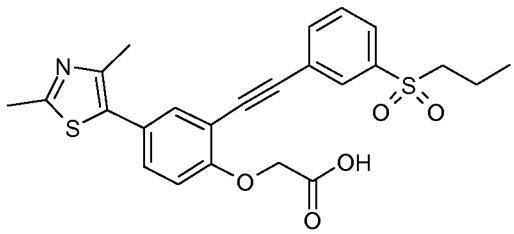
Example 131: [(3-{[3-(propylsulfonyl)phenyl]ethynyl}biphenyl-4-yl)oxy]acetic acid



Following the general method as outlined in Example 37, starting from *tert*-butyl [(3-bromobiphenyl-4-yl)oxy]acetate (Intermediate 188) and 1-ethynyl-3-(propane-1-sulfonyl)-benzene (Intermediate 42), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.20 (1H, bs), 8.02 (1H, t, *J*= 1.6 Hz), 7.92 (1H, m), 7.90 (1H, d, *J*= 1.6 Hz), 7.86 (1H, d, *J*= 2.3 Hz), 7.66-7.75 (4H, m), 7.43-7.48 (2H, m), 7.35 (1H, dt, *J*= 7.3 Hz, *J*= 2.3 Hz), 7.06 (1H, d, *J*= 8.8 Hz), 4.86 (2H, s), 3.36-3.40 (2H, m), 1.57 (2H, sext., *J*= 7.6 Hz), 0.93 (3H, t, *J*= 7.6 Hz). MS (ESI$^-$): 433.1. HPLC (Condition A): Rt 5.20 min (HPLC purity 91.8%).

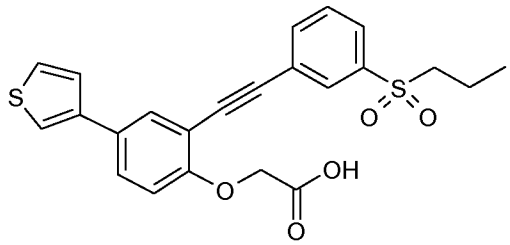
Example 132: (4-(2,4-dimethyl-1,3-thiazol-5-yl)-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-(2,4-dimethyl-1,3-thiazol-5-yl)-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 192), the title compound was obtained as a white solid yield after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.34 (1H, bs), 8.01 (1H, t, *J*= 1.5 Hz), 7.89-7.93 (2H, m), 7.72 (1H, t, *J*= 7.8 Hz), 7.60 (1H, d, *J*= 2.3 Hz), 7.45 (1H, dd, *J*= 8.8 Hz, *J*= 2.3 Hz), 7.06 (1H, d, *J*= 8.8 Hz), 4.86 (2H, s), 3.37 (2H, m), 2.62 (3H, s), 2.36 (3H, s), 1.57 (2H, sext., *J*= 7.6 Hz), 0.93 (3H, t, *J*= 7.6 Hz). MS (ESI$^-$): 468.0. HPLC (Condition A): Rt 3.43 min (HPLC purity 100%).

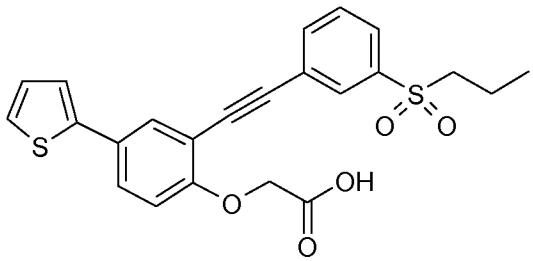
Example 133: [2-{[3-(propylsulfonyl)phenyl]ethynyl}-4-(3-thienyl)phenoxy]acetic acid



A mixutre of *tert*-butyl (4-bromo-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 191, 200 mg; 0.41 mmol), 3-thienylboronic acid (78 mg; 0.61 mmol), caesium fluoride (185 mg; 1.22 mmol) and bis(triphenylphosphine)palladium(II) chloride (28 mg; 0.04 mmol) was placed in a microwave tube. The tube was sealed and degased with nitrogen before adding dioxane (4 ml) and water (2 ml). The reaction mixture was heated at 150 °C for 15 minutes in a microwave reaction system. The reaction mixture was taken up in EtOAc and washed with water and brine. The organic phase was dried over MgSO4, filtered and concentred. The residue was dissolved in DCM (1.00 ml), treated with a 4 N solution of HCl in dioxane (2.0 ml) and stirred for 1 day. The solvents were removed under reduced pressure and the residue purified by preparative HPLC to give the title compound as a white solid.

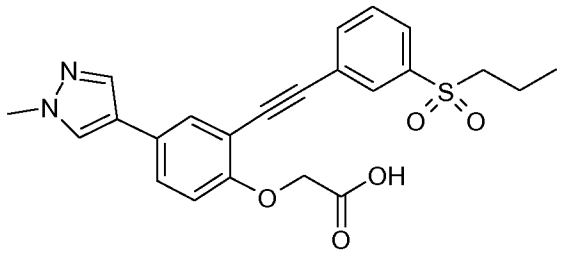
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.17 (1H, bs), 8.01 (1H, t, *J*= 1.5 Hz), 7.86-7.93 (4H, m), 7.70-7.77 (2H, m), 7.64 (1H, dd, *J*= 5.0 Hz, *J*= 2.9 Hz), 7.58 (1H, dd, *J*= 5.0 Hz, *J*= 1.0 Hz), 7.02 (1H, d, *J*= 8.6 Hz), 4.85 (2H, s), 3.37 (2H, m), 1.57 (2H, sext., *J*= 7.5 Hz), 0.93 (3H, t, *J*= 7.5 Hz). MS (ESI$^-$): 439.0. HPLC (Condition A): Rt 4.66 min (HPLC purity 97.3%).

Example 134: [2-{[3-(propylsulfonyl)phenyl]ethynyl}-4-(2-thienyl)phenoxy]acetic acid



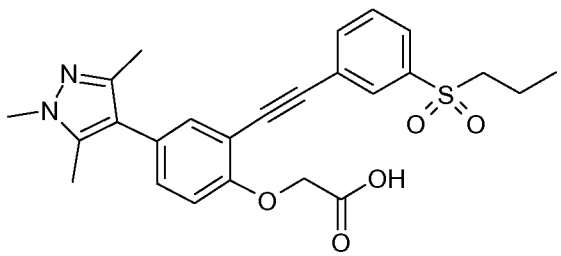
Following the general method as outlined in Example 15, starting from *tert*-butyl [2-{[3-(propylsulfonyl)phenyl]ethynyl}-4-(2-thienyl)phenoxy]acetate (Intermediate 193), the title compound was obtained as a white solid after purification by preparative HPLC. ^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.19 (1H, bs), 8.03 (1H, t, *J*= 1.5 Hz), 7.92 (2H, dd, *J*= 7.8 Hz, *J*= 1.5 Hz), 7.84 (1H, d, *J*= 8.7 Hz, *J*= 2.4 Hz), 7.73 (1H, t, *J*= 7.8 Hz), 7.67 (1H, dd, *J*= 2.4 Hz), 7.52 (1H, dd, *J*= 5.1 Hz, *J*= 1.1 Hz), 7.50 (1H, dd, *J*= 3.6 Hz, J0 1.1 Hz), 7.13 (1H, dd, *J*= 5.1 Hz, *J*= 3.6 Hz), 7.04 (1H, d, *J*= 8.7 Hz), 4.87 (2H, s), 3.37 (2H, m), 1.57 (2H, sext., *J*= 7.5 Hz), 0.93 (3H, t, *J*= 7.5 Hz). MS (ESI$^-$): 439.0. HPLC (Condition A): Rt 4.66 min (HPLC purity 99.7%).

Example 135: (4-(1-methyl-1H-pyrazol-4-yl)-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



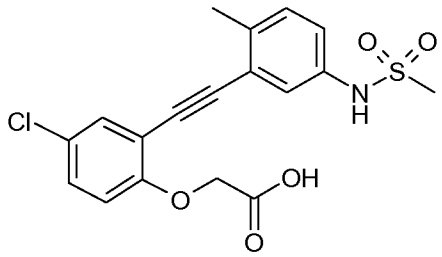
Following the general method as outlined in Example 15, starting from *tert*-butyl (4-(1-methyl-1H-pyrazol-4-yl)-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 194), the title compound was obtained as a white solid in 81% yield. ^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.13 (1H, bs), 7.99 (1H, t, *J*= 1.5 Hz), 7.87-7.93 (2H, m), 7.86 (1H, s), 7.76 (1H, d, *J*= 2.3 Hz), 7.73 (1H, t, *J*= 7.8 Hz), 7.57 (1H, dd, *J*= 8.7 Hz, *J*= 2.3 Hz), 6.97 (1H, d, *J*= 8.7 Hz), 4.83 (2H, s), 3.85 (3H, s), 3.37 (2H, m), 1.57 (2H, sext., *J*= 7.5 Hz), 0.93 (3H, t, *J*= 7.5 Hz). MS (ESI$^-$): 437.1. HPLC (Condition A): Rt 3.71 min (HPLC purity 99.3%).

Example 136: [2-{[3-(propylsulfonyl)phenyl]ethynyl}-4-(1,3,5-trimethyl-1H-pyrazol-4-yl)phenoxy]acetic acid



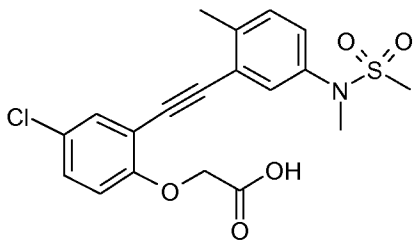
Following the general method as outlined in Example 15, starting from *tert*-butyl [2-{[3-(propylsulfonyl)phenyl]ethynyl}-4-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)phenoxy]acetate (Intermediate 195), the title compound was obtained as a white solid in 79% yield.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.99 (1H, t, *J*= 7.7 Hz), 7.88-7.92 (2H, m), 7.72 (1H, t, *J*= 7.7 Hz), 7.39 (1H, d, *J*= 2.2 Hz), 7.26 (1H, dd, *J*= 8.7 Hz, *J*= 2.2 Hz), 7.01 (1H, d, *J*= 8.7 Hz), 4.86 (2H, s), 3.71 (3H, s), 3.36 (2H, m), 2.21 (3H, s), 2.12 (3H, s), 1.57 (2H, sext., *J*= 7.5 Hz), 0.93 (3H, t, *J*= 7.5 Hz). MS (ESI$^-$): 465.1. HPLC (Condition A): Rt 3.32 min (HPLC purity 95.2%).

Example 137: [4-chloro-2-({2-methyl-5-[(methylsulfonyl)amino]phenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [4-chloro-2-({2-methyl-5-[(methylsulfonyl)amino]phenyl}ethynyl)phenoxy]acetate (Intermediate 196), the title compound was obtained as a pink solid after purification by preparative HPLC.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.18 (1H, bs), 9.73 (1H, s), 7.58 (1H, d, *J*= 2.7 Hz), 7.40 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.28-7.30 (2H, m), 7.16 (1H, dd, *J*= 8.2, *J*= 2.3 Hz), 7.00 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s), 2.98 (3H, s), 2.42 (3H, s). MS (ESI$^-$): 392.0. HPLC (Condition A): Rt 4.17 min (HPLC purity 99.9%).

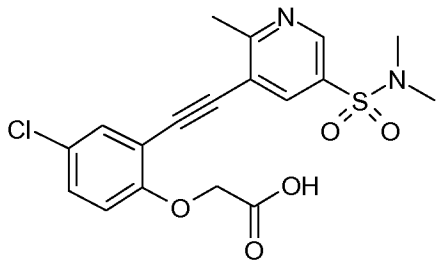
Example 138: [4-chloro-2-({2-methyl-5-[methyl(methylsulfonyl)amino]phenyl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [4-chloro-2-({2-methyl-5-[methyl(methylsulfonyl)amino]phenyl}ethynyl)phenoxy]acetate (Intermediate 196), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.17 (1H, bs), 7.58 (1H, d, *J*= 2.7 Hz), 7.52 (1H, m), 7.42 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.36 (2H, m), 7.02 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 3.24 (3H, s), 2.95 (3H, s), 2.46 (3H, s). MS (ESI$^-$): 406.0. HPLC (Condition A): Rt 4.23 min (HPLC purity 99.8%).

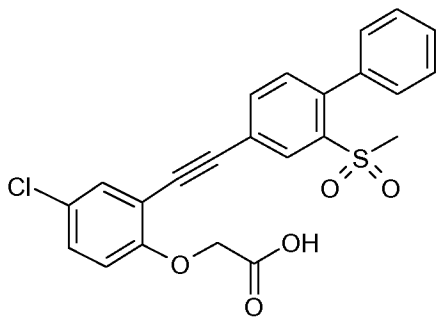
Example 139: [4-chloro-2-({5-[(dimethylamino)sulfonyl]-2-methylpyridin-3-yl}ethynyl)phenoxy]acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [4-chloro-2-({5-[(dimethylamino)sulfonyl]-2-methylpyridin-3-yl}ethynyl)phenoxy]acetate (Intermediate 200) at a temperature of 80 °C, the title compound was obtained as a white solid after filtration from the reaction mixture.

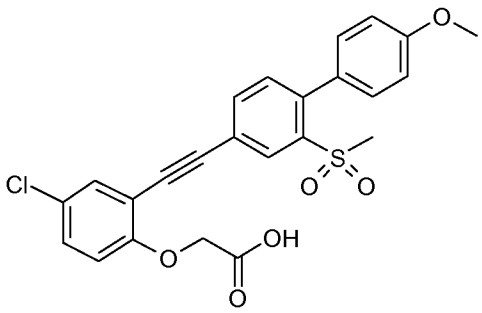
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.4 (1H, bs), 8.77 (1H, d, *J*= 2.2 Hz), 8.18 (1H, d, *J*= 2.2 Hz), 7.70 (1H, d, *J*= 2.7 Hz), 7.48 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.08 (1H, d, *J*= 9.0 Hz), 4.85 (2H, s), 2.79 (3H, s), 2.69 (6H, s). MS (ESI$^-$): 407.1. HPLC (Condition A): Rt 3.93 min (HPLC purity 99.1%).

Example 140: (4-chloro-2-{[2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetic acid



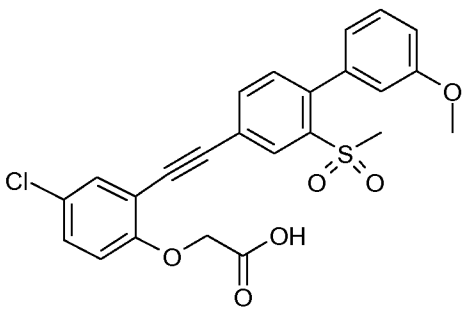
Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetate (Intermediate 204), the title compound was obtained as a white solid after purification by preparative HPLC.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.23 (1H, bs), 8.18 (1H, d, *J*= 1.8 Hz), 7.89 (1H, dd, *J*= 7.9 Hz, *J*= 1.8 Hz), 7.68 (1H, d, *J*= 2.7 Hz), 7.43 (7H, m), 7.02 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 2.88 (3H, s). MS (ESI$^-$): 439.2. HPLC (Condition A): Rt 4.78 min (HPLC purity 98.8%).

Example 141: (4-chloro-2-{[4'-methoxy-2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[4'-methoxy-2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetate (Intermediate 206), the title compound was obtained as a beige solid after purification by preparative HPLC.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.21 (1H, bs), 8.17 (1H, d, *J*= 1.8 Hz), 7.87 (1H, dd, *J*= 8.0 Hz, *J*= 1.8 Hz), 7.67 (1H, d, *J*= 2.7 Hz), 7.43-7.47 (2H, m), 7.38 (2H, d, *J*= 8.7 Hz), 7.00-7.05 (3H, m), 4.85 (2H, s), 3.82 (3H, s), 2.85 (3H, s). MS (ESI$^-$): 469.1. HPLC (Condition A): Rt 4.76 min (HPLC purity 95.7%).

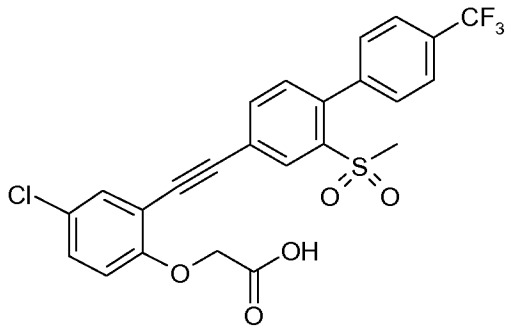
Example 142: (4-chloro-2-{[3'-methoxy-2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[3'-methoxy-2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetate (Intermediate 208), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.17 (1H, d, *J*= 1.8 Hz), 7.89 (1H, dd, *J*= 8.0 Hz, *J*= 1.8 Hz), 7.66 (1H, d, *J*= 2.7 Hz), 7.48 (1H, d, *J*= 8.0 Hz), 7.36-7.45 (2H, m), 6.96-7.06 (4H, m), 4.74 (2H, s), 3.79 (3H, s), 2.90 (3H, s). MS (ESI$^-$): 469.2. HPLC (Condition A): Rt 4.78 min (HPLC purity 99.0%).

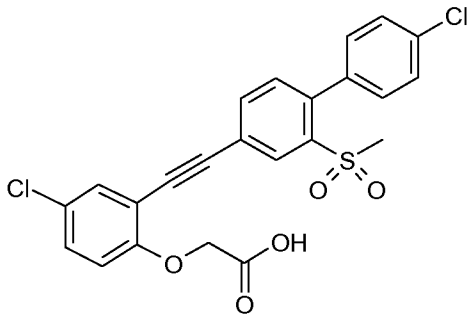
Example 143: (4-chloro-2-{[2-(methylsulfonyl)-4'-(trifluoromethyl)biphenyl-4-yl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[2-(methylsulfonyl)-4'-(trifluoromethyl)biphenyl-4-yl]ethynyl}phenoxy)acetate (Intermediate 210), the title compound was obtained as a beige solid in 70% yield after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.21 (1H, bs), 8.21 (1H, d, *J*= 1.7 Hz), 7.93 (1H, dd, *J*= 7.9 Hz, *J*= 1.7 Hz), 7.83 (2H, d, *J*= 8.1 Hz), 7.65-7.68 (3H, m), 7.51 (1H, d, *J*= 7.9 Hz), 7.46 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.02 (1H, d, *J*= 9.0 Hz), 4.85 (2H, s), 3.03 (3H, s). MS (ESI$^-$): 507.2. HPLC (Condition A): Rt 5.23 min (HPLC purity 98.2%).

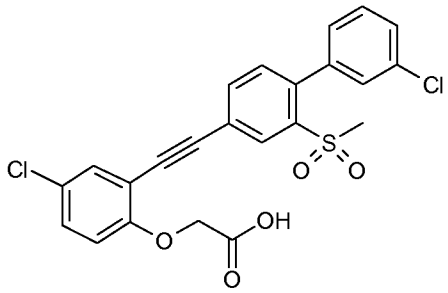
Example 144: (4-chloro-2-{[4'-chloro-2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[4'-chloro-2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetate (Intermediate 212), the title compound was obtained as a beige solid in 55% yield after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.22 (1H, bs), 8.181 (1H, d, *J*= 1.7 Hz), 7.90 (1H, dd, *J*= 7.9 Hz, *J*= 1.7 Hz), 7.67 (1H, d, *J*= 2.7 Hz), 7.531 (2H, d, *J*= 8.6 Hz), 7.43-7.49 (4H, m), 7.02 (1H, d, *J*= 9.0 Hz), 4.85 (2H, s), 2.97(3H, s). MS (ESI$^-$): 473.1. HPLC (Condition A): Rt 5.07 min (HPLC purity 97.7%).

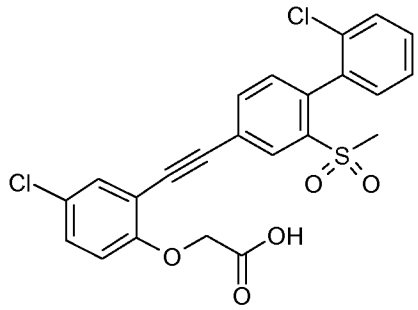
Example 145: (4-chloro-2-{[3'-chloro-2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[3'-chloro-2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetate (Intermediate 214), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.21 (1H, bs), 8.18 (1H, d, *J*= 1.8 Hz), 7.90 (1H, dd, *J*= 7.9 Hz, *J*= 1.8 Hz), 7.68 (1H, d, *J*= 2.7 Hz), 7.44-7.56 (5H, m), 7.40 (1H, dt, *J*= 7.1 Hz, *J*= 1.6 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.85 (2H, s), 2.99 (3H, s). MS (ESI$^-$): 473.2. HPLC (Condition A): Rt 5.04 min (HPLC purity 100%).

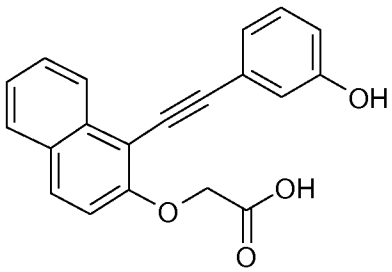
Example 146: (4-chloro-2-{[2'-chloro-2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[2'-chloro-2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetate (Intermediate 216), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.22 (1H, bs), 8.20 (1H, d, *J*= 1.6 Hz), 7.92 (1H, dd, *J*= 7.9 Hz, *J*= 1.6 Hz), 7.67 (1H, d, *J*= 2.7 Hz), 7.57 (1H, m), 7.39-7.50 (5H, m), 7.03 (1H, d, *J*= 9.0 Hz), 4.86 (2H, s), 3.04 (3H, s). MS (ESI$^-$): 473.1 HPLC (Condition A): Rt 4.89 min (HPLC purity 100%).

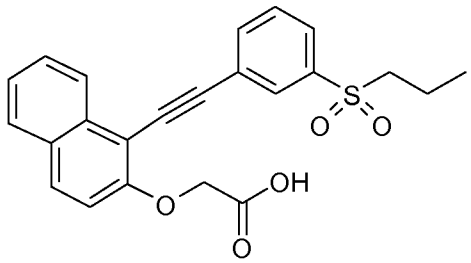
Example 147: ({1-[(3-hydroxyphenyl)ethynyl]-2-naphthyl}oxy)acetic acid



A mixture of (1-bromo-naphthalen-2-yloxy)-acetic acid *tert*-butyl ester (Intermediate 217, 125 mg; 0.37 mmol), 3-hydroxyphenylacetylene (53 mg; 0.44 mmol), palladium(II) chloride (3.3 mg; 0.02 mmol), triphenylphosphine (10 mg; 0.04 mmol) and piperidine (73 µl; 0.74 mmol) in distilled water (1.1 ml) and Acetone (1.4 ml) was stirred overnight at 60 °C. The reaction mixture was extracted by EtOAc and theorganic phases was dried over $MgSO_4$, concentrated to dryness and purified by preparative HPLC. The intermediate obtained was diluted in DCM (1 ml) and treated with a 4 M solution of HCl in dioxane (930 µl). After stirring overnight, the reaction mixture was concentrated to dryness and purified by preparative HPLC to afford the title compound as a beige solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.04 (1H, bs), 9.23 (1H, bS), 8.02 (1H, d, *J*= 9.2 Hz), 7.91 (1H, d, *J*= 8.1 Hz), 7.74 (1H, d, *J*= 8.1 Hz), 7.45-7.50 (1H, m), 7.36-7.40 (2H, m), 7.23 (1H, s), 6.81 (1H, t, *J*= 8.1 Hz); 6.38-6.48 (2H, m), 4.86 (1H, d, *J*= 16.8 Hz), 4.77 (1H, d, *J*= 16.8 Hz). MS (ESI$^+$): 319.0. HPLC (Condition A): Rt 4.13 min (HPLC purity 96.7%).

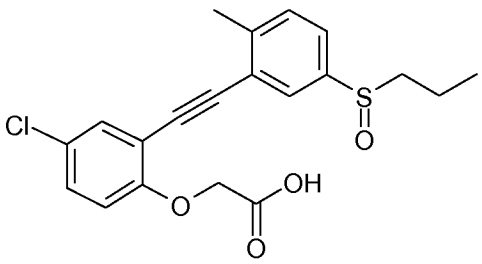
Example 148: [(1-{[3-(propylsulfonyl)phenyl]ethynyl}-2-naphthyl)oxy]acetic acid



A solution of *tert*-butyl [(1-{[3-(propylsulfonyl)phenyl]ethynyl}-2-naphthyl)oxy]acetate (Intermediate 218, 60 mg; 0.13 mmol) in DCM (1.2 mL) was treated with trifluroacetic acid (98 µl; 0.65 mmol). After stirring for 1 hour, the solvents were removed under vacuum to afford a residue, which was purified by preparative HPLC to give the title compound as a beige solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.18 (1H, bs), 8.29 (1H, d, *J*= 8.0 Hz), 8.10 (1H, t, *J*= 1.5 Hz), 8.00-8.04 (2H, m), 7.91-7.96 (2H, m), 7.76 (1H, t, *J*= 8.0 Hz), 7.63-7.68 (1H, m), 7.45-7.50 (1H, m), 7.39 (1H, d, *J*= 9.2 Hz), 5.01 (2H, s), 3.40 (2H, m), 1.60 (2H, sext., *J*= 7.6 Hz), 0.94 (3H, t, *J*= 7.6 Hz). MS (ESI$^-$): 407.1. HPLC (Condition A): Rt 4.88 min.

Example 149: (4-chloro-2-{[2-methyl-5-(propylsulfinyl)phenyl]ethynyl}phenoxy)acetic acid



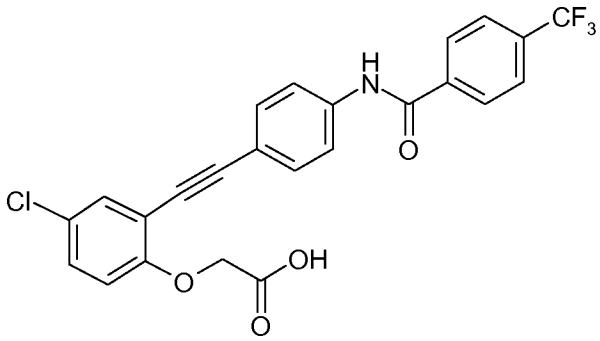
A solution of methyl (4-chloro-2-{[2-methyl-5-(propylsulfinyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 221, 125 mg; 0.31 mmol) in MeOH (5 ml) was treated with a 1M solution of sodium hydroxide in water (0.93 ml; 0.93

mmol). After stirring for 3 hours, the solvent was removed under reduced pressure, the residue was taken up in AcOEt and extracted with 0.1N HCl. The organic phase was dried on $MgSO_4$ and concentrated to give a residue which was triturated in diethyl ether, to afford the title compound as a pale yellow solid (101 mg, 83%).

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.2 (1H, bs), 7.73 (1H, d, *J*= 1.6 Hz), 7.62-7.52 (3H, m), 7.43 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 2.96 (1H, m), 2.77 (1H, m), 2.54 (3H, s), 1.65 (1H, m), 1.46 (1H, m), 0.97 (3H, t, *J*= 7.4 Hz).

MS (ESI$^-$): 389.1. HPLC (Condition A): Rt 4.15 min (HPLC purity 98.8%).

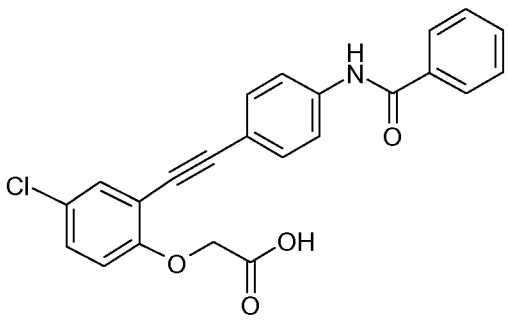
Example 150: {4-chloro-2-[(4-{[4-(trifluoromethyl)benzoyl]amino}phenyl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl [4-chloro-2-({5-[(dimethylamino)sulfonyl]-2-methylpyridin-3-yl}ethynyl)phenoxy]acetate (Intermediate 223), the title compound was obtained as a white solid after purification by preparative HPLC.

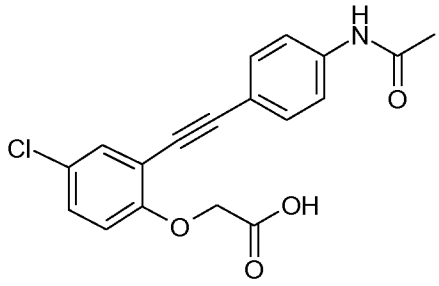
MS (ESI$^-$): 472.1. HPLC (Condition A): Rt 4.92 min (HPLC purity 99.4%).

Example 151: (2-{[4-(benzoylamino)phenyl]ethynyl}-4-chlorophenoxy)acetic acid



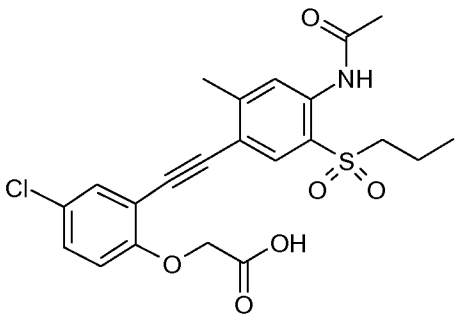
Following the general method as outlined in Example 148, starting from *tert*-butyl (2-{[4-(benzoylamino)phenyl]ethynyl}-4-chlorophenoxy)acetate (Intermediate 224), the title compound was obtained as a white solid after purification by preparative HPLC. ^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.2 (1H, bs), 10.46 (1H, s), 7.98-7.95 (2H, m), 7.90-7.85 (2H, m), 7.65-7.52 (6H, m), 7.38 (1H, dd, *J*= 9.0 Hz, *J*= 2.6 Hz), 6.98 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s). MS (ESI$^-$): 404.1. HPLC (Condition A): Rt 4.42 min (HPLC purity 99.7%).

Example 152: (2-{[4-(acetylamino)phenyl]ethynyl}-4-chlorophenoxy)acetic acid



Following the general method as outlined in Example 148, starting from *tert*-butyl (2-{[4-(acetylamino)phenyl]ethynyl}-4-chlorophenoxy)acetate (Intermediate 225), the title compound was obtained as a white solid after purification by preparative HPLC. ^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.15 (1H, bs), 10.15 (1H, s), 7.64 (2H, d, *J*= 8.7 Hz), 7.52 (1H, d, *J*= 2.7 Hz), 7.47 (2H, d, *J*= 8.7 Hz), 7.38 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 6.98 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 2.07 (3H, s). MS (ESI$^-$): 342.1. HPLC (Condition A): Rt 3.65 min (HPLC purity 99.9%).

Example 153: (2-{[4-(acetylamino)-2-methyl-5-(propylsulfonyl)phenyl]ethynyl}-4-chlorophenoxy)acetic acid

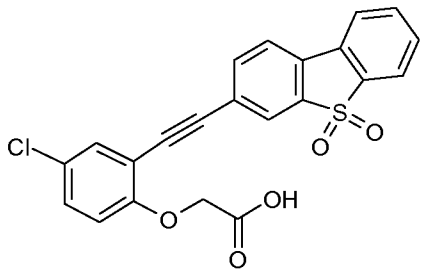


Following the general method as outlined in Example 15, starting from *tert*-butyl (2-{[4-(acetylamino)-2-methyl-5-(propylsulfonyl)phenyl]ethynyl}-4-chlorophenoxy)acetate

(Intermediate 231), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.20 (1H, bs), 9.62 (1H, s), 8.12 (1H, s), 7.89 (1H, s), 7.64 (1H, d, *J*= 2.7 Hz), 7.42 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.02 (1H, d, *J*= 9.0 Hz), 4.823 (2H, s), 3.37 (2H, m), 2.54 (3H, s), 2.15 (3H, s), 1.57 (2H, sext., *J*= 7.5 Hz), 0.93 (3H, t, *J*= 7.5 Hz). MS (ESI$^-$): 462.2. HPLC (Condition A): Rt 4.51 min (HPLC purity 97.9%).

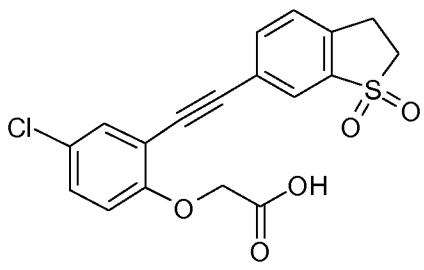
Example 154: {4-chloro-2-[(5,5-dioxidodibenzo[b,d]thien-3-yl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl {4-chloro-2-[(5,5-dioxidodibenzo[b,d]thien-3-yl)ethynyl]phenoxy}acetate (Intermediate 233), the title compound was obtained as a beige solid in 73% yield after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.21 (1H, bs), 8.27 (2H, m), 8.17 (1H, d, *J*= 1.4 Hz), 8.03 (1H, d, *J*= 7.6 Hz), 7.95 (1H, dd, *J*= 8.0 Hz, *J*= 1.4 Hz), 7.84 (1H, dt, *J*= 7.6 Hz, *J*= 1.0 Hz), 7.69 (1H, dt, *J*= 7.6 Hz, *J*= 1.0 Hz), 7.65 (1H, d, *J*= 2.7 Hz), 7.46 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.86 (2H, s). MS (ESI$^-$): 423.0. HPLC (Condition A): Rt 4.56 min (HPLC purity 100%).

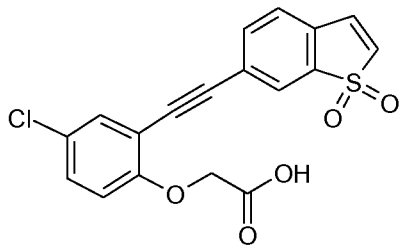
Example 155: {4-chloro-2-[(1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl {4-chloro-2-[(1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetate (Intermediate 235), the title compound was obtained as a beige solid in 93% yield after trituration in DCM / pentane.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.17 (1H, bs), 7.90 (1H,m), 7.80 (1H, dd, *J*= 8.0 Hz, *J*= 1.5 Hz), 7.60-7.63 (2H, m), 7.43 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.02 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 3.65 (2H, t, *J*= 6.8 Hz), 3.40 (2H, t, *J*= 6.8 Hz). MS (ESI$^-$): 375.0. HPLC (Condition A): Rt 3.89 min (HPLC purity 97.8%).

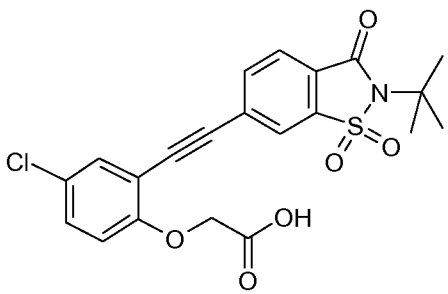
Example 156: {4-chloro-2-[(1,1-dioxido-1-benzothien-6-yl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl {4-chloro-2-[(1,1-dioxido-1-benzothien-6-yl)ethynyl]phenoxy}acetate (Intermediate 237), the title compound was obtained as a beige solid in 82% yield.

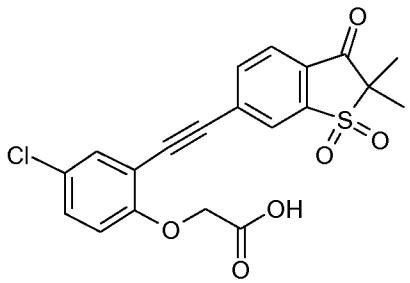
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.19 (1H, bs), 8.04 (1H, m), 7.83 (1H, dd, *J*= 7.9 Hz, *J*= 1.4 Hz), 7.65-7.70 (2H, m), 7.63 (1H, d, *J*= 2.7 Hz), 7.49 (1H, d, *J*= 7.0 Hz), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.85 (2H, s). MS (ESI$^-$): 373.0. HPLC (Condition A): Rt 4.03 min (HPLC purity 94.8%).

Example 157: {2-[(2-*tert*-butyl-1,1-dioxido-3-oxo-2,3-dihydro-1,2-benzisothiazol-6-yl)ethynyl]-4-chlorophenoxy}acetic acid



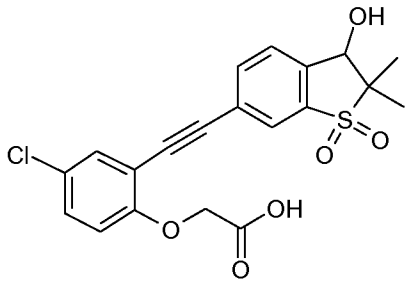
A mixture of (4-chloro-2-ethynylphenoxy)acetic acid (Intermediate 238; 211 mg; 1.00 mmol), 6-bromo-2-*tert*-butyl-1,2-benzisothiazol-3(2*H*)-one-1,1-dioxide (prepared as described in *Tetrahedron,* **2006**, *62*, 7902-7910, 382 mg; 1.20 mmol), dichlorobis(triphenylphosphine)palladium(II) (70 mg; 0.10 mmol) and cuprous iodide (9.5 mg; 0.05 mmol) in anhydrous THF (4 ml) was degassed for 10 minutes then treated with triethylamine (1.00 ml; 7.21 mmol) and the mixture stirred at 60 °C for 16 h.
EtOAc was added and the organic phase washed with a sat. NH_4Cl solution then brine. The organic phase was dried on $MgSO_4$, filtered and concentrated under reduced pressure to give a residue which was purified by preparative HPLC to afford the title compound as a white solid.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.2 (1H, bs), 8.42 (1H, t, *J*= 0.9 Hz), 8.09-8.02 (2H, m), 7.67 (1H, d, *J*= 2.7 Hz), 7.48 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.06 (1H, d, *J*= 9.0 Hz), 4.87 (2H, s), 1.70 (9H, s). MS (ESI$^-$): 446.1. HPLC (Condition A): Rt 4.86 min (HPLC purity 96.6%).

Example 158: {4-chloro-2-[(2,2-dimethyl-1,1-dioxido-3-oxo-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl {4-chloro-2-[(2,2-dimethyl-1,1-dioxido-3-oxo-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetate (Intermediate 243), the title compound was obtained as a yellow solid in 97% yield.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.2 (brs, 1H), 8.38 (m, 1H), 8.11-8.03 (m, 2H), 7.69 (d, *J*= 2.7 Hz, 1H), 7.49 (dd, *J*= 9 - 2.7 Hz, 1H), 7.06 (d, *J*= 9 Hz, 1H), 4.87 (s, 2H), 1.52 (s, 6H). MS (ESI$^-$): 417.1. HPLC (Condition A): Rt 4.53 min (HPLC purity 95.6%).

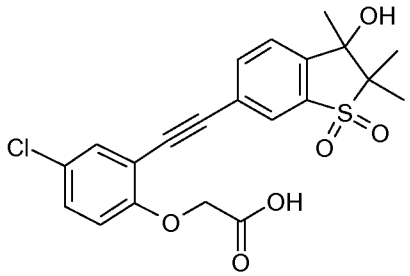
Example 159: {4-chloro-2-[(3-hydroxy-2,2-dimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl {4-chloro-2-[(3-hydroxy-2,2-dimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetate (Intermediate 245), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.2 (brs, 1H), 7.94 (m, 1H), 7.86 (dd, *J*= 8 - 1.5 Hz, 1H), 7.69 (d, *J*= 8 Hz, 1H), 7.62 (d, *J*= 2.7 Hz, 1H), 7.44 (dd, *J*= 2.7 - 9 Hz, 1H), 7.01 (d, *J*= 9 Hz, 1H), 6.58 (brs, 1H), 4.96 (s, 1H), 4.82 (s, 2H), 1.42 (s, 3H), 1.13 (s, 3H). MS (ESI$^-$): 419.2. HPLC (Condition A): Rt 3.89 min (HPLC purity 99.8%).

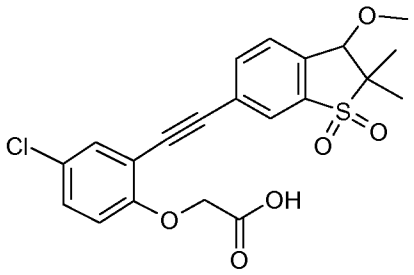
Example 160: {4-chloro-2-[(3-hydroxy-2,2,3-trimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl {4-chloro-2-[(3-hydroxy-2,2,3-trimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetate (Intermediate 247), the title compound was obtained as a yellow solid after purification by preparative HPLC and precipitation from pentane.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.24 – 13.18 (brs, 1H), 7.95 – 7.82 (m, 2H), 7.75 (d, *J*= 8.0, 1H), 7.62 (d, *J*= 2.7, 1H), 7.44 (dd, *J*= 9.0, 2.7, 1H), 7.02 (d, *J*= 9.0, 1H), 6.12 (brs, 1H), 4.83 (s, 2H), 1.48 (s, 3H), 1.34 (s, 3H), 1.21 (s, 3H). MS (ESI$^-$): 433.2. HPLC (Condition A): Rt 3.98 min (HPLC purity 100%).

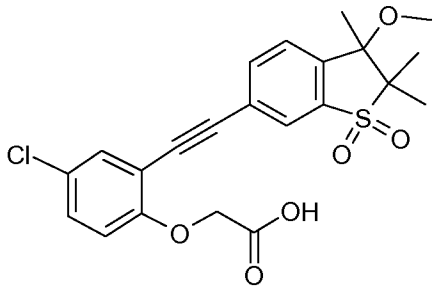
Example 161: {4-chloro-2-[(3-methoxy-2,2-dimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl {4-chloro-2-[(3-methoxy-2,2-dimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetate (Intermediate 249), the title compound was obtained as a yellow solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.97 (brs, 1H), 7.87 (dd, *J*= 1.3, 7.8 Hz, 1H), 7.74 (d, *J*= 8.1 Hz, 1H), 7.61 (d, *J*= 2.8 Hz, 1H), 7.43 (dd, *J*= 2.8, 8.9 Hz, 1H), 7.00 (d, *J*= 8.9 Hz, 1H), 4.80 (s, 2H), 4.76 (s, 1H), 3.56 (s, 3H), 1.42 (s, 3H), 1.27 (s, 3H). MS (ESI$^-$): 433.2. HPLC (Condition A): Rt 4.84 min (HPLC purity 100%).

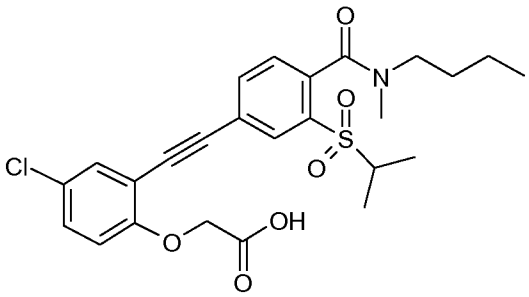
Example 162: {4-chloro-2-[(3-methoxy-2,2,3-trimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl {4-chloro-2-[(3-methoxy-2,2,3-trimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetate (Intermediate 251), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.01 (brs, 1H), 7.97 (d, *J*= 1.2 Hz, 1H), 7.87 (dd, *J*= 1.4, *J*= 8.0 Hz, 1H), 7.82 (d, *J*= 8.1 Hz, 1H), 7.62 (d, *J*= 2.6 Hz, 1H), 7.43 (dd, *J*= 2.6, *J*= 8.9 Hz, 1H), 7.02 (d, *J*= 9.1 Hz, 1H), 4.84 (s, 2H), 3.06 (s, 3H), 1.55 (s, 3H), 1.34 (s, 3H), 1.24 (s, 3H). MS (ESI$^-$): 447.2. HPLC (Condition A): Rt 4.91 min (HPLC purity 99.7%). m.p. = 80-95°C.

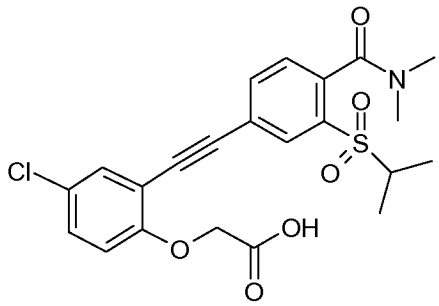
Example 163: (2-{[4-{[butyl(methyl)amino]carbonyl}-3-(isopropylsulfonyl)phenyl]ethynyl}-4-chlorophenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (2-{[4-{[butyl(methyl)amino]carbonyl}-3-(isopropylsulfonyl)phenyl]ethynyl}-4-chlorophenoxy)acetate (Intermediate 254), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.20 (1H, bs), 7.98 (1H, m), 7.93 (1H, *J*= 7.9 Hz, *J*= 1.6 Hz), 7.68 (1H, d, *J*= 2.7 Hz), 7.55 (1H, m), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.02 (1H, d, *J*= 9.0 Hz), 4.85 (2H, s), 3.75 (1H, sept., *J*= 6.9 Hz), 3.43 (1.3H, m), 2.95 (0.7H, m), 2.95 (1.2H, s), 2.72 (1.8H, s), 1.05-1.59 (10H, m), 0.93 (1.8H, t, *J*= 7.3 Hz), 0.74 (1.2H, t, *J*= 7.3 Hz) (high-temperature NMR experiment gave evidence of presence of rotamers). MS (ESI$^-$): 504.2. HPLC (Condition A): HPLC purity 99.0%.

Example 164: (4-chloro-2-{[4-[(dimethylamino)carbonyl]-3-(isopropylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid

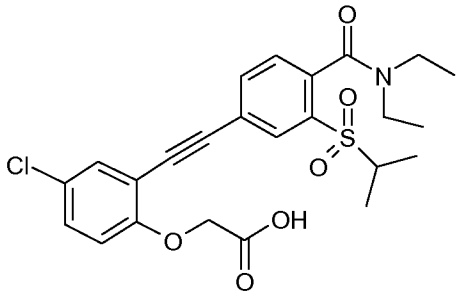


Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[4-[(dimethylamino)carbonyl]-3-(isopropylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 256), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.20 (1H, bs), 7.98 (1H, d, *J*= 1.6 Hz), 7.93 (1H, dd, *J*= 7.8 Hz; *J*= 1.6 Hz), 7.68 (1H, d, *J*= 2.7 Hz), 7.57 (1H, d, *J*= 7.8 Hz), 7.45 (1H, dd,

J= 9.0 Hz, *J*= 2.7 Hz), 7.01 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 3.72 (1H, sept., *J*= 6.9 Hz), 2.98 (3H, s), 2.73 (3H, s), 1.29 (3H, m), 1.05 (3H, m). MS (ESI^-): 432.2. HPLC (Condition A): Rt 3.95 min (HPLC purity 100%). CHN analysis: [$C_{22}H_{22}NO_6ClS$ + 0.15 CH_2Cl_2 +0.5 H_2O] Calculated: C 54.78%,H 4.85%,N 2.87%; Found: C 54.73%,H 4.88%,N 2.98%.

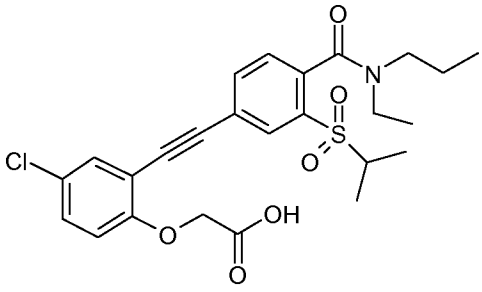
Example 165: (4-chloro-2-{[4-[(diethylamino)carbonyl]-3-(isopropylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[4-[(diethylamino)carbonyl]-3-(isopropylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 258), the title compound was obtained as a white solid in 76% yield after purification by preparative HPLC.

^1H NMR (300MHz, DMSO-d_6) δ [ppm] 13.19 (1H, bs), 7.97 (1H, d, *J*= 1.6 Hz), 7.92 (1H, dd, *J*= 7.8 Hz, *J*= 1.6 Hz), 7.68 (1H, d, *J*= 2.7 Hz), 7.57 (1H, d, *J*= 7.8 Hz), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.02 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 3.75 (1H, sept., *J*= 6.9 Hz), 3.58 (1H, m), 3.30 (1H, m), 2.94-3.12 (2H, m), 1.29 (3H, d, *J*= 6.9 Hz), 1.14 (3H, t, *J*= 7.1 Hz), 1.05 (3H, d, *J*= 6.9 Hz), 1.03 (3H, t, *J*= 7.1 Hz). MS (ESI^-): 490.3. HPLC (Condition A): Rt 4.88 min (HPLC purity 99.9%). CHN analysis: [$C_{24}H_{26}NO_6ClS$ + 0.5 H_2O] Calculated: C 57.31%,H 5.43%,N 2.77%; Found: C 57.27%,H 5.32%,N 3.00%.

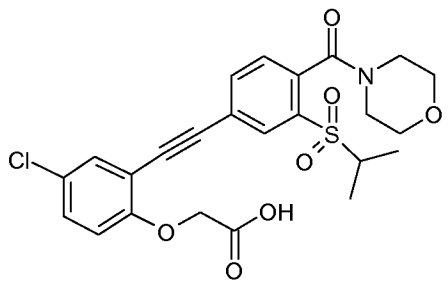
Example 166: (4-chloro-2-{[4-{[ethyl(propyl)amino]carbonyl}-3-(isopropylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[4-{[ethyl(propyl)amino]carbonyl}-3-(isopropylsulfonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 260), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.27 (1H, bs), 7.97 (1H, m), 7.94 (1H, dd, *J*= 7.8 Hz, *J*= 1.6 Hz), 7.68 (1H, d, *J*= 2.7 Hz), 7.56 (1H, m), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.01 (1H, d, *J*= 9.0 Hz), 4.85 (2H, s), 3.73 (1H, m), 3.59 (0.5H, m), 3.44 (0.5H, m), 3.26 (1H, m), 2.79-3.13 (2H, m), 1.40-1.65 (2H, m), 1.28 (3H, d, *J*= 7.0 Hz), 1.13 (1.5H, t, *J*= 7.0 Hz), 1.04 (3H, d, *J*= 7.0 Hz), 1.02 (1.5H, t, *J*= 7.0 Hz), 0.93 (1.5H, t, *J*= 7.0 Hz), 0.69 (1.5H, t, *J*= 7.0 Hz). (high-temperature NMR experiment gave evidence of presence of rotamers) MS (ESI$^-$): 504.3. HPLC (Condition A): Rt 4.72 min (HPLC purity 99.3%). CHN analysis: [$C_{25}H_{28}NO_6ClS$ + 0.2 H_20] Calculated: C 58.70%,H 5.60%,N 2.76%; Found: C 58.49%,H 5.35%,N 2.85%.

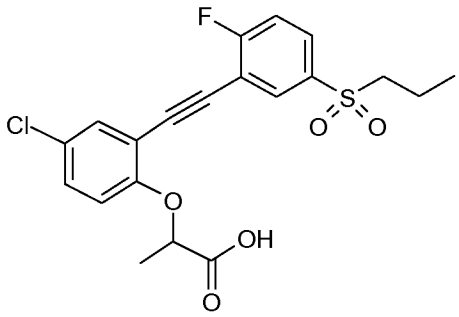
Example 167: (4-chloro-2-{[3-(isopropylsulfonyl)-4-(morpholin-4-ylcarbonyl)phenyl]ethynyl}phenoxy)acetic acid



Following the general method as outlined in Example 15, starting from *tert*-butyl (4-chloro-2-{[3-(isopropylsulfonyl)-4-(morpholin-4-ylcarbonyl)phenyl]ethynyl}phenoxy)acetate (Intermediate 262), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.25 (1H, bs), 7.98 (1H, d, *J*= 1.6 Hz), 7.94 (1H, dd, *J*= 7.8 Hz, *J*= 1.6 Hz), 7.68 (1H, d, *J*= 2.7 Hz), 7.61 (1H, d, *J*= 7.8 Hz), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.01 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 3.53-3.77 (6H, m), 3.02-3.21 (2H, m), 1.30 (3H, d, *J*= 6.8 Hz), 1.07 (3H, d, *J*= 6.8 Hz) (1 remaining proton, probably hidden under the signal of water). MS (ESI$^-$): 504.2. HPLC (Condition A): Rt 3.96 min (HPLC purity 99.7%).

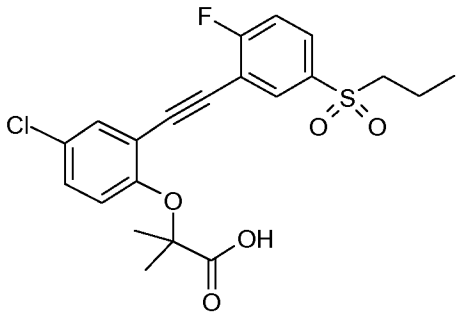
Example 168: 2-(4-chloro-2-{[2-fluoro-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)propanoic acid



A solution of methyl 2-(2-bromo-4-chlorophenoxy)propanoate (Intermediate 263 ; 130 mg; 0.44 mmol), 2-ethynyl-1-fluoro-4-(propane-1-sulfonyl)-benzene (Intermediate 109 ; 110 mg; 0.49 mmol),bis(triphenylphosphine)palladium (II) chloride (9.3 mg; 0.01 mmol), triphenylphosphine (23.2 mg; 0.09 mmol) and cuprous iodide (2.5 mg; 0.01 mmol) in TEA (985 µl) was degassed with nitrogen. The reaction mixture was heated overnight at 80 °C, diluted with EtOAc and washed with sat. ammonium chloride solution and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated to dryness affording a dark brown sticky solid, which was purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc. The intermediate thus obtained was dissolved in a mixture of dioxane (2.6 ml) and water (2.6 ml) and treated with a 4 N solution of HCl in dioxane (1.33 ml). After heating at 100 °C for 16 hours, water was added and the reaction mixture was extrated 3 times with EtOAC. The organic phase was dried over $MgSO_4$, filtered and concentrated to dryness affording a yellow sticky solid, which was triturated in diethylether / pentane to afford the title compound as a white solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.27 (1H, bs), 8.10 (1H, dd, *J*= 6.5 Hz, *J*= 2.3 Hz), 7.98 (1H, m), 7.63-7.69 (2H, m), 7.47 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 6.95 (1H, d, *J*= 9.0 hz), 4.96 (1H, q, *J*= 6.8 Hz), 3.38 (2H, m), 1.50-1.63 (5H, m), 0.93 (3H, t, *J*= 7.5 Hz). MS (ESI$^-$): 423.1. HPLC (Condition A): Rt 4.66 min (HPLC purity 91.9%).

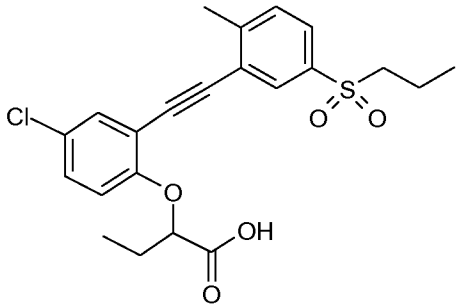
Example 169: 2-(4-chloro-2-{[2-fluoro-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)-2-methylpropanoic acid



Following the general method as outlined in Example 168, starting from 2-(2-bromo-4-chlorophenoxy)-2-methylpropanoate (Intermediate 264), and 2-ethynyl-1-fluoro-4-(propane-1-sulfonyl)-benzene (Intermediate 109) the title compound was obtained as a brown sticky solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.41 (1H, bs), 8.11 (1H, dd, *J*= 6.5 Hz, *J*= 2.4 Hz), 7.98 (1H, ddd, *J*= 8.8 Hz, *J*= 4.7 Hz, *J*= 2.4 Hz), 7.63-7.69 (2H, m), 7.457 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 6.91 (1H, d, *J*= 9.0 Hz), 3.37 (2H, m), 1.51-1.60 (8H, m), 0.93 (3H, t, *J*= 7.4 Hz). MS (ESI$^-$): 437.1. HPLC (Condition A): Rt 4.81 min (HPLC purity 98.9%).

Example 170: 2-(4-chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)butanoic acid

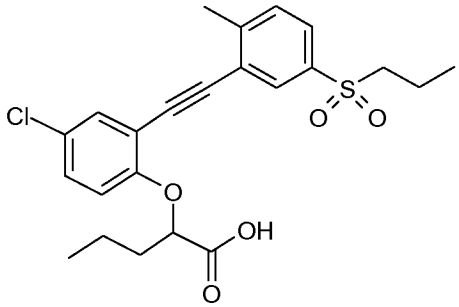


A solution of ethyl 2-(4-chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)butanoate (Intermediate 268; 100 mg; 0.11 mmol) in EtOH (1 ml) was treated with a 1M solution of sodium hydroxide in water (0.16 ml; 0.16 mmol). After stirring at 70 °C for 45 minutes, a 1 N solution of HCl in water (65 µl) was added, the solvents removed under reduced pressure and the residue purified by preparative HPLC to afford the title compound as a beige solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.94 (1H, d, *J*= 2.0 Hz), 7.80 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.65 (1H, d, *J*= 2.7 Hz), 7.62 (1H, d, *J*= 8.0 Hz), 7.42 (1H, dd, *J*= 9.0 Hz, *J*= 2.0 Hz), 6.92 (1H, d, *J*= 9.0 Hz), 4.78 (1H, t, *J*= 5.7 Hz), 2.58 (3H, s), 1.94 (2H, m), 1.54 (2H, sext., *J*= 7.5 Hz), 1.04 (3H, t, *J*= 7.5 Hz), 0.91 (3H, t, *J*= 7.5 Hz) (2 remaining

protons, probably hidden under the peak of water). MS (ESI$^-$): 433.2. HPLC (Condition A): Rt 4.98 min (HPLC purity 98.4%).

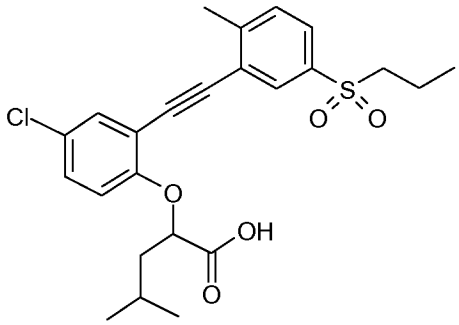
Example 171: 2-(4-chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)pentanoic acid



Following the general method as outlined in Example 170, starting from ethyl 2-(4-chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)pentanoate (Intermediate 269), the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.28 (1H, bs), 7.94 (1H, d, *J*= 2.0 Hz), 7.80 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.65 (1H, d, *J*= 2.7 Hz), 7.63 (1H, d, *J*= 8.0 Hz), 7.43 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 6.92 (1H, d, *J*= 9.0 Hz), 4.85 (1H, t, *J*= 5.8 Hz), 3.30 (2H, m), 2.58 (3H, s), 1.86-1.94 (2H, m), 1.49-1.63 (4H, m), 0.89-0.95 (6H, m). MS (ESI$^-$): 447.2. HPLC (Condition A): Rt 5.69 min (HPLC purity 99.7%).

Example 172: 2-(4-chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)-4-methylpentanoic acid

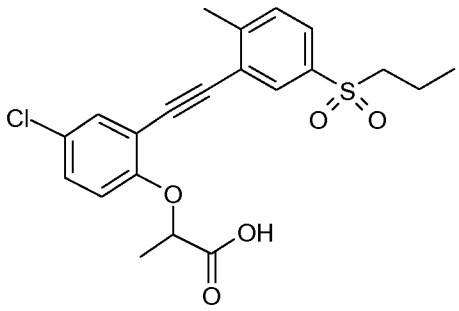


Following the general method as outlined in Example 170, starting from ethyl 2-(4-chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)-4-methylpentanoate

(Intermediate 270), the title compound was obtained as a beige solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.25 (1H, bs), 7.93 (1H, d, *J*= 2.0 Hz), 7.80 (1H, dd, *J*= 8.0 hz, *J*= 2.0 Hz), 7.66 (1H, d, *J*= 2.7 Hz), 7.63 (1H, d, *J*= 8.0 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 6.96 (1H, d, *J*= 9.0 Hz), 4.86 (1H, dd, *J*= 9.0 Hz, *J*= 3.7 Hz), 3.29 (2H, m), 2.58 (3H, s), 1.84-1.99 (2H, m), 1.66-1.77 (1H, m), 1.54 (2H, sext., *J*= 7.5 Hz), 0.89-0.97 (9H, m). MS (ESI$^-$): 461.2. HPLC (Condition A): Rt 5.42 min (HPLC purity 98.5%).

Example 173: 2-(4-chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)propanoic acid



A solution of 4-chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenol (150 mg; 0.43 mmol) and methyl-2-bromopropionate (53 µl; 0.47 mmol) in DME (3 ml) was treated with K_2CO_3 (89 mg, 69 mmol) and heated at 70 °C for 4.5 hours. The reaction mixture was filtered and the filtrate was concentrated affording a sticky solid, which was dissolved in MeOH (1.5 ml) and treated with a 1 N solution of NaOH in water (129 µl) and the micture heated for 1 hour at 70 °C. A 5 N solution of HCl in water (52 µl) was added and the solvents removed under reduced pressure, to give a residue which was purified by preparative HPLC to give the title compound as a white solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 13.26 (1H, bs), 7.95 (1H, d, *J*= 2.0 Hz), 7.80 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.65 (1H, d, *J*= 2.7 Hz), 7.63 (1H, d, *J*= 8.0 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 6.95 (1H, d, *J*= 9.0 Hz), 4.98 (1H, q, *J*= 6.7 Hz), 3.32 (2H, m), 2.59 (3H, s), 1.49-1.62 (5H, m), 0.92 (3H, t, *J*= 7.5 Hz). MS (ESI$^-$): 418.9. HPLC (Condition A): Rt 5.23 min (HPLC purity 98.6%).

Example 174: Preparation of hCRTH2-CHO expressing cell membranes

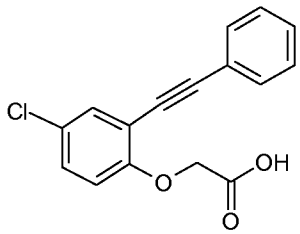
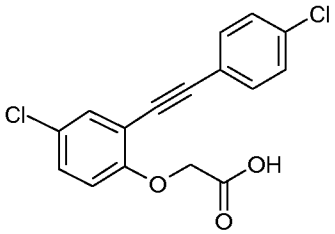
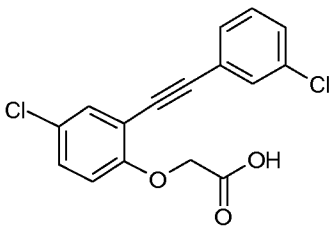
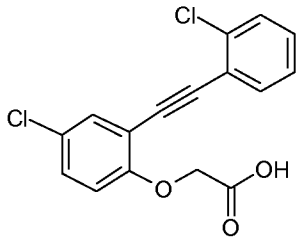
Adherent CHO cells expressing hCRTH2 (Euroscreen, Belgium) were cultured in 225 cm^2 cell culture flasks (Corning, USA) in 30ml of medium. After two rinses of phosphate buffered saline (PBS), cells were harvested in 10ml of PBS containing 1mM EDTA, centrifuged at 500 x g for 5 min at 4°C and frozen at –80°C. The pellet was re-suspended in 50 mM Tris-HCl, pH 7.4, 2mM EDTA, 250mM Sucrose, containing protease inhibitor cocktail tablets, (Complete EDTA-free, Roche, Germany) and incubated 30 min at 4°C. Cells were disrupted by nitrogen cavitation (Parr Instruments, USA) at 4°C (800 p.s.i. for 30 min), and centrifuged at 500 x g for 10min at 4°C. Pellet containing nuclei and cellular debris was discarded and supernatant was centrifuged 60 min at 4°C at 45000 x g. Membrane pellet was re-suspended in storage buffer (10mM HEPES/KOH pH 7.4, 1mM EDTA, 250mM sucrose, protease inhibitor cocktail tablets) using Dounce homogenization and frozen in liquid nitrogen, and stored at –80°C.

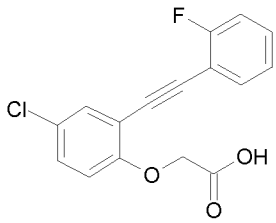
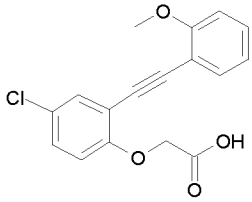
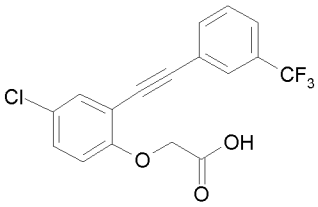
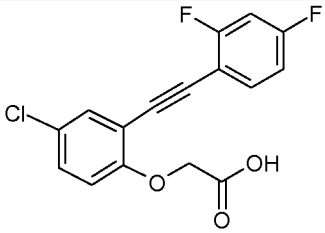
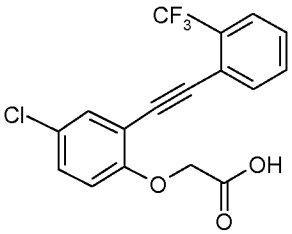
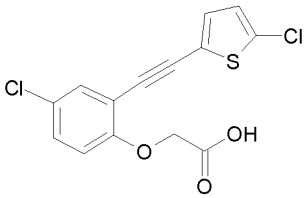
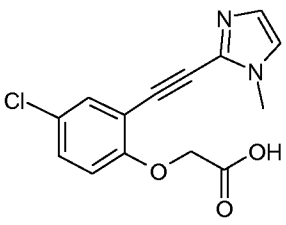
Example 175: Radioligand binding assay

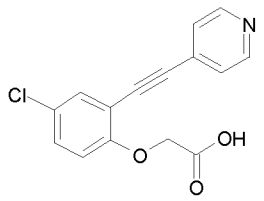
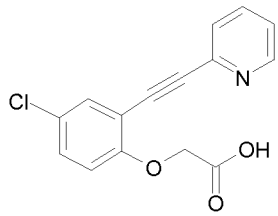
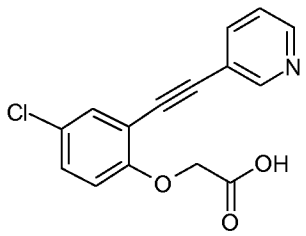
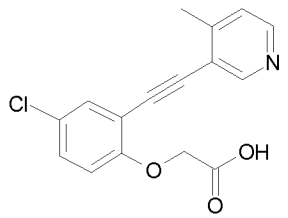
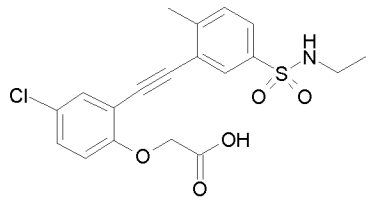
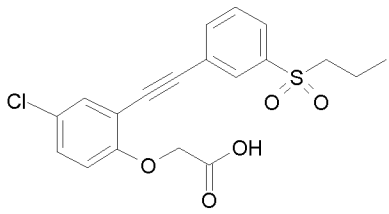
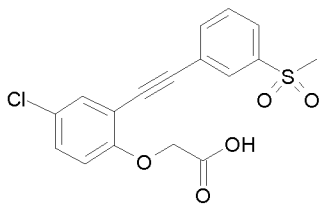
The compounds of the present invention inhibit the binding of PGD2 to its receptor CRTH2. The inhibitory activity can be investigated by a radioligand binding Scintillation Proximity Assay (SPA) (Sawyer et al., Br. J. Pharmocol 2002, 137, 1163-72). The SPA radioligand binding assay was performed at room temperature in binding buffer (10mM HEPES/KOH pH 7.4, 10mM $MnCl_2$, with protease inhibitor cocktail tablets), containing 1.5nM [^{3}H]PGD_2 (Perkin Elmer), 10-50µg/ml of hCRTH2-CHO cell membrane protein and 2mg/ml of Wheat-germ agglutinin Sintillation Proximity Assay beads (RPNQ0001, GE-Healthcare) in a final volume of 100µl in 96 well plates (Corning, USA). Non-specific binding was determined in the presence of 10µM PGD_2 (Cayman, USA). Competing Compounds of Formula (I) were diluted in dimethylsulphoxide so that the total volume of dimethylsulfoxide was kept constant at 1% dimethylsulphoxide (Me_2SO). Serial dilutions of 100µM to 100 pM were prepared and 10 µl each of the compounds of Formula (I) stock solutions were added to the binding assay reagents and incubated for 90 min with agitation at room temperature. Binding activity was determined by using a 1450 Micro-beta scintillation counter (Wallac, UK).

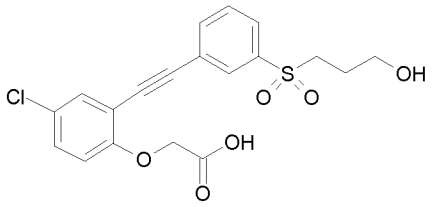
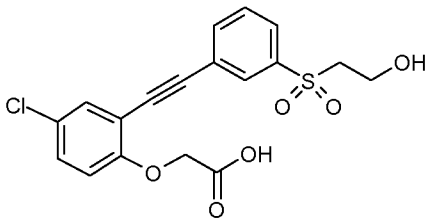
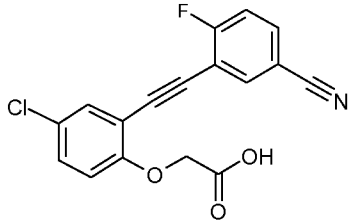
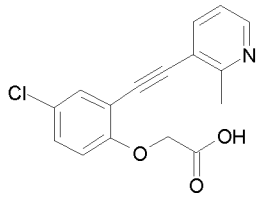
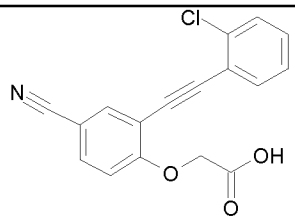
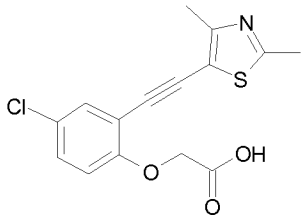
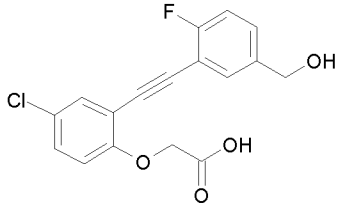
In one embodiment, the compounds of Formula (I) of the present invention inhibit CRTH2 at a concentration of <5μM. In another embodiment, the compounds of Formula (I) of the present invention inhibit CRTH2 at a concentration of <1μM. In a preferred embodiment, the compounds of Formula (I) of the present invention inhibit CRTH2 at a concentration of <0.1μM.

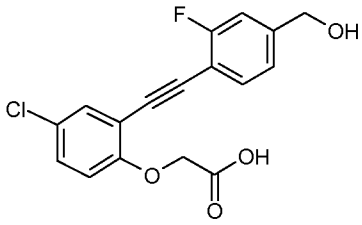
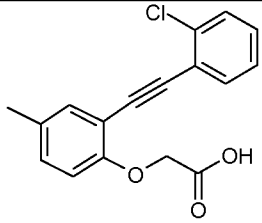
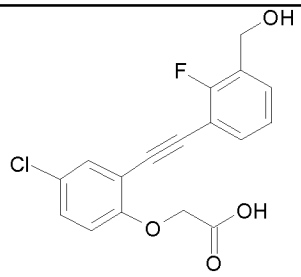
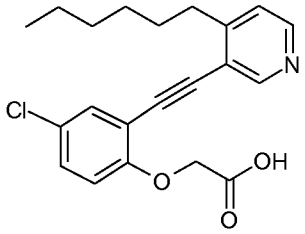
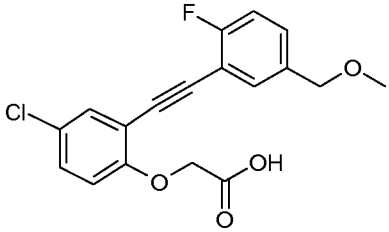
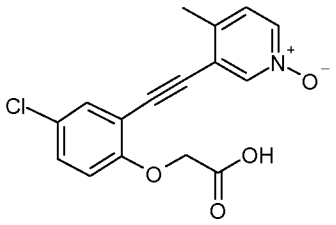
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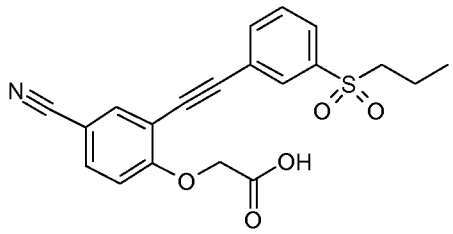
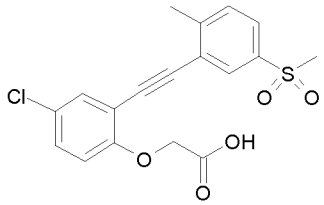
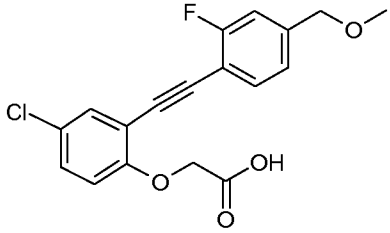
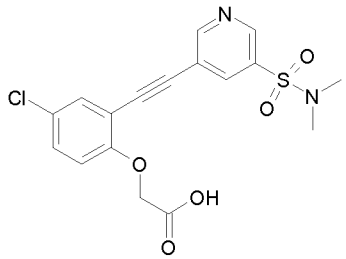
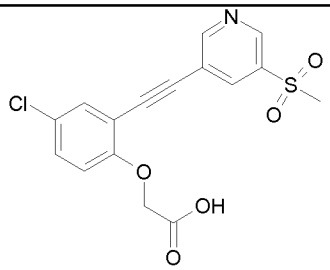
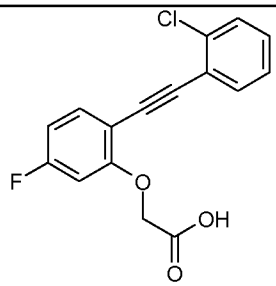
Example	Formula	IC50 binding (μM)
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2		0.091
3		0.026
4		0.015

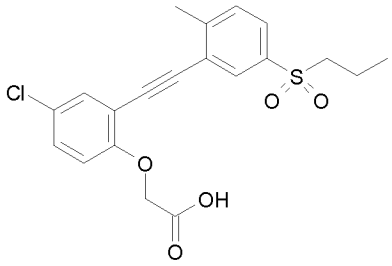
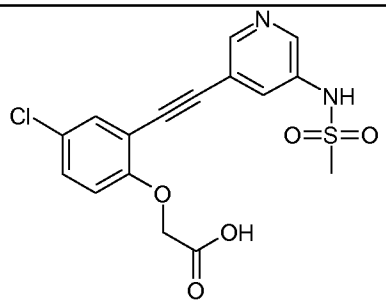
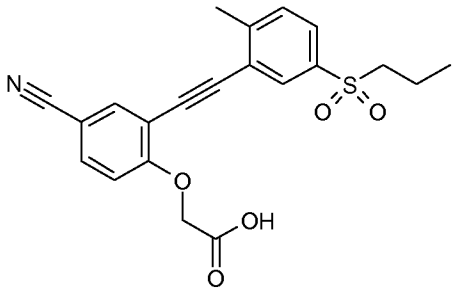
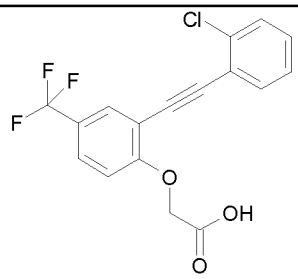
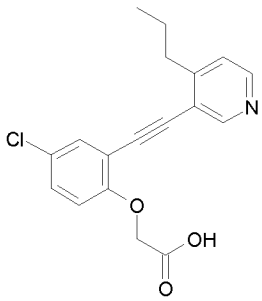
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6		0.229
7		0.111
8		0.123
9		0.030
10		0.267
11		1.765

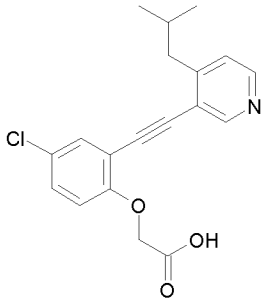
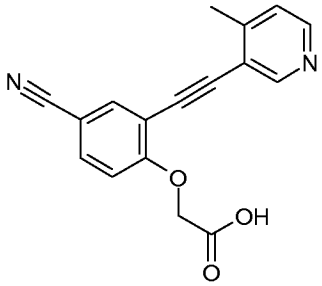
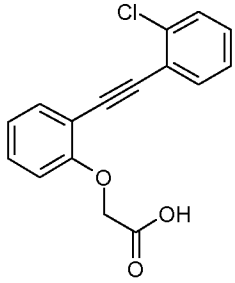
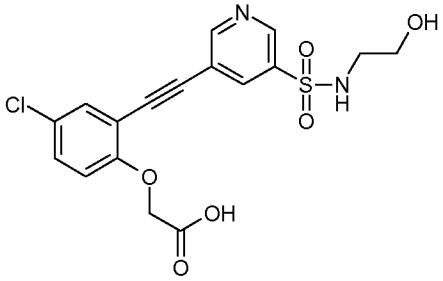
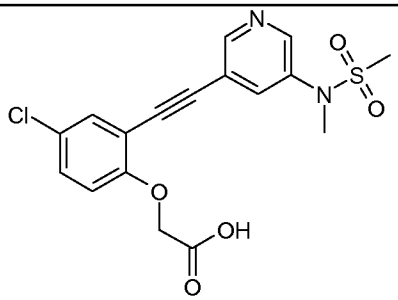
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13		1.445
14		0.146
15		0.030
16		0.006
17		0.010
18		0.019

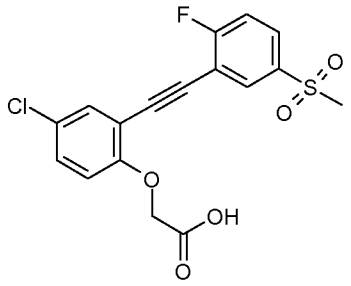
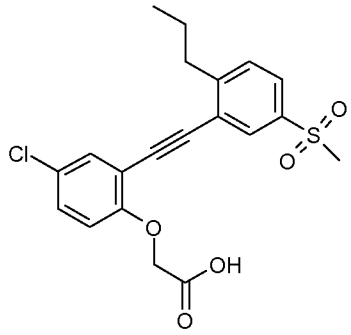
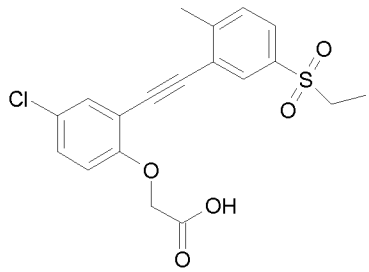
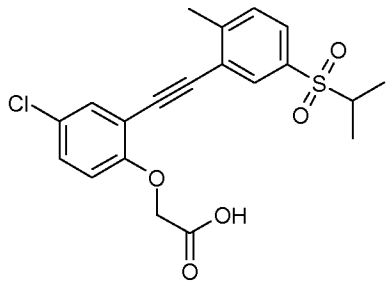
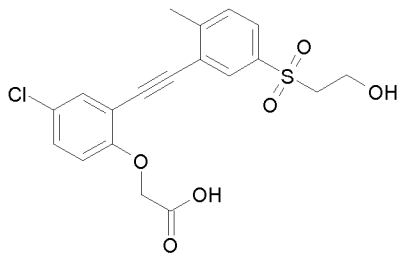
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21		0.046
22		0.175
23		0.030
24		0.102
25		0.089

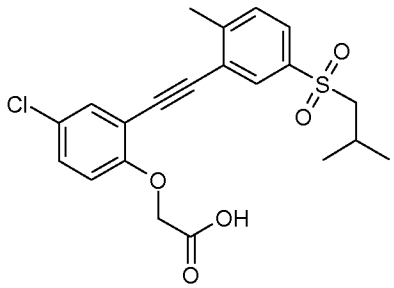
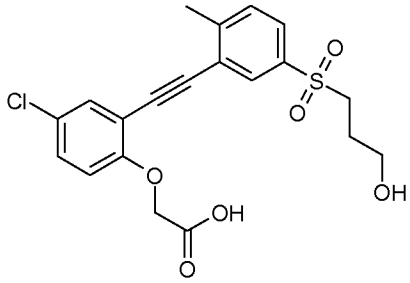
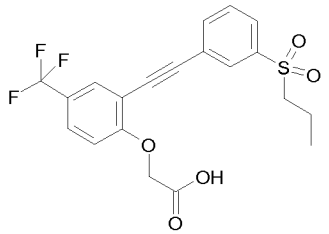
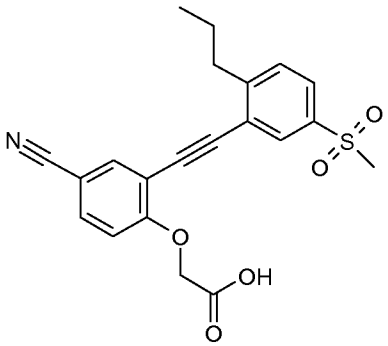
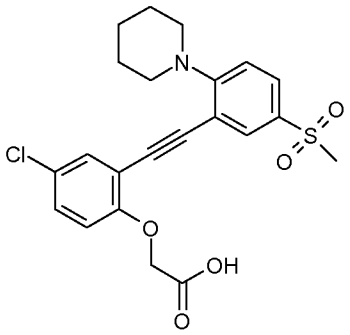
26		0.028
27		0.346
28		0.048
29		0.051
30		0.085
31		0.019

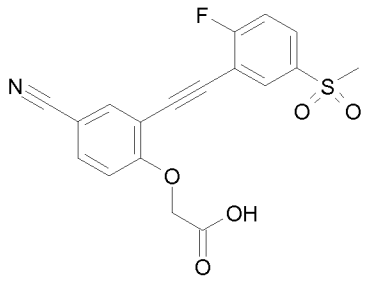
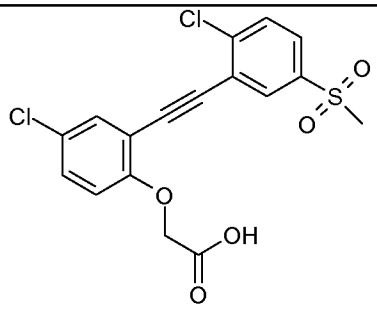
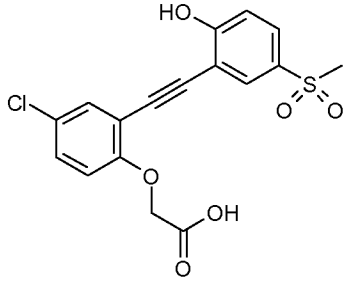
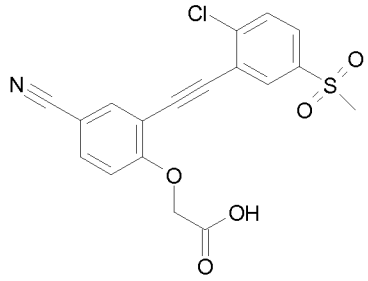
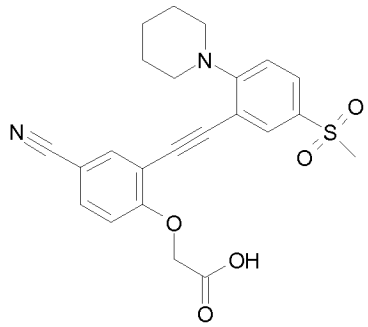
32		0.025
33		0.009
34		0.026
35		0.055
36		0.075
37		5.94

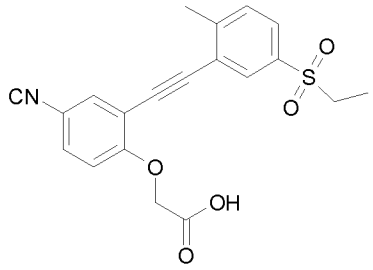
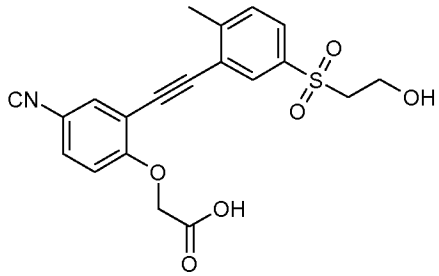
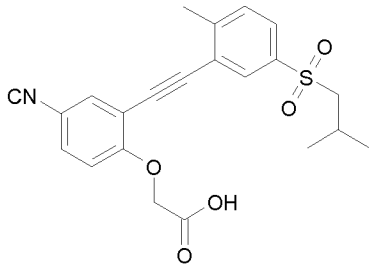
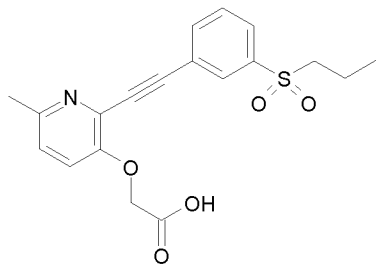
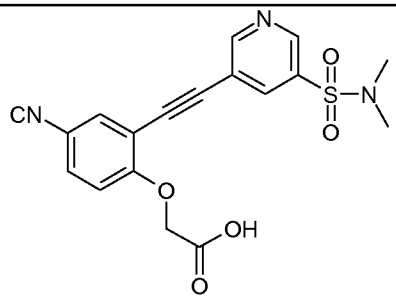
38		0.005
39		0.023
40		0.009
41		0.015
42		0.005

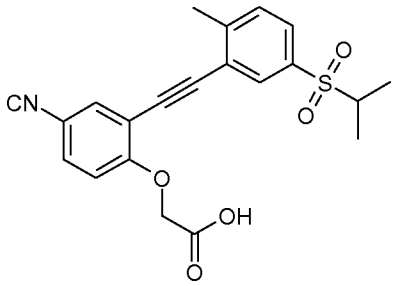
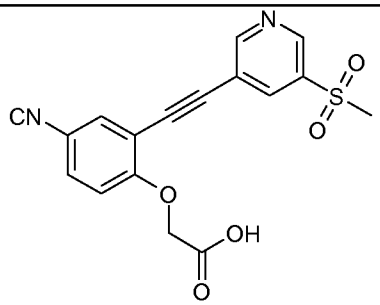
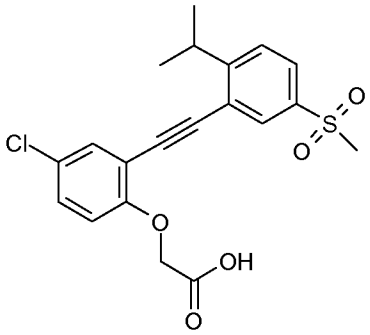
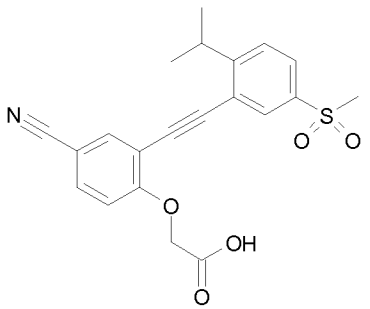
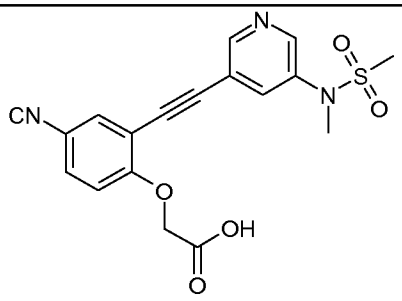
43		0.006
44		0.06
45		0.958
46		0.323
47		0.34

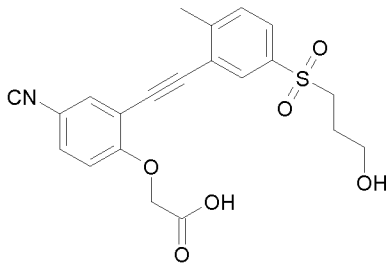
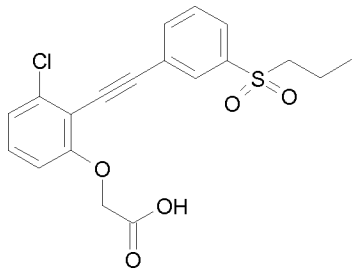
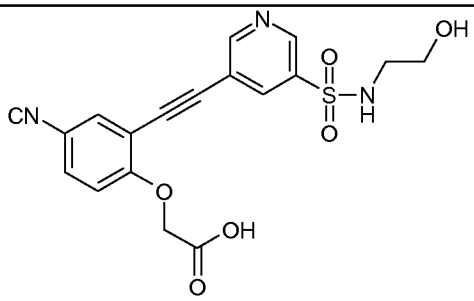
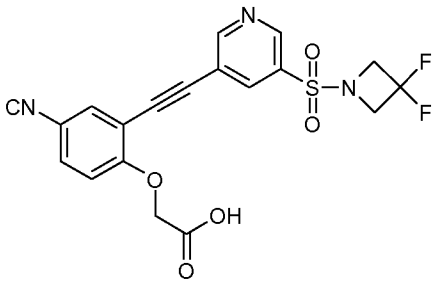
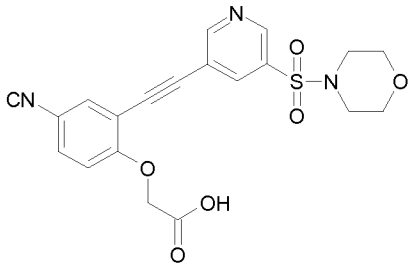
48		0.009
49		0.011
50		0.011
51		0.008
52		0.025

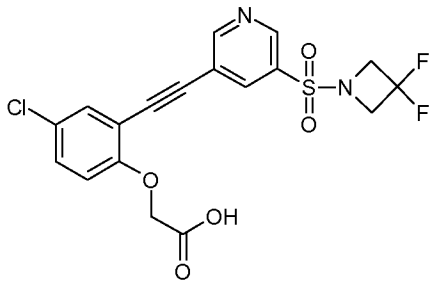
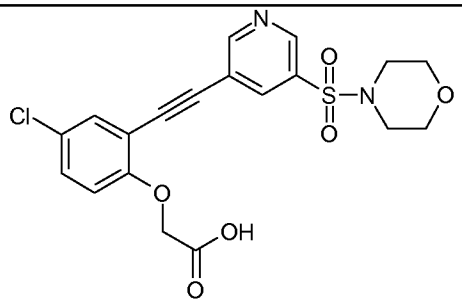
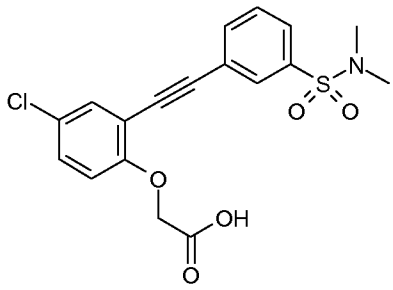
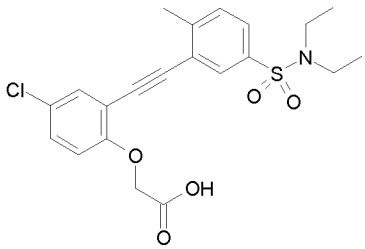
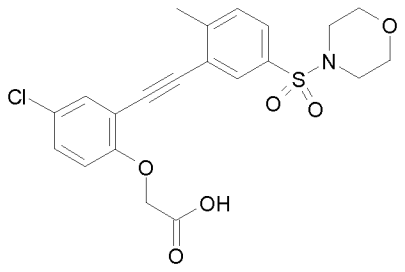
53		0.005
54		0.01
55		0.013
56		0.03
57		0.28

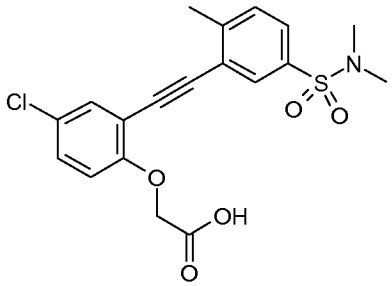
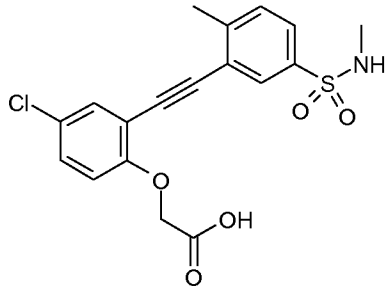
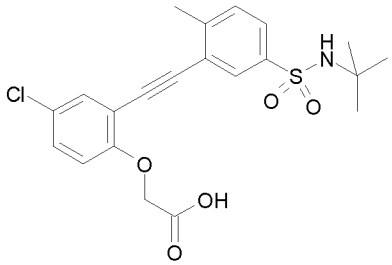
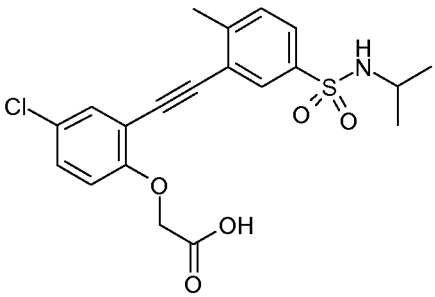
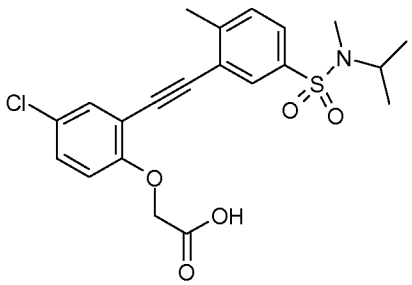
58		0.014
59		0.006
60		0.296
61		0.008
62		0.202

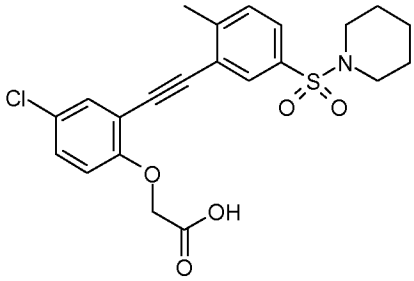
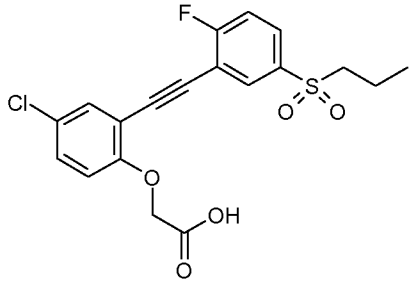
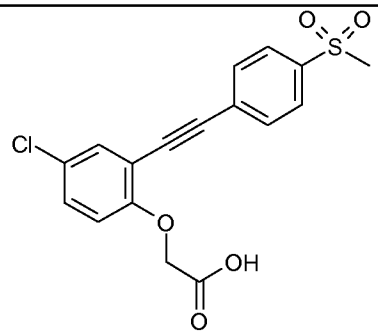
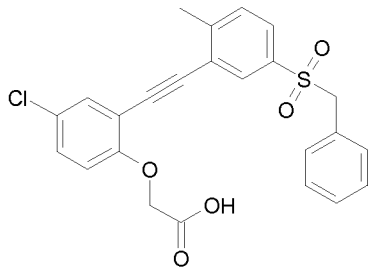
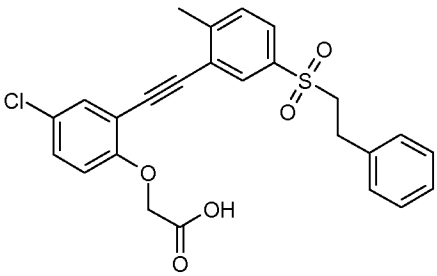
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64		0.136
65		0.009
66		0.193
67		0.086

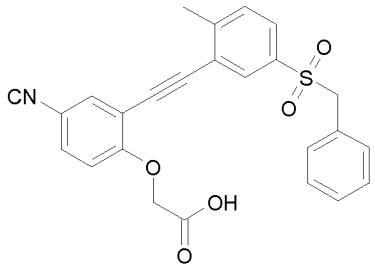
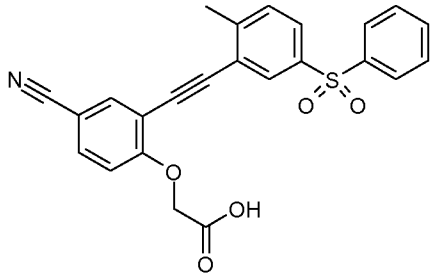
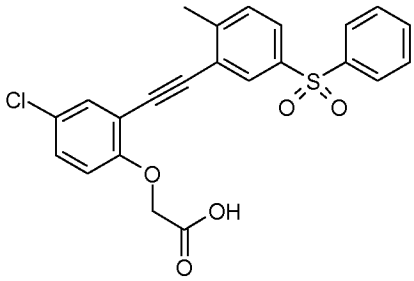
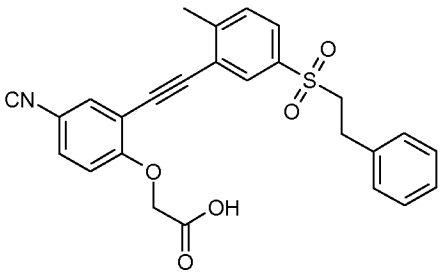
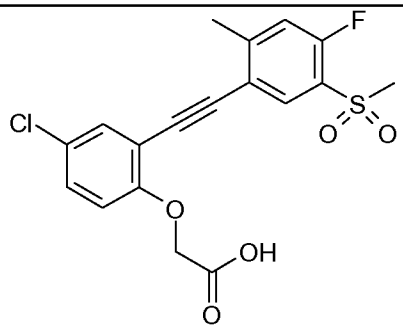
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69		0.186
70		0.007
71		0.016
72		0.364

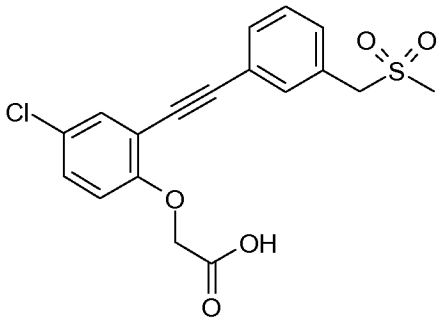
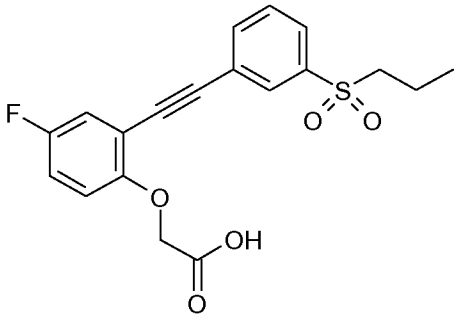
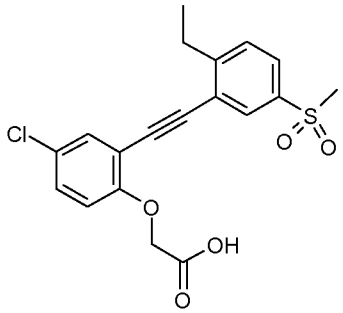
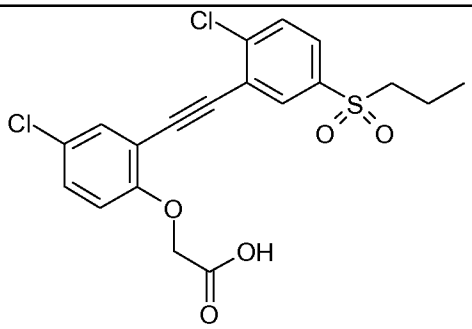
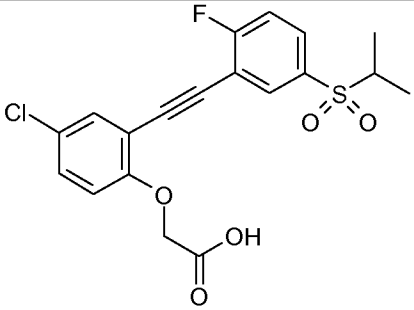
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74		0.07
75		0.372
76		0.171
77		0.36

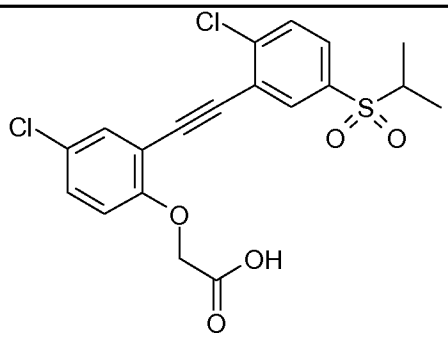
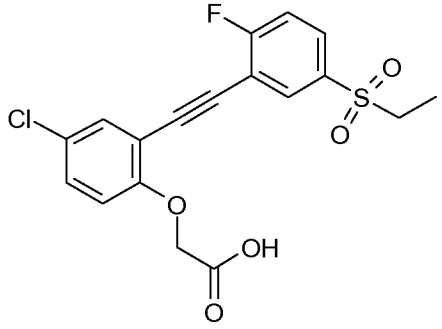
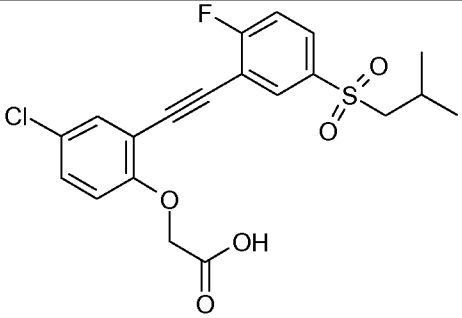
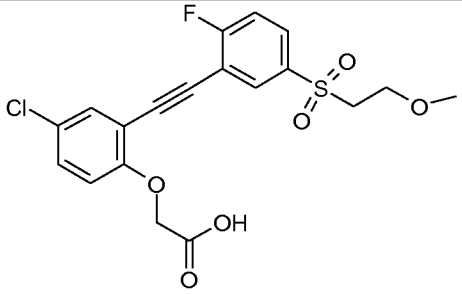
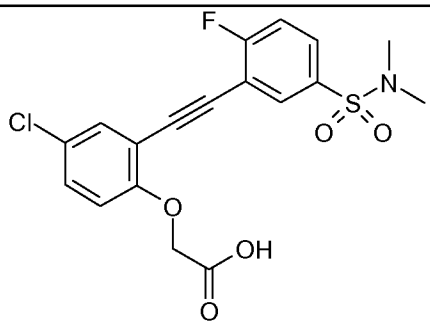
78		0.04
79		0.052
80		0.019
81		0.005
82		0.005

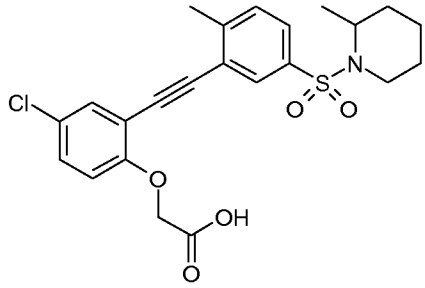
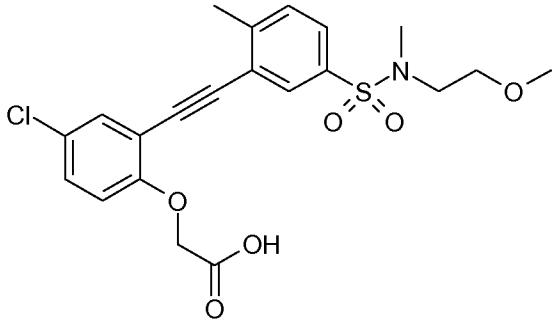
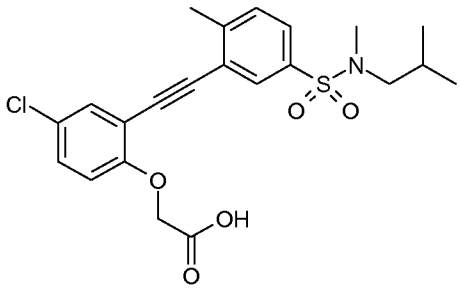
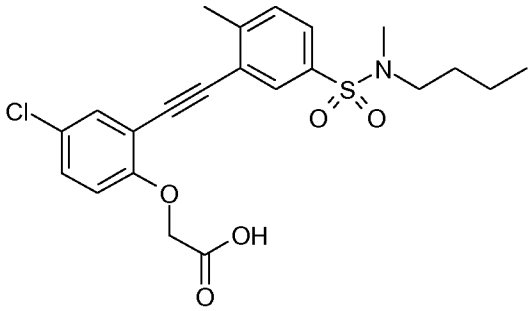
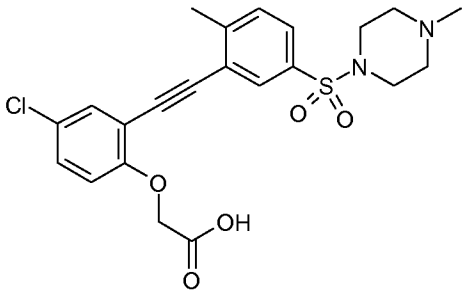
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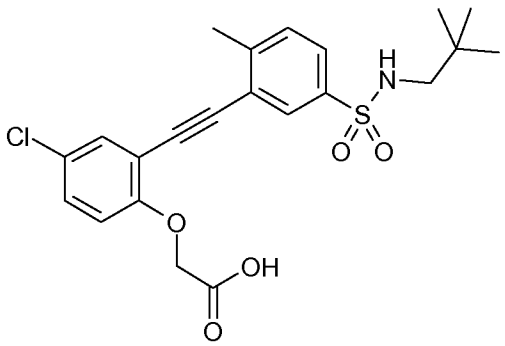
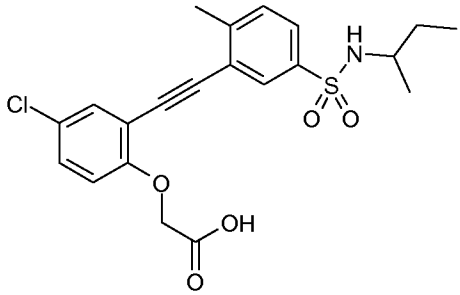
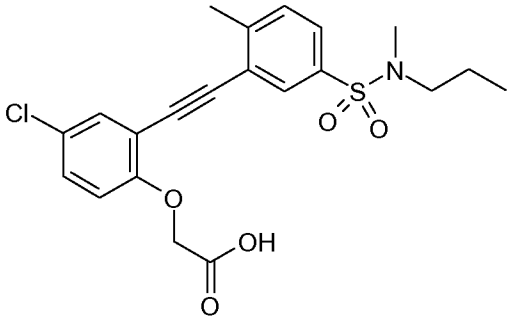
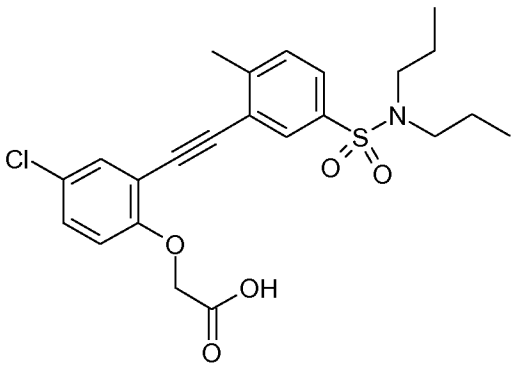
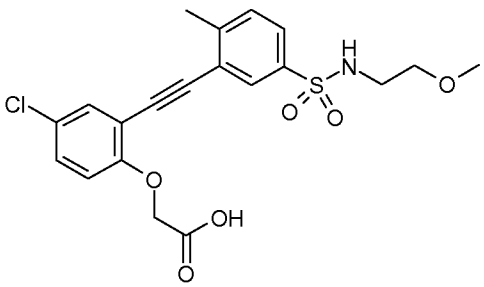
88		0.007
89		0.006
90		0.154
91		0.007
92		0.009

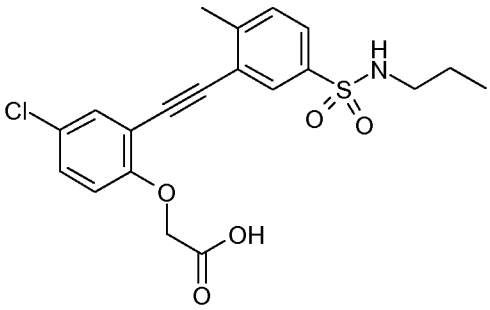
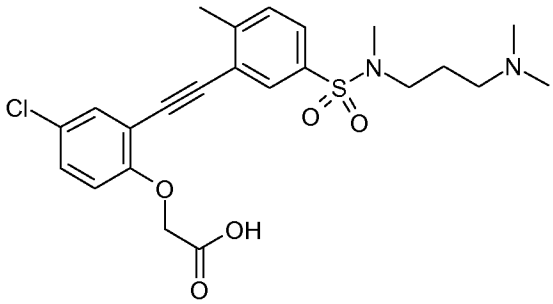
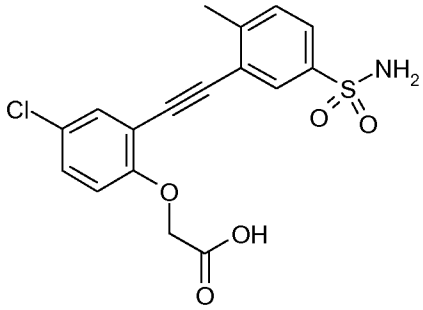
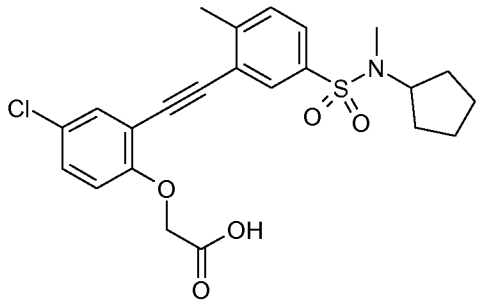
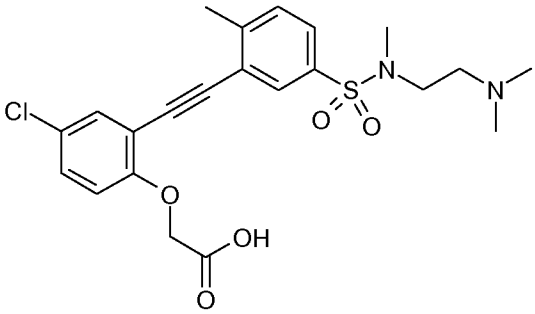
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94		0.011
95		0.009
96		0.007
97		0.008

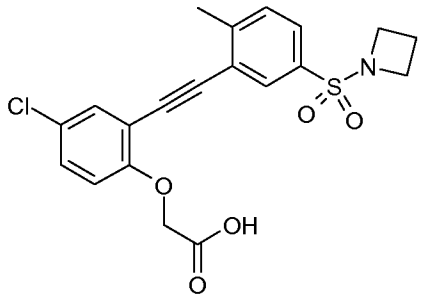
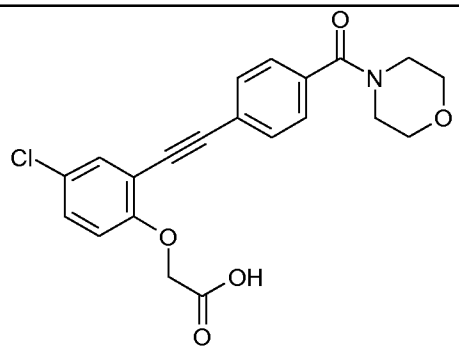
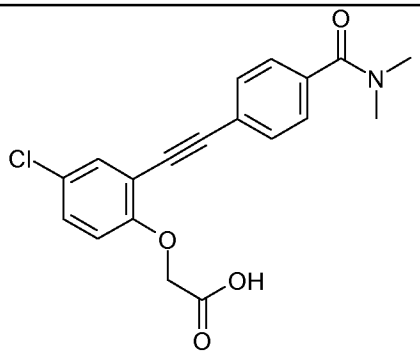
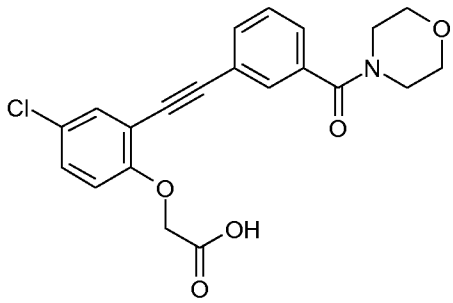
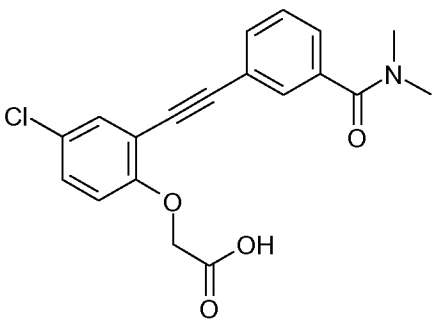
98		0.060
99		0.079
100		0.003
101		0.003
102		0.005

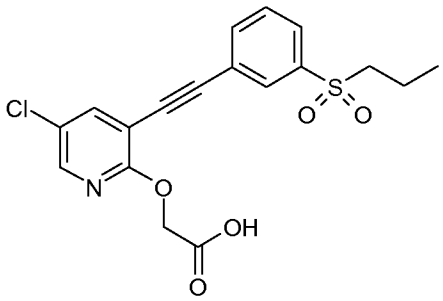
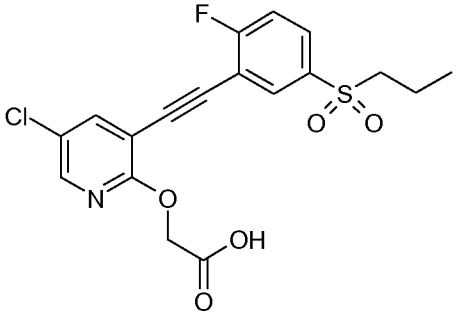
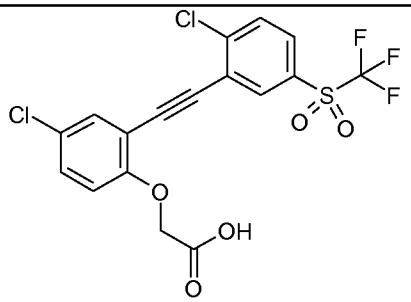
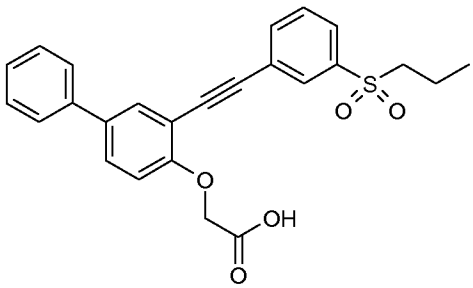
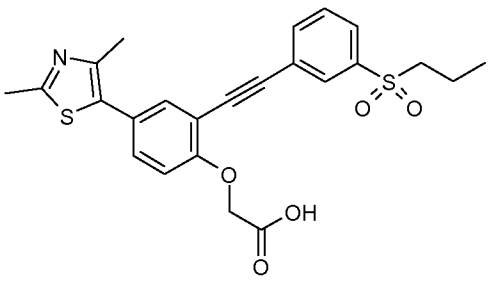
103		0.004
104		0.003
105		0.002
106		0.002
107		0.004

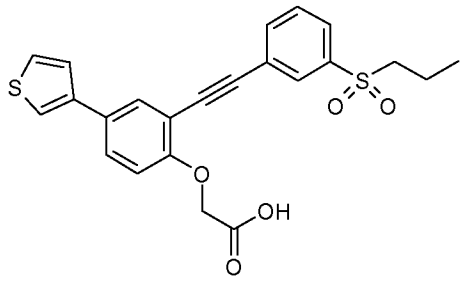
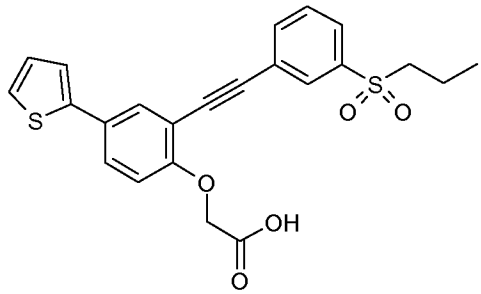
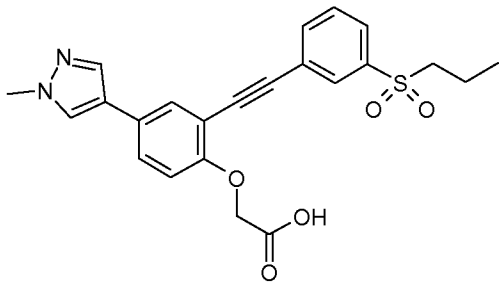
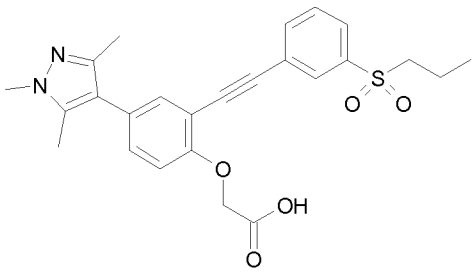
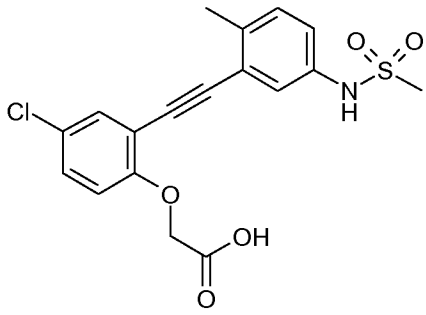
108		0.002
109		0.005
110		0.005
111		0.006
112		0.027

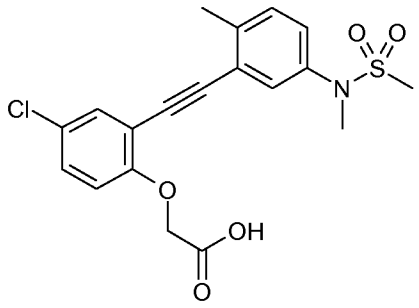
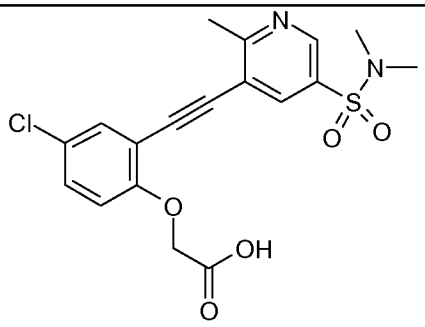
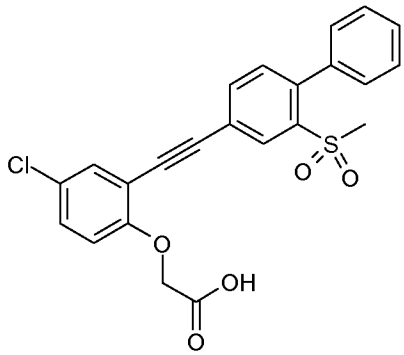
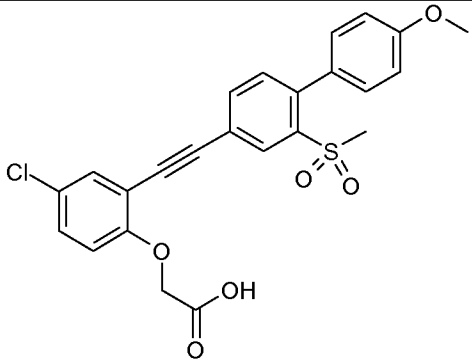
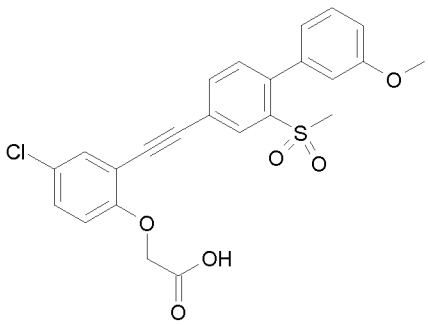
113		0.002
114		0.003
115		0.005
116		0.008
117		0.005

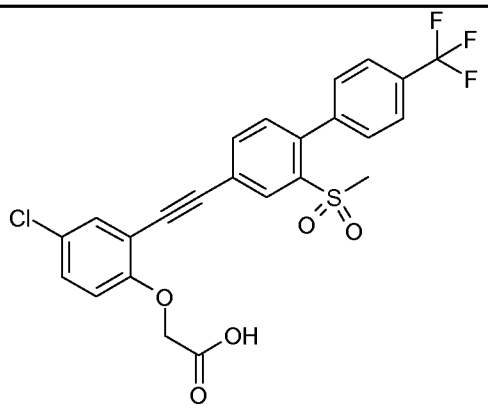
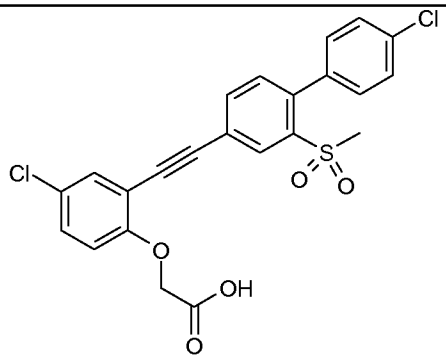
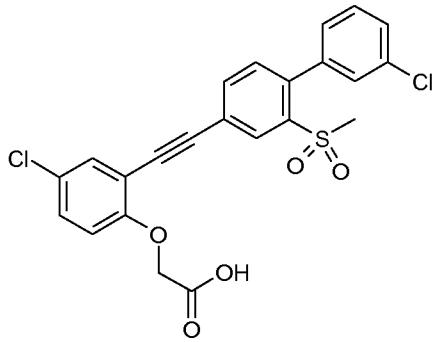
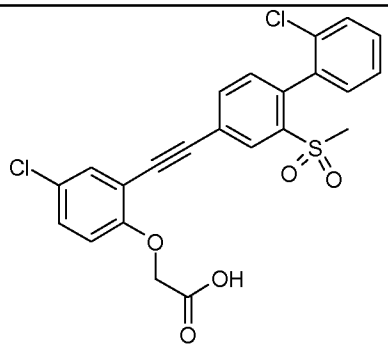
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122		0.452

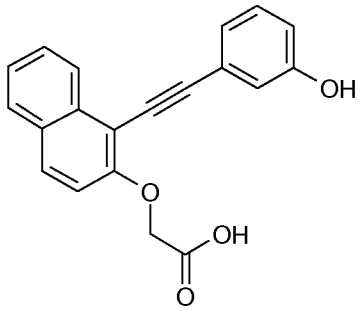
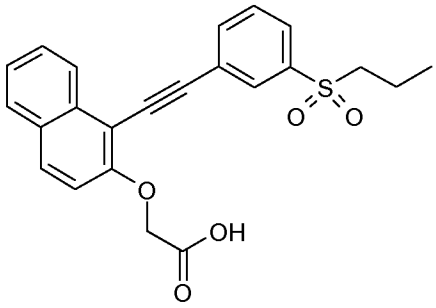
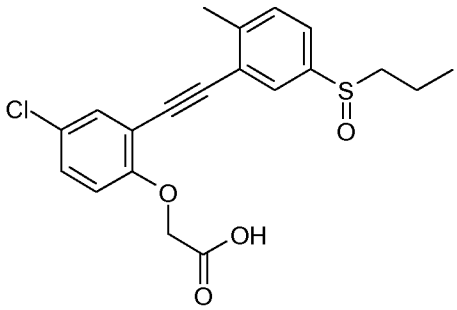
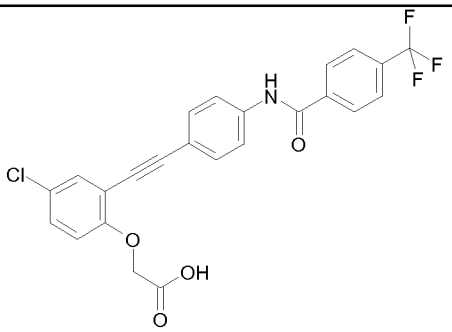
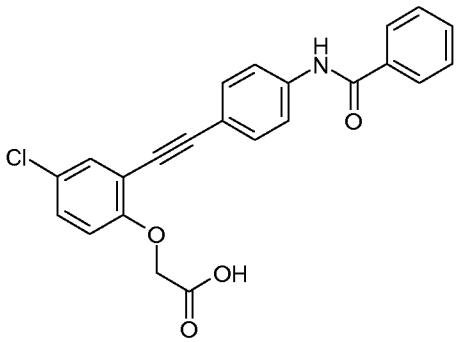
123		0.005
124		0.106
125		0.057
126		0.060
127		0.068

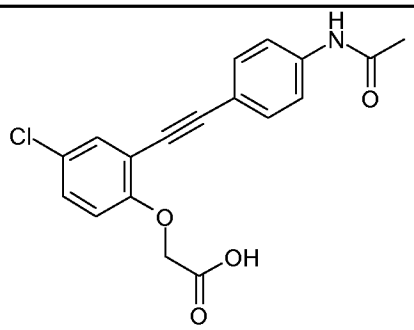
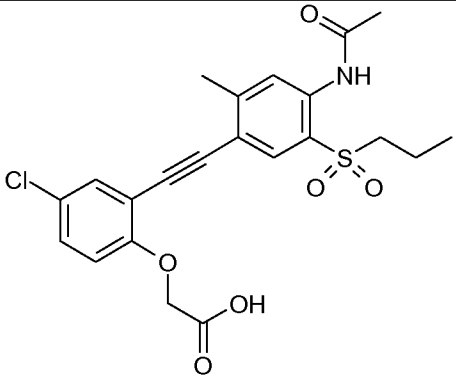
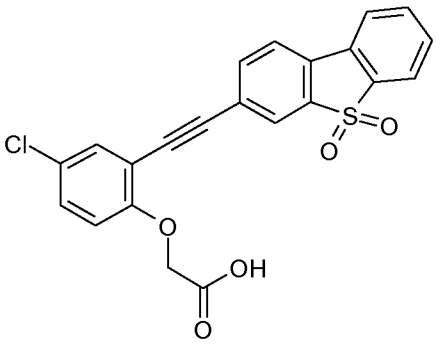
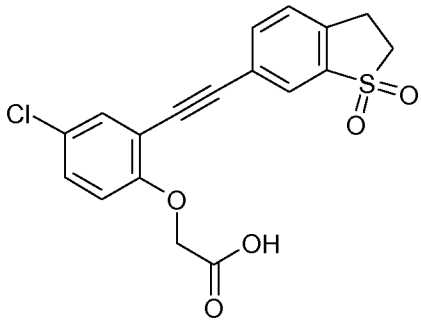
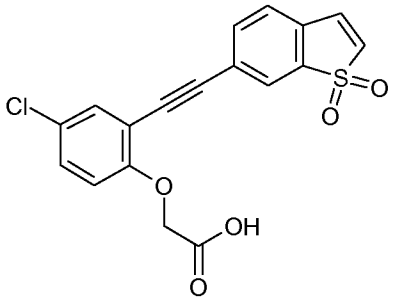
128		0.063
129		0.010
130		0.009
131		0.024
132		0.068

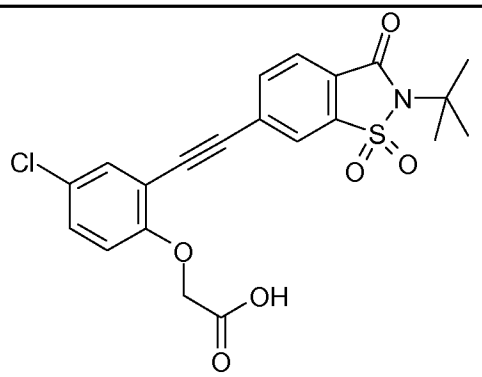
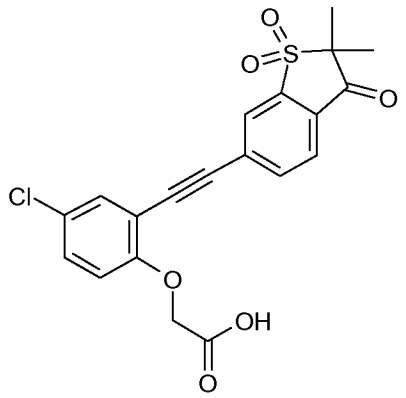
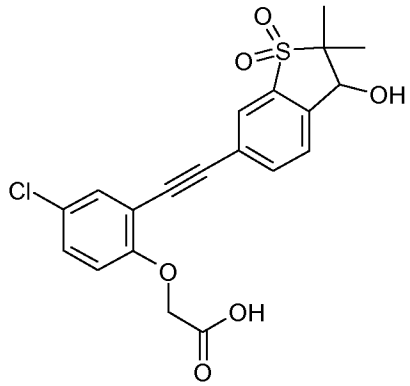
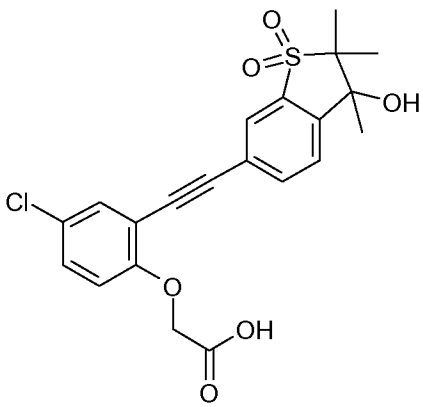
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134		0.015
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137		0.070

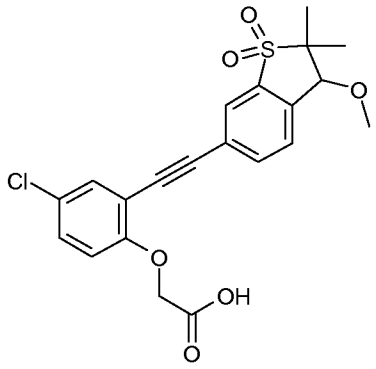
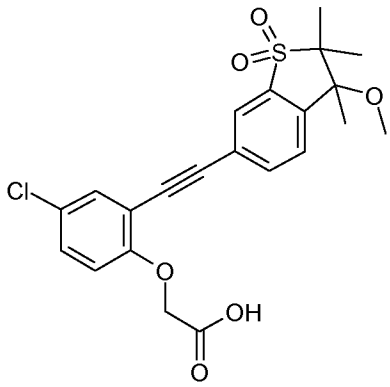
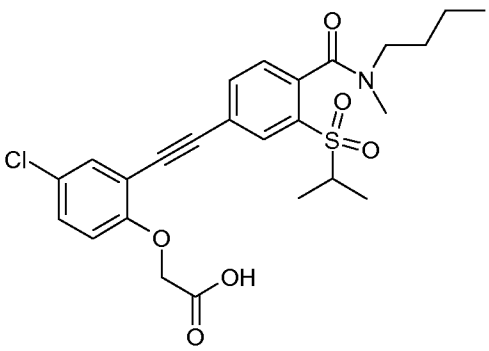
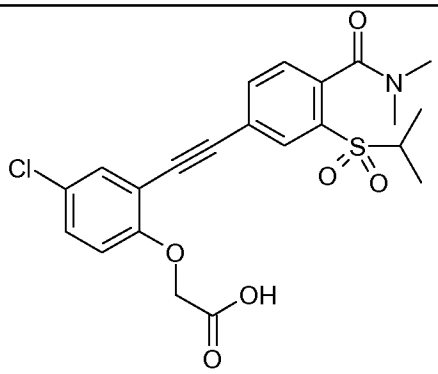
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139		0.051
140		0.006
141		0.008
142		0.009

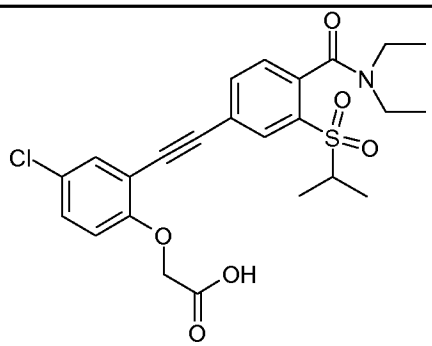
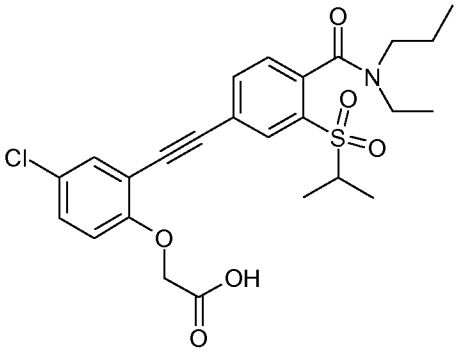
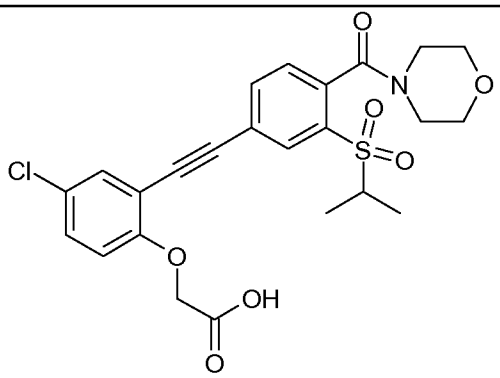
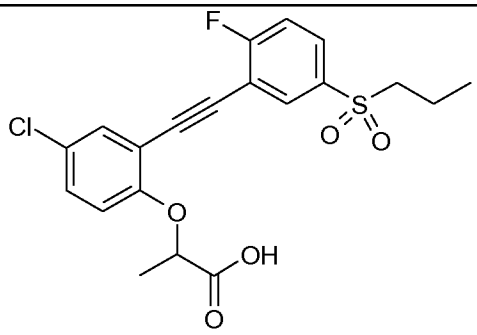
143		0.050
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146		0.004

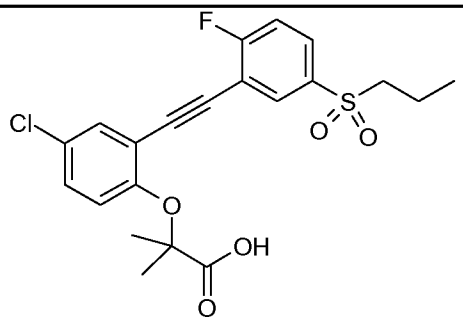
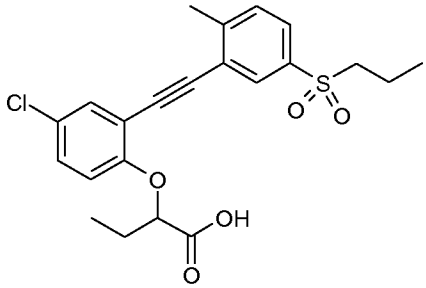
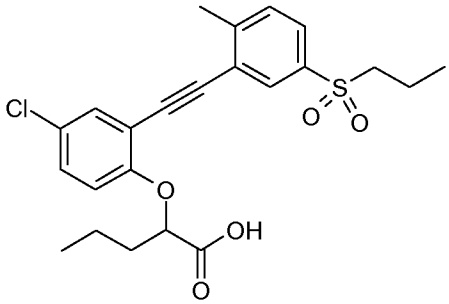
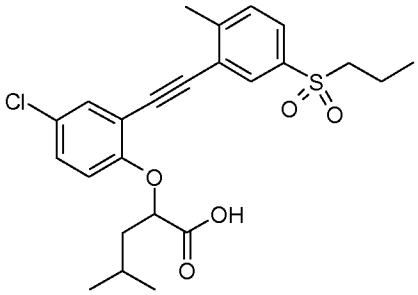
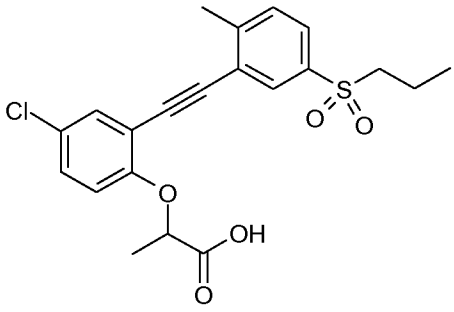
147		0.102
148		0.056
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150		0.267
151		0.028

152		0.028
153		0.001
154		0.014
155		0.029
156		0.032

157		0.017
158		0.034
159		0.037
160		0.032

161		0.024
162		0.029
163		0.032
164		0.075

165		0.053
166		0.043
167		0.100
168		0.003

169		0.287
170		0.035
171		0.066
172		0.060
173		0.001

Example 176: [^{35}S]GTPγS binding assay

The [^{35}S]GTPγS assay measures the increase in guanine nucleotide exchange at G-proteins in cell membranes, resulting from agonist (PGD2) binding to CRTH2. This process can be monitored in vitro by incubating cell membranes containing G-proteins and CRTH2 with GDP and [^{35}S]GTPγS, a radiolabeled, hydrolysis-resistant analogue of GTP (see, Harrison et al., Life Sciences 74, 489-508, 2003). The addition of a Compounds of Formula (I) results in binding to CRTH2 and thus in an inhibition of agonist binding, which can be monitored as inhibition of the stimulation of GTP/GDP exchange.

Briefly, Compounds of Formula (I) are incubated in 96-well scintillating white polystyrene plates (Perkin Elmer, USA) in a final volume of 200µl containing 20mM HEPES/KOH pH 7.4, 3mM $MgCl_2$, 10µg/ml Saponin, 5µM GDP, 75 mM NaCl and 2% of dimethylsulphoxide (DMSO). Reaction is triggered by the addition of 5-10µg of CHO-CRTH2 cell membranes and 0.15 nM [^{35}S]GTPγS. After 60 min incubation at 30°C, reaction is stopped by centrifugation at 700 x g, at 4°C for 10 minutes and supernatant is removed. The radioactivity coming from the [^{35}S]GTPγS bound on centrifuged cell membranes is recorded using a 1450 Micro-beta scintillation counter. For IC50 determination, increasing concentrations of compounds are incubated in presence of a fixed concentration of PGD2 (EC_{80}). For EC_{50} measurements, compounds are incubated without addition of PGD2. Basal [^{35}S]GTPγS activity is determined without addition of any ligands or compounds. 100% [^{35}S]GTPγS activity is measured by the addition of 1µM of PGD2.

In one embodiment, the compounds of Formula (I) of the present invention are antagonists of CRTH2. The results of selected examples are reported in the Table below.

Results:

Example	**IC_{50} (µM)**
3	0.105
4	0.037
20	0.288
26	0.140
32	0.185
35	0.126
38	0.006
40	0.039
42	0.010

48	0.015
56	0.049
58	0.034
59	0.006
95	0.010
102	0.004
140	0.037
168	0.009
173	0.007

In another embodiment, the compounds of Formula (I) of the present invention are partial agonists of CRTH2. For example the compound of Example 44 gave an Emax of 13% (100% being the activity measured by the addition of 1μM of PGD2), with an EC_{50} of 0.040 μM.

In another embodiment, the compounds of Formula (I) of the present invention are inverse agonists of CRTH2. The results of representative examples are reported in the Table below (100% of Emax being the activity measured by the addition of 1μM of PGD2).

Results:

Example	**EMax**
95	-17%
154	-17%
107	-13%
168	-13%
152	-13%
140	-11%

Example 177: Cellular Dielectric Spectroscopy

Cellular Dielectric Spectroscopy (CDS) is a label-free technology based on the measurement of complex impedance changes (delta Z or dZ). Impedance (Z) is related to the ratio of voltage to current as described by Ohm's law (Z = V/I). In order to measure the changes in impedance that occur in response to receptor stimulation, mammalian cells are seeded onto a custom 96-well microtiter plate that contains electrodes at the bottom of each well. Key contributors to the impedance measurements are changes in cell-substrate adherence, changes in cell shape and volume, and changes in cell-cell interactions. These factors individually or collectively affect the flow of current, influencing the magnitude and characteristics of the signal measured. G-protein coupled

receptors ligand-induced activity can be measured using this technology and specific G protein coupling can be identified. Activities of reference agonist and antagonist molecules of CRTH2 have been measured using this assay and similar results were obtained compared to different functional assays.

CHO-CRTH2 cells are cultured in HAM's F12 (Lonza, Switzerland) supplemented with 10% foetal calf serum (PAA, Australia) and 400µg/ml Geneticin. 100000 cells/well are seeded in standard 96W Microplates (MDS Analytical Technologies) and incubated at 37°C in 5% CO_2 for 24 hours. Cells are washed twice with 135µl of cell key buffer (Hank's Balanced Salt Solution 1X (HBSS) (Invitrogen) supplemented with 10mM HEPES pH 7.4 in presence of 1% DMSO). For EC_{50} determination, 15µl of increasing concentration of Compounds of Formula (I) diluted in cell key buffer are added to the cells and agonist activity is then recorded for 25 minutes. For IC_{50} determination, 16.6µl of a fixed concentration of PGD2 (EC80) diluted in cell key buffer is added to the cells-compounds mixture, and antagonist activity is measured during 25 minutes. Results are expressed as the amplitude between the highest and the lowest signal produced (max-min). Basal and maximum activities are measured, respectively in absence or presence of PGD2 (EC_{80}).

In one embodiment, the compounds of Formula (I) of the present invention are antagonists of CRTH2. The results of representative examples are reported in the Table below.

Results:

Example	**IC_{50}(µM)**
15	0.074
17	0.022
35	0.023
38	0.032
42	0.025
43	0.269
48	0.009
53	0.050
54	0.037
56	0.053
59	0.014
67	0.034
70	0.021
71	0.015
86	0.118
87	0.083

89	0.029
95	0.084
100	0.023
101	0.038
102	0.016
103	0.044
107	0.023

In another embodiment, the compounds of Formula (I) of the present invention are partial agonists of CRTH2. The results of representative examples are reported in the Table below.

Results:

Example	EC_{50}(μM)	EMax
15	0.053	46%
44	0.115	59%
48	0.001	12%
55	0.024	62%
58	0.006	32%
131	0.074	68%

Example 178: PGD2-induced Eosinophil Cell Shape assay in Human Whole Blood

The Compounds of Formula (I) were diluted in dimethylsulphoxide so that the total volume of dimethylsulfoxide was kept constant at 2% dimethylsulphoxide (Me_2SO). Serial dilutions of 200 μM to 0.09 μM were prepared. Samples of 90 μl of human blood from healthy volunteers (Centre de Transfusion Sanguine de Genève) were pre-incubated in polypropylene Falcon tubes (BD 352063) for 20 minutes in a water bath at 37 °C with 10 μl of diluted compounds. For CRTH2 activation, 100 μl PGD2 (Cayman 12010) at 20 nM was added (10 nM final) to each tube and cells were maintained at 37 °C. For negative control cells were treated with PBS. After 10 minutes, cell activation was stopped with 120 μl Formaldehyde 10% (4% final, Fluka 41650) and cells were rested for 10 minutes at room temperature. Fixed cells were transferred into polypropylene tubes and then treated for 1 hour in a water bath at 37 °C with 2ml of Triton – Surfact-Amps X-100 (Pierce 28314) at 0.166% (0.13% Triton final). After several washes with PBS (red cells lysed progressively during washes, two washes are necessary), cells were analyzed by flow cytometry on a FACSCalibur. In one embodiment, the compounds of Formula (I) of the present invention are capable of blocking the cell shape change of eosinophils induced by PGD2 in Whole Blood. The results of representative examples are reported in the Table below.

Results:

Example	IC_{50}(μM)
17	0.150
26	0.679
33	0.064
35	0.289
38	0.081
48	0.095
49	1.190
58	0.095
65	0.123
83	0.077
89	0.023
100	0.100
101	0.023
102	0.091
103	0.067
107	0.023
109	0.077
117	0.088

Example 179: In vivo Pharmacokinetic Evaluation in Rat and Mouse.

In order to study the pharmacokinetic (PK) profile of test compounds in vivo, Sprague Dawley male rats or C57BL/6 female mice were dosed intravenously or after oral gavage. For both species, test compounds were dosed in solution at 1 mg/kg for i.v. route (10% ethanol, 10% *N, N*-dimethylacetamide, 30% propylene glycol, 50% water, v/v) and in suspension at 5 mg/kg (0.5% carboxymethylcellulose suspension, containing 0.25% Tween 20 in water) for oral gavage. PK profile in rat was obtained from 3 animals per dosing route and mouse PK profile was determined from 3 animals for each time points. The volume of administration was 2 mL/kg for i.v. dosing in both species and either 5 mL/kg (rat) or 10 mL/kg (mouse) for oral gavage. Blood samples (100 μL/time point) were collected at 0.083 (5 min), 0.25, 0.5, 1, 4, 7 and 24 hours post-dose for i.v. dosing, and at 0.5, 1, 4, 7 and 24 h for oral dosing, into heparin-Li+ containing tubes. For rats, all blood samples were collected trough a catheter in the carotid artery (placed in the artery the day before the experiment), under light isoflurane anesthesia, and stored on ice until centrifugation and plasma isolation. For mouse, blood samples were collected from intracardiac puncture at sacrifice at each time point and processed as described above for the rat. Plasma samples were stored frozen until analysis (-20 °C to -70 °C). For bioanalysis, samples were processed by protein precipitation (acetonitrile, formic acid 0.1%, addition of 3 volumes) after addition of one internal standard and

analysed using a sensitive and selective LC/MS/MS method. An aliquot of the resulting supernatant was subject to LC/MS/MS analysis using a reverse phase column (Waters Xterra, C8, (3.5 µm particle size, 2.1 x 50 mm) and a short gradient (1 min) from (Solvent A) 85% water, 15% acetonitrile and 0.1% formic acid to (Solvent B) 90% acetonitrile, 10% water and 0.1% formic acid followed by isocratic conditions of Solvent B for 3.5 min at 0.4 mL/min. Column effluent was monitored using a Sciex API 4000 triple quadrupole mass spectrometer with a Turbo V electrospray ion source. Unknown concentrations of test compounds were determined using a calibration curve ranging from 1 to 3000 ng/mL.

Pharmacokinetic profile in mice of representative compounds

Compound	Clearance iv (1 mg/Kg) (L/Kg/h)	AUC po (5 mg/Kg) (h*ng/ml)	Oral bioavailability
Example 17	0.3	5768	37%
Example 35	0.8	6213	95%
Example 38	1.0	3685	80%
Example 89	0.4	6752	63%
Example 101	1.0	5795	110%
Example 102	0.35	18691	130%
Example 103	0.7	4889	64%
Example 107	0.6	4880	58%
Example 154	0.1	30942	57%

Pharmacokinetic profile in rat of a representative compound

	Clearance iv (1 mg/Kg) (L/Kg/h)	AUC po (5 mg/Kg) (h*ng/ml)	Oral bioavailability
Example 17	0.4	3695	28%

Example 180: OVA-induced lung eosinophilia in mice

BALB/c mice (6 - 8 weeks old) were immunized with ovalbumin (10 µg i.p) on day 0 and 7. In order to elicit a local inflammatory response in the lung, mice were challenged between day's 15 – 17 with a nebulised solution of ovalbumin (10 µg/ml; De Vilibiss

Ultraneb 2000, once daily for 30 min during the 3 days). On each separate day between 15 and 17 each animal received via oral gavage the test compound, at t -1 h and t +7 h with respect to OVA exposure at t =0 h. Eight hours after the final OVA challenge, bronchoalveolar lavage (BAL) was then carried out. Total cell numbers in the BAL fluid samples were measured using a haemocytometer. Cytospin smears of the BAL fluid samples were prepared by centrifugation at 1200 rpm for 2 min at room temperature and stained using a DiffQuik stain system (Dade Behring) for differential cell counts. Compounds of Formula (I) of the present invention were tested at 3, 10 and 30 mg/Kg. Selected compounds showed a significative decrease of cell numbers in BALF. For example the compounds of Examples 38 and 89 showed the % inhibition of total cells and eosinophils as showed in the table below.

Compound	Dose (mg/kg)	% inhibition total cells (mean ± s.e.m.)	% inhibition eosinophils (mean ± s.e.m.)
Dexamethasone	1	88 ± 11	90 ± 10
Example 38	3	21 ± 13	29 ± 14
	10	42 ± 14	54 ± 16
	30	67 ± 8	81 ± 7
Example 89	3	12 ± 15	19 ± 18
	10	19 ± 8	27 ± 10
	30	44 ± 10	55 ± 11

Example 181: FITC 1 week model

Fluorescein isothiocyanate (FITC) induced contact hypersensitivity (CHS) is a commonly used model for atopic dermatitis (AD). The hapten FITC is a small molecule that is able to elicit an immune response only when attached to a larger carrier such as a protein. It is reactive towards e-amino groups (lysine). The immune response to FITC sensitization and challenge is Th2 cytokine driven (IL-4, IL-5, IL-6, IL-10 and IL-13) and associated with elevated serum IgE levels. The skin inflammation at the site of the challenge is characterized by edema and eosinophil infiltrations.

Female 9 week old Balb/C mice were sensitized on days 0 and 1 with 0.5% FITC in aectone/dibuthylphtalate (A/DBP). One group (sham) was sensitized with A/DBP alone. On day 6 all the mice including the sham group were challenged on the right ear (inner and outer surface) with 0.5% FITC in A/DBP. The mice were treated with the compounds via oral gavage 1 h before and 7 h after the challenge. The baseline ear thickness was measured before the challenge and 24 h after the challenge. At the end of the experiment (24 h after the challenge) the mice were sacrificed. Serum and plasma samples were taken. The challenged ear was excised and stored at -80 °C. Compounds of Formula (I) of the present invention were tested at 3, 10 and 30 mg/Kg. Selected compounds showed a significative decrease of ear swelling. For example the compounds of Examples 38, 89 and 154 showed the % inhibition of ear swelling as showed in the table below.

Compound	dose (mg/kg)	% inhibition (mean ± s.e.m.)
Example 38	30	52 ± 12
	10	56 ± 12
	3	23 ± 16
Example 89	30	48 ± 11
	10	54 ± 16
	3	36 ± 19
Example 154	30	54 ± 17
	10	49 ± 9
	3	41 ±9

Example 182: Preparation of a pharmaceutical formulation

Formulation 1 – Tablets

A compound of formula (I) is admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 240-270 mg tablets (80-90 mg of active compound according to the invention per tablet) in a tablet press.

Formulation 2 – Capsules

A compound of formula (I) is admixed as a dry powder with a starch diluent in an approximate 1:1 weight ratio. The mixture is filled into 250 mg capsules (125 mg of active compound according to the invention per capsule).

Formulation 3 – Liquid

A compound of formula (I) (1250 mg), sucrose (1.75 g) and xanthan gum (4 mg) are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously prepared solution of microcrystalline cellulose and sodium carboxymethyl cellulose (11:89, 50 mg) in water. Sodium benzoate (10 mg), flavor, and color are diluted with water and added with stirring. Sufficient water is then added to produce a total volume of 5 mL.

Formulation 4 – Tablets

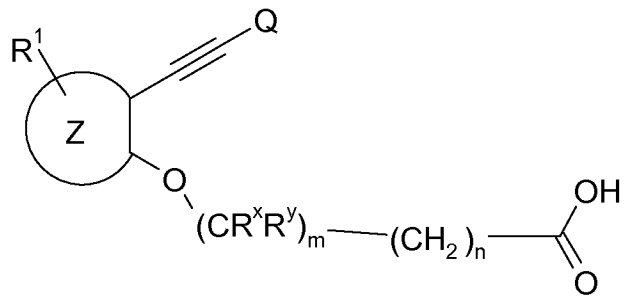
A compound of formula (I) is admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 450-900 mg tablets (150-300 mg of active compound according to the invention) in a tablet press.

Formulation 5 – Injection

A compound of formula (I) is dissolved in a buffered sterile saline injectable aqueous medium to a concentration of approximately 5 mg/mL.

Claims:

1. A compound of Formula (I)



(I)

as well as its ester derivatives, its geometrical isomers, its optically active enantiomers, diastereoisomers and its racemates forms, and tautomers, or a pharmaceutically acceptable derivative thereof,

wherein :

R^1 is H, Hal, A, CN, NO_2, OA, CF_3, OCF_3, Ar or Het,

Q is Ar, Het,

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

m is 0, 1 or 2 wherein n+m is not 0,

Z is phenyl, naphthyl or pyridinyl,

A is branched or linear alkyl having 1 to 12 C-atoms, wherein one or more, preferably 1 to 7 H-atoms may be replaced by Hal, OR^3, CN or $N(R^3)_2$ and wherein one or more, preferably 1 to 7 non-adjacent CH_2-groups may be replaced by O, NR^3 or S and/or by CH=CH- or -C≡C- groups, or denotes cycloalkyl or cycloalkylalkylen having 3 to 7 ring C atoms,

Hal is F, Cl, Br or I,

Ar denotes a monocyclic or bicyclic, unsaturated or aromatic carbocyclic ring having 6 to 14 carbon atoms which may be unsubstituted or monosubstituted, disubstituted or trisubstituted or tetrasubstituted by Hal, A, $-CH_2OA$, $-CH_2SO_2A$ -

CH_2OR^3, $-OR^3$, CF_3, $-OCF_3$, $-N(R^3)_2$, NO_2, -CN, $-NR^3COA$, $-NR^3COAr'$, $-NR^3SO_2A$, $-COR^3$, $CON(R^3)_2$, COHet, $-SO_2N(R^3)_2$, -SOA, $-SO_2A$, Het, or by SO_2T , SOT , Ar',

T denotes $-(CH_2)_p$-Ar' or $-(CH_2)_p$-Het',

p is 0, 1, 2, 3 or 4,

Ar' denotes a monocyclic or bicyclic, unsaturated or aromatic carbocyclic ring having 6 to 14 carbon atoms which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, $-CH_2OA$, $-CH_2OR^3$, $-OR^3$, $-CF_3$, $-OCF_3$,

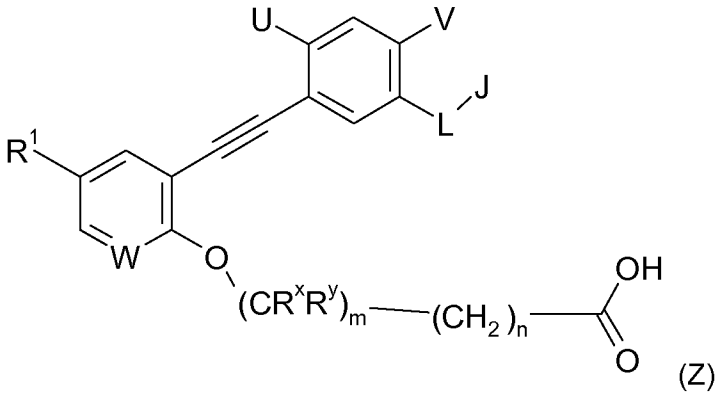
Het' denotes a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic ring, having 1 to 4 N, O and/or S atoms, which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, CH_2OA, OR^3, CF_3, OCF_3,

Het denotes a monocyclic or bicyclic or tricyclic, saturated, unsaturated or aromatic heterocyclic ring, having 1 to 4 N, O, S atoms, and/or 1 SO_2 and/or CO groups and/or NO groups, which may be unsubstituted or monosubstituted, disubstituted or trisubstituted or tetrasubstituted by Hal, A, CH_2OA, OR^3, CF_3, OCF_3, $N(R^3)_2$, NO_2, CN, NR^3COA, NR^3SO_2A, COR^3, $SO_2N(R^3)_2$, SOA, SO_2A, SO_2T,

R^3 is H or A,

R^x, R^y independently denote H, a linear or branched alkyl having 1 to 8 carbon atoms optionally substituted with OH, Hal, CN, or R^x and R^y together form a carbocyclic ring having 3 to 7 carbon atoms, optionally substituted by OH, Hal, CN,

2. A compound according to claim 1 wherein the compound is of Formula (Z),



(Z)

Wherein R^1, R^x, R^y, m and n are as defined in claim 1,

L denotes SO_2, SO, or O;

W denotes C or N, preferably C,

U denotes H, Hal, R^Z,

V denotes H, Ar', R^Z, COR^Z, $CONHR^Z$, and if linked to J also –CO-, -$CONR^Z$, or an arylen,

J denotes R^Z, NHR^Z, $N(R^Z)_2$, $(CH_2)_sAr'$, wherein s is 0 or 1; and if linked to V also $–NR^Z$, or $(CH_2)_sAr''$; or when L is O, J also denotes H,

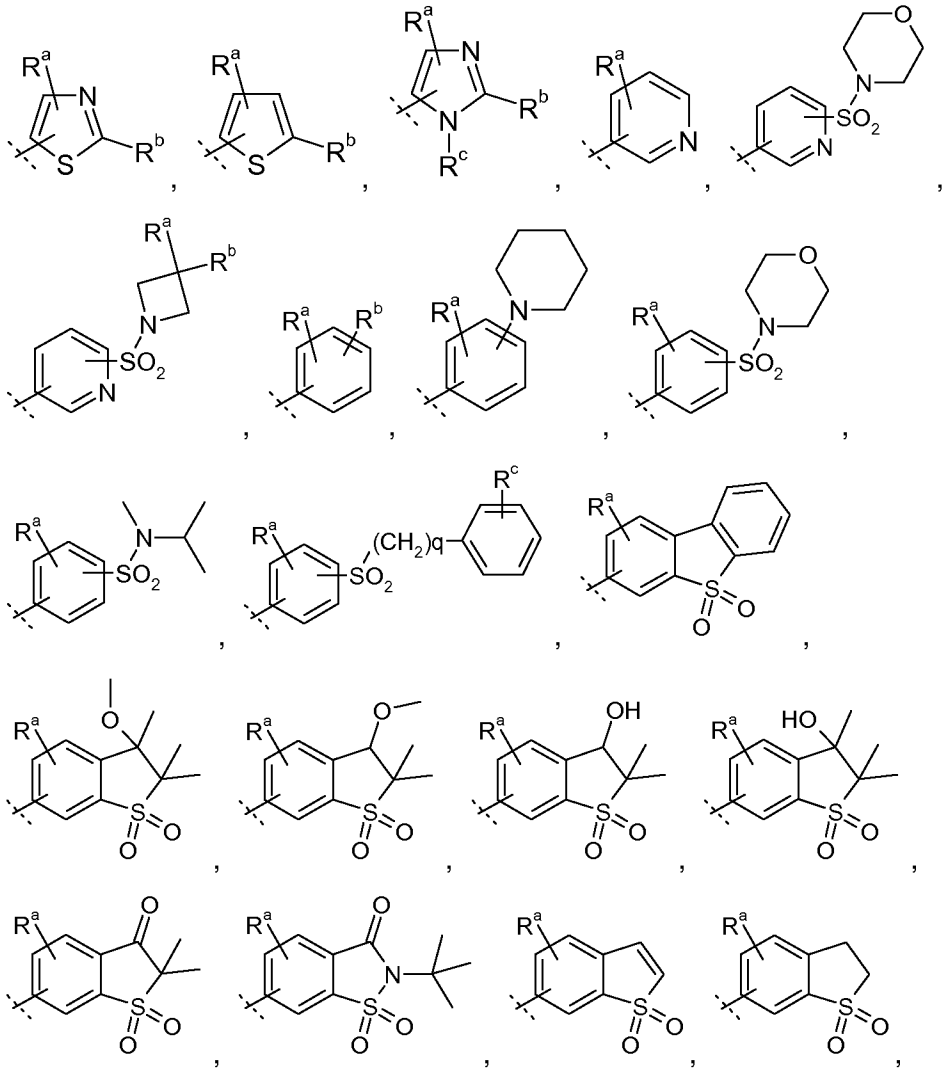
and wherein J and V may be linked to each other to form a ring,

R^Z denotes a linear or branched alkyl or alkenyl having 1 to 6 carbon atoms, optionally substituted by OH, OCH_3,

Ar'' denotes an arylen which may be further substituted by 1 or 2 groups selected from OR^3, Hal, CF_3, wherein R^3 is as defined in claim 1,

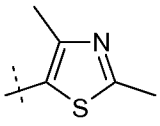
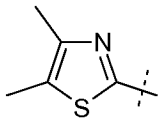
as well as their ester derivatives, their geometrical isomers, their optically active enantiomers, diastereoisomers and their racemates forms, and tautomers, or a pharmaceutically acceptable derivative thereof.

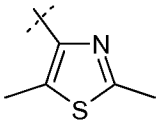
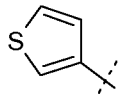
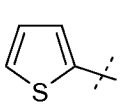
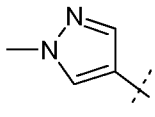
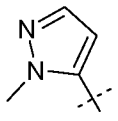
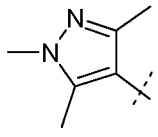
3. A compound according to claim 1 wherein Q is selected from the following groups:



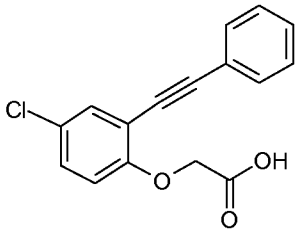
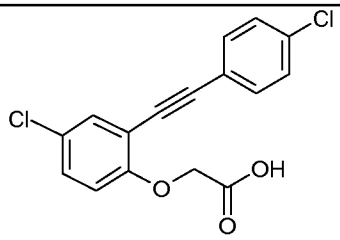
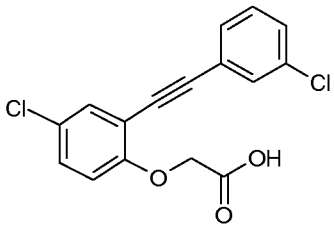
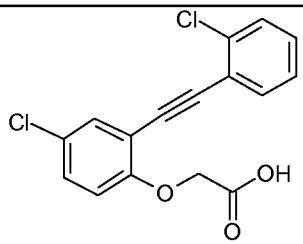
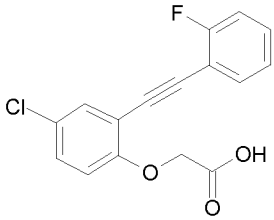
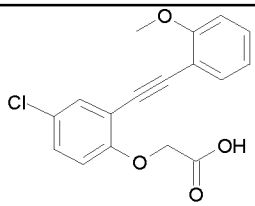
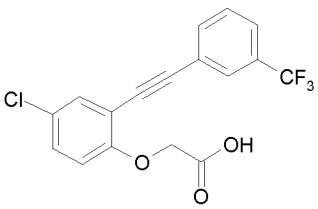
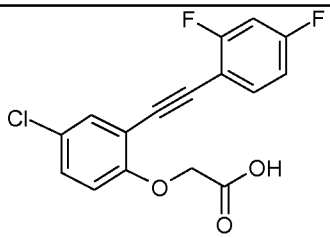
wherein R^a, R^b independently from one another denotes an alkyl group having 1 to 6 carbon atoms, H, Hal, CN, OH, CF_3, -OMe, -OEt, $(CH_2)_qCH_3$, -$(CH_2)_q(CH)(CH_3)_2$, -$SO_2NH(CH_2)_qCH_3$, -$SO_2NH(CH_2)_qC(CH_3)_3$, -$SO_2N(C_2H_5)_2$, -$SO_2N(CH_3)_2$, -$SO_2(CH_2)_qCH_3$, -$SO_2(CH)(CH_3)_2$, -$SO_2(CH_2)_qCH(CH_3)_2$, -$SO_2NH(CH_2)_qOH$, -$SO_2(CH_2)_qOH$, -$SO_2NH(CH_2)_qO(CH_2)_qCH_3$, -$SO_2(CH_2)_qO(CH_2)_qCH_3$, $N(CH_3)$-SO_2-$(CH_2)_qCH_3$, -Ar' or $-(CH_2)Ar'$, SO_2T,
wherein q denotes 0, 1, 2, 3 or 4,
and wherein R^c denotes H, Me, or Et.

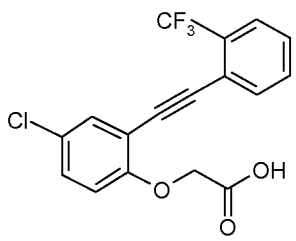
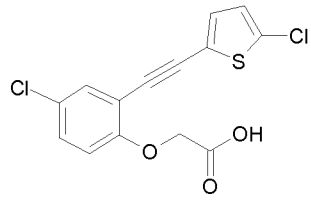
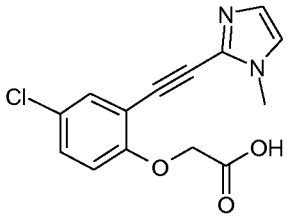
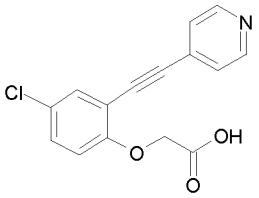
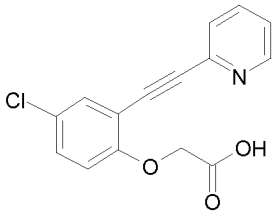
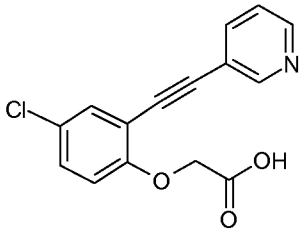
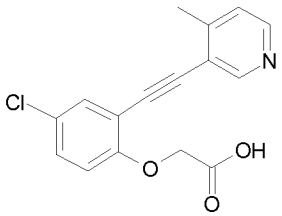
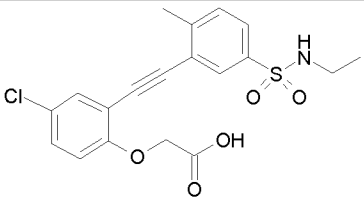
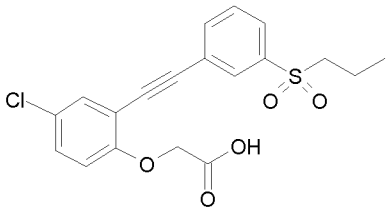
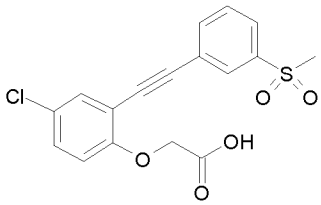
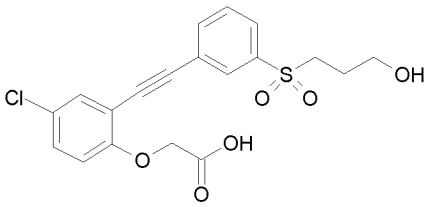
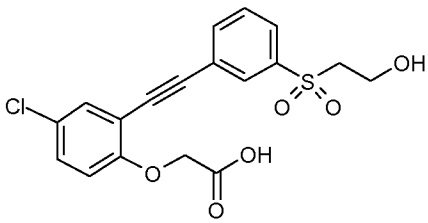
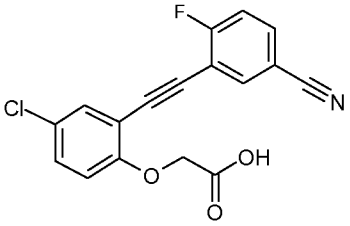
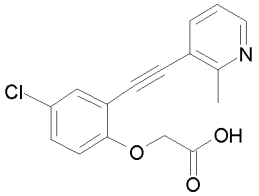
4. A compound according to claim 1 or 2 wherein R^1 denotes one of the following groups : H, Cl, F, CN, -CH_3, -CF_3, a phenyl group obtionally substituted by an

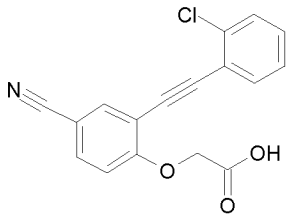
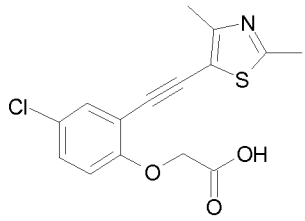
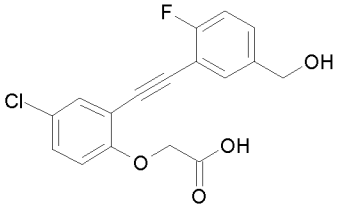
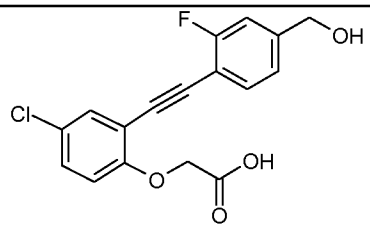
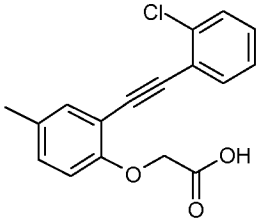
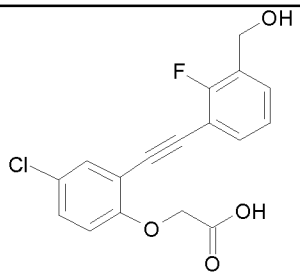
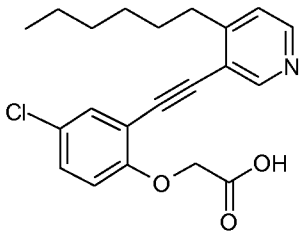
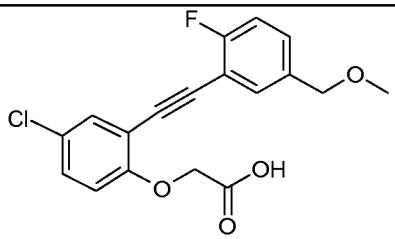
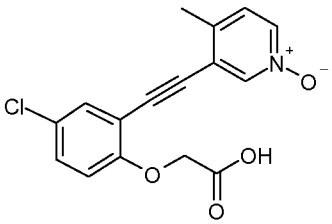
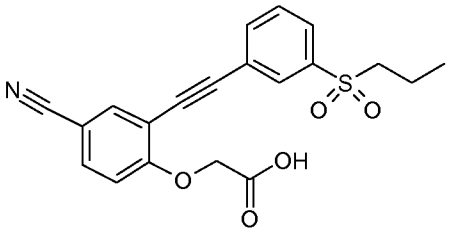
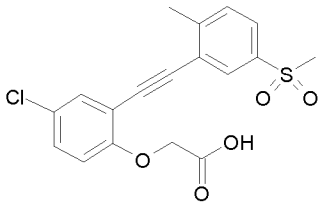
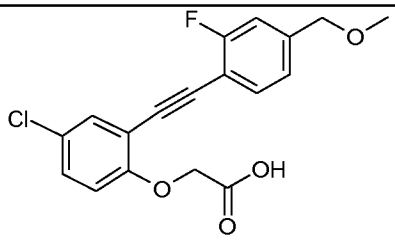
alkyl having 1 to 6 carbon atoms, or  ,  ,

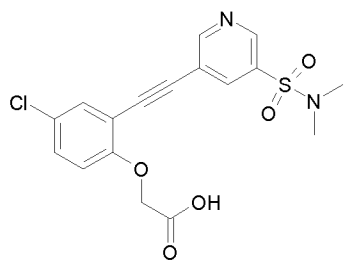
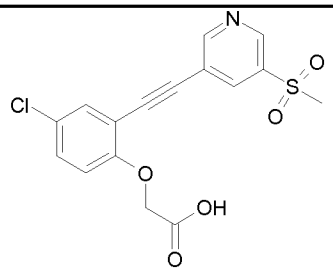
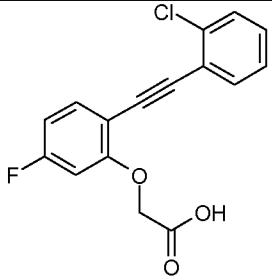
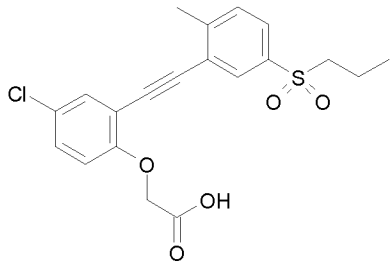
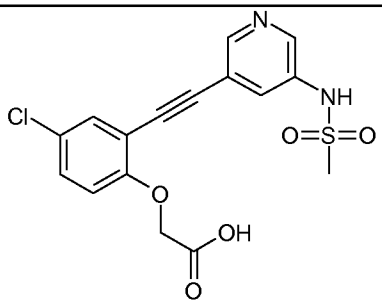
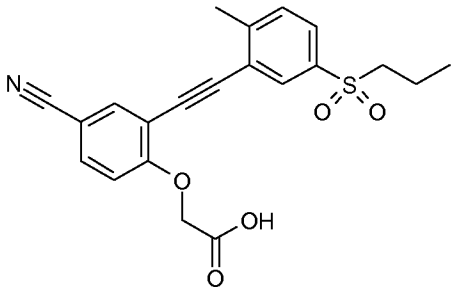
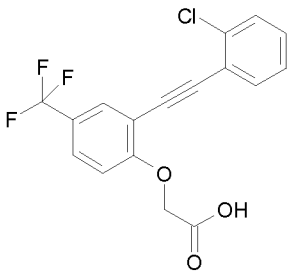
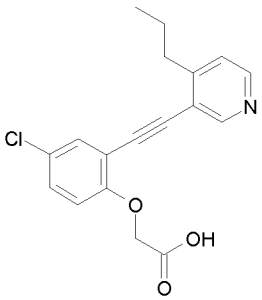
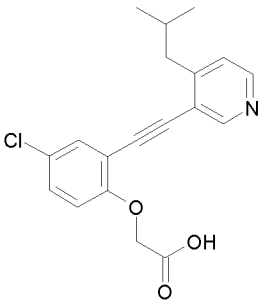
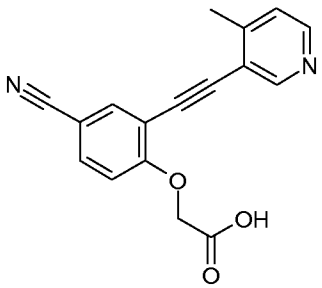
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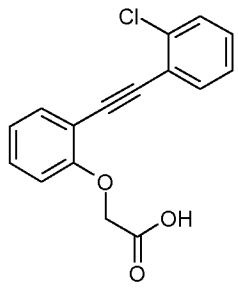
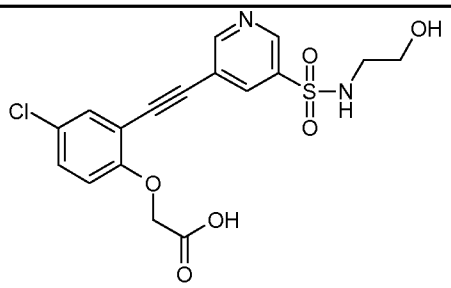
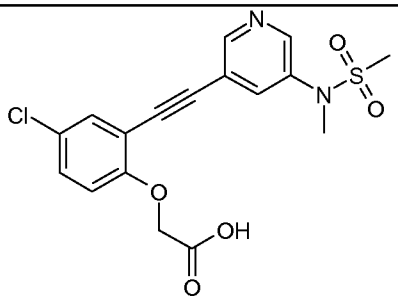
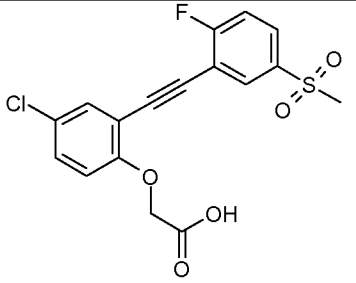
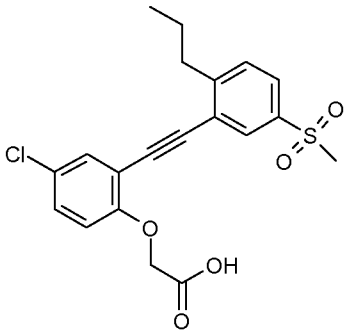
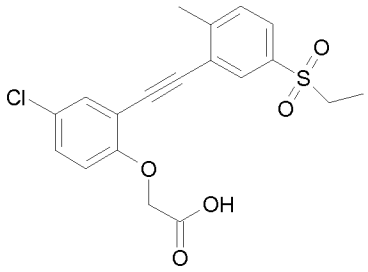
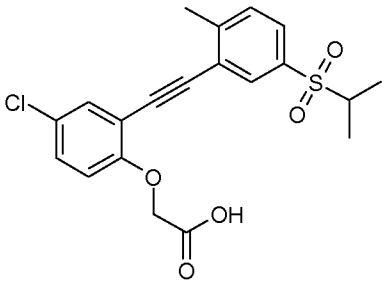
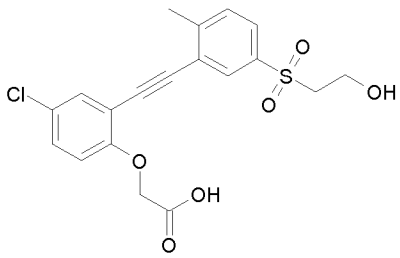
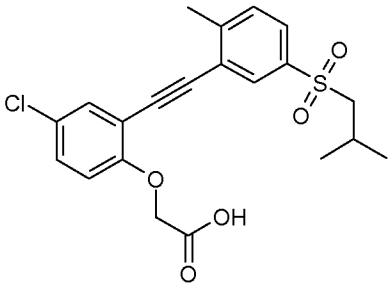
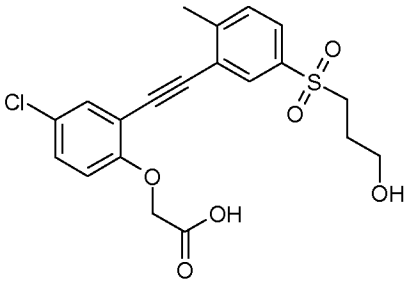
5. A compound according to the preceding claims selected from the following group:

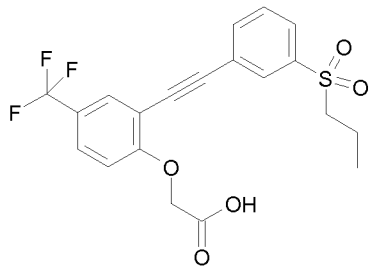
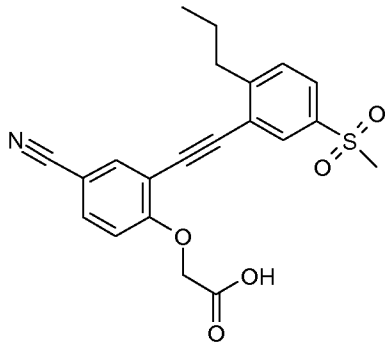
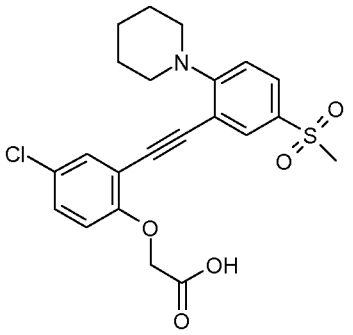
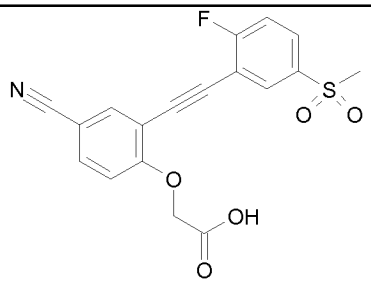
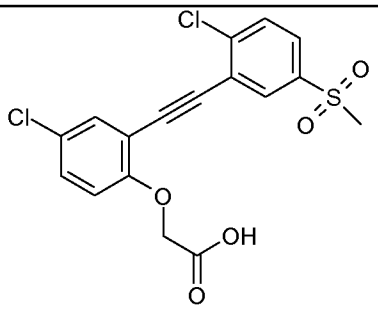
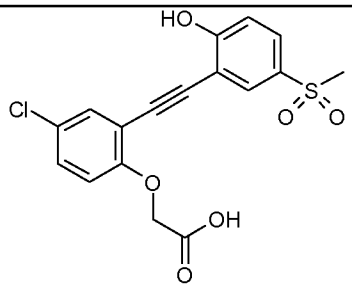
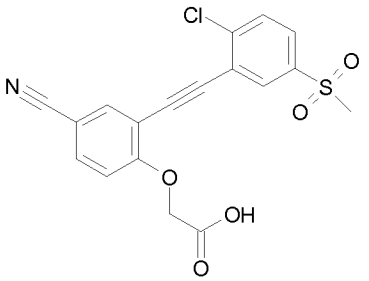
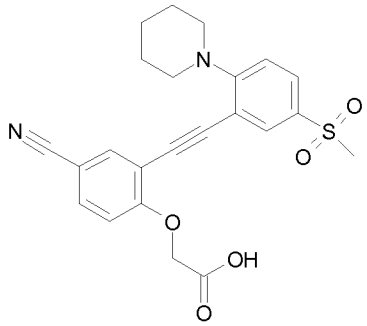
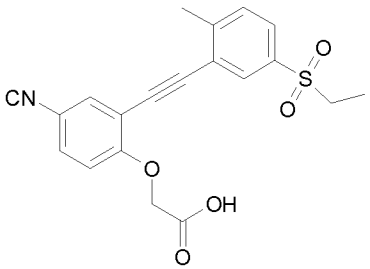
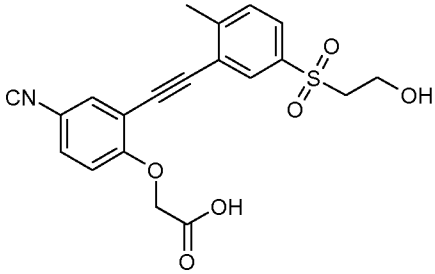
Ex.	Formula	Ex.	Formula
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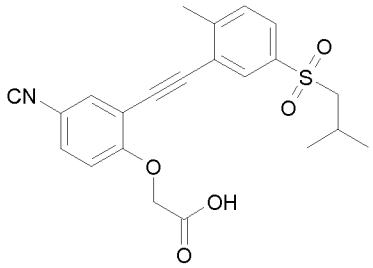
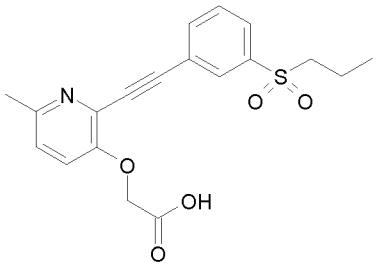
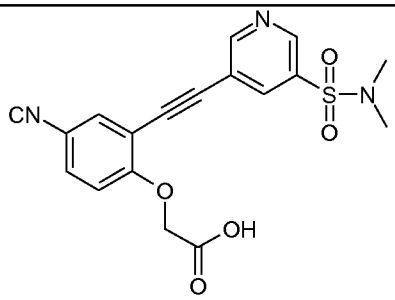
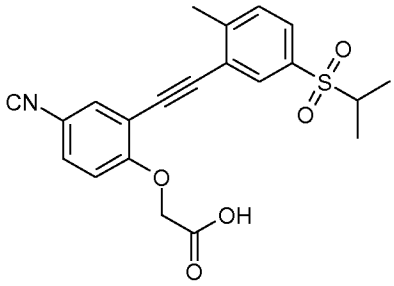
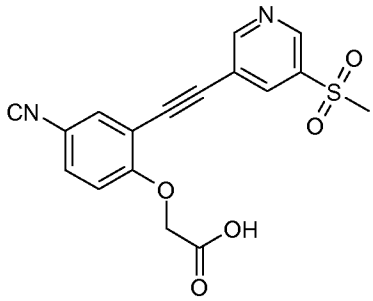
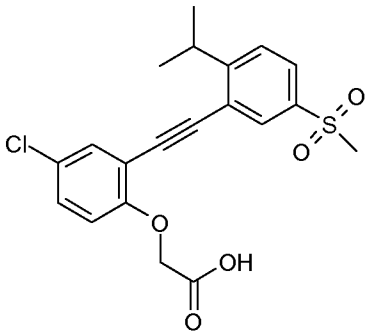
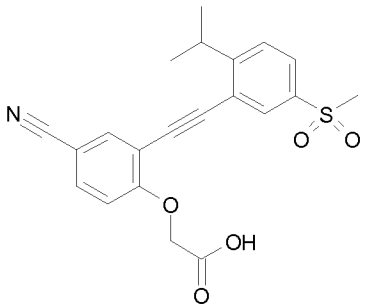
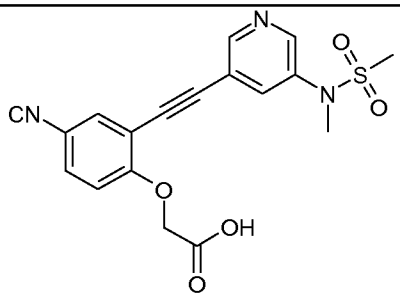
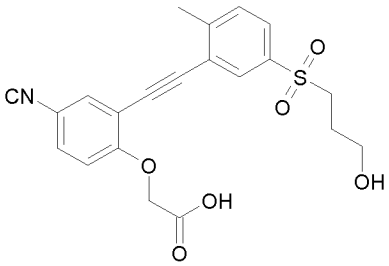
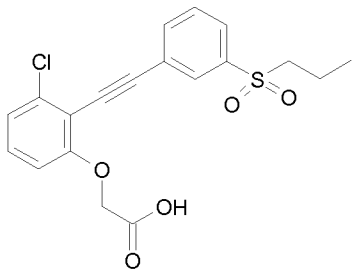
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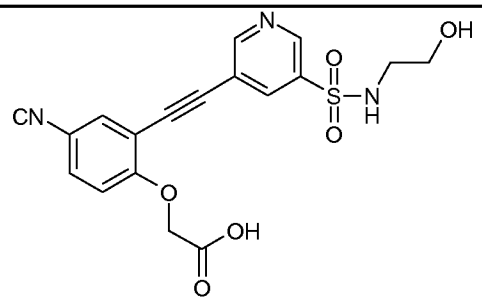
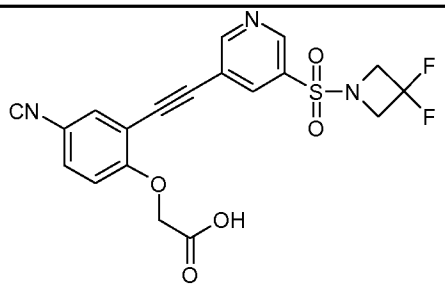
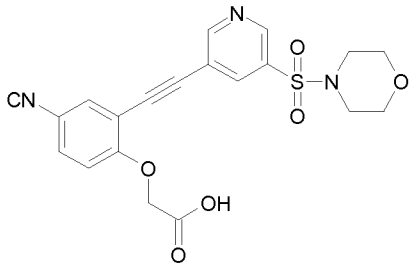
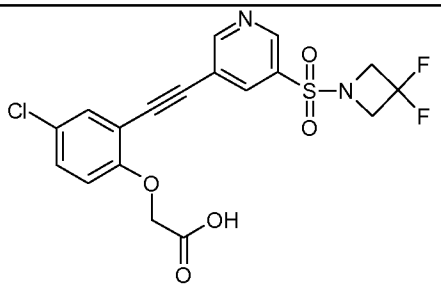
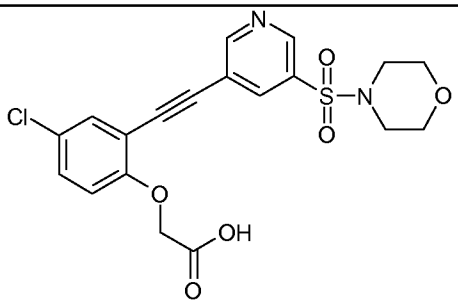
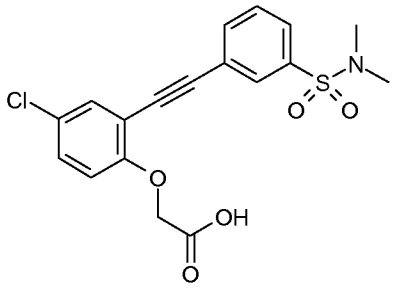
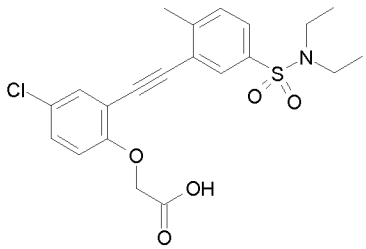
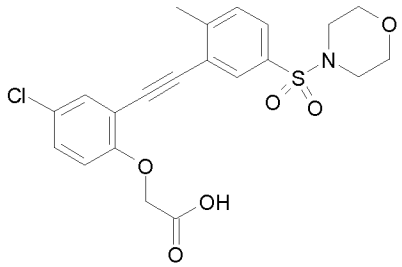
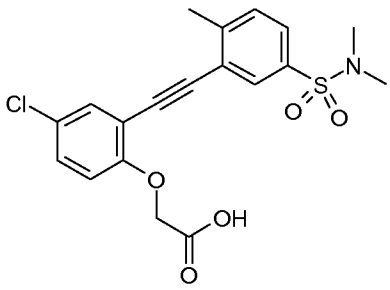
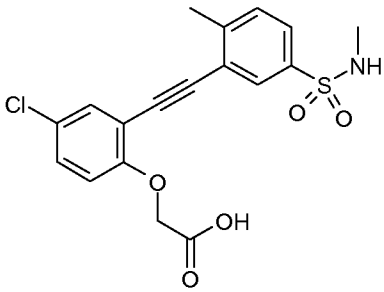
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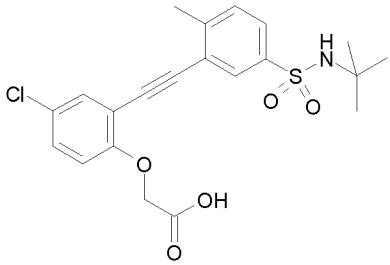
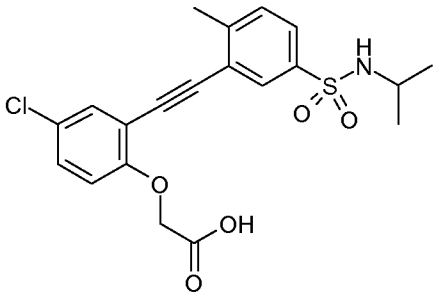
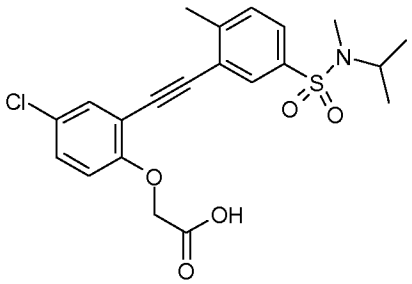
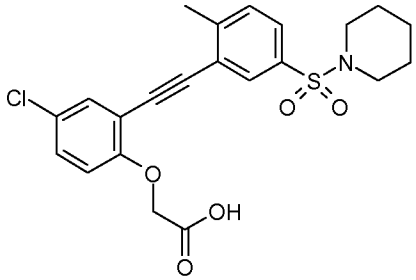
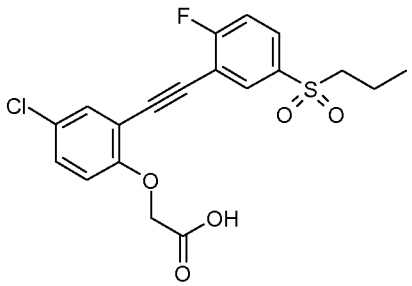
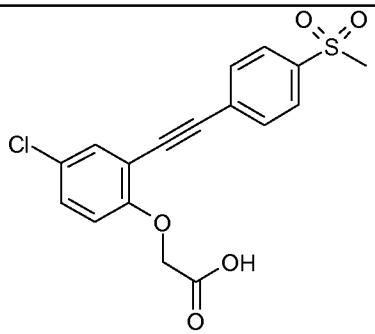
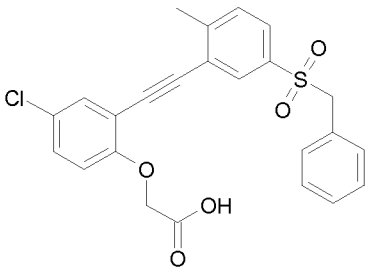
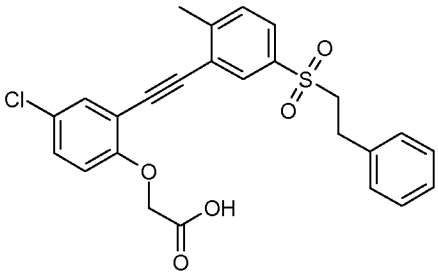
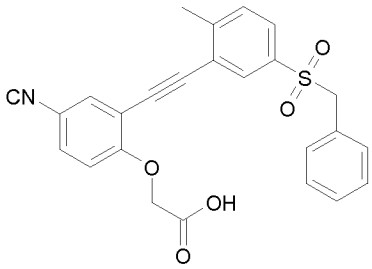
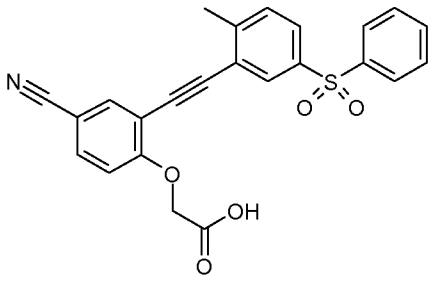
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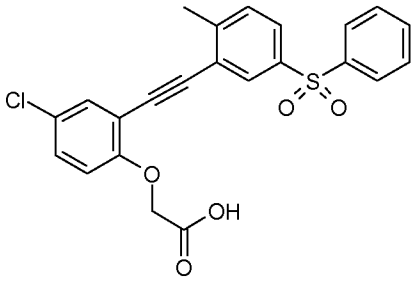
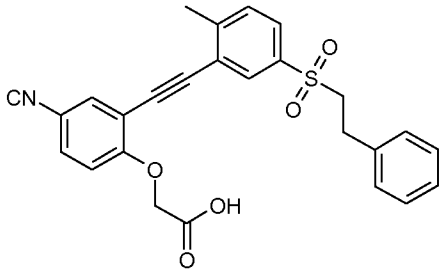
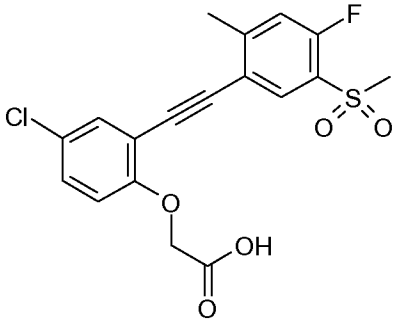
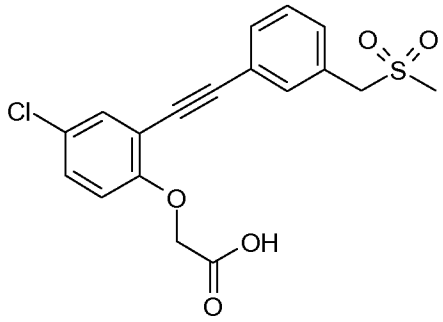
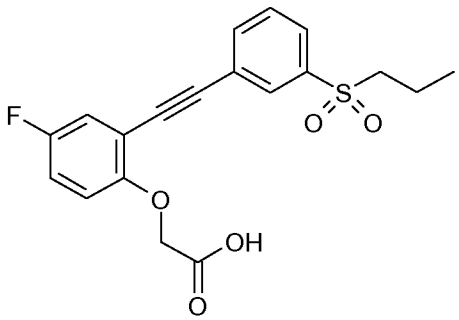
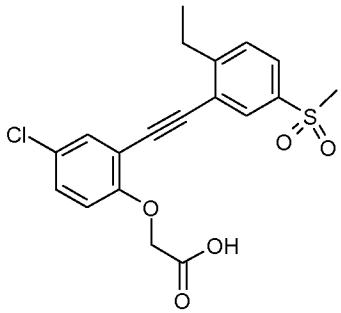
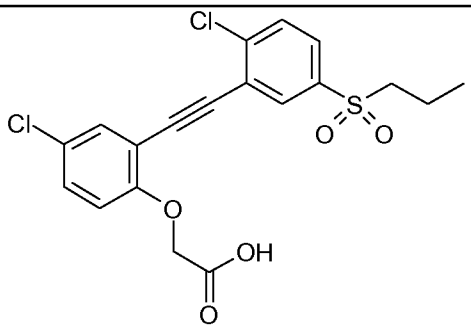
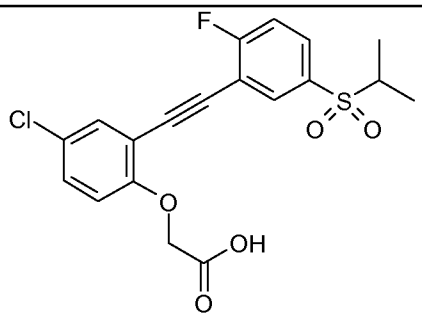
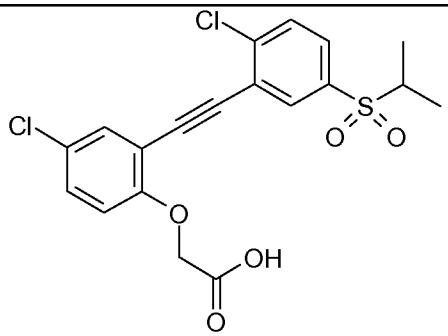
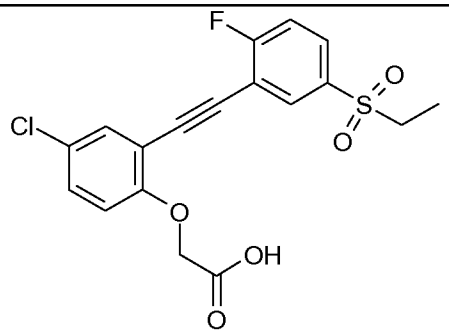
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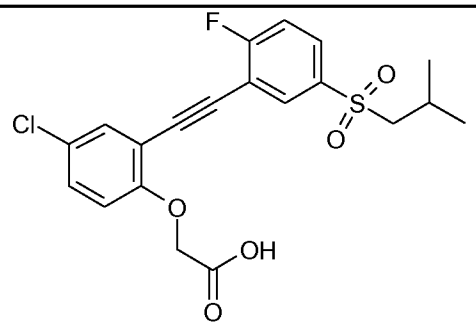
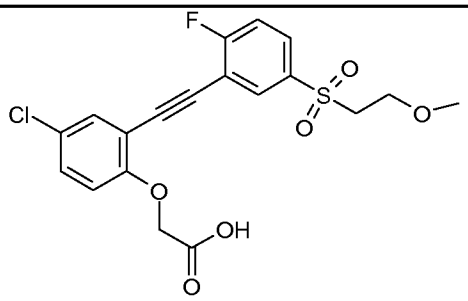
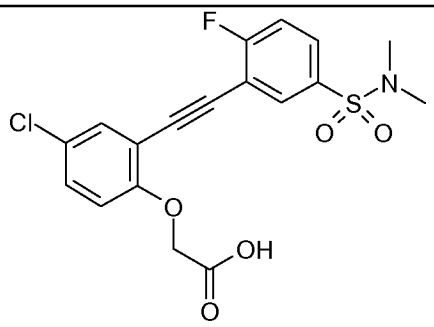
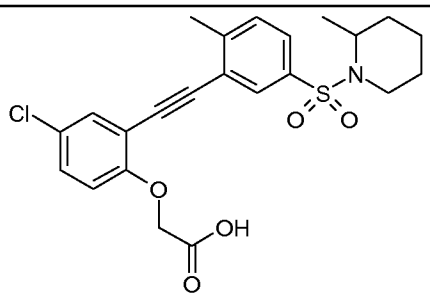
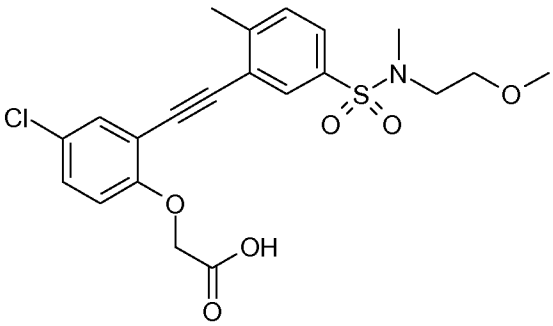
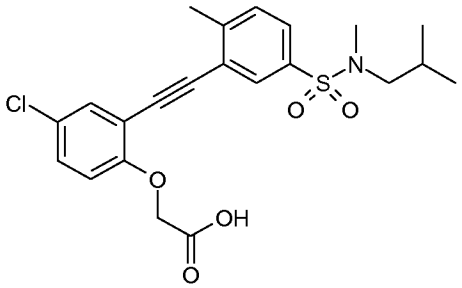
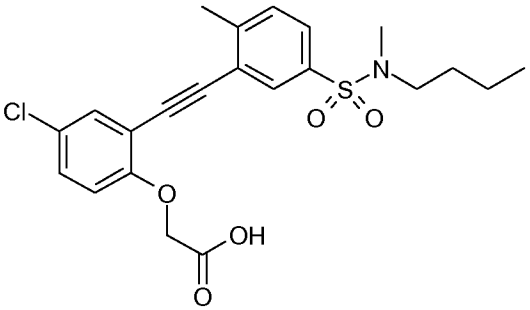
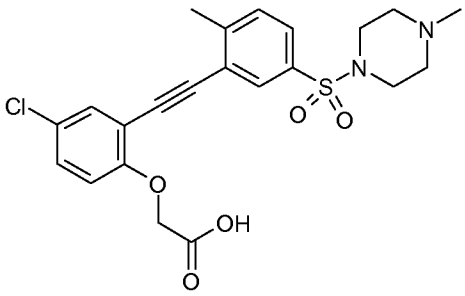
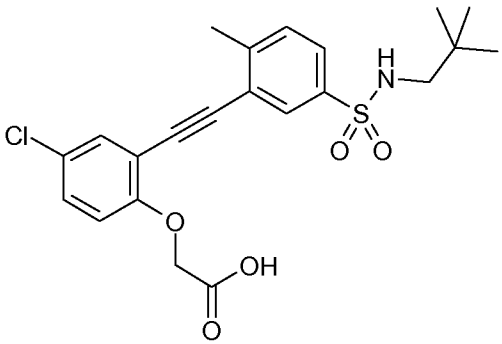
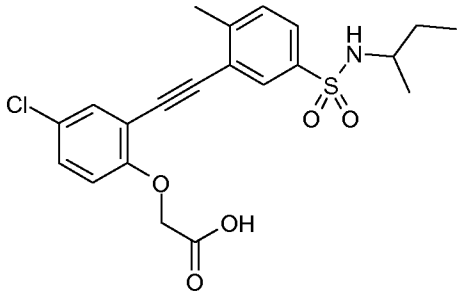
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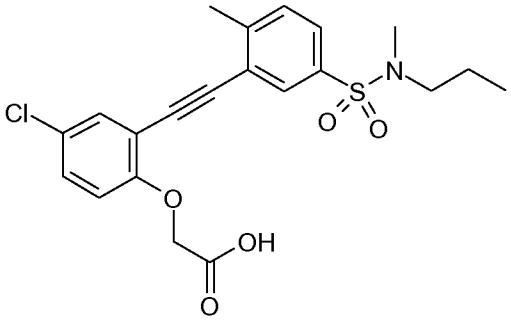
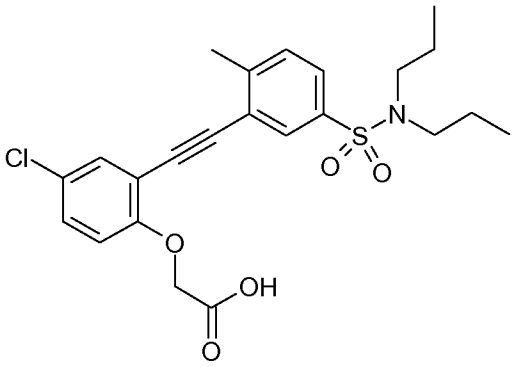
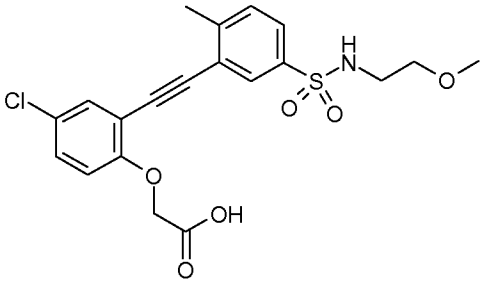
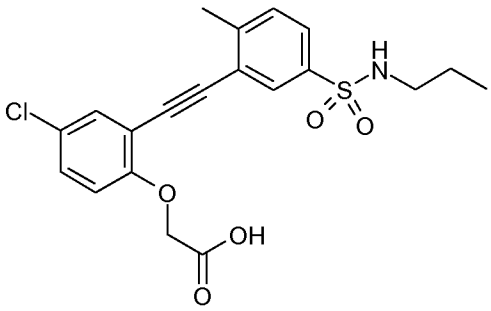
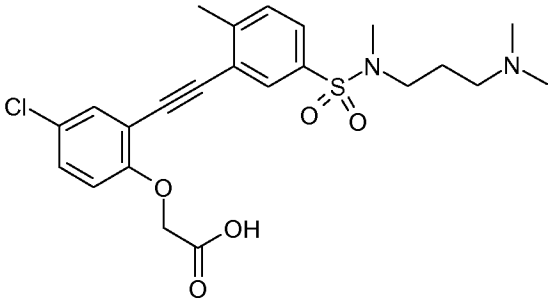
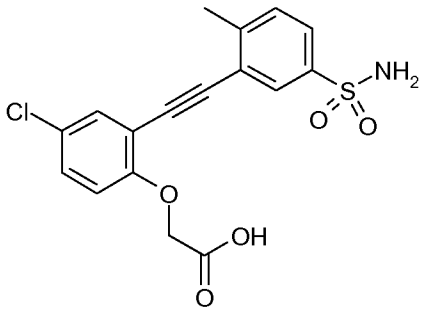
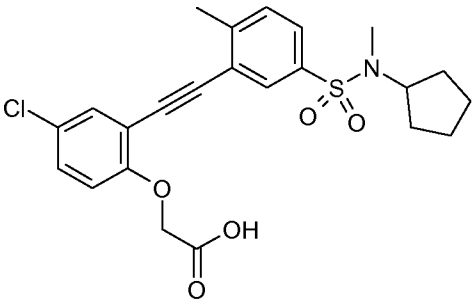
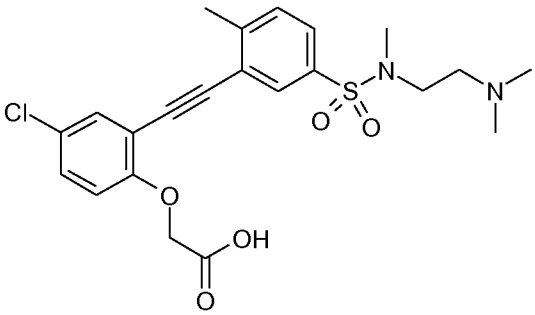
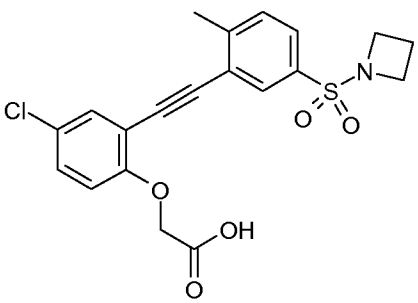
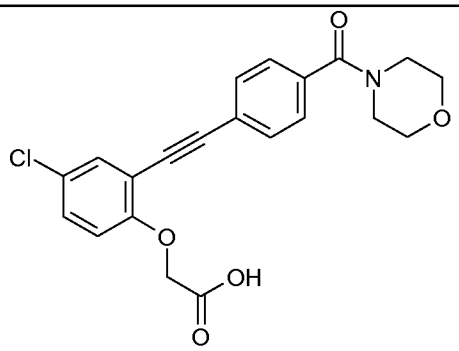
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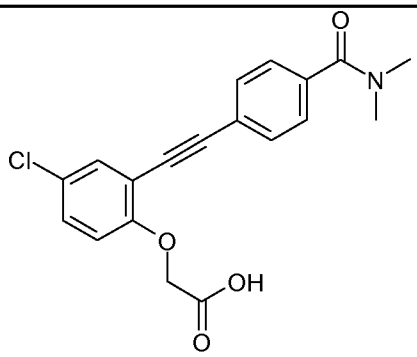
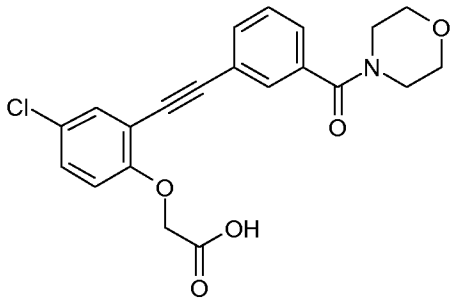
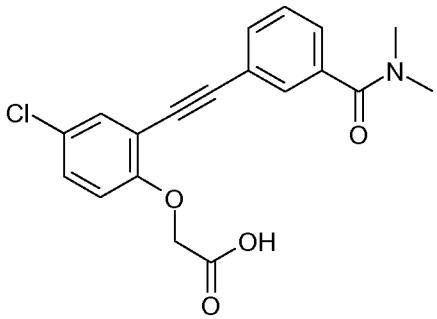
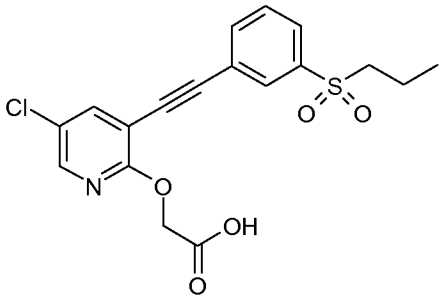
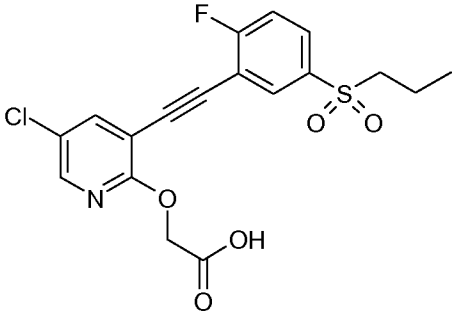
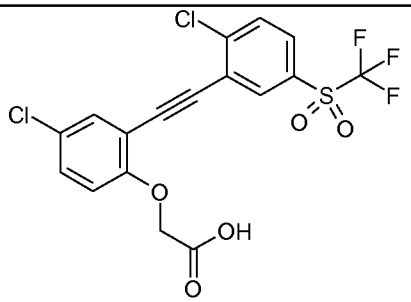
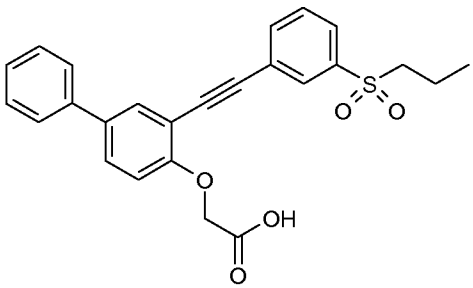
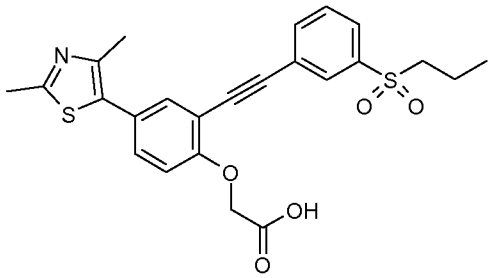
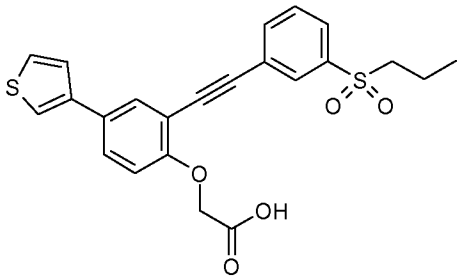
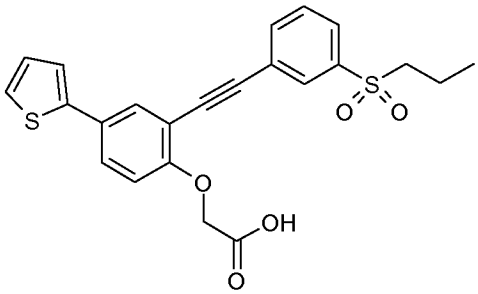
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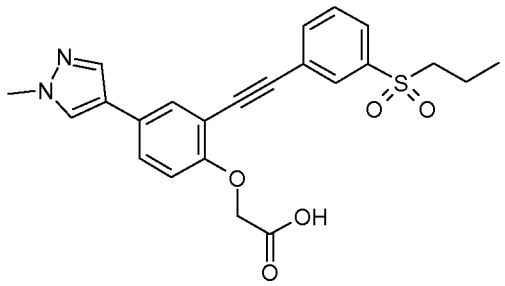
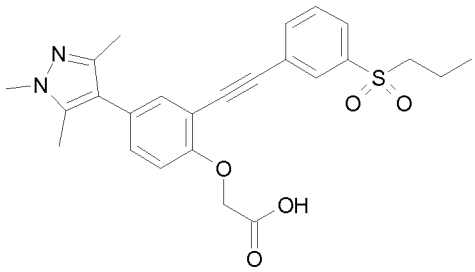
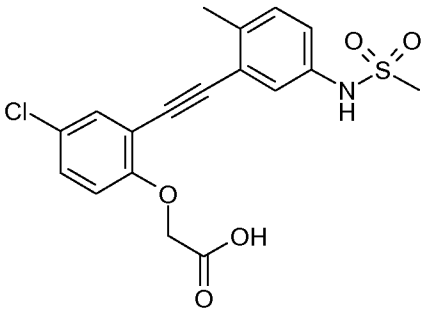
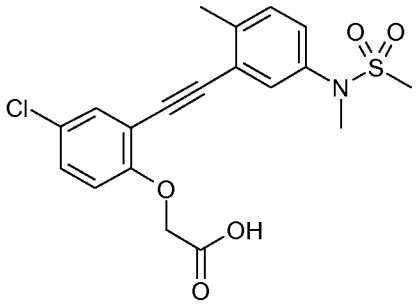
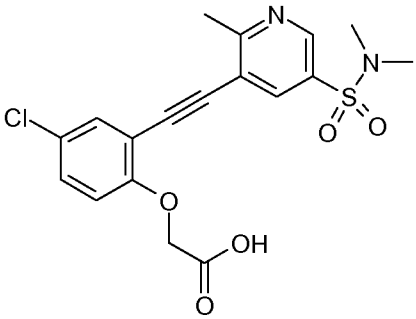
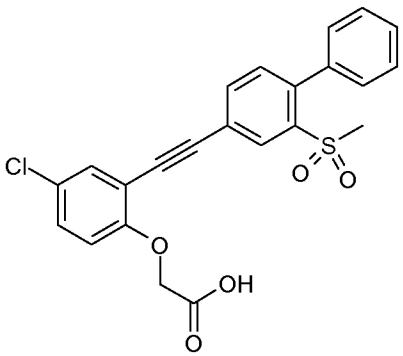
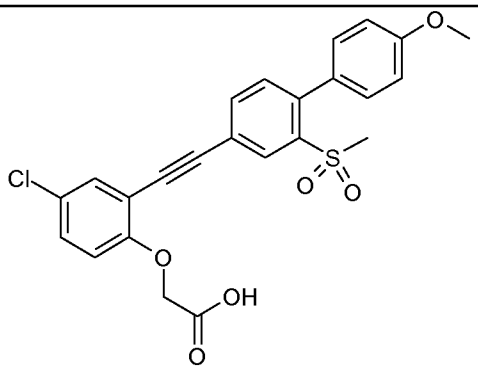
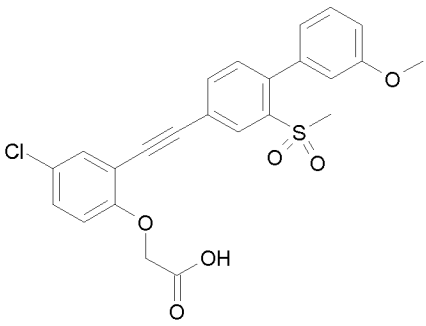
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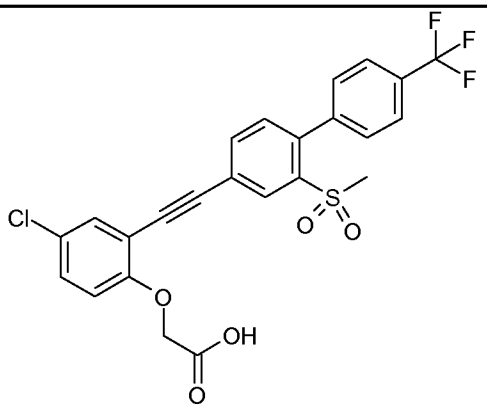
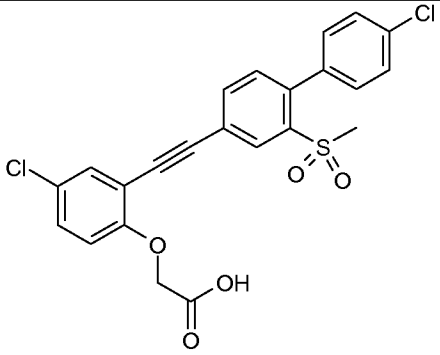
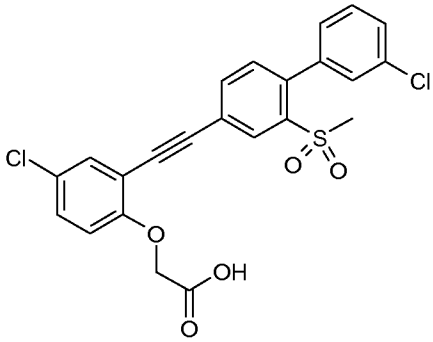
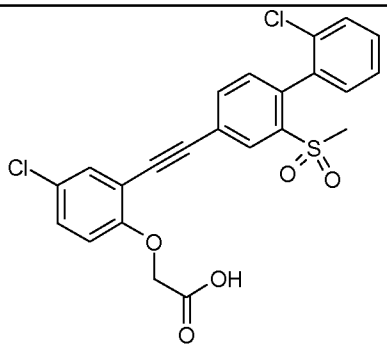
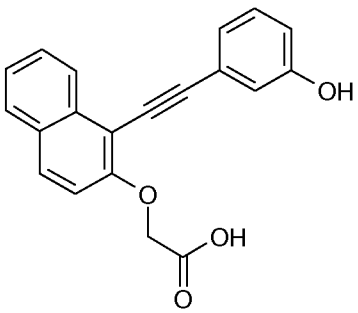
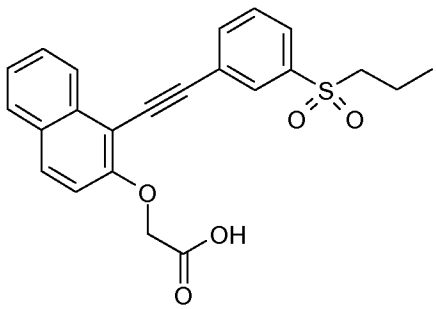
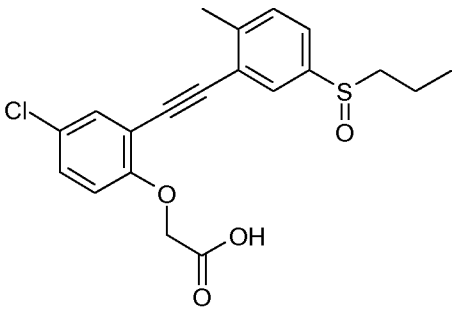
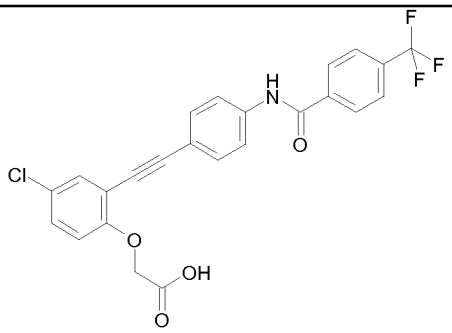
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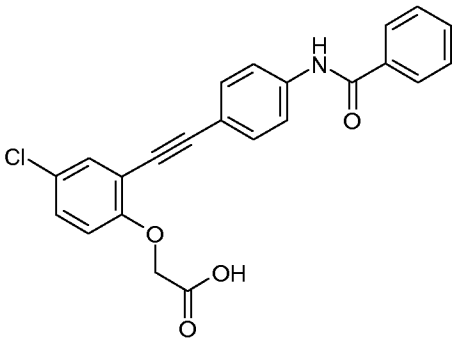
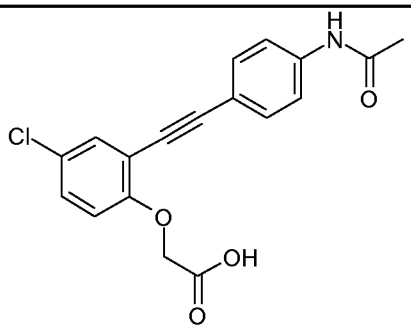
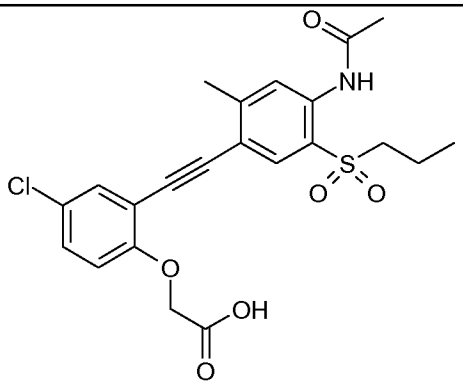
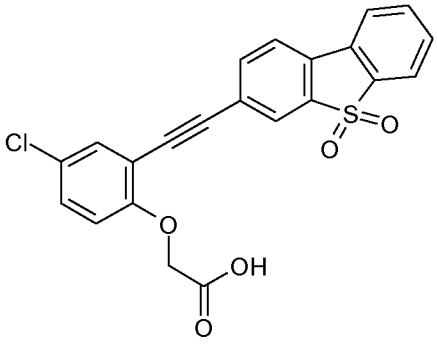
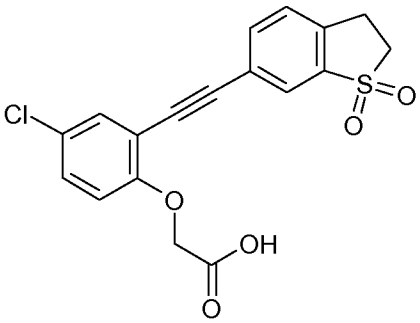
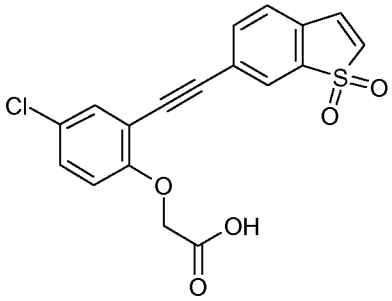
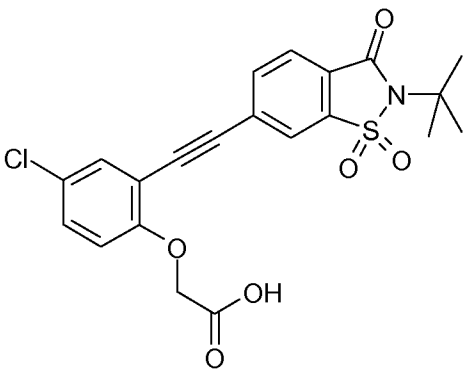
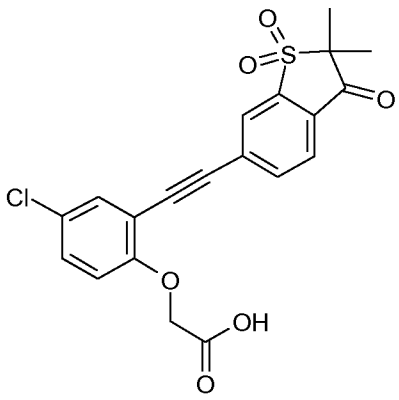
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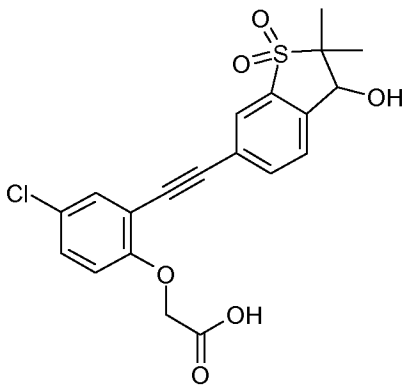
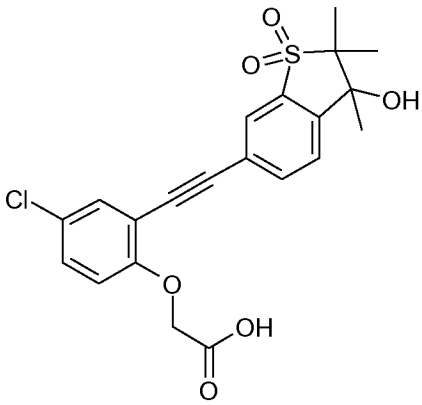
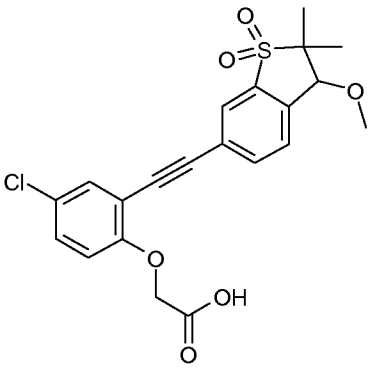
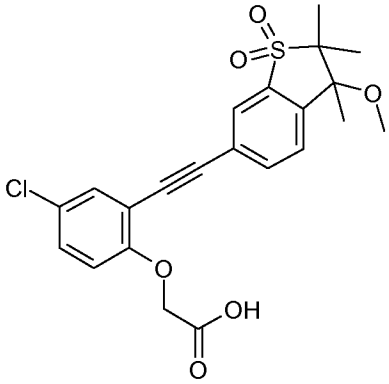
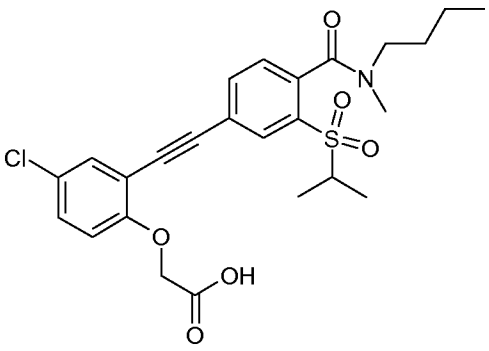
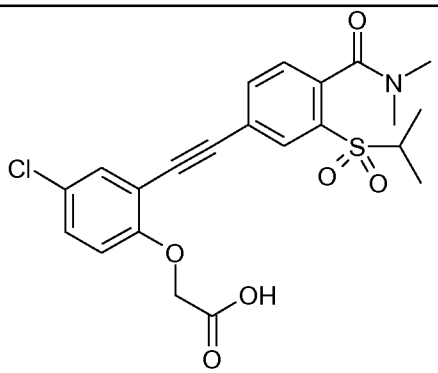
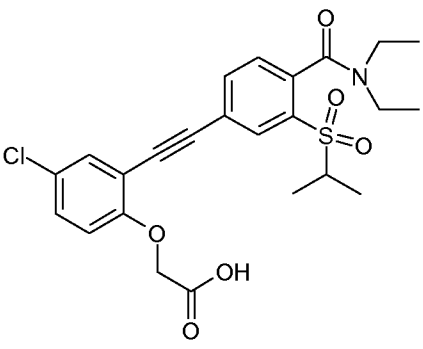
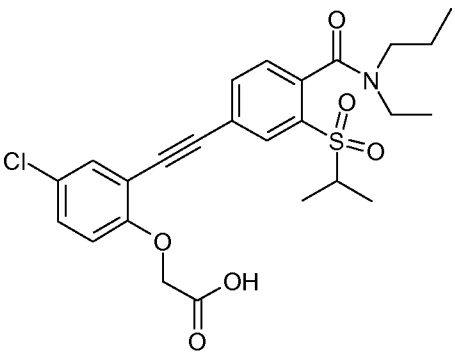
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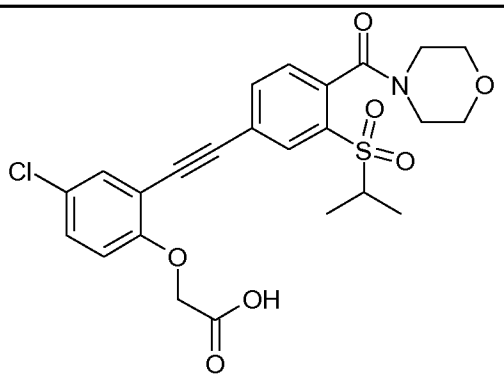
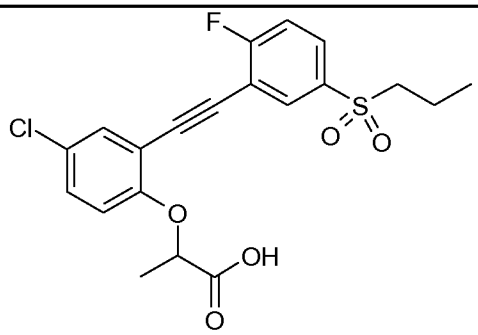
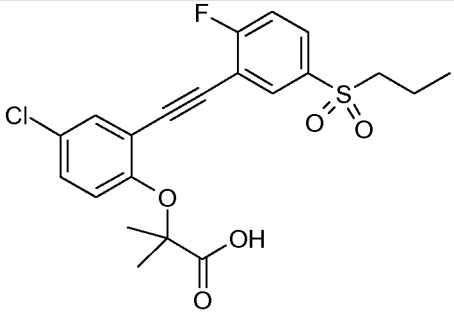
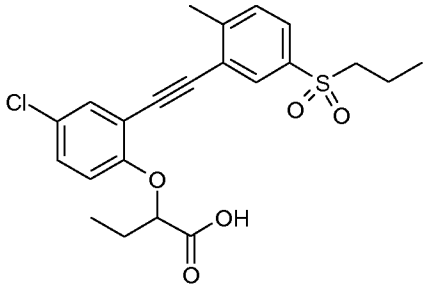
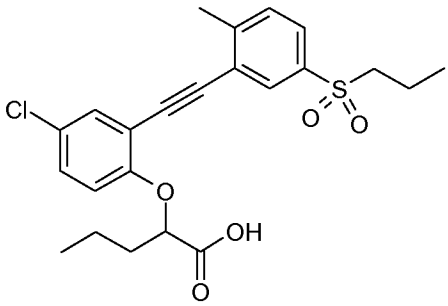
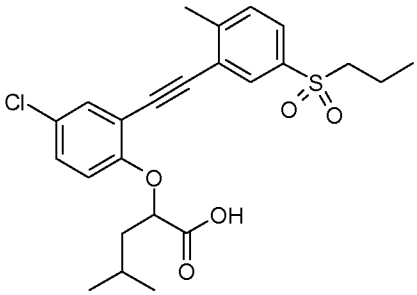
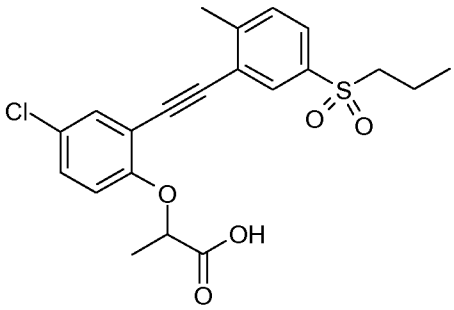
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6. A pharmaceutical composition containing at least one compound of Formula (I) according to claim 1 and a pharmaceutically acceptable carrier, diluent or excipient thereof.

7. A kit consisting of separate packs of :

(a) an effective amount of a compound of formula (I) and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and

(b) an effective amount of a further medicament active ingredient.

8. A compound of Formula (I) according to claim 1 for use as a medicament.

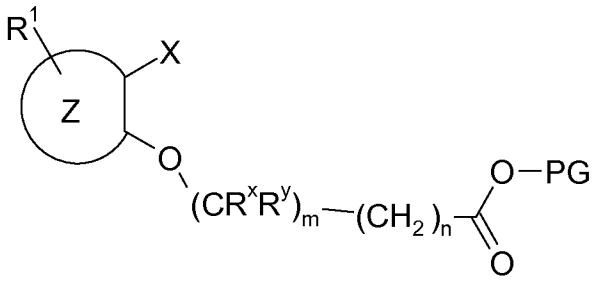
9. A compound of Formula (I) according to claim 1 for use in the treatment and/or prevention of allergic disease, inflammatory dermatoses, inflammatory diseases and neurodegenerative disorders.

10. A compound according to claim 9 wherein said disease is selected from the group consisting of allergic asthma, allergic rhitinitis, allergic conjunctivitis, systemic anaphylaxis, COPD, rheumatoid arthtitis, osteoarthritis, inflammatory bowel disease, ulcerative colitis, Crohn disease, or hypersensitivity response.

11. A compound according to claim 9 wherein said inflammatory dermatosis is selected from the group consisting of atopic dermatitis, contact hypersensitivity, allergic contact dermititis, eczema, myositis, chronic urticaria/chronic, idiopatic/ autoimmune urticaria, drug induced exanthems, photodermatosis or polymorphous light eruption and myosotis.

12. A compound according to claim 8 for use in the modulation of CRTH2 activity.

13. A process for the preparation of compounds of Formula (I) according to claim 1 wherein compounds of Formula (II)



(II)

wherein R^1, X, m and n are as defined in claim 1, and wherein PG denotes a protecting group,
are reacting with compounds of Formula (III)



(III)

wherein X denotes Cl, Br, I, or trifluoromethanesulfonate and wherein Q is as defined in claim 1 in the presence of a catalyst.

14. A process according to claim 13 wherein the catalyst is selected from dichlorobis(triphenylphosphine)palladium(II) or 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II), $Pd(OAc)_2$, $Pd_2(dba)_3$, or Pd/C

15. A process according to claim 14 further comprising the step of removing the protecting group.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/051567

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C59/70 A61P7/06 A61P37/00 A61P25/28 A61P17/00
A61K31/192 C07D213/30 C07D213/65 C07D213/71 C07D213/76
C07D233/64 C07D277/24 C07D333/28 C07D401/12 C07D295/096

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)
C07C C07D A61P A61K

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, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KANAZAWA, CHIKASHI ET AL: "Phosphazene base-catalyzed intramolecular cyclization for efficient synthesis of benzofurans via carbon-carbon bond formation" CHEMICAL COMMUNICATIONS, vol. 35, 2009, pages 5248-5250, XP008121080 ISSN: 1359-7345 DOI: 10.1039/b913588j table 3; compounds 1h, 1i, 1l, 1m, 1n, 3a	1
A	WO 2007/062773 A (7TM PHARMA AS [DK]; RECEVEUR JEAN-MARIE [DK]; CHRISTENSEN ANN [DK]; GR) 7 June 2007 (2007-06-07) cited in the application the whole document	1-15

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[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
9 April 2010	16/04/2010

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/051567

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A	figure 1; table 1; compounds 8ah, 9ah,10ah	1-5

INTERNATIONAL SEARCH REPORT

Information on patent family members

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