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### Novel caspase inhibitors

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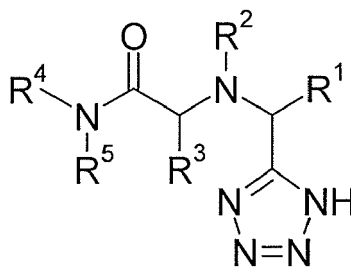
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(54) **NOVEL CASPASE INHIBITORS**

(57) The present invention provides novel compounds of formula (I) that are potent and selective non-covalent caspase inhibitors. These compounds may be used for the treatment of inflammatory diseases.



(I)

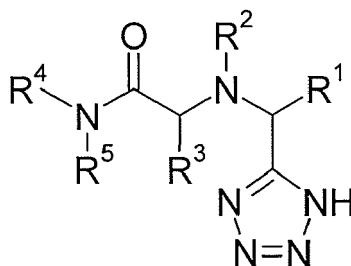
## Description

**[0001]** The present invention provides novel compounds that are potent and selective non-covalent caspase inhibitors. These compounds may be used for the treatment of inflammatory diseases.

**[0002]** Caspase-1 is the key enzyme driving inflammation through the activation of IL1b and IL18. It plays a key driving role in diseases such as Alzheimer, Parkinson, stroke, diabetes, multiple sclerosis, amyotrophic lateral sclerosis. Caspase-1 inhibitors are therefore of great interest for the treatment of a variety of diseases.

**[0003]** Several caspase inhibitors have already been elucidated in clinical trials and are all covalent inhibitors (e.g. Belnacasan, Pralnacasan). None of the compounds showed sufficient efficacy to be approved for use for any of the applications suggested to date. Covalent inhibitors might have secondary targets and therefore show toxic side effects. On the other hand non covalent inhibitors might be more selective and exhibit less side effects. Therefore, we present here a class of noncovalent Caspase-1 inhibitors.

**[0004]** The present invention provides compounds of formula (I):



(I)

wherein

$R^1$  is a hydrogen atom or an alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl group, all of which groups may optionally be substituted;

$R^2$  is a hydrogen atom or an alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl group, all of which groups may optionally be substituted;

$R^3$  is a hydrogen atom or an alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl group, all of which groups may optionally be substituted;

$R^4$  is a hydrogen atom or an alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl group, all of which groups may optionally be substituted; and

$R^5$  is a hydrogen atom or an alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl group, all of which groups may optionally be substituted;

or a pharmaceutically acceptable salt, ester, solvate or hydrate or a pharmaceutically acceptable formulation thereof.

**[0005]** In the following, preferred embodiments of the present invention are disclosed. It is preferred that the preferred embodiments may be combined in any manner:

Preferably,  $R^1$  is alkylcycloalkyl containing 4 to 16 carbon atoms; heteroalkylcycloalkyl containing 4 to 16 atoms selected from C, O, S and N; aralkyl containing 7 to 16 carbon atoms; or heteroaralkyl containing 6 to 16 atoms selected from C, O, S and N; wherein all these groups may optionally be substituted.

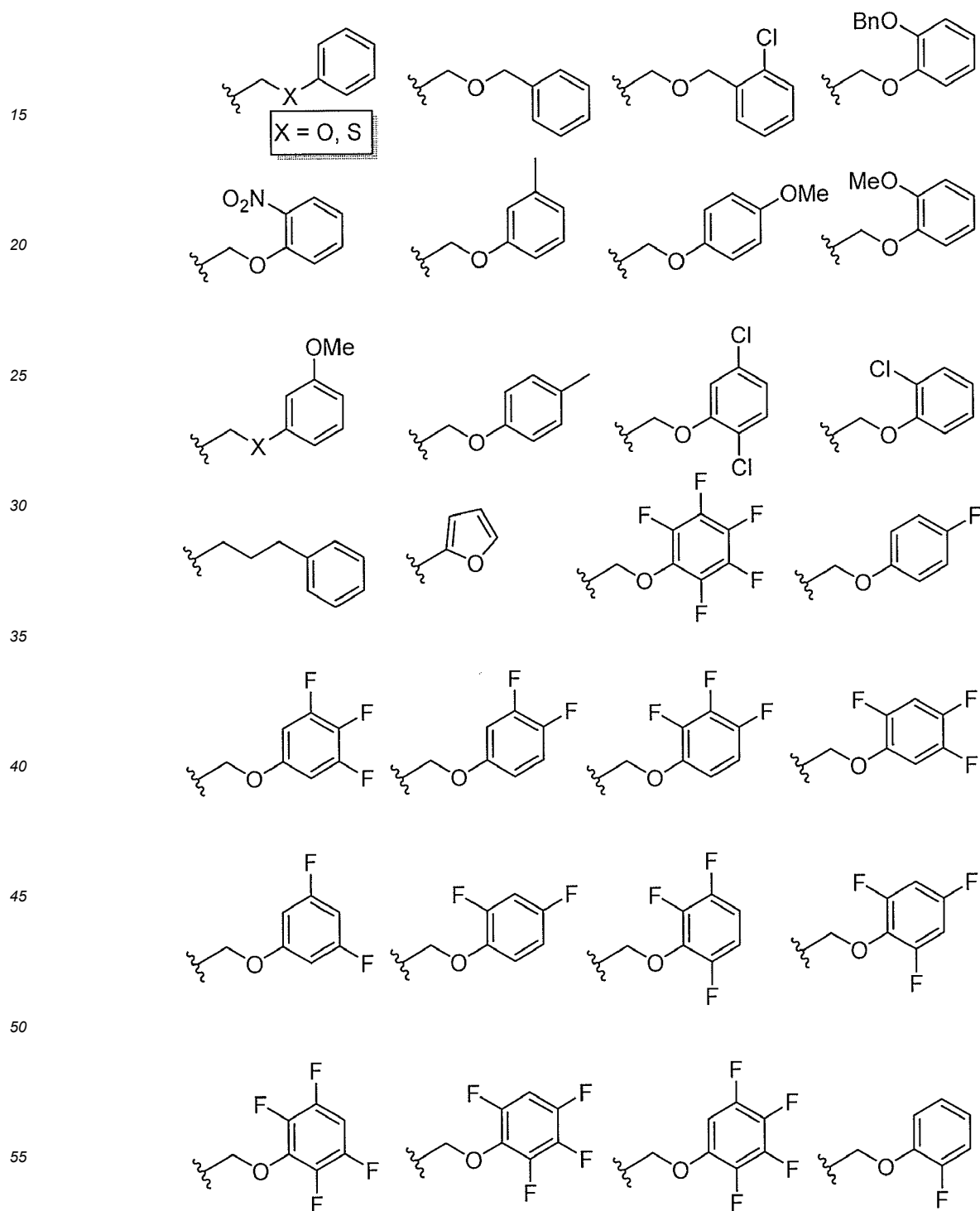
**[0006]** More preferably,  $R^1$  is a group of formula  $-CH_2-X-R^{10}$  wherein X is O, S or NH (especially O) and  $R^{10}$  is a cycloalkyl, heterocycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl group, all of which groups may optionally be substituted. Preferably,  $R^{10}$  is cycloalkyl containing one or two rings and 3 to 10 carbon atoms; alkylcycloalkyl containing one or two rings and 4 to 16 carbon atoms; heterocycloalkyl containing one or two rings and 3 to 10 ring atoms selected from C, O, S and N; heteroalkylcycloalkyl containing one or two rings and 4 to 16 atoms selected from C, O, S and N; phenyl; naphthyl; heteroaryl containing one or two rings and 5 to 10 ring atoms selected from C, O, S and N; aralkyl containing one or two rings and 7 to 16 carbon atoms; or heteroaralkyl containing one or two rings and 6 to 16 atoms selected from C, O, S and N; wherein all these groups may optionally be substituted by halogen, OH,  $NO_2$ , OMe, Me, =O,  $NH_2$ , NHMe or  $NMe_2$  or a group of formula  $-O-CH_2CH_2-O-$  or  $-O-CH_2-O-$ .

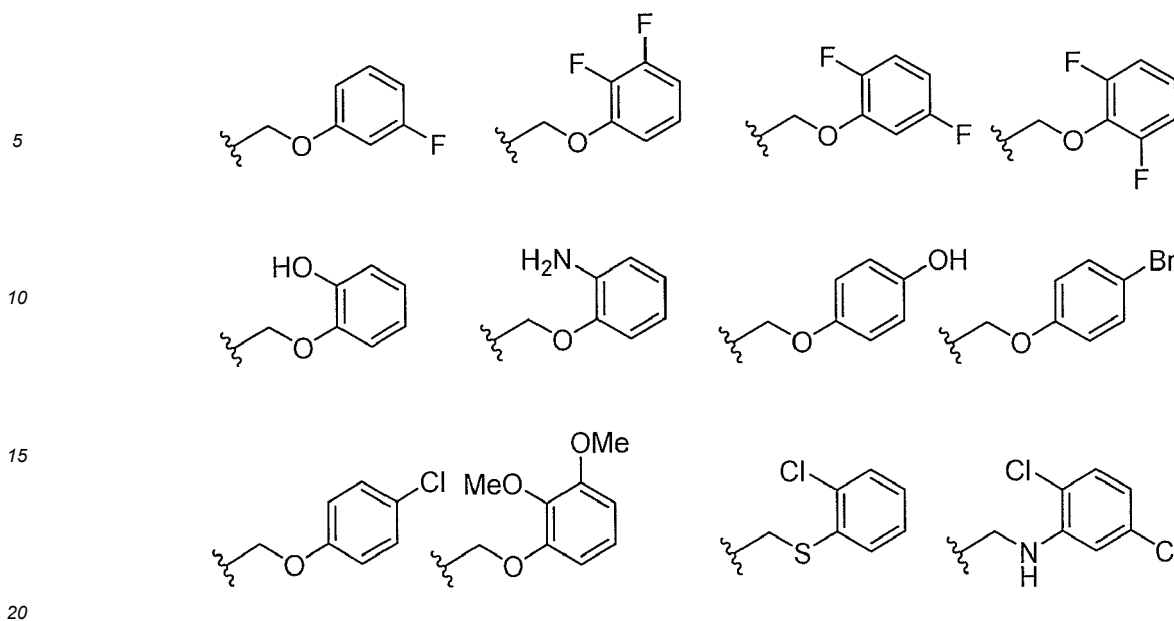
**[0007]** More preferably, R<sup>10</sup> is phenyl, naphthyl or a heteroaryl group containing one or two rings and 5 to 10 ring atoms selected from C, O, S and N, wherein all these groups may optionally be substituted by halogen, OH, NO<sub>2</sub>, OMe, Me, NH<sub>2</sub>, NHMe or NMe<sub>2</sub> or a group of formula -O-CH<sub>2</sub>CH<sub>2</sub>-O- or -O-CH<sub>2</sub>-O-.

**[0008]** Especially preferably, R<sup>10</sup> is phenyl or a heteroaryl group containing 5 or 6 ring atoms selected from C, O, S and N, wherein all these groups may optionally be substituted by halogen, OH, NO<sub>2</sub>, OMe, Me, NH<sub>2</sub>, NHMe or NMe<sub>2</sub> or a group of formula -O-CH<sub>2</sub>CH<sub>2</sub>-O- or -O-CH<sub>2</sub>-O-.

**[0009]** Most preferably, R<sup>10</sup> is a phenyl group which may optionally be substituted by halogen, OH, NO<sub>2</sub>, OMe, Me, NH<sub>2</sub>, NHMe or NMe<sub>2</sub> or a group of formula -O-CH<sub>2</sub>CH<sub>2</sub>-O- or -O-CH<sub>2</sub>-O-.

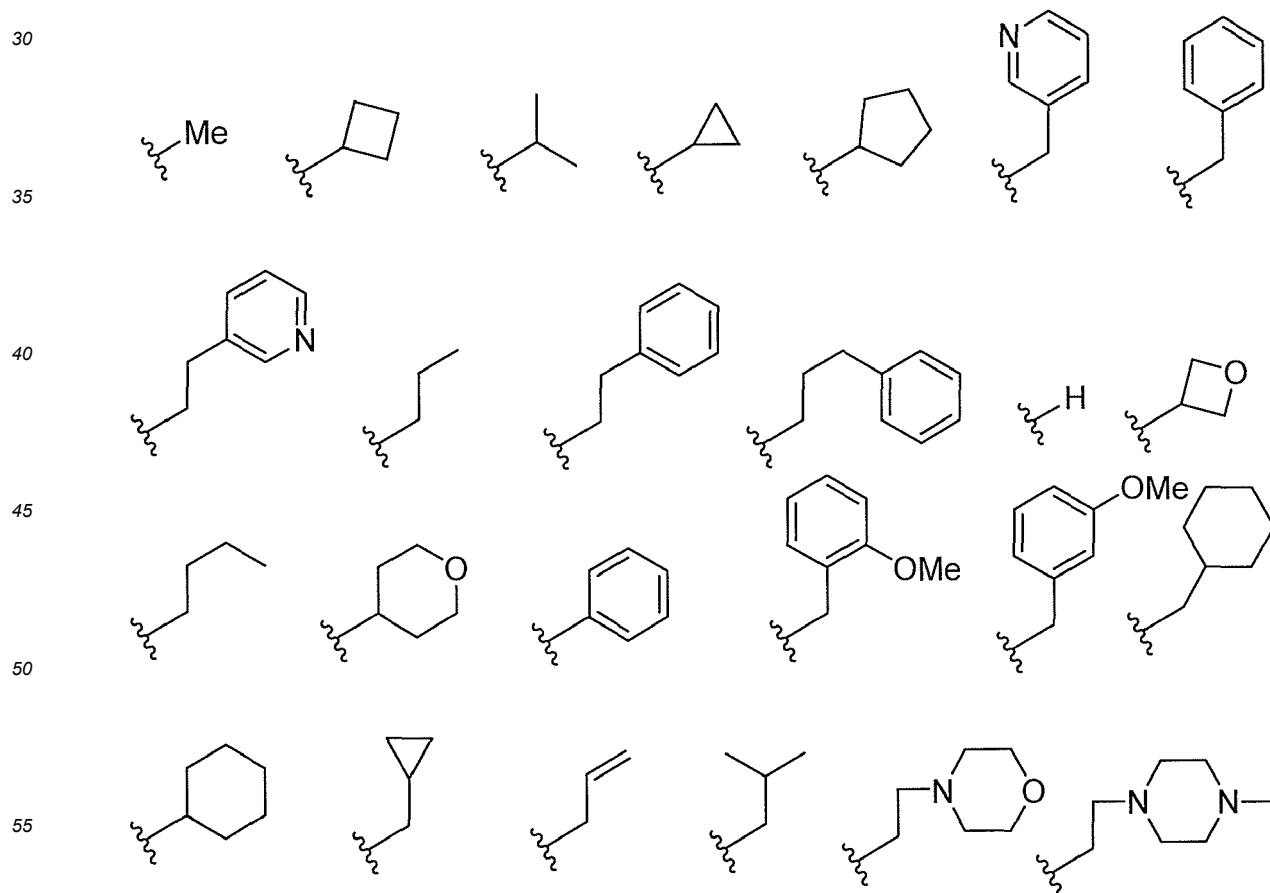
**[0010]** Especially preferably, R<sup>1</sup> is selected from the following groups:





**[0011]** Further preferably,  $R^2$  is Ci-6 alkyl;  $C_{2-6}$  alkenyl;  $C_{1-6}$  alkynyl; heteroalkyl containing 1 to 6 carbon atoms and 1 to 4 heteroatoms selected from O, S and N;  $C_{3-7}$  cycloalkyl;  $C_{4-10}$  alkylcycloalkyl; heterocycloalkyl containing 3 to 7 ring atoms selected from C, O, S and N; heteroalkylcycloalkyl containing 4 to 10 atoms selected from C, O, S and N; phenyl; heteroaryl containing 5 or 6 ring atoms selected from C, O, S and N; aralkyl containing 7 to 12 carbon atoms; or heteroaralkyl containing 6 to 12 atoms selected from C, O, S and N; wherein all these groups may optionally be substituted by halogen, OH,  $NO_2$ , OMe, Me, =O,  $NH_2$ , NHMe or  $NMe_2$ .

**[0012]** More preferably,  $R^2$  is selected from the following groups:



[0013] Especially preferably, R<sup>2</sup> is methyl.

[0014] Moreover preferably, R<sup>3</sup> is hydrogen.

[0015] Further preferably, R<sup>4</sup> is hydrogen.

[0016] Moreover preferably, R<sup>5</sup> is an aryl, heteroaryl, aralkyl or heteroaralkyl group, all of which groups may optionally be substituted.

[0017] Further preferably, R<sup>5</sup> is a group of formula -Ar-L-Cy, wherein Ar is an arylene, heteroarylene, aralkylene or heteroaralkylene group, all of which groups may optionally be substituted; L is a bond, -O-, -NH-, -S- or a C<sub>1-4</sub> alkyl group or a heteroalkyl group containing 1 to 6 atoms selected from C, O, S and N; and Cy is a cycloalkyl, heterocycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl group, all of which groups may optionally be substituted.

[0018] Further preferably, Ar is an optionally substituted phenylene group or an optionally substituted heteroarylene group containing 5 or 6 ring atoms selected from C, O, S and N.

[0019] Especially preferably, Ar is an optionally substituted phenylene group.

[0020] Moreover preferably, Ar is unsubstituted or substituted by a halogen atom or a methoxy group.

[0021] Further preferably, L is -O-, -CH<sub>2</sub>O- or -OCH<sub>2</sub>-; especially -O-.

[0022] Moreover preferably, Cy is cycloalkyl containing one or two rings and 3 to 10 carbon atoms; heterocycloalkyl containing one or two rings and 3 to 10 ring atoms selected from C, O, S and N; phenyl; naphthyl; or heteroaryl containing one or two rings and 5 to 10 ring atoms selected from C, O, S and N; all of which groups may optionally be substituted.

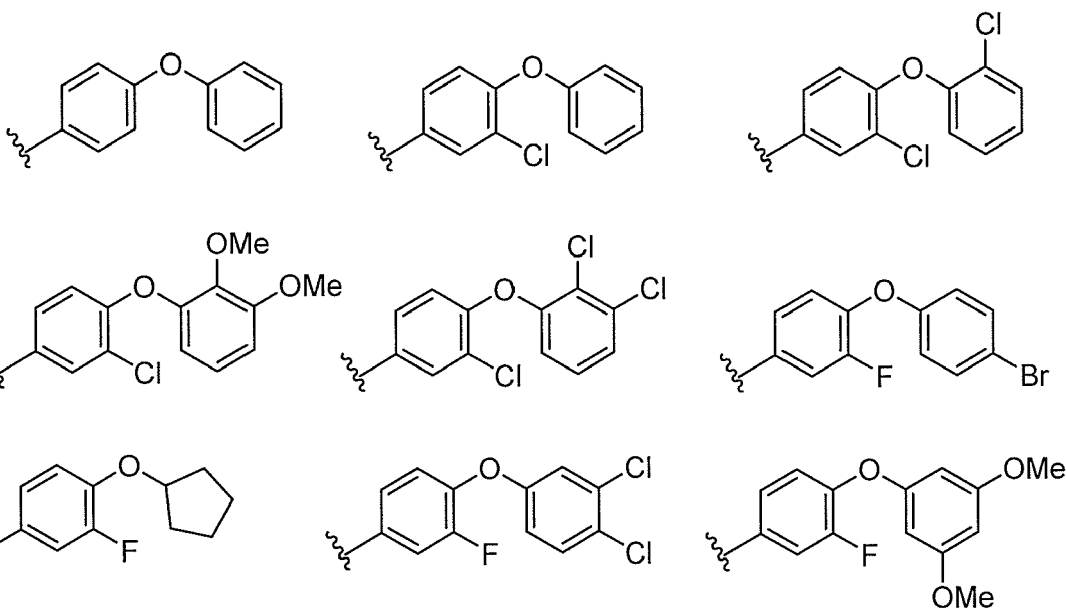
[0023] More preferably, Cy is phenyl, naphthyl or heteroaryl containing one or two rings and 5 to 10 ring atoms selected from C, O, S and N; all of which groups may optionally be substituted.

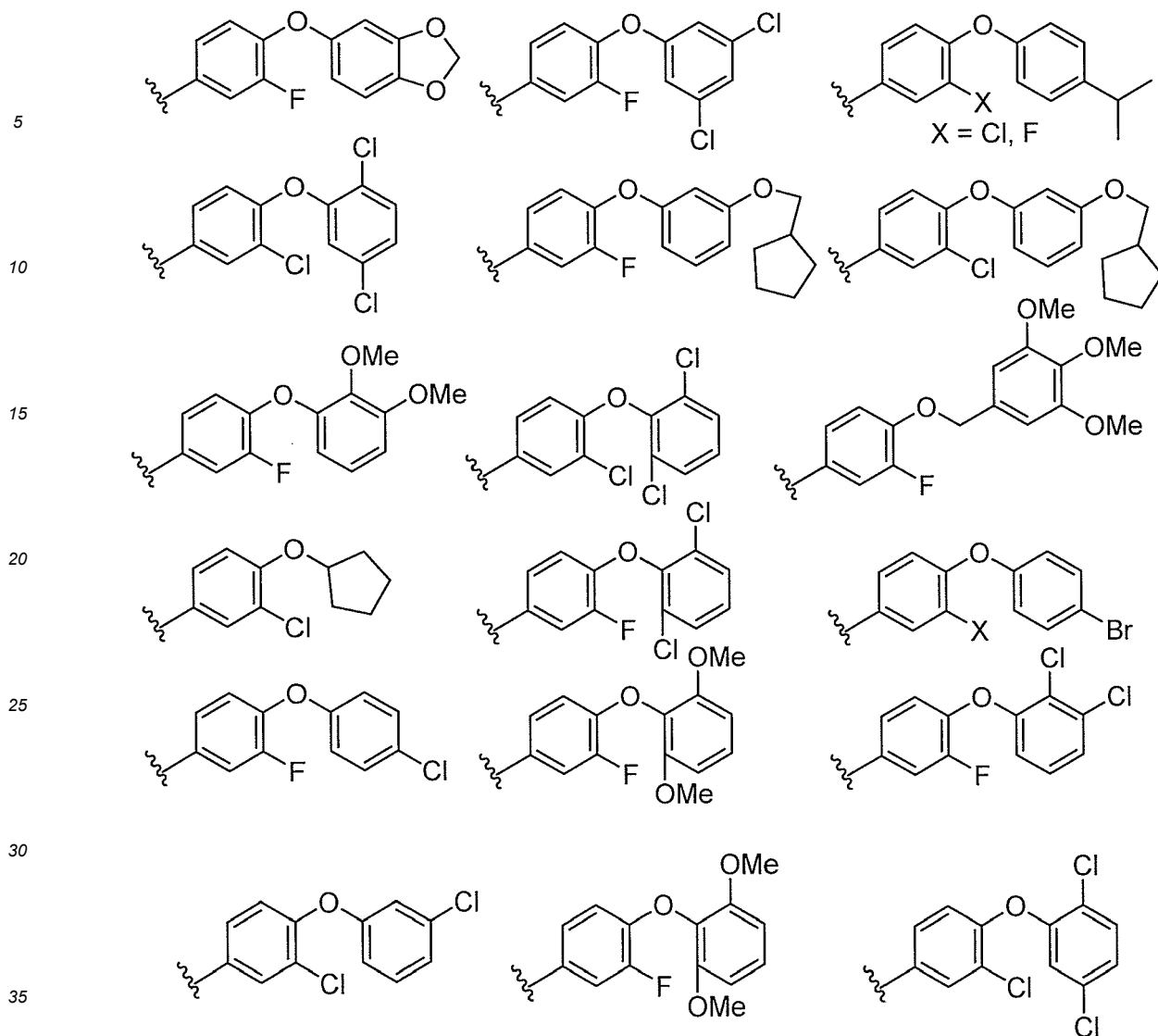
[0024] Further preferably, Cy is phenyl or heteroaryl containing 5 or 6 ring atoms selected from C, O, S and N; all of which groups may optionally be substituted.

[0025] Most preferably, Cy is an optionally substituted phenyl group.

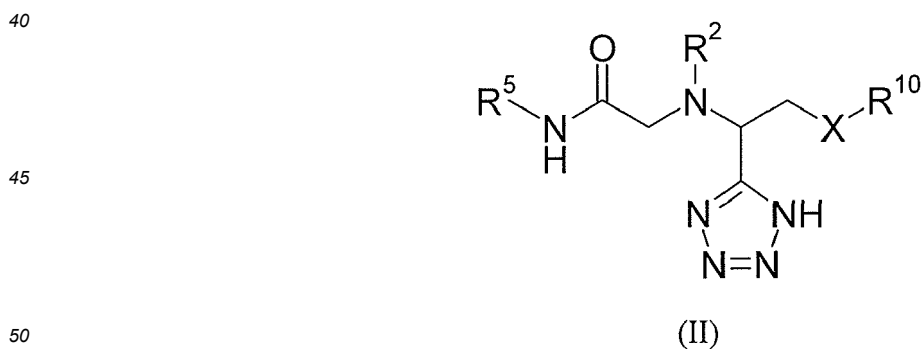
[0026] Further preferably, Cy is unsubstituted or substituted by halogen, O-C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkyl or a group of formula -O-CH<sub>2</sub>CH<sub>2</sub>-O- or -O-CH<sub>2</sub>-O-.

[0027] More preferably, R<sup>5</sup> is selected from the following groups:





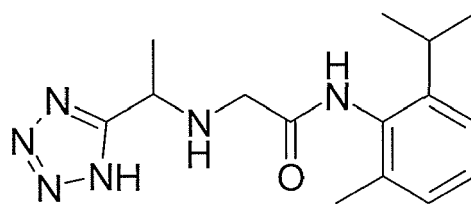
[0028] Especially preferably, the compounds of the present invention have the following formula (II):



wherein X, R<sup>2</sup>, R<sup>3</sup> and R<sup>10</sup> are as defined above.

[0029] Further preferably, the following compound is excluded from the scope of the present invention:

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10 **[0030]** The expression alkyl refers to a saturated, straight-chain or branched hydrocarbon group that contains from 1 to 20 carbon atoms, preferably from 1 to 12 carbon atoms, especially from 1 to 6 (e.g. 1, 2, 3 or 4) carbon atoms, for example a methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, n-hexyl, 2,2-dimethylbutyl or n-octyl group. Furthermore, the term alkyl refers to groups in which one or more hydrogen atoms have been replaced by a halogen atom (preferably F or Cl) such as, for example, a 2,2,2-trichloroethyl or a trifluoromethyl group.

15 **[0031]** The expressions alkenyl and alkynyl refer to at least partially unsaturated, straight-chain or branched hydrocarbon groups that contain from 2 to 20 carbon atoms, preferably from 2 to 12 carbon atoms, especially from 2 to 6 (e.g. 2, 3 or 4) carbon atoms, for example an ethenyl (vinyl), propenyl (allyl), iso-propenyl, butenyl, ethinyl, propinyl, butinyl, acetylenyl, propargyl, isoprenyl or hex-2-enyl group. Preferably, alkenyl groups have one or two (especially preferably one) double bond(s), and alkynyl groups have one or two (especially preferably one) triple bond(s). Furthermore, the terms alkenyl and alkynyl refer to groups in which one or more hydrogen atoms have been replaced by a halogen atom (preferably F or Cl).

20 **[0032]** The expression heteroalkyl refers to an alkyl, alkenyl or alkynyl group in which one or more (preferably 1, 2 or 3) carbon atoms have been replaced by an oxygen, nitrogen, phosphorus, boron, selenium, silicon or sulfur atom (preferably by an oxygen, sulfur or nitrogen atom) or a SO group or a SO<sub>2</sub> group. The expression heteroalkyl furthermore refers to a carboxylic acid or to a group derived from a carboxylic acid, such as, for example, acyl, acylalkyl, alkoxy-carbonyl, acyloxy, acyloxyalkyl, carboxyalkylamide or alkoxy-carbonyloxy.

25 **[0033]** Preferably, a heteroalkyl group contains from 1 to 12 carbon atoms and from 1 to 4 heteroatoms selected from oxygen, nitrogen and sulphur (especially oxygen and nitrogen). Especially preferably, a heteroalkyl group contains from 1 to 6 (e.g. 1, 2, 3 or 4) carbon atoms and 1, 2 or 3 (especially 1 or 2) hetero atoms selected from oxygen, nitrogen and sulphur (especially oxygen and nitrogen). The term C<sub>1</sub>-C<sub>6</sub> heteroalkyl refers to a heteroalkyl group containing from 1 to 6 carbon atoms and 1, 2 or 3 heteroatoms selected from O, S and/or N (especially O and/or N). The term C<sub>1</sub>-C<sub>4</sub> heteroalkyl refers to a heteroalkyl group containing from 1 to 4 carbon atoms and 1, 2 or 3 heteroatoms selected from O, S and/or N (especially O and/or N). Furthermore, the term heteroalkyl refers to groups in which one or more hydrogen atoms have been replaced by a halogen atom (preferably F or Cl).

30 **[0034]** Examples of heteroalkyl groups are groups of formulae: R<sup>a</sup>-O-Y<sup>a</sup>-, R<sup>a</sup>-S-Y<sup>a</sup>-, R<sup>a</sup>-N(R<sup>b</sup>)-Y<sup>a</sup>-, R<sup>a</sup>-CO-Y<sup>a</sup>-, R<sup>a</sup>-O-CO-Y<sup>a</sup>-, R<sup>a</sup>-CO-O-Y<sup>a</sup>-, R<sup>a</sup>-CO-N(R<sup>b</sup>)-Y<sup>a</sup>-, R<sup>a</sup>-N(R<sup>b</sup>)-CO-Y<sup>a</sup>-, R<sup>a</sup>-O-CO-N(R<sup>b</sup>)-Y<sup>a</sup>-, R<sup>a</sup>-N(R<sup>b</sup>)-CO-O-Y<sup>a</sup>-, R<sup>a</sup>-N(R<sup>b</sup>)-CO-N(R<sup>c</sup>)-Y<sup>a</sup>-, R<sup>a</sup>-O-CO-O-Y<sup>a</sup>-, R<sup>a</sup>-N(R<sup>b</sup>)-C(=NR<sup>d</sup>)-N(R<sup>c</sup>)-Y<sup>a</sup>-, R<sup>a</sup>-CS-Y<sup>a</sup>-, R<sup>a</sup>-O-CS-Y<sup>a</sup>-, R<sup>a</sup>-CS-O-Y<sup>a</sup>-, R<sup>a</sup>-CS-N(R<sup>b</sup>)-Y<sup>a</sup>-, R<sup>a</sup>-N(R<sup>b</sup>)-CS-Y<sup>a</sup>-, R<sup>a</sup>-O-CS-N(R<sup>b</sup>)-Y<sup>a</sup>-, R<sup>a</sup>-N(R<sup>b</sup>)-CS-O-Y<sup>a</sup>-, R<sup>a</sup>-N(R<sup>b</sup>)-CS-N(R<sup>c</sup>)-Y<sup>a</sup>-, R<sup>a</sup>-O-CS-O-Y<sup>a</sup>-, R<sup>a</sup>-S-CO-Y<sup>a</sup>-, R<sup>a</sup>-CO-S-Y<sup>a</sup>-, R<sup>a</sup>-S-CO-N(R<sup>b</sup>)-Y<sup>a</sup>-, R<sup>a</sup>-N(R<sup>b</sup>)-CO-S-Y<sup>a</sup>-, R<sup>a</sup>-S-CO-O-Y<sup>a</sup>-, R<sup>a</sup>-O-CO-S-Y<sup>a</sup>-, R<sup>a</sup>-S-CO-S-Y<sup>a</sup>-, R<sup>a</sup>-S-CS-Y<sup>a</sup>-, R<sup>a</sup>-CS-S-Y<sup>a</sup>-, R<sup>a</sup>-S-CS-N(R<sup>b</sup>)-Y<sup>a</sup>-, R<sup>a</sup>-N(R<sup>b</sup>)-CS-S-Y<sup>a</sup>-, R<sup>a</sup>-S-CS-O-Y<sup>a</sup>-, R<sup>a</sup>-O-CS-S-Y<sup>a</sup>-, wherein R<sup>a</sup> being a hydrogen atom, a C<sub>1</sub>-C<sub>6</sub> alkyl, a C<sub>2</sub>-C<sub>6</sub> alkenyl or a C<sub>2</sub>-C<sub>6</sub> alkynyl group; R<sup>b</sup> being a hydrogen atom, a C<sub>1</sub>-C<sub>6</sub> alkyl, a C<sub>2</sub>-C<sub>6</sub> alkenyl or a C<sub>2</sub>-C<sub>6</sub> alkynyl group; R<sup>c</sup> being a hydrogen atom, a C<sub>1</sub>-C<sub>6</sub> alkyl, a C<sub>2</sub>-C<sub>6</sub> alkenyl or a C<sub>2</sub>-C<sub>6</sub> alkynyl group; R<sup>d</sup> being a hydrogen atom, a C<sub>1</sub>-C<sub>6</sub> alkyl, a C<sub>2</sub>-C<sub>6</sub> alkenyl or a C<sub>2</sub>-C<sub>6</sub> alkynyl group and Y<sup>a</sup> being a direct bond, a C<sub>1</sub>-C<sub>6</sub> alkylene, a C<sub>2</sub>-C<sub>6</sub> alkenylene or a C<sub>2</sub>-C<sub>6</sub> alkynylene group, wherein each heteroalkyl group contains at least one carbon atom and one or more hydrogen atoms may be replaced by fluorine or chlorine atoms.

45 **[0035]** Specific examples of heteroalkyl groups are methoxy, trifluoromethoxy, ethoxy, n-propyloxy, isopropyloxy, butoxy, *tert*-butyloxy, methoxymethyl, ethoxymethyl, -CH<sub>2</sub>CH<sub>2</sub>OH, -CH<sub>2</sub>OH, methoxyethyl, 1-methoxyethyl, 1-ethoxyethyl, 2-methoxyethyl or 2-ethoxyethyl, methyl-amino, ethylamino, propylamino, isopropylamino, dimethylamino, diethylamino, isopropyl-ethylamino, methylamino methyl, ethylamino methyl, diisopropylamino ethyl, methylthio, ethylthio, isopropylthio, enol ether, dimethylamino methyl, dimethylamino ethyl, acetyl, propionyl, butyryloxy, acetyloxy, methoxycarbonyl, ethoxycarbonyl, propionyloxy, acetylamino or propionylamino, carboxymethyl, carboxyethyl or carboxypropyl, N-ethyl-N-methylcarbamoyl or N-methylcarbamoyl. Further examples of heteroalkyl groups are nitrile, isonitrile, cyanate, thiocyanate, isocyanate, isothiocyanate and alkyl nitrile groups.

50 **[0036]** The expression cycloalkyl refers to a saturated or partially unsaturated (for example, a cycloalkenyl group) cyclic group that contains one or more rings (preferably 1 or 2), and contains from 3 to 14 ring carbon atoms, preferably from 3 to 10 (especially 3, 4, 5, 6 or 7) ring carbon atoms. The expression cycloalkyl refers furthermore to groups in which one or more hydrogen atoms have been replaced by fluorine, chlorine, bromine or iodine atoms or by OH, =O, SH, =S, NH<sub>2</sub>, =NH, N<sub>3</sub> or NO<sub>2</sub> groups, thus, for example, cyclic ketones such as, for example, cyclohexanone, 2-cyclohexenone or cyclopentanone. Further specific examples of cycloalkyl groups are a cyclopropyl, cyclobutyl, cy-



clopentyl, spiro[4,5]decanyl, norbornyl, cyclohexyl, cyclopentenyl, cyclohexadienyl, decalanyl, bicyclo[4.3.0]nonyl, tetraline, cyclopentylcyclohexyl, fluorocyclohexyl or cyclohex-2-enyl group.

**[0037]** The expression heterocycloalkyl refers to a cycloalkyl group as defined above in which one or more (preferably 1, 2, 3 or 4) ring carbon atoms have been replaced by an oxygen, nitrogen, silicon, selenium, phosphorus or sulfur atom (preferably by an oxygen, sulfur or nitrogen atom) or a SO group or a SO<sub>2</sub> group. A heterocycloalkyl group has preferably 1 or 2 ring(s) containing from 3 to 10 (especially 3, 4, 5, 6 or 7) ring atoms (preferably selected from C, O, N and S). The expression heterocycloalkyl refers furthermore to groups that are substituted by fluorine, chlorine, bromine or iodine atoms or by OH, =O, SH, =S, NH<sub>2</sub>, =NH, N<sub>3</sub> or NO<sub>2</sub> groups. Examples are a piperidyl, prolanyl, imidazolidinyl, piperazinyl, morpholinyl, urotro-pinyl, pyrrolidinyl, tetrahydrothiophenyl, tetrahydropyranyl, tetrahydrofuryl or 2-pyrazolinyl group and also lactames, lactones, cyclic imides and cyclic anhydrides.

**[0038]** The expression alkylcycloalkyl refers to groups that contain both cycloalkyl and also alkyl, alkenyl or alkynyl groups in accordance with the above definitions, for example alkylcyclo-alkyl, cycloalkylalkyl, alkylcycloalkenyl, alkenyl-cycloalkyl and alkynylcycloalkyl groups. An alkylcycloalkyl group preferably contains a cycloalkyl group that contains one or two rings having from 3 to 10 (especially 3, 4, 5, 6 or 7) ring carbon atoms, and one or two alkyl, alkenyl or alkynyl groups (especially alkyl groups) having 1 or 2 to 6 carbon atoms.

**[0039]** The expression heteroalkylcycloalkyl refers to alkylcycloalkyl groups as defined above in which one or more (preferably 1, 2, 3, 4 or 5) carbon atoms have been replaced by an oxygen, nitrogen, silicon, selenium, phosphorus or sulfur atom (preferably by an oxygen, sulfur or nitrogen atom) or a SO group or a SO<sub>2</sub> group. A heteroalkylcycloalkyl group preferably contains 1 or 2 rings having from 3 to 10 (especially 3, 4, 5, 6 or 7) ring atoms, and one or two alkyl, alkenyl, alkynyl or heteroalkyl groups (especially alkyl or heteroalkyl groups) having from 1 or 2 to 6 carbon atoms. Examples of such groups are alkylheterocycloalkyl, alkylheterocycloalkenyl, alkenylheterocycloalkyl, alkynylheterocycloalkyl, heteroalkylcycloalkyl, heteroalkylheterocycloalkyl and heteroalkylheterocycloalkenyl, the cyclic groups being saturated or mono-, di- or tri-unsaturated.

**[0040]** The expression aryl refers to an aromatic group that contains one or more rings containing from 6 to 14 ring carbon atoms, preferably from 6 to 10 (especially 6) ring carbon atoms. The expression aryl refers furthermore to groups in which one or more hydrogen atoms have been replaced by fluorine, chlorine, bromine or iodine atoms or by OH, SH, NH<sub>2</sub>, N<sub>3</sub> or NO<sub>2</sub> groups. Examples are the phenyl, naphthyl, biphenyl, 2-fluorophenyl, aniliny, 3-nitrophenyl or 4-hydroxyphenyl group.

**[0041]** The expression heteroaryl refers to an aromatic group that contains one or more rings containing from 5 to 14 ring atoms, preferably from 5 to 10 (especially 5 or 6 or 9 or 10) ring atoms, and contains one or more (preferably 1, 2, 3, 4 or 5) oxygen, nitrogen, phosphorus or sulfur ring atoms (preferably O, S or N). The expression heteroaryl refers furthermore to groups in which one or more hydrogen atoms have been replaced by fluorine, chlorine, bromine or iodine atoms or by OH, SH, N<sub>3</sub>, NH<sub>2</sub> or NO<sub>2</sub> groups. Examples are pyridyl (e.g. 4-pyridyl), imidazolyl (e.g. 2-imidazolyl), phenylpyrrolyl (e.g. 3-phenylpyrrolyl), thiazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, thiadiazolyl, indolyl, indazolyl, tetrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, isoxazolyl, indazolyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzthiazolyl, pyridazinyl, quinolinyl, isoquinolinyl, pyrrolyl, purinyl, carbazolyl, acridinyl, pyrimidyl, 2,3'-bifuryl, pyrazolyl (e.g. 3-pyrazolyl) and isoquinolinyl groups.

**[0042]** The expression aralkyl refers to groups containing both aryl and also alkyl, alkenyl, alkynyl and/or cycloalkyl groups in accordance with the above definitions, such as, for example, arylalkyl, arylalkenyl, arylalkynyl, arylcycloalkyl, arylcycloalkenyl, alkylarylalkyl and alkylarylalkenyl groups. Specific examples of aralkyls are toluene, xylene, mesitylene, styrene, benzyl chloride, o-fluorotoluene, 1H-indene, tetraline, dihydronaphthalene, indanone, phenylcyclopentyl, cumene, cyclohexylphenyl, fluorene and indane. An aralkyl group preferably contains one or two aromatic ring systems (1 or 2 rings) containing from 6 to 10 carbon atoms and one or two alkyl, alkenyl and/or alkynyl groups containing from 1 or 2 to 6 carbon atoms and/or a cycloalkyl group containing 5 or 6 ring carbon atoms.

**[0043]** The expression heteroaralkyl refers to an aralkyl group as defined above in which one or more (preferably 1, 2, 3 or 4) carbon atoms have been replaced by an oxygen, nitrogen, silicon, selenium, phosphorus, boron or sulfur atom (preferably oxygen, sulfur or nitrogen), that is to say to groups containing both aryl or heteroaryl, respectively, and also alkyl, alkenyl, alkynyl and/or heteroalkyl and/or cycloalkyl and/or heterocycloalkyl groups in accordance with the above definitions. A heteroaralkyl group preferably contains one or two aromatic ring systems (1 or 2 rings) containing from 5 or 6 to 10 ring carbon atoms and one or two alkyl, alkenyl and/or alkynyl groups containing 1 or 2 to 6 carbon atoms and/or a cycloalkyl group containing 5 or 6 ring carbon atoms, wherein 1, 2, 3, 4, 5 or 6 of these carbon atoms have been replaced by oxygen, sulfur or nitrogen atoms.

**[0044]** Examples are arylheteroalkyl, arylheterocycloalkyl, arylheterocycloalkenyl, arylalkyl-heterocycloalkyl, arylalkenylheterocycloalkyl, arylalkynylheterocycloalkyl, arylalkylhetero-cycloalkenyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylalkylcycloalkyl, heteroarylalkylcycloalkenyl, heteroarylalkylheterocycloalkyl, heteroarylalkylheterocycloalkenyl, heteroarylalkylcycloalkyl, heteroarylalkylheterocycloalkenyl, heteroarylalkylheterocycloalkyl, heteroarylalkylheterocycloalkenyl and heteroarylalkylhetero-cycloalkyl groups, the cyclic groups being saturated or mono-, di- or tri-unsaturated. Specific examples are a tetrahydroisoquinolinyl, benzoyl, 2- or 3-ethylindolyl, 4-methylpy-

ridino, 2-, 3- or 4-methoxyphenyl, 4-ethoxyphenyl, 2-, 3- or 4-carboxyphenylalkyl group.

**[0045]** The term halogen or halogen atom refers to F, Cl, Br or I.

**[0046]** The expression "optionally substituted" especially refers to groups in which one, two, three or more hydrogen atoms may have been replaced by fluorine, chlorine, bromine or iodine atoms or by OH, =O, SH, =S, NH<sub>2</sub>, =NH, SO<sub>3</sub>H, N<sub>3</sub> or NO<sub>2</sub> groups. This expression refers furthermore especially to groups that may be substituted by one, two, three or more preferably unsubstituted C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>2</sub>-C<sub>10</sub> alkynyl, C<sub>1</sub>-C<sub>10</sub> heteroalkyl, C<sub>3</sub>-C<sub>18</sub> cyclo-alkyl, C<sub>2</sub>-C<sub>17</sub> heterocycloalkyl, C<sub>4</sub>-C<sub>20</sub> alkylcycloalkyl, C<sub>2</sub>-C<sub>19</sub> heteroalkylcycloalkyl, C<sub>6</sub>-C<sub>18</sub> aryl, C<sub>1</sub>-C<sub>17</sub> heteroaryl, C<sub>7</sub>-C<sub>20</sub> aralkyl or C<sub>2</sub>-C<sub>19</sub> heteroaralkyl groups. This expression refers furthermore especially to groups that may be substituted by one, two, three or more preferably unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> heteroalkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>9</sub> heterocycloalkyl, C<sub>7</sub>-C<sub>12</sub> alkylcycloalkyl, C<sub>2</sub>-C<sub>11</sub> heteroalkylcycloalkyl, C<sub>6</sub>-C<sub>10</sub> aryl, C<sub>1</sub>-C<sub>9</sub> heteroaryl, C<sub>7</sub>-C<sub>12</sub> aralkyl or C<sub>2</sub>-C<sub>11</sub> heteroaralkyl groups.

**[0047]** Preferred substituents are halogen, methyl, methoxy, OH, =O, NH<sub>2</sub>, NHMe, NMe<sub>2</sub>, NO<sub>2</sub>, CN, CF<sub>3</sub>, ethyl, n-propyl and isopropyl.

**[0048]** According to a preferred embodiment, all alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, aralkyl and heteroaralkyl groups described herein may optionally be substituted.

**[0049]** When an aryl, heteroaryl, cycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, heterocycloalkyl, aralkyl or heteroaralkyl group contains more than one ring, these rings may be bonded to each other via a single or double bond or these rings may be annulated.

**[0050]** The compounds of the present invention are cell penetrable, they do not covalently bind to the active site cysteine of caspase-1, they show reasonable water solubility and the synthesis of these compounds is short, convergent and cheap.

**[0051]** The present invention further provides pharmaceutical compositions comprising one or more compounds of formula (I) as defined herein or a pharmaceutically acceptable ester, prodrug, hydrate, solvate or salt thereof, optionally in combination with a pharmaceutically acceptable carrier.

**[0052]** It is a further object of the present invention to provide a compound of formula (I) as defined herein or a pharmaceutical composition as defined herein for the preparation of a medicament for the treatment of inflammatory diseases.

**[0053]** Preferably the compounds of the present invention may be used for the treatment and/or prevention of inflammatory diseases.

**[0054]** A therapeutically effective amount of a compound in accordance with this invention means an amount of compound that is effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. Determination of a therapeutically effective amount is within the skill in the art.

**[0055]** The therapeutically effective amount or dosage of a compound according to this invention can vary within wide limits and may be determined in a manner known in the art. Such dosage may be adjusted to the individual requirements in each particular case including the specific compound being administered, the route of administration, the condition being treated, as well as the patient being treated.

**[0056]** Examples of pharmacologically acceptable salts of sufficiently basic compounds of formula (I) are salts of physiologically acceptable mineral acids like hydrochloric, hydrobromic, sulfuric and phosphoric acid; or salts of organic acids like methanesulfonic, p-toluenesulfonic, lactic, acetic, trifluoroacetic, citric, succinic, fumaric, maleic and salicylic acid. Further, a sufficiently acidic compound of formula (I) may form alkali or earth alkali metal salts, for example sodium, potassium, lithium, calcium or magnesium salts; ammonium salts; or organic base salts, for example methylamine, dimethylamine, trimethylamine, triethylamine, ethylenediamine, ethanolamine, choline hydroxide, meglumin, piperidine, morpholine, tris-(2-hydroxyethyl)amine, lysine or arginine salts; all of which are also further examples of salts of formula (I). Compounds of formula (I) may be solvated, especially hydrated. The hydratization/hydration may occur during the process of production or as a consequence of the hygroscopic nature of the initially water free compounds of formula (I). The solvates and/or hydrates may e.g. be present in solid or liquid form.

**[0057]** It should be appreciated that certain compounds of formula (I) may have tautomeric forms from which only one might be specifically mentioned or depicted in the following description, different geometrical isomers (which are usually denoted as cis/trans isomers or more generally as (E) and (Z) isomers) or different optical isomers as a result of one or more chiral carbon atoms (which are usually nomenclatured under the Cahn-Ingold-Prelog or R/S system). All these tautomeric forms, geometrical or optical isomers (as well as racemates and diastereomers) and polymorphous forms are included in the invention. Since the compounds of formula (I) may contain asymmetric C-atoms, they may be present either as achiral compounds, mixtures of diastereomers, mixtures of enantiomers or as optically pure compounds. The present invention comprises both all pure enantiomers and all pure diastereomers, and also the mixtures thereof in any mixing ratio.

**[0058]** The therapeutic use of compounds according to formula (I), their pharmacologically acceptable salts, solvates and hydrates, respectively, as well as formulations and pharmaceutical compositions also lie within the scope of the

present invention.

**[0059]** The pharmaceutical compositions according to the present invention comprise at least one compound of formula (I) as an active ingredient and, optionally, carrier substances and/or adjuvants.

**[0060]** The present invention also relates to pro-drugs which are composed of a compound of formula (I) and at least one pharmacologically acceptable protective group which will be cleaved off under physiological conditions, such as an alkoxy-, arylalkoxy-, acyl-, acyloxymethyl group (e.g. pivaloyloxymethyl), an 2-alkyl-, 2-aryl- or 2-arylalkyl-oxycarbonyl-2-alkylidene ethyl group or an acyloxy group as defined herein, e.g. ethoxy, benzyloxy, acetyl or acetyloxy or, especially for a compound of formula (I), carrying a hydroxy group (-OH): a sulfate, a phosphate (-OPO<sub>3</sub> or -OCH<sub>2</sub>OPO<sub>3</sub>) or an ester of an amino acid.

**[0061]** Preferably, the present invention also relates to a prodrug, a biohydrolyzable ester, a biohydrolyzable amide, a polymorph, tautomer, stereoisomer, metabolite, N-oxide, biohydrolyzable carbamate, biohydrolyzable ether, physiologically functional derivative, atropisomer, or in vivo-hydrolysable precursor, diastereomer or mixture of diastereomers, chemically protected form, affinity reagent, complex, chelate and a stereoisomer of the compounds of formula (I).

**[0062]** As used herein, the term pharmaceutically acceptable ester especially refers to esters which hydrolyze in vivo and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanolic, alkenolic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include, but are not limited to, formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

**[0063]** As mentioned above, therapeutically useful agents that contain compounds of formula (I), their solvates, salts or formulations are also comprised in the scope of the present invention. In general, compounds of formula (I) will be administered by using the known and acceptable modes known in the art, either alone or in combination with any other therapeutic agent.

**[0064]** For oral administration such therapeutically useful agents can be administered by one of the following routes: oral, e.g. as tablets, dragees, coated tablets, pills, semisolids, soft or hard capsules, for example soft and hard gelatine capsules, aqueous or oily solutions, emulsions, suspensions or syrups, parenteral including intravenous, intramuscular and subcutaneous injection, e.g. as an injectable solution or suspension, rectal as suppositories, by inhalation or insufflation, e.g. as a powder formulation, as microcrystals or as a spray (e.g. liquid aerosol), transdermal, for example via an transdermal delivery system (TDS) such as a plaster containing the active ingredient or intranasal. For the production of such tablets, pills, semisolids, coated tablets, dragees and hard, e.g. gelatine, capsules the therapeutically useful product may be mixed with pharmaceutically inert, inorganic or organic excipients as are e.g. lactose, sucrose, glucose, gelatine, malt, silica gel, starch or derivatives thereof, talc, stearic acid or their salts, dried skim milk, and the like. For the production of soft capsules one may use excipients as are e.g. vegetable, petroleum, animal or synthetic oils, wax, fat, polyols. For the production of liquid solutions, emulsions or suspensions or syrups one may use as excipients e.g. water, alcohols, aqueous saline, aqueous dextrose, polyols, glycerin, lipids, phospholipids, cyclodextrins, vegetable, petroleum, animal or synthetic oils. Especially preferred are lipids and more preferred are phospholipids (preferred of natural origin; especially preferred with a particle size between 300 to 350 nm) preferred in phosphate buffered saline (pH = 7 to 8, preferred 7.4). For suppositories one may use excipients as are e.g. vegetable, petroleum, animal or synthetic oils, wax, fat and polyols. For aerosol formulations one may use compressed gases suitable for this purpose, as are e.g. oxygen, nitrogen and carbon dioxide. The pharmaceutically useful agents may also contain additives for conservation, stabilization, e.g. UV stabilizers, emulsifiers, sweetener, aromatizers, salts to change the osmotic pressure, buffers, coating additives and antioxidants.

**[0065]** In general, in the case of oral or parenteral administration to adult humans weighing approximately 80 kg, a daily dosage of about 10 mg to about 10,000 mg, preferably from about 20 mg to about 1,000 mg, should be appropriate, although the upper limit may be exceeded when indicated. The daily dosage can be administered as a single dose or in divided doses, or for parenteral administration, it may be given as continuous infusion or subcutaneous injection.

**[0066]** Examples for inflammatory diseases are:

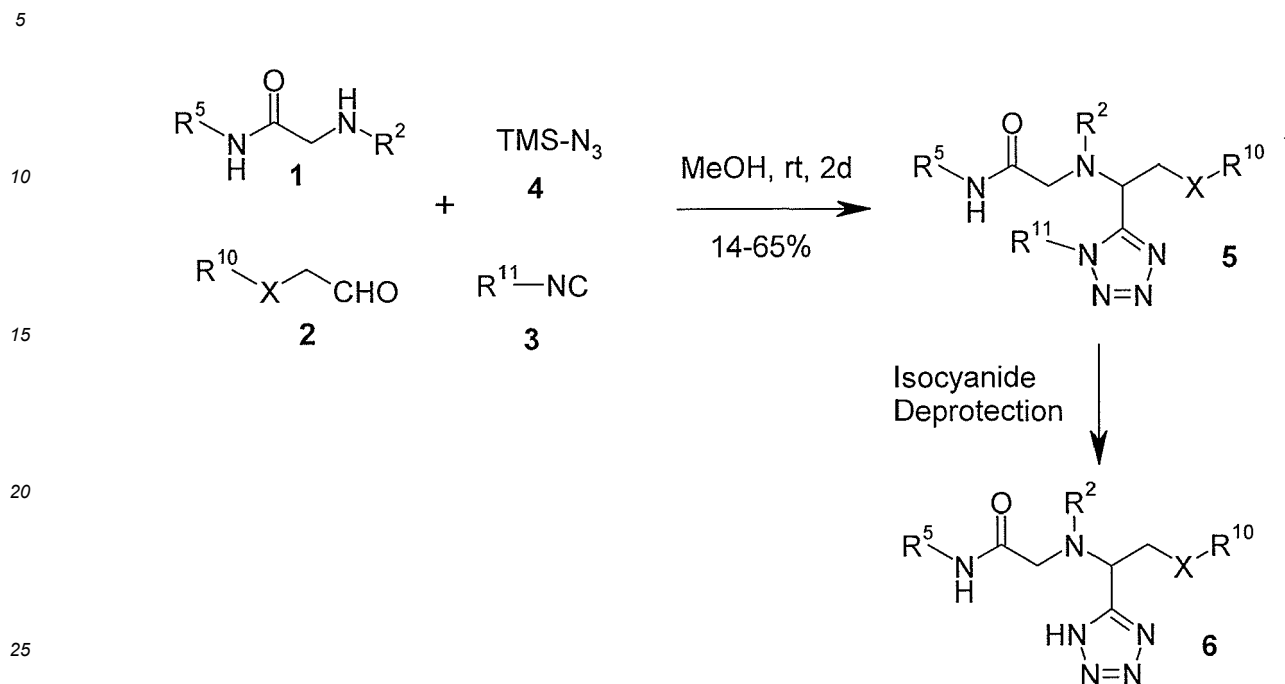
Cancer, inflammatory bowel disease, arthritis, rheumatoid arthritis, autoimmune diseases, appendicitis, salpingitis, Crohn's disease, peritonitis, colitis, atherosclerosis, asthma, ulcerative colitis, cervicitis, ankylosing spondylitis, pneumonia, thrombosis, metabolic syndrome, erythema, vaginitis, vasculitis, gout, and urethritis.

#### Examples

**[0067]** The compounds of the present invention may be synthesized using the Ugi four-component reaction (U-4CR).

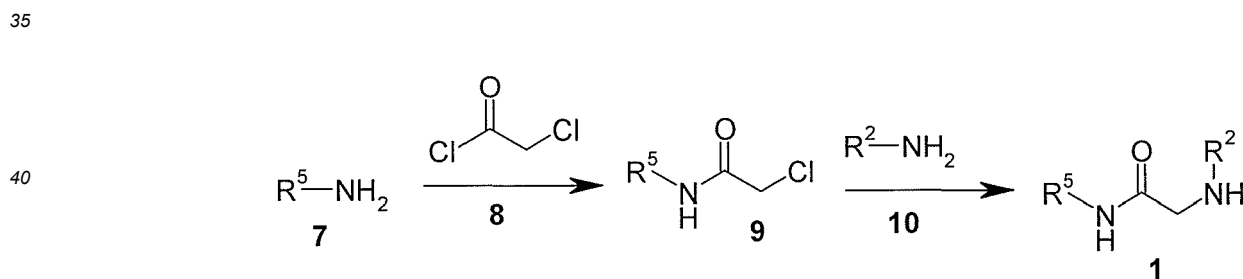
**[0068]** As shown in Scheme 1, an Ugi reaction, using secondary amine **1**, aldehyde **2**, isocyanide **3**, and trimethylsilyl azide **4**, in methanol gave the desired condensation product **5** after stirring at room temperature for 2 days. The corresponding isocyanide-deprotected product **6** was obtained by the subsequent deprotection of Ugi-product **5**.

## Scheme 1. Ugi reaction and isocyanide deprotection.



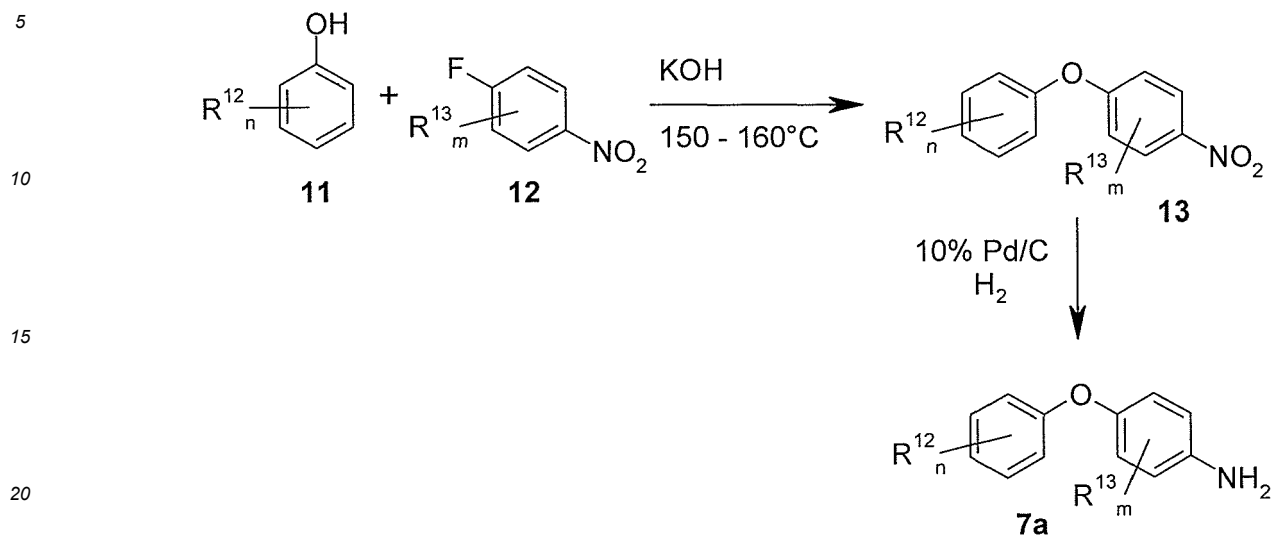
[0069] Therein,  $R^{11}$  is the residue of a suitable cleavable isocyanide such as  $-\text{CH}_2\text{CH}_2\text{CN}$ ,  $-\text{C}(\text{CH}_3)_3$ ,  $-\text{C}(\text{Me})_2\text{CH}_2\text{C}(\text{CH}_3)_3$ ,  $-\text{benzyl}$ ,  $-\text{p-MeO benzyl}$ ,  $-\text{trityl}$  or  $-(3,4)\text{dimethoxy benzyl}$ .

[0070] Secondary amines **1** were synthesized as illustrated in Scheme 2 by coupling a primary amine **7** to 2-chloroacetyl chloride **8** to give the corresponding amide **9** followed by the coupling of a primary amine **10**.

Scheme 2. Synthesis of secondary amines **1**

[0071] Some primary amines **7a** were synthesized according to scheme 3. Thereby a coupling reaction between phenol derivative **11** and 4-fluoronitrobenzene derivative **12** was carried out, followed by reduction of the formed nitro-derivative **13** by Pd/C,  $\text{H}_2$  to give primary amine **7a**.

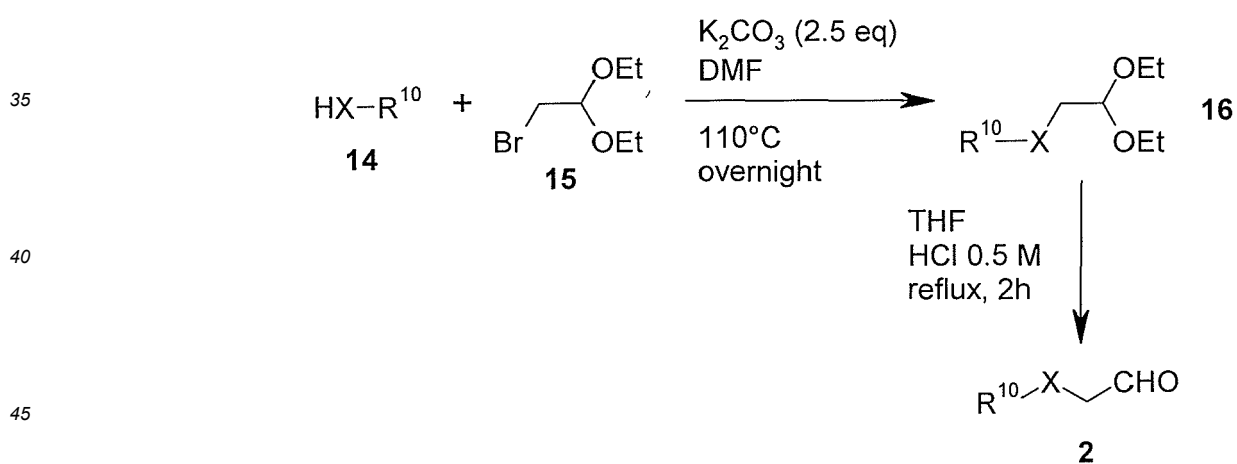
## Scheme 3. Synthesis of primary certain amines 7a



[0072] Therein n is an integer of from 0 to 5, m is an integer of from 0 to 4 and R<sup>11</sup> and R<sup>12</sup> are independently suitable substituents.

[0073] Aldehydes 2 were synthesized as illustrated in Scheme 4 by first coupling an alcohol, amine or thiol derivative 14 with 2-bromo-1,1-diethoxyethane 15 to give the corresponding coupled product 16 followed by hydrolysis by HCl to form aldehyde 2.

## Scheme 4. Synthesis of Aldehydes 2



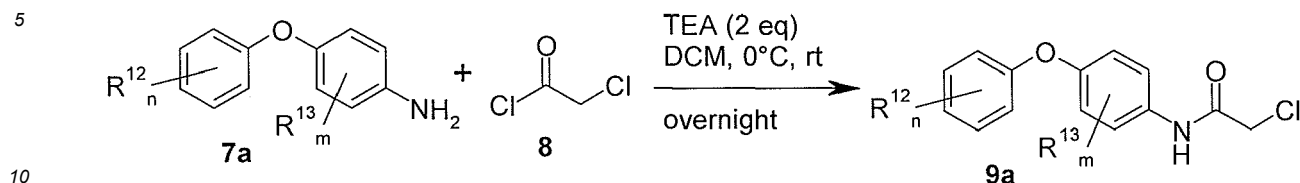
General procedures:

50 Synthesis of certain secondary amines 1a:

Method 1: General procedure for the coupling reaction of aniline derivative 7a and 2-chloroacetyl chloride 8

[0074]

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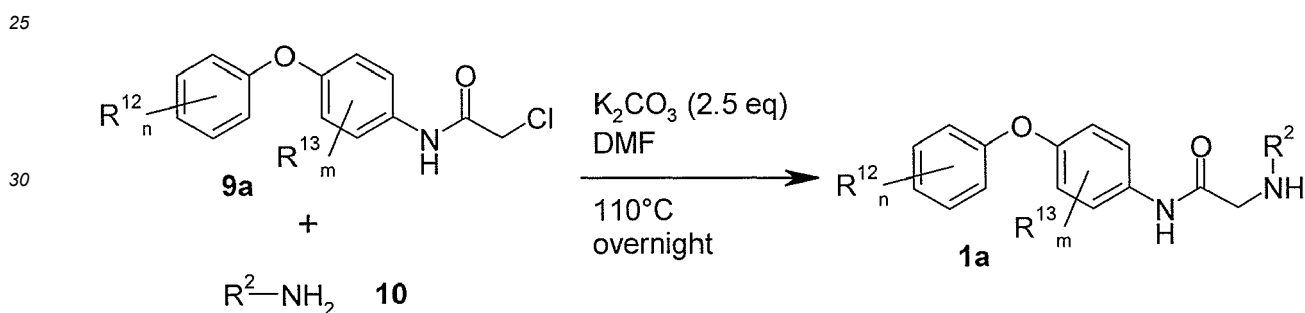
**Scheme 5.** Coupling reaction of aniline derivative **7a** and 2-chloroacetyl chloride **8**

[0075] 4-phenoxyaniline derivative **7a** (4 mmol) and TEA (8 mmol) were added to 60 ml DCM at 0°C in a round-bottomed flask (RBF). The 2-chloroacetyl chloride **8** (4.4 mmol, 0.35 ml) in 5 ml DCM was slowly added to the reaction mixture through a dropping funnel. The reaction mixture was stirred overnight (reaction monitored by TLC). Then, the reaction mixture was added to water and extracted with DCM. The solvent was removed under reduced pressure and the residue was purified by flash chromatography using petroleum ether:ethyl acetate on silica gel to afford product **9a**.

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**Method 2: General procedure for the coupling reaction of 9a and primary amine 10**

20 [0076]

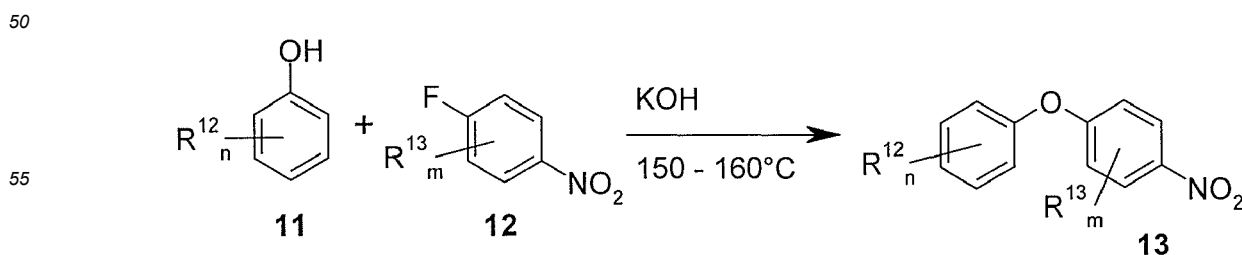
**Scheme 6.** Coupling reaction of **9a** and primary amine **10**

[0077] 2-Chloro-N-(4-phenoxyphenyl)acetamide derivative **9a** (2.7 mmol) and primary amine **10** (4.05 mmol) were added to 10 ml DMF in a RBF. Then  $K_2CO_3$  (931 mg, 6.75 mmol) was added to the reaction mixture, heated to 60 °C and stirred overnight (reaction monitored by TLC). Then, the reaction mixture was added to water and extracted with ethyl acetate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography using petroleum ether:ethyl acetate on silica gel to afford product **1a**.

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**Method 3: General procedure for the coupling reaction of phenol derivative 11 and 4-fluoronitrobenzene derivative 12**

45 [0078]

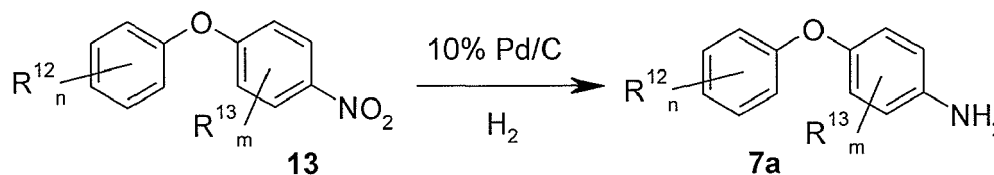
**Scheme 7.** Coupling reaction of phenol derivative **11** and 4-fluoronitrobenzene derivative **12**

[0079] KOH (1 eq.) was dissolved in phenol derivative **11** (3eq). Then, 4-fluoronitrobenzene derivative **12** (1 eq.) was added to the solution. The mixture was heated in an oil-bath at 150-160°C for 30 min. Then, the mixture was poured into a diluted NaOH solution (3 mmol, 3 ml 1,0 M). The solid product was collected on a filter. It was recrystallized from alcohol: petroleum ether (7:3) to yield product **13**.

**Method 4: General method for the reduction of nitro-derivative 13**

[0080]

**Scheme 8. Reduction of nitro-derivative 13**



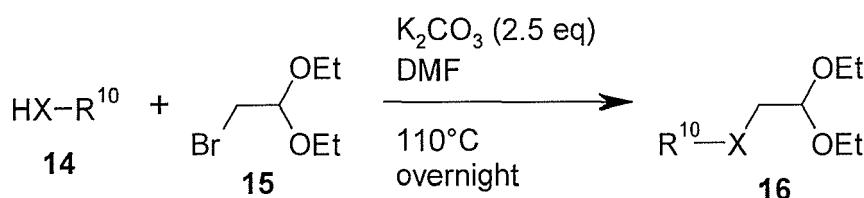
[0081] Nitro-derivative **13** (4 mmol) was dissolved in 50 ml ethyl acetate. The solution was flushed with nitrogen. 175 mg of 10% Pd/C were added to the solution. The flask was placed in an PARR apparatus and shaken thereon. The reaction was monitored by TLC (ethyl acetate: petroleum ether 30:70). Then, the reaction mixture was filtered over Celite and the solvent evaporated to yield product **7a**.

**Synthesis of aldehyde 2:**

**Method 5: General procedure for the coupling reaction with 2-bromo-1,1-diethoxyethane**

[0082]

**Scheme 9. Coupling reaction with 2-bromo-1,1-diethoxyethane**

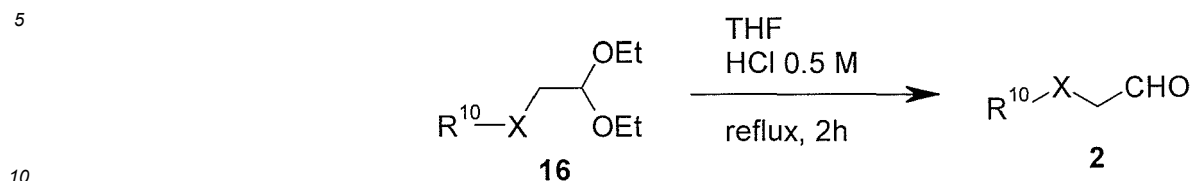


[0083] Phenol, aniline or thiol derivative **14** (5 mmol) and  $\text{K}_2\text{CO}_3$  (12.5 mmol) were dissolved in 5 ml DMF in a RBF. 2-Bromo-1,1-diethoxyethane **15** (900  $\mu\text{l}$ , 5 mmol) was slowly added to the reaction mixture. The reaction mixture was heated to 110 °C and stirred overnight (reaction monitored by TLC). Then, the reaction mixture was added to water and extracted with DCM. The solvent was removed under reduced pressure and the residue was purified by flash chromatography by using petroleum ether:ethyl acetate on silica gel to afford product **16**.

**Method 6: General procedure for the hydrolysis reaction**

[0084] Reference: J. Org. Chem., 1997, 62(14), 4552-4553,

## Scheme 10. Aldehyde synthesis by hydrolysis reaction



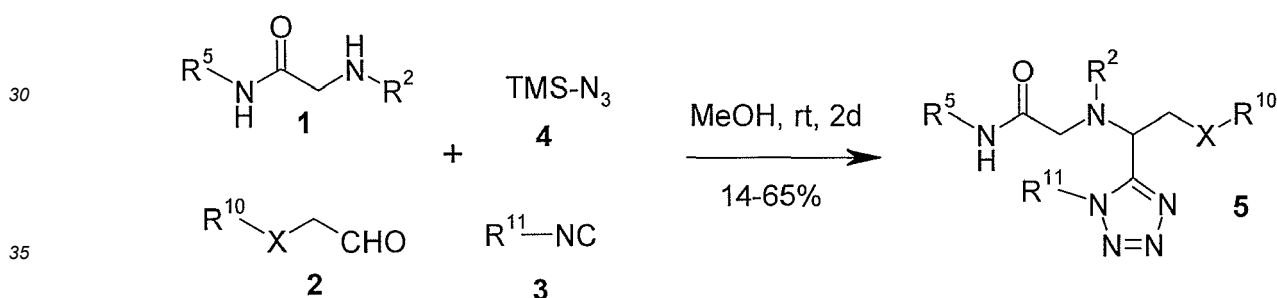
[0085] A solution of 1-(2,2-diethoxyethoxy)-phenol/aniline/thiol derivative **16** (3.4 mmol) in THF (15 mL) and HCl (0.5 M, 20 mL) was refluxed for 1-4 h. The solution was cooled and diluted with water (30 mL) and the product was extracted with ethyl acetate. The combined organic layers were dried ( $\text{MgSO}_4$ ) and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography using petroleum ether:ethyl acetate on silica gel to afford product **2**.

## General procedures for the Ugi reaction and deprotection:

## 20 Method 7: General procedure for Ugi reaction

[0086]

## 25 Scheme 11. Ugi reaction

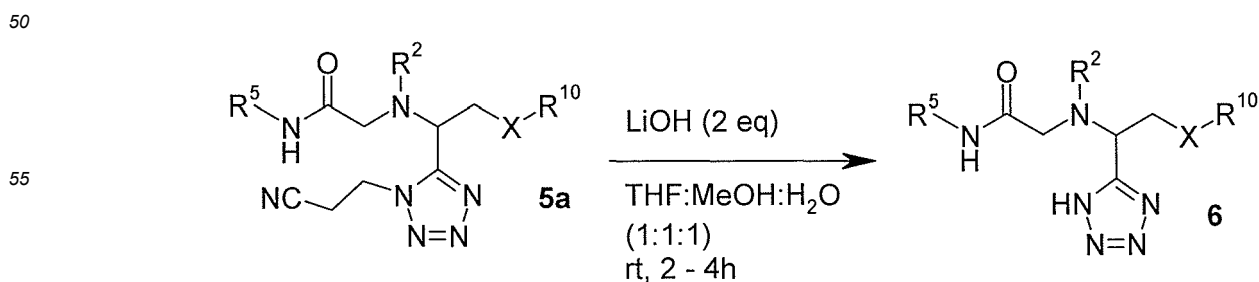


[0087] To a solution of amine **1** (1 mmol) in MeOH (1 mL), aldehyde **2** (1 mmol), isocyanide **3** (1 mmol) and trimethylsilyl azide **4** (1 mmol) were added. The reaction mixture stirred at rt for 24-48h. The solvent was removed under reduced pressure followed by purification by flash chromatography on silica gel eluted with hexane-ethyl acetate to afford product **5**.

## Method 8: General procedure for isocyanide (3-isocyanopropanenitrile) deprotection from a certain Ugi-product 5a

45 [0088]

## Scheme 12. Deprotection of Ugi-product 5a





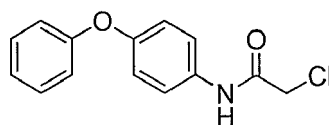
## EP 3 666 769 A1

**[0089]** 2-((2-(2-chlorophenoxy)-1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)-ethyl)(methyl)amino)-N-(4-phenoxyphenyl)acetamide (110 mg, 0.2 mmol) was added to THF:MeOH:H<sub>2</sub>O (1:1:1, 4 ml) and cooled to 0 °C in a 25 ml RBF followed by the addition of LiOH (17 mg, 0.4 mmol) to the reaction mixture and allowed to stir at rt for 2 h. Then, the solvent was removed under reduced pressure and the residue was dissolved in water and cooled in ice. Addition of HCl (1 N) gave a precipitated product. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel and eluted with methanol:DCM to afford product **6**.

Following examples were prepared by using Method 1: Method for coupling reaction of aniline derivative and 2-chloroacetyl chloride

### Example 1: 2-chloro-N-(4-phenoxyphenyl)acetamide

**[0090]**

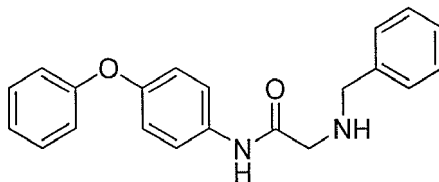


**[0091]** White solid, Yield: 8.5 gm (60 %); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.21 (s, 1H), 7.51 (d, *J* = 8.9, 2H), 7.38 - 7.30 (m, 2H), 7.10 (t, *J* = 7.4, 1H), 7.04 - 6.97 (m, 4H), 4.20 (s, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 163.7, 157.2, 154.4, 131.9, 129.8, 123.3, 121.9, 119.5, 118.7, 42.9 ppm. (ESI) *m/z* calculated [M+H]<sup>+</sup>: 262.70; found [M+H]<sup>+</sup>: 262.07.

Following examples were prepared by using Method 2: General procedure for coupling reaction of aniline derivative **9** and 2-chloroacetyl chloride

### Example 2: 2-(benzylamino)-N-(4-phenoxyphenyl)acetamide

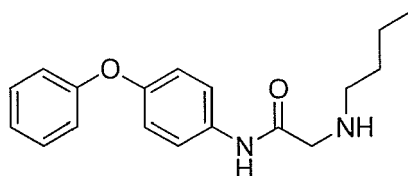
**[0092]**



**[0093]** Yellow solid, Yield: 370 mg (42 %); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.24 (s, 1H), 7.52 (d, *J* = 8.9, 2H), 7.38 - 7.29 (m, 7H), 7.08 (t, *J* = 7.3, 1H), 7.02 - 6.95 (m, 4H), 3.86 (s, 2H), 3.44 (s, 2H), 1.61 (s, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 169.5, 153.3, 139.1, 133.2, 129.7, 128.8, 128.7, 128.1, 127.6, 127.5, 127.4, 123.0, 121.1, 119.8, 118.3, 54.1, 52.4 ppm. (ESI) *m/z* calculated [M+H]<sup>+</sup>: 333.15; found [M+H]<sup>+</sup>: 333.29.

### Example 3: 2-(butylamino)-N-(4-phenoxyphenyl)acetamide

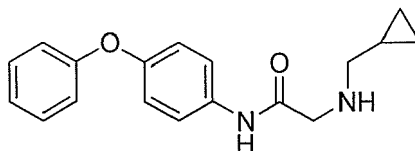
**[0094]**



**[0095]** Pale yellow liquid, Yield: 447 mg (50 %); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.36 (s, 1H), 7.56 (d, *J* = 8.9, 2H), 7.34 - 7.29 (m, 2H), 7.07 (t, *J* = 7.4, 1H), 7.02 - 6.96 (m, 4H), 3.37 (s, 2H), 2.68 (t, *J* = 7.0, 2H), 1.58 (s, 1H), 1.55 - 1.47 (m, 2H), 1.46 - 1.35 (m, 2H), 0.95 (t, *J* = 7.3, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 170.0, 157.7, 153.2, 133.4, 129.7, 123.0, 121.4, 121.0, 119.8, 119.7, 118.3, 53.0, 50.1, 32.3, 20.3, 14.0 ppm. MS (ESI) *m/z* calculated [M+H]<sup>+</sup>: 299.17; found

[M+H]<sup>+</sup>: 299.31**Example 4: 2-((cyclopropylmethyl)amino)-N-(4-phenoxyphenyl)acetamide**

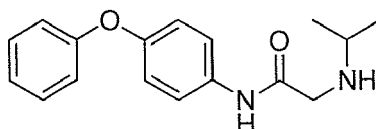
[0096]



[0097] Yellow solid, Yield: 85 mg (41 %); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.38 (s, 1H), 7.57 (d, *J* = 8.9, 2H), 7.32 (t, *J* = 7.9, 2H), 7.08 (t, *J* = 7.4, 1H), 7.02 - 6.96 (m, 4H), 3.40 (d, *J* = 12.9, 2H), 2.55 (d, *J* = 6.9, 2H), 1.82 (s, 1H), 1.03 - 0.92 (m, 1H), 0.57 - 0.50 (m, 2H), 0.17 (q, *J* = 5.0, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 169.9, 133.4, 129.7, 122.9, 121.0, 119.8, 118.3, 55.3, 52.7, 11.3, 3.5 ppm.

**Example 5: 2-(isopropylamino)-N-(4-phenoxyphenyl)acetamide**

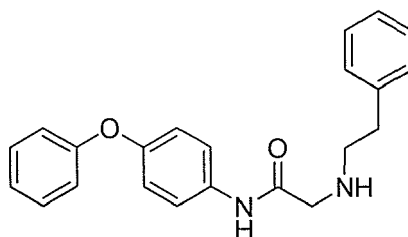
[0098]



[0099] Brown liquid, Yield: 860 mg (76 %); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.43 (s, 1H), 7.56 (d, *J* = 8.9, 2H), 7.31 (t, *J* = 7.9, 2H), 7.07 (t, *J* = 7.3, 1H), 7.03 - 6.94 (m, 4H), 3.38 (s, 2H), 2.94 - 2.80 (m, 1H), 1.69 (s, 2H), 1.12 (d, *J* = 6.3, 6H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 170.4, 157.7, 153.16, 133.4, 129.7, 122.9, 121.0, 119.8, 118.3, 50.8, 49.9, 23.1 ppm. MS (ESI) *m/z* calculated [M+H]<sup>+</sup>: 285.15; found [M+H]<sup>+</sup>: 285.27.

**Example 6: 2-(phenethylamino)-N-(4-phenoxyphenyl)acetamide**

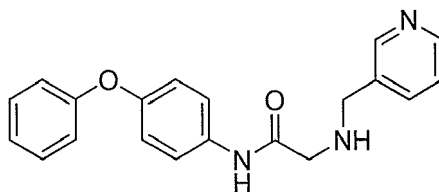
[0100]



[0101] Yellow liquid, Yield: 511 mg (51 %); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.08 (s, 1H), 7.38 - 7.29 (m, 6H), 7.26 - 7.21 (m, 3H), 7.07 (t, *J* = 7.4, 1H), 7.00 - 6.93 (m, 4H), 3.36 (s, 2H), 2.97 (t, *J* = 6.5, 2H), 2.82 (t, *J* = 6.5, 2H), 1.60 (s, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 169.6, 153.1, 139.5, 133.3, 129.7, 128.8, 128.7, 126.5, 122.9, 121.0, 119.7, 118.3, 52.6, 51.2, 36.4 ppm. MS (ESI) *m/z* calculated [M+H]<sup>+</sup>: 347.17; found [M+H]<sup>+</sup>: 347.33.

**Example 7: N-(4-phenoxyphenyl)-2-((pyridin-3-ylmethyl)amino)acetamide**

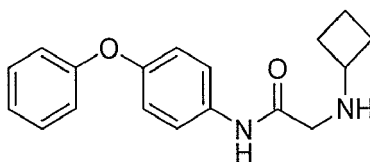
[0102]



10 **[0103]** Brown liquid, Yield: 409 mg (50 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.15 (s, 1H), 8.61 (d,  $J = 1.9$ , 1H), 8.57 - 8.52 (m, 1H), 7.69 - 7.65 (m, 1H), 7.52 (d,  $J = 8.9$ , 2H), 7.34 - 7.28 (m, 3H), 7.08 (t,  $J = 7.4$ , 1H), 7.00 - 6.95 (m, 4H), 3.87 (s, 2H), 3.43 (s, 2H), 1.98 (s, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  169.1, 157.6, 153.4, 149.6, 149.0, 148.3, 135.8, 134.9, 134.5, 133.1, 129.7, 123.6, 123.1, 121.2, 119.7, 118.4, 52.4, 51.4 ppm. MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 334.15; found  $[\text{M}+\text{H}]^+$ : 334.26

15 **Example 8: 2-(cyclobutylamino)-N-(4-phenoxyphenyl)acetamide**

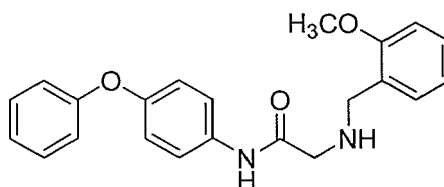
**[0104]**



25 **[0105]** White liquid, Yield: 379 mg (43 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.26 (s, 1H), 7.55 (d,  $J = 8.9$ , 2H), 7.32 (t,  $J = 7.9$ , 2H), 7.07 (t,  $J = 7.4$ , 1H), 7.03 - 6.95 (m, 4H), 3.36 - 3.24 (m, 3H), 2.33 - 2.20 (m, 2H), 1.81 - 1.69 (m, 3H), 1.68 - 1.56 (m, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  169.9, 157.7, 153.2, 133.3, 129.7, 123.0, 121.5, 121.1, 119.8, 119.7, 118.4, 118.3, 54.2, 49.99, 30.8, 14.5 ppm.

30 **Example 9: 2-((2-methoxybenzyl)amino)-N-(4-phenoxyphenyl)acetamide**

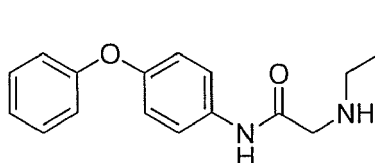
**[0106]**



40 **[0107]** Brown liquid, Yield: 409 mg (50 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.94 (s, 1H), 7.46 (d,  $J = 8.9$ , 2H), 7.32 (M, 2H), 7.09 (t,  $J = 7.4$ , 1H), 7.01 - 6.95 (m, 5H), 3.91 (s, 1H), 3.86 (s, 2H), 3.44 (s, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  168.5, 157.9, 157.4, 153.8, 132.9, 132.1, 130.0, 129.8, 123.2, 122.0, 121.4, 119.6, 118.6, 111.4, 60.4, 59.4, 56.2 ppm.

45 **Example 10: N-(4-phenoxyphenyl)-2-(propylamino)acetamide**

**[0108]**



55 **[0109]** Brown liquid, Yield: 580 mg (51 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.42 (s, 1H), 7.57 (d,  $J = 8.9$ , 1H), 7.49 (d,  $J = 9.0$ , 1H), 7.36 - 7.29 (m, 2H), 7.13 - 7.06 (m, 1H), 7.05 - 6.93 (m, 4H), 3.45 (s, 1H), 3.41 (s, 1H), 2.67 (t,  $J = 7.1$ , 1H),

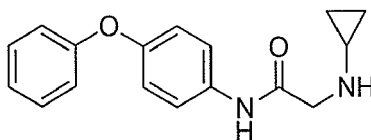
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2.64 - 2.56 (m, 1H), 1.62 - 1.51 (m, 2H), 0.98 (t,  $J = 7.4$ , 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  169.6, 153.2, 133.3, 129.7, 123.0, 121.1, 119.7, 118.6, 118.3, 57.2, 52.6, 52.0, 23.0, 11.6 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 285.15; found  $[\text{M}+\text{H}]^+$ : 285.27.

### 5 Example 11: 2-(cyclopropylamino)-N-(4-phenoxyphenyl)acetamide

[0110]

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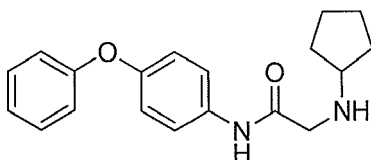


15 [0111] Brown liquid, Yield: 860 mg (76 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.98 (s, 1H), 7.55 - 7.49 (m, 2H), 7.36 - 7.28 (m, 2H), 7.07 (t,  $J = 7.4$ , 1H), 7.01 - 6.94 (m, 4H), 3.49 (s, 2H), 2.29 (tt,  $J = 6.7$ , 3.6, 1H), 2.02 (s, 1H), 0.57 - 0.50 (m, 2H), 0.46 - 0.40 (m, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.0, 157.7, 153.3, 133.2, 129.7, 123.0, 121.1, 119.8, 119.6, 118.3, 53.2, 31.5, 6.6. MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 283.14; found  $[\text{M}+\text{H}]^+$ : 283.25.

### 20 Example 12: 2-(cyclopropylamino)-N-(4-phenoxyphenyl)acetamide

[0112]

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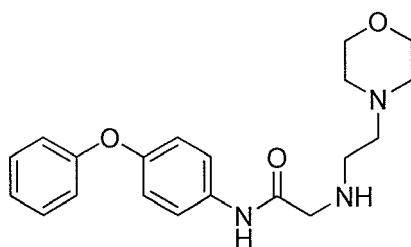
30 [0113] Brown liquid, Yield: 1047 mg (84 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.41 (s, 1H), 7.56 (d,  $J = 8.9$ , 2H), 7.36 - 7.29 (m, 2H), 7.07 (t,  $J = 7.4$ , 1H), 7.03 - 6.92 (m, 4H), 3.38 (s, 2H), 3.16 (p,  $J = 6.2$ , 1H), 1.87 - 1.82 (m, 2H), 1.74 - 1.69 (m, 2H), 1.62 - 1.56 (m, 2H), 1.44 - 1.33 (m, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.3, 157.7, 153.1, 133.4, 129.7, 122.9, 121.0, 119.8, 118.3, 60.6, 51.7, 33.0, 23.7 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 311.17; found  $[\text{M}+\text{H}]^+$ : 311.28.

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### Example 13: 2-((2-morpholinoethyl)amino)-N-(4-phenoxyphenyl)acetamide

[0114]

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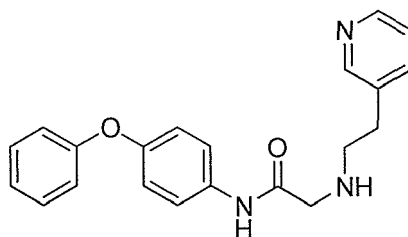
50 [0115] Brown liquid, Yield: 1070 mg (75 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.41 (s, 1H), 7.56 (d,  $J = 8.9$ , 2H), 7.31 (t,  $J = 7.9$ , 2H), 7.07 (t,  $J = 7.4$ , 1H), 7.01 - 6.95 (m, 4H), 3.73 - 3.68 (m, 4H), 3.39 (s, 2H), 2.83 - 2.75 (m, 2H), 2.57 - 2.48 (m, 2H), 2.46 (s, 4H), 2.16 (s, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  169.9, 157.6, 153.3, 133.3, 129.7, 123.0, 121.2, 119.7, 118.3, 66.9, 58.1, 53.7, 53.0, 46.3 ppm. MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 356.19; found  $[\text{M}+\text{H}]^+$ : 356.33.

### Example 14: N-(4-phenoxyphenyl)-2-((2-(pyridin-3-yl)ethyl)amino)acetamide

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[0116]

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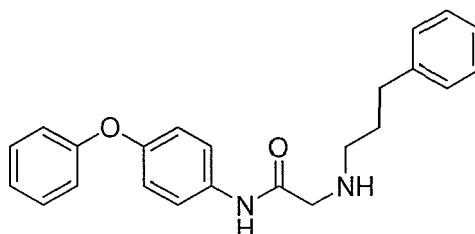


10 **[0117]** Brown liquid, Yield: 1070 mg (77 %);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.37 (s, 1H), 8.54 (d,  $J = 4.7$ , 1H), 7.62 (td,  $J = 7.7$ , 1.8, 1H), 7.48 (d,  $J = 8.9$ , 2H), 7.31 (t,  $J = 8.0$ , 2H), 7.23 - 7.14 (m, 2H), 7.07 (t,  $J = 7.4$ , 1H), 6.98 (d,  $J = 8.8$ , 4H), 3.40 (s, 2H), 3.13 (t,  $J = 6.3$ , 2H), 3.01 (t,  $J = 6.3$ , 2H), 2.17 (s, 1H). MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 348.16; found  $[\text{M}+\text{H}]^+$ : 348.30.

15 **Example 15: N-(4-phenoxyphenyl)-2-((3-phenylpropyl)amino)acetamide**

**[0118]**

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30 **[0119]** Yellow solid, Yield: 1.83 gm (86 %);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.28 (s, 1H), 7.53 (d,  $J = 8.8$ , 2H), 7.36 - 7.27 (m, 4H), 7.20 (t,  $J = 7.7$ , 3H), 7.08 (t,  $J = 7.2$ , 1H), 6.99 (t,  $J = 8.7$ , 4H), 3.37 (s, 2H), 2.75 - 2.67 (m, 4H), 1.94 - 1.81 (m, 2H), 1.54 (s, 1H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  169.78, 157.70, 153.20, 141.55, 133.32, 129.71, 128.51, 128.31, 126.05, 122.97, 121.05, 119.80, 118.29, 52.95, 49.85, 33.50, 31.77 ppm. MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 361.18; found  $[\text{M}+\text{H}]^+$ : 361.30.

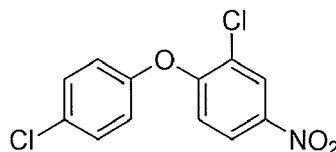
30

35 **Following examples were prepared by using Method 3: General procedure for coupling reaction of phenol derivative and 4-fluoronitrobenzene derivatives**

**Example 16: 2-chloro-1-(4-chlorophenoxy)-4-nitrobenzene**

**[0120]**

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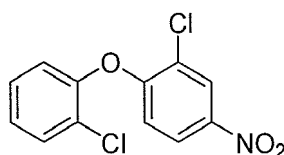
45

**[0121]** White crystals, Yield: 0,2458 gm (87%);  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.39 (s, 1H), 8.08 (d,  $J = 9.1$ , 1H), 7.41 (d,  $J = 8.9$ , 2H), 7.04 (d,  $J = 8.8$ , 2H), 6.91 (d,  $J = 9.1$ , 1H).

50 **Example 17: 2-chloro-1-(2-chlorophenoxy)-4-nitrobenzene**

**[0122]**

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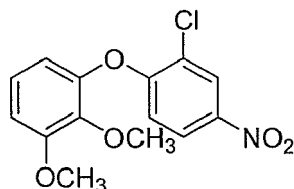
[0123] White crystals, Yield: 0,2053 gm (72 %),  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.40 (d,  $J = 2.6$ , 1H), 8.04 (dd,  $J = 9.1$ , 2.4, 1H), 7.54 (dd,  $J = 8.0$ , 1.3, 1H), 7.37 (td,  $J = 7.6$ , 1.1, 1H), 7.31 - 7.27 (m, 1H), 7.17 (dd,  $J = 8.0$ , 1.3, 1H), 6.69 (d,  $J = 9.1$ , 1H).  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  158.2, 149.9, 142.8, 131.4, 128.6, 127.2, 126.7, 126.6, 124.1, 123.6, 122.6, 115.5.

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### Example 18: 1-(2-chloro-4-nitrophenoxy)-2,3-dimethoxybenzene

[0124]

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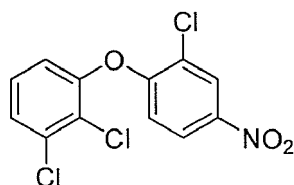
[0125] Brown viscous liquid, Yield: 0,8616 gm (70%),  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.37 (d,  $J = 2.6$ , 1H), 8.01 (dd,  $J = 9.1$ , 2.7, 1H), 7.11 (t,  $J = 8.3$ , 1H), 6.88 (dd,  $J = 8.4$ , 1.0, 1H), 6.77 - 6.73 (m, 2H), 3.91 (s, 3H), 3.81 - 3.78 (m, 3H).  $^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  159.1, 154.4, 147.3, 142.3, 141.1, 126.3, 124.4, 123.6, 123.4, 115.4, 114.3, 110.1, 61.3, 56.2.

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### Example 19: 1,2-dichloro-3-(2-chloro-4-nitrophenoxy)benzene

[0126]

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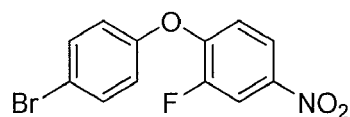
[0127] Yellow solid, Yield: 1,3448 g (99%),  $^1\text{H-NMR}$  (500 MHz, DMSO):  $\delta$  8.53 (d,  $J = 2.7$ , 1H), 8.18 (dd,  $J = 9.1$ , 2.7, 1H), 7.67 (dd,  $J = 8.2$ , 1.1, 1H), 7.52 (t,  $J = 8.2$ , 1H), 7.38 (dd,  $J = 8.2$ , 1.1, 1H), 7.06 (d,  $J = 9.1$ , 1H).  $^{13}\text{C-NMR}$  (126 MHz, DMSO):  $\delta$  157.3, 151.3, 143.6, 133.8, 130.1, 128.3, 126.8, 125.1, 124.5, 123.6, 121.4, 117.7.

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### Example 20: 1-(4-bromophenoxy)-2-fluoro-4-nitrobenzene

[0128]

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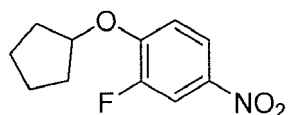
[0129] Green powder, Yield: 1,1648 gm (93%),  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.10 (dd,  $J = 10.2$ , 2.6, 1H), 8.01 (ddd,  $J = 9.1$ , 2.0, 1.3, 1H), 7.57 - 7.50 (m, 2H), 7.03 - 6.95 (m, 3H).  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  153.7, 151.8, 150.1, 142.7, 133.0, 120.9, 120.6, 118.6, 117.7, 113.0.

50

### Example 21: 1-(cyclopentyloxy)-2-fluoro-4-nitrobenzene

[0130]

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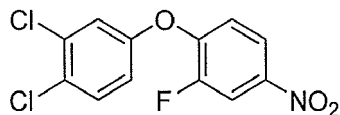
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**[0131]** Dark brown oil, Yield: 0,6773 gm (75%),  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.03 (d,  $J = 9.1$ , 1H), 7.97 (dd,  $J = 10.7$ , 2.6, 1H), 7.01 (t,  $J = 8.5$ , 1H), 4.96 - 4.88 (m, 1H), 2.03 - 1.61 (m, 8H).  $^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  152.7, 152.2, 150.7, 120.8, 114.0, 112.3, 81.8, 32.8, 24.0.

### 5 Example 22: 1,2-dichloro-4-(2-fluoro-4-nitrophenoxy)benzene

**[0132]**

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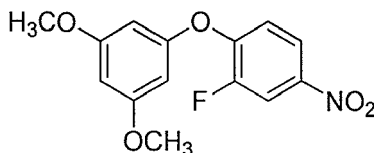


**[0133]** Green powder, Yield: 1,282 gm (99%),  $^1\text{H-NMR}$  (500 MHz, DMSO):  $\delta$  8.39 (dd,  $J = 10.7$ , 2.4, 1H), 8.14 - 8.08 (m, 1H), 7.75 (d,  $J = 8.8$ , 1H), 7.63 (d,  $J = 2.7$ , 1H), 7.35 (t,  $J = 8.6$ , 1H), 7.26 (dd,  $J = 8.5$ , 2.4, 1H).  $^{13}\text{C-NMR}$  (125 MHz, DMSO):  $\delta$  154.5, 152.2, 149.7, 143.7, 132.9, 132.5, 128.0, 121.9, 121.7, 120.5, 120.1, 113.9.

### 15 Example 23: 1-(3,5-dimethoxyphenoxy)-2-fluoro-4-nitrobenzene

**[0134]**

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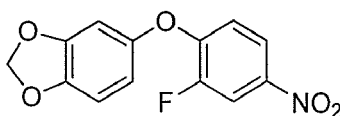
**[0135]** Brown solid, Yield: 0,8055 gm, (69%),  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.12 - 8.09 (m, 1H), 8.03 - 8.00 (m, 1H), 7.10 - 7.05 (m, 1H), 6.36 (t,  $J = 2.2$ , 1H), 6.26 (d,  $J = 2.1$ , 2H), 3.81 (s, 6H).  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  161.9, 156.4, 152.2, 150.9, 142.8, 120.6, 118.5, 113.17, 98.1, 97.4, 55.6.

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### Example 24: 5-(2-fluoro-4-nitrophenoxy)benzo[d][1,3]dioxole

**[0136]**

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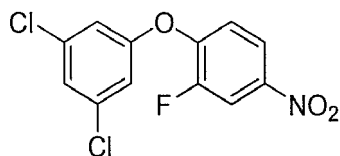
**[0137]** Dark brown solid, Yield: 1,4343 gm (129%),  $^1\text{H-NMR}$  (500 MHz, DMSO):  $\delta$  8.31 (dd,  $J = 10.8$ , 2.7, 1H), 8.08 (d,  $J = 9.1$ , 1H), 7.07 (t,  $J = 8.7$ , 1H), 7.01 (d,  $J = 8.4$ , 1H), 6.97 (d,  $J = 2.4$ , 1H), 6.70 (dd,  $J = 8.4$ , 2.4, 1H), 6.09 (d,  $J = 20.5$ , 2H).  $^{13}\text{C-NMR}$  (125 MHz, DMSO):  $\delta$  151.9, 151.3, 148.9, 148.8, 145.4, 142.3, 121.8, 118.0, 113.3, 113.1, 109.1, 103.0, 102.5.

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### Example 25: 1-(3,5-dichlorophenoxy)-2-fluoro-4-nitrobenzene

**[0138]**

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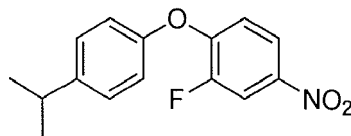


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**[0139]** Yellow powder, Yield: 1,247 gm (99%),  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.13 (dd,  $J = 10.0$ , 2.6, 1H), 8.10 - 8.06 (m, 1H), 7.23 (t,  $J = 1.5$ , 1H), 7.19 - 7.13 (m, 1H), 6.96 (d,  $J = 1.6$ , 2H).  $^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  156.4, 152.7, 148.9, 136.2, 125.3, 120.8, 120.8, 120.4, 117.4, 113.8.

**Example 26: 2-fluoro-1-(4-isopropylphenoxy)-4-nitrobenzene****[0140]**

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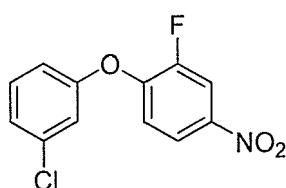
10

**[0141]** Brown oil, Yield: 0,9113 gm (83%),  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.07 (dd,  $J = 10.3, 2.6$ , 1H), 7.98 - 7.93 (m, 1H), 7.28 (d,  $J = 8.4$ , 2H), 7.02 (d,  $J = 8.4$ , 2H), 6.94 (t,  $J = 8.5$ , 1H), 2.95 (dt,  $J = 13.8, 6.9$ , 1H), 1.27 (d,  $J = 7.0$ , 6H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  152.4, 152.0, 151.8, 146.3, 142.3, 128.2, 120.5, 119.7, 117.5, 113.1, 33.6, 24.0.

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**Example 27: 1-(3-chlorophenoxy)-2-fluoro-4-nitrobenzene****[0142]**

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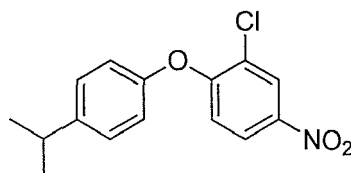
25

**[0143]** Brown powder, Yield: 1,0404 gm (97%),  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.11 (dd,  $J = 10.1, 2.3$ , 1H), 8.03 (d,  $J = 9.0$ , 1H), 7.35 (t,  $J = 8.1$ , 1H), 7.23 (d,  $J = 8.0$ , 1H), 7.11 - 7.03 (m, 2H), 6.98 (dd,  $J = 8.2, 1.2$ , 1H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  155.7, 152.5, 150.1, 143.3, 135.6, 131.0, 125.5, 120.7, 119.6, 119.2, 117.3, 113.4.

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**Example 28: 2-chloro-1-(4-isopropylphenoxy)-4-nitrobenzene****[0144]**

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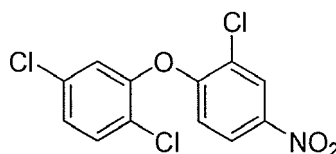
40

**[0145]** Light brown solid, Yield: 1516mg (87%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.37 (d,  $J = 2.6$ , 1H), 8.03 (dd,  $J = 9.1, 2.7$ , 1H), 7.29 (d,  $J = 8.5$ , 2H), 7.02 (d,  $J = 8.5$ , 2H), 6.86 (d,  $J = 9.1$ , 1H), 2.95 (dt,  $J = 13.8, 6.9$ , 1H), 1.28 (d,  $J = 6.9$ , 6H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  159.5, 152.3, 146.6, 142.4, 128.3, 126.5, 124.3, 123.6, 120.1, 116.3, 33.6, 24.1.

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**Example 29: 1,4-dichloro-2-(2-chloro-4-nitrophenoxy)benzene****[0146]**

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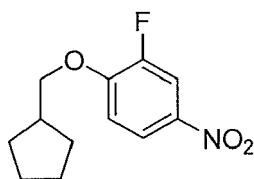
55

**[0147]** White solid, Yield: 2175mg (99%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.41 (d,  $J = 2.6$ , 1H), 8.09 (dd,  $J = 9.1, 2.6$ , 1H), 7.47 (d,  $J = 8.6$ , 1H), 7.25 (dd,  $J = 8.6, 2.3$ , 1H), 7.14 (d,  $J = 2.3$ , 1H), 6.79 (d,  $J = 9.1$ , 1H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  157.4, 150.5, 143.4, 133.8, 131.9, 127.2, 126.8, 125.0, 124.6, 123.7, 122.4, 116.4.



**Example 30: 1-(cyclopentylmethoxy)-2-fluoro-4-nitrobenzene****[0148]**

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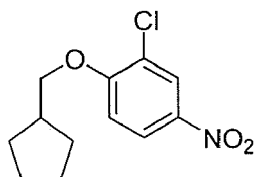
10

**[0149]** Dark brown oil, Yield: 1284mg (89 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.06 - 8.01 (m, 1H), 7.98 (dd,  $J$  = 10.7, 2.7, 1H), 7.02 (t,  $J$  = 8.5, 1H), 4.01 (d,  $J$  = 6.9, 2H), 2.49 - 2.39 (m, 1H), 1.93 - 1.84 (m, 2H), 1.70 - 1.59 (m, 4H), 1.42 - 1.33 (m, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  153.2, 151.2, 140.6, 120.9, 112.9, 112.3, 73.9, 38.8, 29.4, 25.4.

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**Example 31: 2-chloro-1-(cyclopentylmethoxy)-4-nitrobenzene****[0150]**

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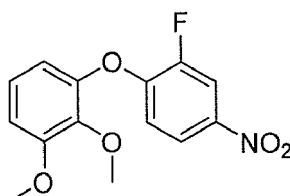
25

**[0151]** Dark brown oil, Yield: 1273mg (83%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.29 (d,  $J$  = 2.7, 1H), 8.14 (dd,  $J$  = 9.1, 2.7, 1H), 6.97 (d,  $J$  = 9.1, 1H), 4.02 (d,  $J$  = 6.8, 2H), 2.51 - 2.40 (m, 1H), 1.89 (td,  $J$  = 12.2, 7.4, 2H), 1.73 - 1.58 (m, 4H), 1.46 - 1.37 (m, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  159.9, 140.9, 126.0, 124.0, 123.5, 111.7, 73.9, 38.8, 29.4, 25.4.

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**Example 32: 1-(2-fluoro-4-nitrophenoxy)-2,3-dimethoxybenzene****[0152]**

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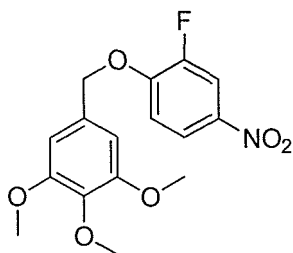
**[0153]** Dark brown solid, Yield: 1321mg (75%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.08 (dd,  $J$  = 10.3, 2.6, 1H), 7.95 - 7.91 (m, 1H), 7.10 (t,  $J$  = 8.3, 1H), 6.87 (d,  $J$  = 8.4, 1H), 6.83 (t,  $J$  = 8.6, 1H), 6.74 (d,  $J$  = 8.3, 1H), 3.91 (s, 3H), 3.80 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  154.4, 151.7, 151.3, 147.4, 142.1, 141.1, 124.3, 120.5, 116.6, 113.9, 112.9, 110.0, 61.2, 56.2.

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**Example 33: 5-((2-fluoro-4-nitrophenoxy)methyl)-1,2,3-trimethoxybenzene****[0154]**

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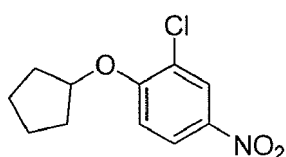
55



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**[0155]** Brown/red solid, Yield: 1821mg (94%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.06 - 8.00 (m, 2H), 7.09 (t,  $J = 8.3$ , 1H), 6.66 (s, 2H), 5.17 (s, 2H), 3.88 (s, 6H), 3.86 (s, 3H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  153.6, 152.3, 151.4, 141.1, 138.2, 130.5, 120.8, 113.8, 112.5, 104.6, 71.8, 60.9, 56.2.

15 **Example 34: 2-chloro-1-(cyclopentyloxy)-4-nitrobenzene**

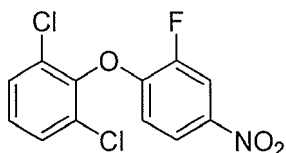
**[0156]**



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**[0157]** Dark brown oil, Yield: 1165mg (80%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.28 (d,  $J = 2.7$ , 1H), 8.13 (dd,  $J = 9.1$ , 2.7, 1H), 6.97 (d,  $J = 9.1$ , 1H), 4.92 (tt,  $J = 5.5$ , 2.6, 1H), 2.04 - 1.93 (m, 4H), 1.86 (ddd,  $J = 15.8$ , 8.1, 2.7, 2H), 1.73 - 1.64 (m, 2H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  159.0, 140.7, 126.1, 123.9, 123.8, 112.8, 81.9, 32.8, 24.0.

30 **Example 35: 1,3-dichloro-2-(2-fluoro-4-nitrophenoxy)benzene**

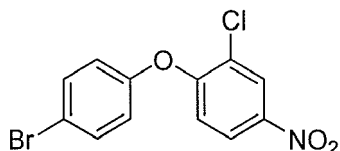
**[0158]**



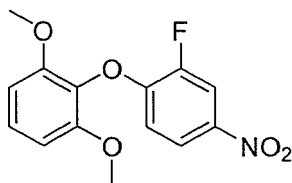
40  
**[0159]** Light yellow solid, Yield: 1924mg (99%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.13 (dd,  $J = 10.2$ , 2.6, 1H), 7.95 (ddd,  $J = 9.0$ , 2.4, 1.4, 1H), 7.46 (d,  $J = 8.1$ , 2H), 7.25 (t,  $J = 6.7$ , 1H), 6.63 (t,  $J = 8.5$ , 1H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  151.9, 149.8, 147.9, 142.7, 129.5, 129.3, 127.7, 120.5, 114.9, 113.3.

45 **Example 36: 1-(4-bromophenoxy)-2-chloro-4-nitrobenzene**

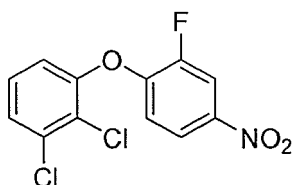
**[0160]**



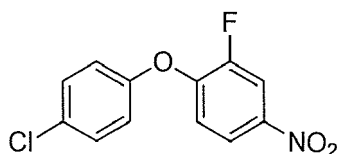
55  
**[0161]** Light yellow solid, Yield: 2166mg (99%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.38 (d,  $J = 2.7$ , 1H), 8.07 (dd,  $J = 9.1$ , 2.6, 1H), 7.58 - 7.53 (m, 2H), 7.00 - 6.94 (m, 2H), 6.91 (d,  $J = 9.1$ , 1H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  158.4, 153.8, 143.1, 133.4, 126.7, 125.1, 123.7, 121.7, 118.5, 117.3.

**Example 37: 2-(2-fluoro-4-nitrophenoxy)-1,3-dimethoxybenzene****[0162]**

**[0163]** Dark brown solid, Yield: 1289 mg (99%);  $^1\text{H NMR}$  (500 MHz, DMSO)  $\delta$  8.28 (dd,  $J = 11.0, 2.7$ , 1H), 8.01 (dd,  $J = 9.1, 1.5$ , 1H), 7.31 (t,  $J = 8.5$ , 1H), 6.88 (d,  $J = 8.5$ , 2H), 6.72 (t,  $J = 8.8$ , 1H), 3.76 (s, 6H).  $^{13}\text{C NMR}$  (126 MHz, DMSO)  $\delta$  152.7, 151.8, 150.6, 141.6, 129.7, 127.6, 121.8, 115.3, 113.4, 106.0, 56.6.

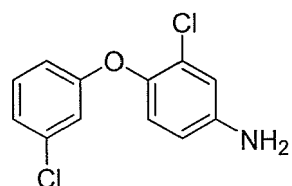
**Example 38: 1,2-dichloro-3-(2-fluoro-4-nitrophenoxy)benzene****[0164]**

**[0165]** Yellow solid, Yield: 1160mg (96%),  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.12 (dd,  $J = 10.1, 2.6$ , 1H), 8.00 (d,  $J = 9.1$ , 1H), 7.42 (d,  $J = 8.1$ , 1H), 7.31 - 7.25 (m, 1H), 7.05 (d,  $J = 8.2$ , 1H), 6.86 (t,  $J = 8.5$ , 1H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  151.3, 151.2, 149.8, 142.9, 134.6, 128.2, 127.5, 125.2, 120.6, 119.6, 117.4, 113.2.

**Example 39: 1-(4-chlorophenoxy)-2-fluoro-4-nitrobenzene****[0166]**

**[0167]** Yellow solid, Yield: 1897 mg (99%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.10 (dd,  $J = 10.2, 2.6$ , 1H), 8.01 (ddd,  $J = 9.1, 2.4, 1.5$ , 1H), 7.42 - 7.37 (m, 2H), 7.06 - 7.01 (m, 2H), 6.99 (d,  $J = 8.2$ , 1H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  153.4, 152.4, 150.7, 143.0, 130.4, 129.5, 120.7, 120.6, 118.4, 113.4.

Following examples were prepared by using Method 4: Method for reduction of nitro-derivative

**Example 40: 3-chloro-4-(3-chlorophenoxy)aniline****[0168]**

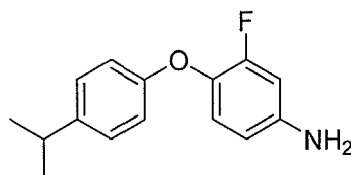
**[0169]** Dark brown solid, Yield: 1060 mg (73%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.19 (t,  $J = 8.1$ , 1H), 7.01 - 6.97 (m, 1H),

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6.93 - 6.90 (m, 1H), 6.84 (t,  $J = 2.1$ , 1H), 6.78 (dd,  $J = 8.6, 2.5$ , 2H), 6.58 (dd,  $J = 8.6, 2.7$ , 1H), 3.70 (s, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  159.2, 144.5, 142.6, 135.0, 130.3, 127.5, 123.7, 122.3, 116.6, 116.4, 114.6, 114.4. MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 255.11; found  $[\text{M}+\text{H}]^+$ : 254.12

### 5 Example 41: 3-fluoro-4-(4-isopropylphenoxy)aniline

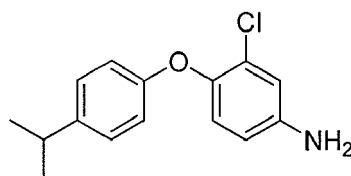
[0170]



[0171] Light brown solid Yield: 635 mg (71 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.12 (d,  $J = 8.6$ , 2H), 6.90 (t,  $J = 8.8$ , 1H), 6.84 (d,  $J = 8.6$ , 2H), 6.51 (dd,  $J = 12.0, 2.6$ , 1H), 6.43 - 6.34 (m, 1H), 3.67 (s, 2H), 2.86 (dt,  $J = 13.8, 6.9$ , 1H), 1.23 (s, 3H), 1.21 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  156.7, 155.3, 144.2, 142.7, 135.0, 127.3, 123.8, 115.8, 110.8, 103.8, 33.3, 24.2. MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 246.30; found  $[\text{M}+\text{H}]^+$ : 246.23.

### 20 Example 42: 3-chloro-4-(4-isopropylphenoxy)aniline

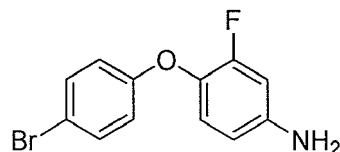
[0172]



[0173] Black solid, Yield: 1242 mg (95%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.13 (d,  $J = 8.5$ , 2H), 6.87 (t,  $J = 7.9$ , 1H), 6.81 (d,  $J = 8.5$ , 2H), 6.77 (s, 1H), 6.57 - 6.49 (m, 1H), 3.40 (s, 2H), 2.86 (dt,  $J = 13.8, 6.9$ , 1H), 1.23 (s, 3H), 1.21 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  156.3, 144.0, 143.7, 142.7, 127.4, 123.1, 117.3, 116.6, 116.2, 114.6, 33.4, 24.2. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 262.75; found  $[\text{M}+\text{H}]^+$ : 262.19

### 35 Example 43: 4-(4-bromophenoxy)-3-fluoroaniline

[0174]

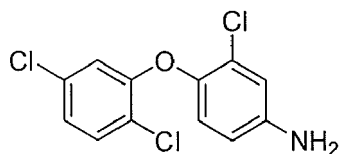


[0175] Brown solid, Yield: 838mg (80%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39 - 7.35 (m, 1H), 6.91 (t,  $J = 8.7$ , 1H), 6.80 (d,  $J = 8.9$ , 1H), 6.54 - 6.48 (m, 1H), 6.43 (dd,  $J = 8.6, 2.1$ , 1H), 3.71 (s, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  157.9, 155.2, 144.8, 133.0, 132.4, 123.9, 120.0, 117.6, 110.9, 103.9. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 283.11; found  $[\text{M}+\text{H}]^+$ : 282.25

### 50 Example 44: 3-chloro-4-(2,5-dichlorophenoxy)aniline

[0176]

## EP 3 666 769 A1



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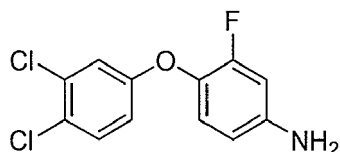
**[0177]** Brown solid, Yield: 1413 mg (79%); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.34 (d, *J* = 8.5, 1H), 6.97 - 6.94 (m, 1H), 6.91 (d, *J* = 8.6, 1H), 6.79 (d, *J* = 2.7, 1H), 6.60 (t, *J* = 2.4, 1H), 6.59 (dd, *J* = 8.6, 2.6, 1H), 3.72 (s, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 154.4, 144.9, 142.2, 133.0, 131.1, 127.2, 123.4, 123.0, 121.5, 116.7, 116.4, 114.6. Mass: MS (ESI) *m/z* calculated [M+H]<sup>+</sup>: 289.06; found [M+H]<sup>+</sup>: 288.06

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### Example 45: 4-(3,4-dichlorophenoxy)-3-fluoroaniline

**[0178]**

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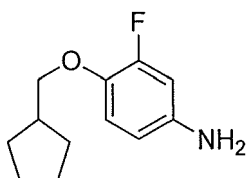
**[0179]** Brown solid, Yield: 619mg (57%); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.35 (d, *J* = 8.9, 1H), 7.00 (d, *J* = 2.9, 1H), 6.97 - 6.91 (m, 1H), 6.81 (dd, *J* = 8.9, 2.9, 1H), 6.54 (dd, *J* = 12.0, 2.7, 1H), 6.46 (ddd, *J* = 9.7, 5.7, 4.1, 1H), 3.77 (s, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 157.8, 155.0, 145.2, 133.5, 133.0, 130.8, 125.5, 124.0, 117.6, 115.5, 111.0, 103.7. Mass: MS (ESI) *m/z* calculated [M-H]<sup>-</sup>: 271.10; found [M-H]<sup>-</sup>: 272.17

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### Example 46: 4-(cyclopentylmethoxy)-3-fluoroaniline

**[0180]**

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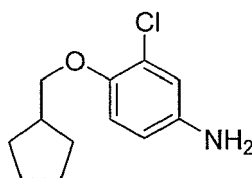
**[0181]** Brown liquid; Yield: 1036 mg (99%); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.79 (t, *J* = 8.9, 1H), 6.43 (dd, *J* = 12.7, 2.7, 1H), 6.33 (ddd, *J* = 8.7, 2.6, 1.2, 1H), 3.79 (d, *J* = 7.1, 2H), 3.51 (t, *J* = 23.8, 2H), 2.33 (dt, *J* = 15.0, 7.5, 1H), 1.88 - 1.75 (m, 2H), 1.67 - 1.51 (m, 4H), 1.39 - 1.29 (m, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 153.8, 141.3, 139.6, 118.1, 110.4, 104.1, 75.5, 39.3, 29.4, 25.4. Mass: MS (ESI) *m/z* calculated [M+H]<sup>+</sup>: 210.26; found [M+H]<sup>+</sup>: 210.18

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### Example 47: 3-chloro-4-(cyclopentylmethoxy)aniline

**[0182]**

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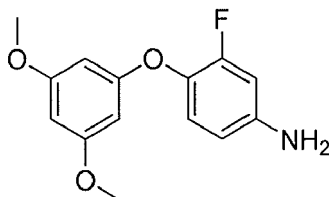
**[0183]** Black oil, Yield: 982 mg (87%); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.79 - 6.75 (m, 1H), 6.73 (d, *J* = 2.7, 1H), 6.52 (dd, *J* = 8.6, 2.8, 1H), 3.80 (d, *J* = 6.9, 2H), 3.64 - 3.22 (m, 2H), 2.37 (dt, *J* = 14.9, 7.4, 1H), 1.90 - 1.75 (m, 2H), 1.71 - 1.51 (m, 4H), 1.38 (td, *J* = 14.0, 7.1, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 147.8, 140.8, 124.2, 117.2, 116.3, 114.3, 74.7, 39.2, 29.4, 25.5. Mass: MS (ESI) *m/z* calculated [M+H]<sup>+</sup>: 226,72; found [M+H]<sup>+</sup>: 226,14

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**Example 48: 4-(3,5-dimethoxyphenoxy)-3-fluoroaniline****[0184]**

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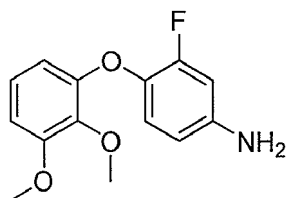


15

**[0185]** Dark brown solid, Yield: 660 mg (96%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.92 (t,  $J = 8.7$ , 1H), 6.52 - 6.47 (m, 1H), 6.43 - 6.40 (m, 1H), 6.14 (t,  $J = 2.1$ , 1H), 6.09 (d,  $J = 2.1$ , 2H), 3.73 (s, 6H), 3.69 (s, 2H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  161.5, 160.7, 155.2, 144.6, 134.1, 124.1, 110.9, 103.7, 94.7, 94.4, 55.4. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 224.27; found  $[\text{M}+\text{H}]^+$ : 264.20

**Example 49: 4-(2,3-dimethoxyphenoxy)-3-fluoroaniline****[0186]**

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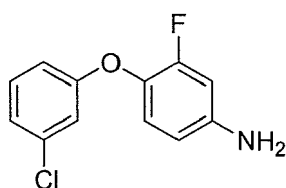
30

**[0187]** Brown solid, Yield: 1053 mg (90%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.89 (td,  $J = 8.6$ , 2.4, 2H), 6.63 (dd,  $J = 8.4$ , 1.1, 1H), 6.50 (dd,  $J = 12.1$ , 2.7, 1H), 6.42 - 6.34 (m, 2H), 3.93 (s, 3H), 3.88 (s, 3H), 3.63 (s, 2H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  155.8, 153.9, 152.9, 144.1, 139.0, 135.1, 123.4, 123.2, 110.7, 109.3, 106.6, 103.8, 61.1, 56.2. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 264.27; found  $[\text{M}+\text{H}]^+$ : 264.20

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**Example 50: 4-(3-chlorophenoxy)-3-fluoroaniline****[0188]**

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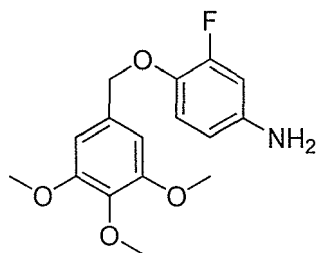
45

**[0189]** Light brown solid, Yield: 842 mg (92%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.19 (t,  $J = 8.1$ , 1H), 7.01 - 6.97 (m, 1H), 6.92 (t,  $J = 8.7$ , 1H), 6.88 (t,  $J = 2.1$ , 1H), 6.81 (dd,  $J = 8.3$ , 2.3, 1H), 6.51 (dd,  $J = 11.9$ , 2.4, 1H), 6.44 (d,  $J = 8.3$ , 1H), 3.88 (s, 2H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  159.5, 155.0, 144.9, 134.9, 130.3, 124.1, 122.3, 116.1, 115.9, 114.2, 110.9, 103.9. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 238.66; found  $[\text{M}+\text{H}]^+$ : 238.10

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**Example 51: 3-fluoro-4-((3,4,5-trimethoxybenzyl)oxy)aniline****[0190]**

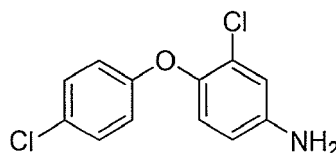
55



**[0191]** Dark brown solid, Yield: 1614 mg (99%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.83 (t,  $J = 8.9$ , 1H), 6.65 (s, 2H), 6.47 (dd,  $J = 12.6, 2.7$ , 1H), 6.36 - 6.32 (m, 1H), 4.96 (s, 2H), 3.87 (d,  $J = 7.4$ , 6H), 3.84 (s, 3H), 3.54 (s, 2H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  153.8, 153.3, 141.9, 133.6, 132.8, 119.1, 110.4, 105.9, 104.6, 104.0, 73.5, 60.9, 56.1. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 308.32; found  $[\text{M}+\text{Na}]^+$ : 330.22

**Example 52: 3-chloro-4-(4-chlorophenoxy)aniline**

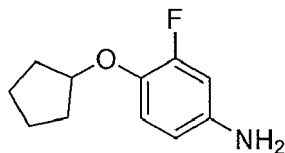
**[0192]**



**[0193]** Dark brown solid, Yield: 767 mg (96%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 - 7.20 (m, 2H), 6.89 (d,  $J = 8.6$ , 1H), 6.82 - 6.79 (m, 2H), 6.78 (d,  $J = 2.7$ , 1H), 6.57 (dd,  $J = 8.6, 2.7$ , 1H), 3.68 (s, 2H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  157.1, 144.3, 143.1, 129.5, 127.1, 123.4, 118.4, 117.4, 116.6, 114.6. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 255.11; found  $[\text{M}+\text{H}]^+$ : 254.12

**Example 53: 4-(cyclopentyloxy)-3-fluoroaniline**

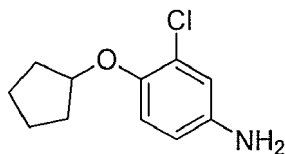
**[0194]**



**[0195]** Dark brown oil, Yield: 498 mg (85%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.79 (t,  $J = 8.9$ , 1H), 6.47 - 6.42 (m, 1H), 6.37 - 6.33 (m, 1H), 4.69 - 4.59 (m, 1H), 3.50 (s, 2H), 1.93 - 1.70 (m, 6H), 1.69 - 1.51 (m, 2H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  154.6, 141.3, 138.3, 119.9, 110.4, 104.0, 82.6, 32.7, 23.7. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 196.24; found  $[\text{M}+\text{H}]^+$ : 196.23

**Example 54: 3-chloro-4-(cyclopentyloxy)aniline**

**[0196]**



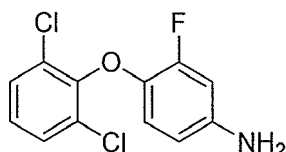
**[0197]** Dark brown oil, Yield: 899 mg (97 %);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.78 (d,  $J = 8.6$ , 1H), 6.72 (d,  $J = 2.7$ , 1H), 6.52 (dd,  $J = 8.6, 2.8$ , 1H), 4.66 (dt,  $J = 5.3, 2.5$ , 1H), 3.59 (s,  $J = 125.6, 12.1$ , 2H), 1.95 - 1.72 (m, 6H), 1.67 - 1.51 (m, 2H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  146.6, 140.8, 125.0, 118.0, 117.2, 114.3, 82.1, 32.7, 23.8. Mass: MS (ESI)  $m/z$

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calculated  $[M+H]^+$ : 212,69; found  $[M+H]^+$ : 212,23

### Example 55: 4-(2,6-dichlorophenoxy)-3-fluoroaniline

5 [0198]



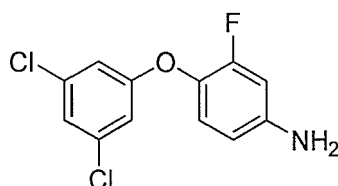
10

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[0199] Brown solid, Yield: 1239 mg (81%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36 (d,  $J = 8.1$ , 2H), 7.11 (t,  $J = 8.1$ , 1H), 6.53 (dt,  $J = 11.9$ , 3.6, 1H), 6.39 (t,  $J = 8.9$ , 1H), 6.27 (dd,  $J = 8.7$ , 1.1, 1H), 3.57 (s, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  152.3, 147.9, 142.5, 137.1, 129.2, 126.1, 123.1, 116.8, 110.2, 104.2. Mass: MS (ESI)  $m/z$  calculated  $[M+H]^+$ : 273.10; found  $[M+H]^+$ : 272.10, 274.12

### Example 56: 4-(3,5-dichlorophenoxy)-3-fluoroaniline

20 [0200]



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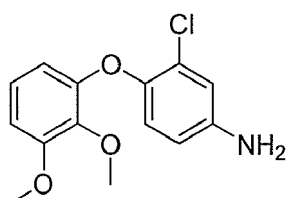
30

[0201] Light yellow solid, Yield: 957 mg (95%); Mass: MS (ESI)  $m/z$  calculated  $[M-H]^-$ : 271.10; found  $[M-H]^-$ : 271.23

### Example 57: 3-chloro-4-(2,3-dimethoxyphenoxy)aniline

[0202]

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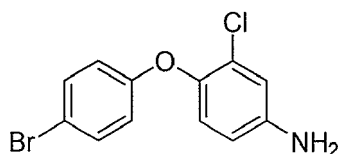
[0203] Brown solid, Yield: 575 mg (86%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.90 (t,  $J = 8.4$ , 1H), 6.85 (d,  $J = 8.6$ , 1H), 6.78 (d,  $J = 2.7$ , 1H), 6.65 (dd,  $J = 9.5$ , 8.4, 1H), 6.54 (dd,  $J = 8.6$ , 2.7, 1H), 6.31 (dd,  $J = 8.3$ , 1.0, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 3.50 (s,  $J = 108.4$ , 35.3, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  154.0, 151.6, 143.9, 143.7, 139.0, 123.4, 122.4, 120.0, 116.6, 114.5, 109.6, 106.7, 61.1, 56.1. Mass: MS (ESI)  $m/z$  calculated  $[M-H]^-$ : 278.79; found  $[M-H]^-$ : 278.08

### Example 58: 4-(4-bromophenoxy)-3-chloroaniline

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[0204]

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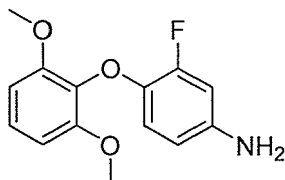
**[0205]** Brown solid, Yield: 1212 mg (71%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39 - 7.35 (m, 1H), 7.28 (dd,  $J = 8.3, 7.6$ , 1H), 6.93 - 6.85 (m, 2H), 6.79 (dd,  $J = 7.0, 2.6$ , 1H), 6.77 - 6.72 (m, 1H), 6.57 (dd,  $J = 8.6, 2.5$ , 1H), 3.70 (d,  $J = 72.5$ , 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  157.6, 144.3, 143.8, 132.4, 129.6, 123.4, 122.2, 117.9, 116.3, 114.7. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 299.56; found  $[\text{M}+\text{H}]^+$ : 298.10, 300.09.

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### Example 59: 4-(2,6-dimethoxyphenoxy)-3-fluoroaniline

**[0206]**

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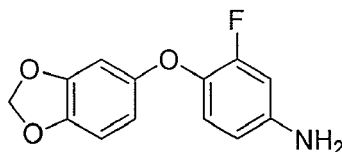
**[0207]** White solid, Yield: 817 mg (71%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.10 (t,  $J = 8.4$ , 1H), 6.63 (d,  $J = 8.4$ , 2H), 6.49 (dd,  $J = 12.4, 2.6$ , 1H), 6.45 (t,  $J = 9.0$ , 1H), 6.26 - 6.20 (m, 1H), 3.78 (s, 6H), 3.48 (s, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  153.5, 152.5, 141.3, 139.1, 133.2, 125.2, 116.8, 110.1, 105.5, 104.1, 56.3. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 264.10; found  $[\text{M}+\text{H}]^+$ : 264.20.

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### Example 60: 4-(benzo[d][1,3]dioxol-5-yloxy)-3-fluoroaniline

**[0208]**

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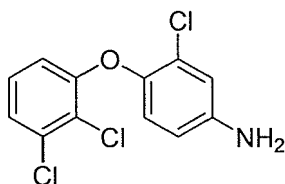
**[0209]** Black solid, Yield: 766 mg (66%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.23 (ddd,  $J = 13.7, 11.9, 2.4$ , 1H), 8.05 - 7.79 (m, 1H), 6.99 (t,  $J = 8.6$ , 1H), 6.79 (dd,  $J = 8.3, 7.1$ , 1H), 6.63 (d,  $J = 2.4$ , 1H), 6.57 - 6.52 (m, 1H), 6.01 (d,  $J = 6.4$ , 2H), 3.95 - 3.40 (m, 1H). Mass: MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 248.23; found  $[\text{M}+\text{H}]^+$ : 248.06, 248.21

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### Example 61: 3-chloro-4-(2,3-dichlorophenoxy)aniline

**[0210]**

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**[0211]** Brown solid, Yield: 750 mg (87%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.14 (dd,  $J = 8.1, 1.2$ , 1H), 7.06 - 7.02 (m, 1H), 6.90 - 6.87 (m, 1H), 6.78 (d,  $J = 2.7$ , 1H), 6.59 - 6.54 (m, 2H), 3.71 (s, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  155.3, 144.7, 142.7, 134.1, 127.2, 123.9, 123.2, 122.2, 120.8, 116.6, 114.5, 114.2. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 289.55; found  $[\text{M}+\text{H}]^+$ : 288.03

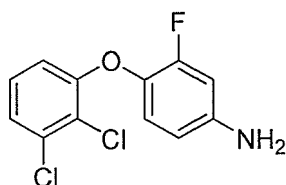
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### Example 62: 4-(2,3-dichlorophenoxy)-3-fluoroaniline

**[0212]**

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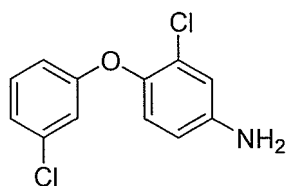
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[0213] Dark brown solid, Yield: 883 mg (85%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.14 (d,  $J = 8.1$ , 1H), 7.05 (t,  $J = 8.2$ , 1H), 6.91 (t,  $J = 8.7$ , 1H), 6.64 (d,  $J = 8.3$ , 1H), 6.51 (dd,  $J = 12.0, 2.2$ , 1H), 6.43 (d,  $J = 8.5$ , 1H), 3.74 (s, 2H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  155.8, 154.7, 145.1, 133.8, 130.6, 127.2, 123.8, 123.6, 116.2, 113.8, 110.9, 103.7. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 272,00; found  $[\text{M}+\text{H}]^+$ : 272,03.

Example 63: 3-chloro-4-(3-chlorophenoxy)aniline

15 [0214]

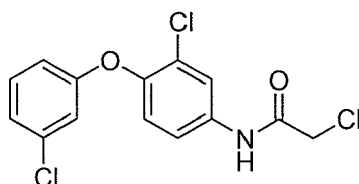


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[0215] Dark brown solid, Yield: 1060 mg (73%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.19 (t,  $J = 8.1$ , 1H), 7.01 - 6.97 (m, 1H), 6.93 - 6.90 (m, 1H), 6.84 (t,  $J = 2.1$ , 1H), 6.78 (dd,  $J = 8.6, 2.5$ , 2H), 6.58 (dd,  $J = 8.6, 2.7$ , 1H), 3.70 (s, 2H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  159.2, 144.5, 142.6, 135.0, 130.3, 127.5, 123.7, 122.3, 116.6, 116.4, 114.6, 114.4. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 254.01; found  $[\text{M}+\text{H}]^+$ : 254.12.

30 Following examples were prepared by using Method 1: Method for coupling reaction of aniline derivative and 2-chloroacetyl chloride

Example 64: 2-chloro-N-(3-chloro-4-(3-chlorophenoxy)phenyl)acetamide

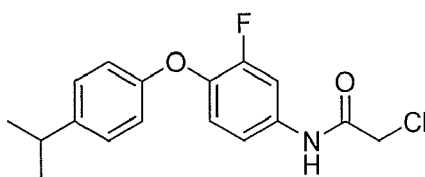
35 [0216]



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[0217] Light brown solid, Yield: 1210 mg (92%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.26 (s, 1H), 7.80 (d,  $J = 2.6$ , 1H), 7.43 (dd,  $J = 8.8, 2.6$ , 1H), 7.24 (t,  $J = 8.2$ , 1H), 7.06 (t,  $J = 8.5$ , 2H), 6.91 (t,  $J = 2.1$ , 1H), 6.82 (dd,  $J = 8.3, 2.3$ , 1H), 4.21 (s, 2H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  163.9, 157.9, 148.5, 135.2, 133.9, 130.6, 127.0, 123.4, 122.6, 122.1, 119.9, 117.5, 115.4, 42.8. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}-\text{H}]^-$ : 329,59; found  $[\text{M}-\text{H}]^-$ : 330.06, 329,87

Example 65: 2-chloro-N-(3-fluoro-4-(4-isopropylphenoxy)phenyl)acetamide

50 [0218]



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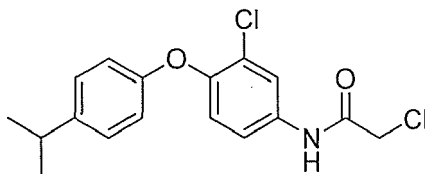
**[0219]** Light brown solid, Yield: 600 mg (78%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.23 (s, 1H), 7.63 (dd,  $J = 12.0, 2.5$ , 1H), 7.19 - 7.16 (m, 2H), 7.16 - 7.12 (m, 1H), 7.02 (t,  $J = 8.8$ , 1H), 6.92 - 6.86 (m, 2H), 4.20 (s, 2H), 2.89 (hept,  $J = 6.8$ , 1H), 1.24 (s, 3H), 1.23 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  163.8, 155.2, 154.0, 143.9, 141.2, 133.0, 127.6, 121.8, 117.1, 116.0, 109.7, 42.8, 33.4, 24.1. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}-\text{H}]^-$ : 320.78; found  $[\text{M}-\text{H}]^-$ : 320, 18.

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### Example 66: 2-chloro-N-(3-chloro-4-(4-isopropylphenoxy)phenyl)acetamide

**[0220]**

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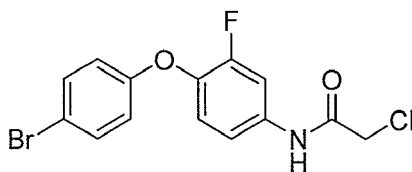
**[0221]** Light brown powder, Yield: 1412 mg (93%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.23 (s, 1H), 7.75 (d,  $J = 2.6$ , 1H), 7.35 (dd,  $J = 8.8, 2.6$ , 1H), 7.22 - 7.14 (m, 2H), 6.96 (d,  $J = 8.8$ , 1H), 6.91 - 6.86 (m, 2H), 4.19 (s, 2H), 2.89 (dt,  $J = 13.8, 6.9$ , 1H), 1.25 - 1.23 (m, 6H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  163.9, 154.8, 150.1, 144.1, 132.8, 127.7, 126.0, 122.6, 120.7, 119.8, 117.8, 42.8, 33.5, 24.1. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}-\text{H}]^-$ : 337.23; found  $[\text{M}-\text{H}]^-$ : 336.30, 336.50.

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### Example 67: N-(4-(4-bromophenoxy)-3-fluorophenyl)-2-chloroacetamide

**[0222]**

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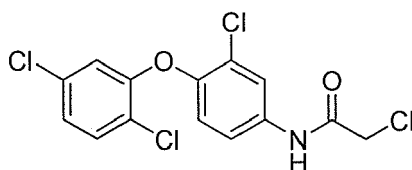
**[0223]** Brown solid, Yield: 823 mg (82%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.27 (s, 1H), 7.68 - 7.63 (m, 1H), 7.44 - 7.39 (m, 2H), 7.18 (d,  $J = 8.7$ , 1H), 7.08 - 7.03 (m, 1H), 6.86 - 6.81 (m, 2H), 4.21 (s, 2H), 2.76 (s, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  163.9, 155.7, 153.1, 140.1, 133.8, 132.6, 122.4, 118.6, 116.2, 115.6, 109.8, 42.8. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}-\text{H}]^-$ : 357.59; found  $[\text{M}-\text{H}]^-$ : 357.82.

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### Example 68: 2-chloro-N-(3-chloro-4-(2,5-dichlorophenoxy)phenyl)acetamide

**[0224]**

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**[0225]** Brown solid, Yield: 977 mg (99%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.31 (s, 1H), 7.82 (d,  $J = 2.6$ , 1H), 7.44 (dd,  $J = 8.8, 2.6$ , 1H), 7.40 - 7.37 (m, 1H), 7.06 - 7.03 (m, 1H), 6.98 (dd,  $J = 8.2, 3.6$ , 1H), 6.74 (d,  $J = 2.3$ , 1H), 4.21 (s, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  164.0, 153.1, 148.1, 134.2, 133.2, 131.4, 126.4, 124.4, 122.8, 122.7, 121.2, 119.9, 118.3, 42.8. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}-\text{H}]^-$ : 365.03; found  $[\text{M}-\text{H}]^-$ : 364, 19.

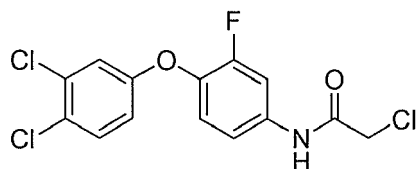
50

### Example 69: 2-chloro-N-(4-(3,4-dichlorophenoxy)-3-fluorophenyl)acetamide

**[0226]**

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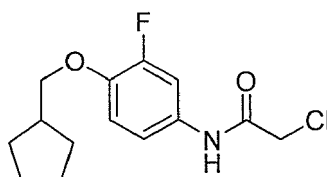
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10 [0227] Dark red solid, Yield: 630 mg (86%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.31 (s, 1H), 7.68 (dd,  $J = 11.9, 2.2$ , 1H), 7.36 (d,  $J = 8.8$ , 1H), 7.24 - 7.18 (m, 1H), 7.10 (t,  $J = 8.7$ , 1H), 7.03 (d,  $J = 2.7$ , 1H), 6.82 (dd,  $J = 8.8, 2.6$ , 1H), 4.22 (d,  $J = 7.8$ , 2H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  164.1, 156.6, 154.1, 139.4, 134.3, 133.3, 131.0, 126.5, 122.8, 122.8, 118.5, 110.0, 42.8, 40.5. Mass: MS (ESI)  $m/z$  calculated  $[\text{M-H}]^-$ : 347.58; found  $[\text{M-H}]^-$ : 347.87, 349.89.

Example 70: 2-chloro-N-(4-(cyclopentylmethoxy)-3-fluorophenyl)acetamide

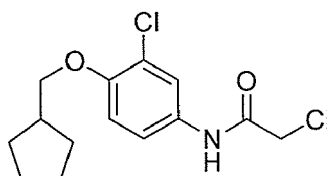
15 [0228]



25 [0229] Brown solid, Yield: 619 mg (45%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.15 (s, 1H), 7.45 (dd,  $J = 12.5, 2.6$ , 1H), 7.15 - 7.11 (m, 1H), 6.93 (t,  $J = 8.9$ , 1H), 4.18 (s, 2H), 3.89 (d,  $J = 7.0$ , 2H), 2.44 - 2.33 (m, 1H), 1.84 (ddd,  $J = 12.0, 9.0, 5.2$ , 2H), 1.68 - 1.54 (m, 4H), 1.41 - 1.31 (m, 2H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  163.7, 153.4, 147.9, 129.8, 115.9, 115.4, 109.5, 74.1, 42.8, 39.1, 29.4, 25.4. Mass: MS (ESI)  $m/z$  calculated  $[\text{M-H}]^-$ : 285.74; found  $[\text{M-H}]^-$ : 283.97.

Example 71: 2-chloro-N-(3-chloro-4-(cyclopentylmethoxy)phenyl)acetamide

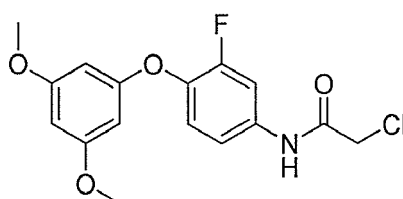
30 [0230]



40 [0231] Dark brown solid, Yield: 1204 mg (99%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.16 (s, 1H), 7.58 (d,  $J = 2.6$ , 1H), 7.37 (dd,  $J = 8.8, 2.6$ , 1H), 6.89 (d,  $J = 8.9$ , 1H), 4.18 (s, 2H), 3.88 (d,  $J = 6.8$ , 2H), 2.41 (dt,  $J = 14.8, 7.4$ , 1H), 1.85 (td,  $J = 11.9, 7.0$ , 2H), 1.72 - 1.54 (m, 4H), 1.40 (td,  $J = 14.1, 7.3$ , 2H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  163.9, 152.4, 129.9, 123.3, 122.8, 119.9, 113.7, 73.6, 42.8, 39.0, 29.4, 25.5. Mass: MS (ESI)  $m/z$  calculated  $[\text{M-H}]^-$ : 301.19; found  $[\text{M-H}]^-$ : 300.10, 300.49.

Example 72: 2-chloro-N-(4-(3,5-dimethoxyphenoxy)-3-fluorophenyl)acetamide

45 [0232]



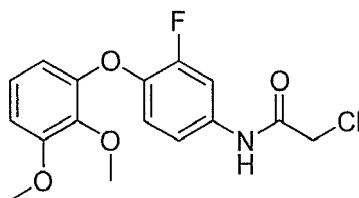
[0233] Light brown solid, Yield: 530 mg (71%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.27 (s, 1H), 7.64 (dd,  $J = 11.9, 2.5$ , 1H),

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7.19 -7.14 (m, 1H), 7.08 (t,  $J = 8.7$ , 1H), 6.20 (t,  $J = 2.2$ , 1H), 6.12 (d,  $J = 2.2$ , 2H), 4.21 (s, 2H), 3.75 (s, 6H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  163.9, 161.6, 159.3, 154.1, 140.2, 133.6, 122.6, 116.1, 109.6, 95.7, 95.3, 55.5, 42.8. Mass: MS (ESI)  $m/z$  calculated  $[\text{M-H}]^-$ : 338.75; found  $[\text{M-H}]^-$ : 338.06.

#### 5 Example 73: 2-chloro-N-(4-(2,3-dimethoxyphenoxy)-3-fluorophenyl)acetamide

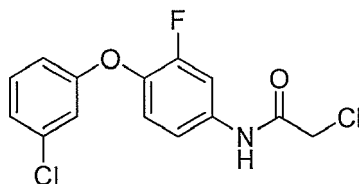
[0234]



[0235] Brown solid, Yield: 1106 mg (81%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.21 (s, 1H), 7.64 (dd,  $J = 12.1, 2.5$ , 1H), 7.12 -7.08 (m, 1H), 6.96 (td,  $J = 8.5, 6.0$ , 2H), 6.72 (dd,  $J = 8.4, 1.1$ , 1H), 6.51 (d,  $J = 8.4$ , 1H), 4.20 (s, 2H), 3.90 (s, 3H), 3.88 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  163.7, 154.3, 152.3, 152.1, 141.7, 132.7, 123.7, 120.6, 115.9, 111.4, 109.7, 109.5, 107.9, 61.1, 56.2, 42.8. Mass: MS (ESI)  $m/z$  calculated  $[\text{M-H}]^-$ : 339.75; found  $[\text{M-H}]^-$ : 338.06.

#### 25 Example 74: 2-chloro-N-(4-(3-chlorophenoxy)-3-fluorophenyl)acetamide

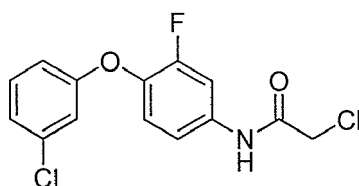
[0236]



[0237] Light brown solid, Yield: 980 mg (92%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.35 (s, 1H), 7.67 (dd,  $J = 11.9, 2.5$ , 1H), 7.24 - 7.19 (m, 2H), 7.09 (t,  $J = 8.7$ , 1H), 7.07 - 7.04 (m, 1H), 6.93 (t,  $J = 2.1$ , 1H), 6.84 (dd,  $J = 8.3, 2.2$ , 1H), 4.20 (d,  $J = 2.4$ , 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  164.0, 155.7, 155.2, 139.6, 134.2, 130.5, 129.7, 123.2, 122.8, 117.1, 116.2, 114.9, 109.8, 42.8. Mass: MS (ESI)  $m/z$  calculated  $[\text{M-H}]^-$ : 313.14; found  $[\text{M-H}]^-$ : 313.88.

#### 40 Example 75: 2-chloro-N-(3-fluoro-4-((3,4,5-trimethoxybenzyl)oxy)phenyl)acetamide

[0238]



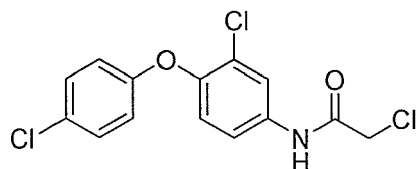
[0239] Red/brown solid, Yield: 513 mg (28%); Mass: MS (ESI)  $m/z$  calculated  $[\text{M-H}]^-$ : 382.8; found  $[\text{M-H}]^-$ : 382.07, 382.26.

#### 55 Example 76: 2-chloro-N-(3-chloro-4-(4-chlorophenoxy)phenyl)acetamide

[0240]

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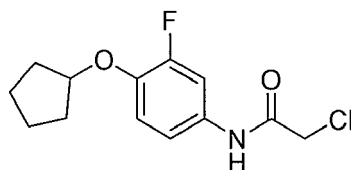


10 [0241] Light brown solid, Yield: 850mg (92%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.26 (s, 1H), 7.78 (d,  $J = 2.6$ , 1H), 7.40 (dd,  $J = 8.8$ , 2.6, 1H), 7.28 (dt,  $J = 6.1$ , 3.6, 2H), 7.00 (dd,  $J = 9.0$ , 4.0, 1H), 6.89 - 6.85 (m, 2H), 4.21 (s, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  163.9, 155.7, 149.0, 133.6, 129.8, 128.4, 126.7, 122.6, 121.5, 119.9, 118.7, 42.8. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}-\text{H}]^-$ : 329.59; found  $[\text{M}-\text{H}]^-$ : 328.37.

Example 77: 2-chloro-N-(4-(cyclopentyloxy)-3-fluorophenyl)acetamide

15 [0242]

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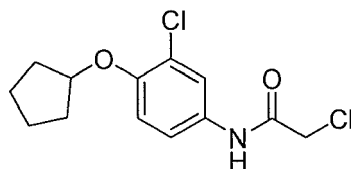
25 [0243] Brown/red solid, Yield: 551mg (99%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.21 (s, 1H), 7.46 - 7.40 (m, 1H), 7.12 (d,  $J = 0.8$ , 1H), 6.93 (t,  $J = 8.9$ , 1H), 4.78 (s, 1H), 4.18 (s, 2H), 1.89 - 1.85 (m, 2H), 1.86 - 1.79 (m, 4H), 1.62 (d,  $J = 2.9$ , 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  163.8, 152.9, 143.5, 129.9, 116.9, 116.0, 109.6, 81.6, 50.8, 42.8, 32.7, 23.8. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}-\text{H}]^-$ : 270.72; found  $[\text{M}-\text{H}]^-$ : 270.06.

Example 78: 2-chloro-N-(3-chloro-4-(cyclopentyloxy)phenyl)acetamide

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[0244]

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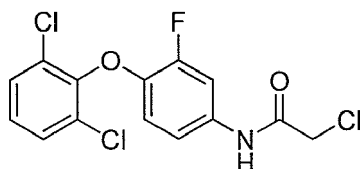


40 [0245] Light brown solid, Yield: 582 mg (99%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.14 (s, 0H), 7.60 (d,  $J = 2.6$ , 1H), 7.39 (dd,  $J = 8.9$ , 2.7, 1H), 6.93 (d,  $J = 8.9$ , 1H), 4.81 (dd,  $J = 7.8$ , 3.8, 1H), 4.21 (s, 2H), 1.98 - 1.82 (m, 6H), 1.65 (td,  $J = 8.4$ , 5.0, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  163.7, 158.2, 151.4, 129.7, 122.8, 119.8, 115.2, 81.2, 42.8, 32.8, 23.9. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}-\text{H}]^-$ : 287.17; found  $[\text{M}-\text{H}]^-$ : 286.12, 288.07.

Example 79: 2-chloro-N-(4-(2,6-dichlorophenoxy)-3-fluorophenyl)acetamide

[0246]

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[0247] White solid, Yield: 724 mg (99%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.18 (s, 1H), 7.62 (dd,  $J = 12.1$ , 2.5, 1H), 7.40 (t,  $J = 6.2$ , 2H), 7.17 (t,  $J = 8.1$ , 1H), 7.08 - 7.03 (m, 1H), 6.53 (t,  $J = 8.9$ , 1H), 4.19 (s, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  163.8, 148.7, 129.6, 129.3, 127.9, 126.7, 124.5, 121.2, 115.7, 109.8, 42.8, 30.9. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}-\text{H}]^-$ :

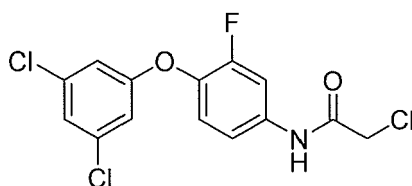
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H]: 347,58; found [M-H]<sup>-</sup>: 347,87.

#### Example 80: 2-chloro-N-(4-(3,5-dichlorophenoxy)-3-fluorophenyl)acetamide

5 [0248]

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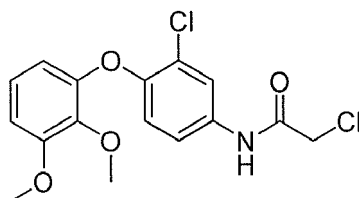
15 [0249] Light brown solid, Yield: 396 mg (43%); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.28 (s, 1H), 7.71 (dd, *J* = 11.9, 2.5, 1H), 7.24 (dd, *J* = 8.8, 1.3, 1H), 7.12 (t, *J* = 8.7, 1H), 7.07 (t, *J* = 1.7, 1H), 6.82 (d, *J* = 1.6, 2H), 4.22 (s, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 163.9, 157.0, 153.3, 138.7, 135.7, 134.8, 123.3, 116.3, 115.3, 109.8, 100.0, 42.8. Mass: MS (ESI) *m/z* calculated [M-H]<sup>-</sup>: 347,58; found [M-H]<sup>-</sup>: 347,94.

#### Example 81: 2-chloro-N-(3-chloro-4-(2,3-dimethoxyphenoxy)phenyl)acetamide

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[0250]

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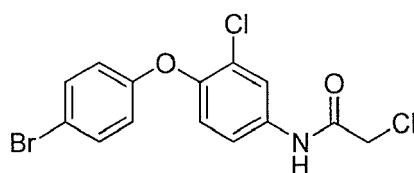
30

35 [0251] Light brown solid, Yield: 441 mg (63%), <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.21 (s, 1H), 7.76 (t, *J* = 7.1, 1H), 7.30 (dd, *J* = 8.8, 2.6, 1H), 7.01 - 6.95 (m, 1H), 6.86 (d, *J* = 8.8, 1H), 6.74 (dd, *J* = 8.3, 1.0, 1H), 6.50 (dd, *J* = 8.3, 1.2, 1H), 4.19 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 163.8, 154.2, 150.2, 149.7, 140.2, 132.5, 123.8, 122.5, 121.9, 119.7, 119.3, 112.0, 108.2, 61.2, 56.2, 42.8. Mass: MS (ESI) *m/z* calculated [M-H]<sup>-</sup>: 355,20; found [M-H]<sup>-</sup>: 355,93.

#### Example 82: N-(4-(4-bromophenoxy)-3-chlorophenyl)-2-chloroacetamide

40 [0252]

45



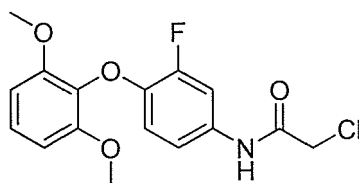
50

55 [0253] Light brown solid, Yield: 1096 mg (73%); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.25 (d, *J* = 8.4, 1H), 7.78 (dd, *J* = 6.1, 2.6, 1H), 7.42 (dd, *J* = 7.1, 5.1, 1H), 7.38 (dd, *J* = 8.9, 2.7, 1H), 7.35 - 7.30 (m, 1H), 7.00 (t, *J* = 8.5, 1H), 6.96 - 6.92 (m, 1H), 6.83 - 6.79 (m, 1H), 4.20 (s, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 163.9, 156.6, 149.2, 132.7, 129.8, 123.4, 121.7, 121.3, 121.1, 119.1, 117.7, 42.8. Mass: MS (ESI) *m/z* calculated [M-H]<sup>-</sup>: 374,04; found [M-H]<sup>-</sup>: 374,14.

#### Example 83: 2-chloro-N-(4-(2,6-dimethoxyphenoxy)-3-fluorophenyl)acetamide

55 [0254]

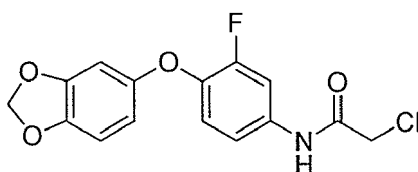
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 [0255] Light brown solid, Yield: 572 mg (53%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.13 (s, 1H), 7.51 (dt,  $J = 22.9, 11.4$ , 1H), 7.15 (t,  $J = 8.4$ , 1H), 7.00 (d,  $J = 8.9$ , 1H), 6.65 (d,  $J = 8.5$ , 2H), 6.58 (t,  $J = 8.9$ , 1H), 4.17 (s, 2H), 3.79 (s, 6H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  163.6, 153.3, 151.6, 130.7, 125.8, 115.7, 115.6, 109.5, 105.4, 103.0, 100.0, 56.3, 42.8. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}-\text{H}]^-$ : 338,75; found  $[\text{M}-\text{H}]^-$ : 338,12.0.

Example 84: N-(4-(benzo[d][1,3]dioxol-5-yloxy)-3-fluorophenyl)-2-chloroacetamide

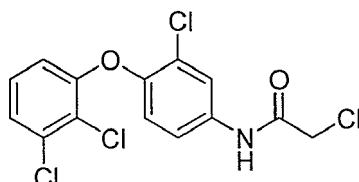
15 [0256]



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 [0257] Dark brown solid, Yield: 219 mg (23%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.22 (s, 1H), 7.61 (dd,  $J = 12.0, 2.5$ , 1H), 7.16 - 7.11 (m, 1H), 7.01 - 6.95 (m, 1H), 6.73 (d,  $J = 8.4$ , 1H), 6.56 (d,  $J = 2.5$ , 1H), 6.43 (dd,  $J = 8.4, 2.5$ , 1H), 5.97 (s, 2H), 4.20 (s, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  163.8, 153.4, 152.7, 148.4, 143.7, 141.8, 132.8, 121.1, 116.0, 110.0, 109.70, 108.2, 101.6, 100.6, 42.8. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}-\text{H}]^-$ : 322,70; found  $[\text{M}-\text{H}]^-$ : 322,00.

Example 85: 2-chloro-N-(3-chloro-4-(2,3-dichlorophenoxy)phenyl)acetamide

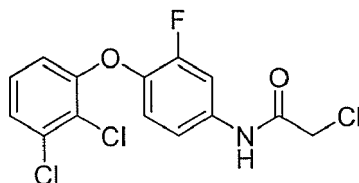
30 [0258]



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 [0259] Red/brown solid, Yield: 313 mg (99%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.24 (s, 1H), 7.80 (d,  $J = 2.5$ , 1H), 7.41 (dd,  $J = 8.8, 2.6$ , 1H), 7.25 (dd,  $J = 8.2, 1.3$ , 1H), 7.15 - 7.10 (m, 1H), 6.95 (d,  $J = 8.8$ , 1H), 6.70 (dd,  $J = 8.3, 1.2$ , 1H), 4.20 (d,  $J = 13.8$ , 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.7, 164.1, 153.8, 148.7, 133.7, 127.5, 125.3, 122.7, 122.2, 120.8, 119.9, 119.0, 116.4, 42.8. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}-\text{H}]^-$ : 364,03; found  $[\text{M}-\text{H}]^-$ : 364,00.

Example 86: 2-chloro-N-(4-(2,3-dichlorophenoxy)-3-fluorophenyl)acetamide

45 [0260]



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 [0261] Red/brown solid, Yield: 1067 mg (99%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.27 (s, 1H), 7.69 (dd,  $J = 11.9, 2.5$ , 1H), 7.23 (dd,  $J = 8.1, 1.2$ , 1H), 7.18 (dd,  $J = 6.1, 4.5$ , 1H), 7.11 (t,  $J = 8.2$ , 1H), 7.02 (t,  $J = 8.7$ , 1H), 6.74 (d,  $J = 8.3$ , 1H), 4.21 (s, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  163.8, 154.4, 152.7, 134.3, 127.9, 127.4, 125.1, 124.5, 121.8, 118.4, 116.1,



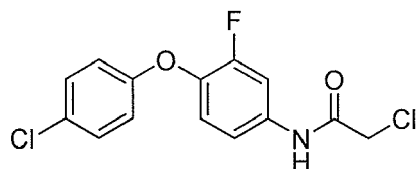
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115.6, 109.8, 42.8. Mass: MS (ESI) m/z calculated [M-H]<sup>-</sup>: 347.58; found [M-H]<sup>-</sup>: 346.25, 348.26.

### Example 87: 2-chloro-N-(4-(4-chlorophenoxy)-3-fluorophenyl)acetamide

5 [0262]

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[0263] Light pink solid, Yield: 1353 mg (86%); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.26 (s, 1H), 7.68 - 7.64 (m, 1H), 7.29 - 7.25 (m, 2H), 7.20 - 7.16 (m, 1H), 7.06 (t, J = 8.7, 1H), 6.91 - 6.87 (m, 2H), 4.21 (s, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 163.8, 155.5, 153.1, 140.3, 133.9, 129.7, 128.2, 122.3, 118.2, 116.2, 109.8, 42.8. Mass: MS (ESI) m/z calculated [M-H]<sup>-</sup>: 313.14; found [M-H]<sup>-</sup>: 312.97.

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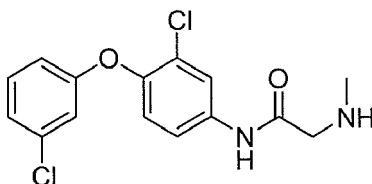
Following examples were synthesized by using Method 2: Method for coupling reaction of primary amines 9 and 2-chloroacetyl chloride

### Example 88: N-(3-chloro-4-(3-chlorophenoxy)phenyl)-2-(methylamino)acetamide

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[0264]

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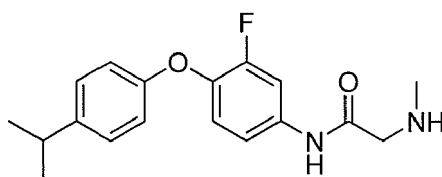
[0265] Brown oil, Yield: 878 mg (77%); <sup>1</sup>H NMR 500 MHz, CDCl<sub>3</sub>) δ 9.53 (s, 1H), 7.92 (d, J = 2.5, 1H), 7.44 (dd, J = 8.8, 2.5, 1H), 7.19 (t, J = 8.2, 1H), 7.00 (d, J = 8.7, 2H), 6.88 (t, J = 2.1, 1H), 6.78 (dd, J = 8.3, 2.3, 1H), 3.34 (s, 2H), 2.46 (s, 3H), 2.19 (s, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 170.2, 158.2, 147.0, 135.4, 135.0, 130.6, 126.6, 123.0, 122.3, 121.7, 119.3, 117.1, 115.1, 54.9, 36.7. Mass: MS (ESI) m/z calculated [M-H]<sup>-</sup>: 324.19; found [M-H]<sup>-</sup>: 323.24, 323.37.

### Example 89: N-(3-fluoro-4-(4-isopropylphenoxy)phenyl)-2-(methylamino)acetamide

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[0266]

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[0267] Yellow oil, Yield: 506mg (80%); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.51 (s, 1H), 7.76 (dd, J = 12.5, 2.3, 1H), 7.16 (d, J = 8.8, 1H), 7.12 (d, J = 8.5, 2H), 6.96 (t, J = 8.8, 1H), 6.86 (d, J = 8.5, 2H), 3.29 (d, J = 9.4, 2H), 2.90-2.78 (m, 1H), 2.41 (s, 3H), 2.18 (s, 1H), 1.20 (d, J = 7.1, 6H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 170.2, 155.6, 154.0, 143.5, 139.7, 134.8, 127.5, 122.0, 116.7, 115.5, 108.9, 54.9, 36.6, 33.3, 24.1. Mass: MS (ESI) m/z calculated [M-H]<sup>-</sup>: 315.38; found [M-H]<sup>-</sup>: 315.11, 315.37.

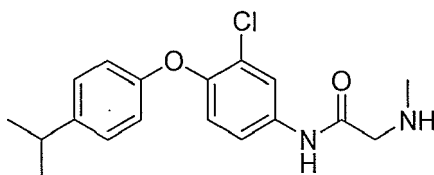
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### Example 90: N-(3-chloro-4-(4-isopropylphenoxy)phenyl)-2-(methylamino)acetamide

[0268]

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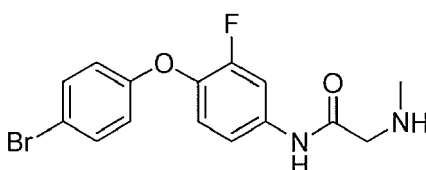
[0269] Brown oil, Yield: 538 mg (77%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.36 (s, 1H), 7.83 (d,  $J = 2.5$ , 1H), 7.39 (dd,  $J = 8.8$ , 2.6, 1H), 7.17 - 7.12 (m, 2H), 6.94 (d,  $J = 8.8$ , 1H), 6.87 - 6.82 (m, 2H), 3.32 (s, 2H), 2.87 (dt,  $J = 16.5$ , 6.9, 1H), 2.46 (d,  $J = 2.8$ , 3H), 1.91 (s, 1H), 1.23 (dd,  $J = 6.9$ , 3.7, 6H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.0, 155.2, 148.7, 143.7, 134.3, 127.6, 126.0, 121.7, 121.1, 119.1, 117.4, 54.9, 36.8, 33.4, 24.1. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 333.82; found  $[\text{M}+\text{H}]^+$ : 333.31.

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**Example 91: N-(4-(4-bromophenoxy)-3-fluorophenyl)-2-(methylamino)acetamide**

[0270]

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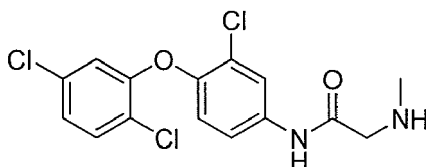
[0271] Light brown oil, Yield: 290 mg (71%),  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.45 (s, 1H), 7.74 (dt,  $J = 12.4$ , 3.3, 1H), 7.40 - 7.34 (m, 2H), 7.19 (dd,  $J = 10.7$ , 5.1, 1H), 7.02 (t,  $J = 8.8$ , 1H), 6.83 - 6.77 (m, 2H), 3.34 (s, 2H), 2.45 (d,  $J = 16.8$ , 3H), 2.03 (s, 1H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.1, 157.0, 154.1, 138.7, 135.4, 132.5, 129.7, 122.6, 118.3, 115.6, 109.0, 54.9, 36.8. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 353.02; found  $[\text{M}+\text{H}]^+$ : 353.14.

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**Example 92: N-(3-chloro-4-(2,5-dichlorophenoxy)phenyl)-2-(methylamino)acetamide**

[0272]

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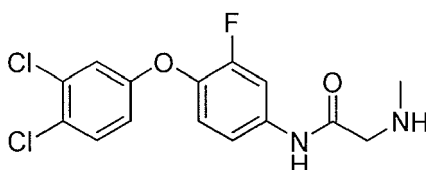
[0273] Brown oil, Yield: 717 mg (91%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.54 (s, 1H), 7.94 (d,  $J = 2.5$ , 1H), 7.45 (dt,  $J = 7.5$ , 3.8, 1H), 7.37 - 7.32 (m, 1H), 7.02 - 6.96 (m, 2H), 6.70 (d,  $J = 2.3$ , 1H), 3.36 (s, 2H), 2.47 (s, 3H), 2.21 (s, 1H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.2, 153.3, 146.8, 135.6, 133.1, 131.3, 126.1, 124.0, 122.3, 121.8, 121.5, 119.3, 117.7, 54.9, 36.8. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}-\text{H}]^-$ : 357.00; found  $[\text{M}-\text{H}]^-$ : 357.24.

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**Example 93: N-(4-(3,4-dichlorophenoxy)-3-fluorophenyl)-2-(methylamino)acetamide**

[0274]

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[0275] Light brown oil, Yield: 117 mg (38%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.45 (s, 1H), 7.76 (dd,  $J = 12.3$ , 2.5, 1H), 7.34 (d,  $J = 8.9$ , 1H), 7.23 (ddd,  $J = 8.8$ , 2.3, 1.3, 1H), 7.06 (t,  $J = 8.7$ , 1H), 7.01 (d,  $J = 2.9$ , 1H), 6.80 (dd,  $J = 8.9$ , 2.9,

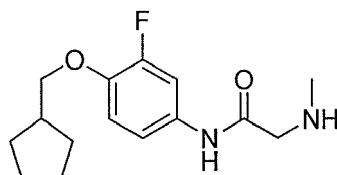
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1H), 3.36 (s, 2H), 2.50 (s, 3H), 1.95 (d,  $J = 18.4$ , 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.0, 157.0, 154.2, 138.0, 135.9, 133.1, 130.9, 126.1, 122.9, 118.2, 116.0, 115.5, 109.0, 54.9, 36.9. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 343.03; found  $[\text{M}+\text{H}]^+$ : 343.19.

#### 5 Example 94: N-(4-(cyclopentylmethoxy)-3-fluorophenyl)-2-(methylamino)acetamide

[0276]

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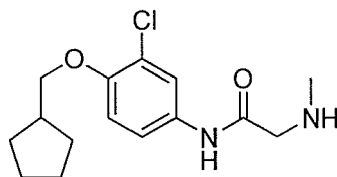
[0277] Pink solid, Yield: 354 mg (74%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.32 (s, 1H), 7.55 (dt,  $J = 8.5, 4.2$ , 1H), 7.14 (dt,  $J = 7.8, 3.9$ , 1H), 6.92 - 6.86 (m, 1H), 3.85 (d,  $J = 7.0$ , 2H), 3.31 (s, 2H), 2.45 (s, 3H), 2.38 - 2.31 (m, 1H), 2.22 (s, 1H), 1.86 - 1.77 (m, 2H), 1.68 - 1.52 (m, 4H), 1.39 - 1.30 (m, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  169.7, 152.4, 143.6, 131.4, 115.5, 115.1, 108.6, 74.1, 54.7, 39.0, 36.5, 29.3, 25.3. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 281.34; found  $[\text{M}+\text{H}]^+$ : 281.31

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#### Example 95: N-(3-chloro-4-(cyclopentylmethoxy)phenyl)-2-(methylamino)acetamide

[0278]

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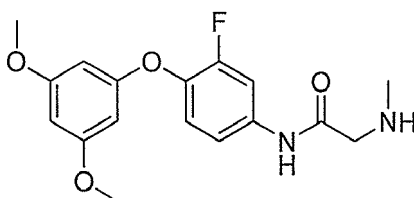
[0279] Brown oil, Yield: 193 mg (33%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.29 (s, 1H), 7.67 (d,  $J = 2.6$ , 1H), 7.36 (dt,  $J = 9.7, 4.8$ , 1H), 6.84 (d,  $J = 8.9$ , 1H), 3.84 (d,  $J = 6.9$ , 2H), 3.29 (s, 2H), 2.44 (s, 3H), 2.41 - 2.31 (m, 1H), 2.24 (s, 1H), 1.88 - 1.76 (m, 2H), 1.71 - 1.51 (m, 4H), 1.38 (td,  $J = 14.2, 7.2$ , 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  169.8, 151.3, 131.3, 122.9, 121.8, 119.1, 113.8, 73.6, 54.8, 39.0, 36.6, 29.3, 25.4. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 297.79; found  $[\text{M}+\text{H}]^+$ : 297.17.

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#### Example 96: N-(4-(3,5-dimethoxyphenoxy)-3-fluorophenyl)-2-(methylamino)acetamide

[0280]

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[0281] Brown oil, Yield: 193 mg (74%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.41 (s, 1H), 7.73 (dd,  $J = 12.3, 2.4$ , 1H), 7.19 (dd,  $J = 5.4, 4.1$ , 1H), 7.06 (t,  $J = 8.8$ , 1H), 6.18 (t,  $J = 2.2$ , 1H), 6.10 (d,  $J = 2.2$ , 2H), 3.72 (d,  $J = 6.8$ , 6H), 3.34 (s, 2H), 2.48 (s, 3H), 1.97 (s, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.0, 161.6, 159.7, 154.1, 138.8, 135.2, 122.8, 115.3, 108.9, 95.4, 95.0, 55.4, 54.9, 36.8. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 335.34; found  $[\text{M}+\text{H}]^+$ : 335.20.

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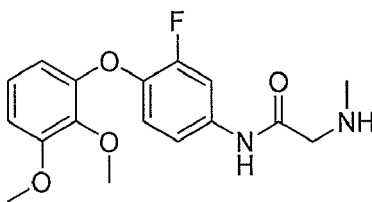
#### Example 97: N-(4-(2,3-dimethoxyphenoxy)-3-fluorophenyl)-2-(methylamino)acetamide

[0282]

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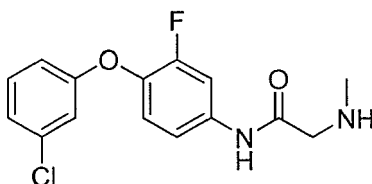


10 **[0283]** Brown oil, Yield: 400 mg (39%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.41 (s, 1H), 7.73 (dd,  $J = 12.5, 2.4$ , 1H), 7.17-7.12 (m, 1H), 6.94 (td,  $J = 8.6, 5.2$ , 2H), 6.69 (dd,  $J = 8.4, 1.2$ , 1H), 6.46 (dd,  $J = 8.3, 0.7$ , 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.33 (s, 2H), 2.46 (s, 3H), 2.13 (s, 1H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.0, 154.0, 153.5, 150.6, 140.2, 139.6, 134.4, 123.7, 121.0, 115.2, 110.7, 108.7, 107.6, 61.0, 56.1, 54.8, 36.7. Mass: MS (ESI)  $m/z$  calculated  $[\text{M-H}]^-$ : 333.35; found  $[\text{M-H}]^-$ : 333.31.

15 **Example 98: N-(4-(3-chlorophenoxy)-3-fluorophenyl)-2-(methylamino)acetamide**

**[0284]**

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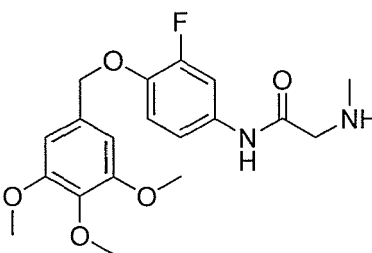
**[0285]** Brown oil, Yield: 336 mg (70%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.53 (s, 1H), 7.77 (dd,  $J = 12.3, 2.3$ , 1H), 7.25 - 7.16 (m, 2H), 7.02 (dt,  $J = 8.5, 7.1$ , 2H), 6.91 (t,  $J = 2.0$ , 1H), 6.81 (dd,  $J = 8.3, 2.2$ , 1H), 3.36 (s, 2H), 2.47 (s, 3H), 2.44 - 2.35 (m, 1H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.0, 158.6, 154.2, 138.3, 135.6, 134.9, 130.5, 129.7, 122.9, 122.8, 116.7, 115.6, 114.7, 108.9, 54.8, 36.6. Mass: MS (ESI)  $m/z$  calculated  $[\text{M+H}]^+$ : 309.20; found  $[\text{M+H}]^+$ : 309.20.

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**Example 99: N-(3-fluoro-4-((3,4,5-trimethoxybenzyl)oxy)phenyl)-2-(methylamino)acetamide**

**[0286]**

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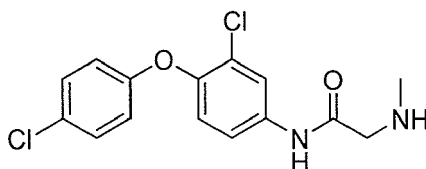
45 **[0287]** Dark brown oil, Yield: 251 mg (99%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.24 (s, 1H), 7.56 (dd,  $J = 12.8, 2.2$ , 1H), 7.16 (d,  $J = 8.8$ , 1H), 6.95 (t,  $J = 8.9$ , 1H), 6.66 (s, 2H), 5.04 (s, 2H), 3.87 (s, 6H), 3.84 (s, 3H), 3.36 (s, 2H), 2.50 (s, 3H), 1.96 (d,  $J = 18.0$ , 1H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  169.4, 153.4, 152.8, 143.0, 137.7, 132.2, 132.1, 116.8, 115.0, 108.7, 104.5, 72.4, 60.9, 56.1, 54.8, 36.8. Mass: MS (ESI)  $m/z$  calculated  $[\text{M+H}]^+$ : 379.39; found  $[\text{M+H}]^+$ : 379.34.

50 **Example 100: N-(3-chloro-4-(4-chlorophenoxy)phenyl)-2-(methylamino)acetamide**

**[0288]**

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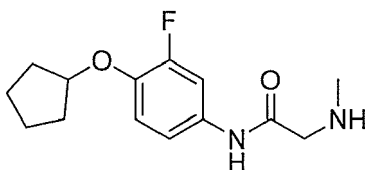


10 **[0289]** Brown oil, Yield: 345 mg (82%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.46 (s, 1H), 7.86 (d,  $J = 2.1$ , 1H), 7.42 (dd,  $J = 8.7$ , 2.2, 1H), 7.23 (d,  $J = 8.7$ , 3H), 6.97 (d,  $J = 8.9$ , 1H), 6.81 (dd,  $J = 13.9$ , 8.0, 2H), 3.34 (s, 2H), 2.45 (d,  $J = 14.6$ , 3H), 2.22 (s, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.2, 156.0, 147.7, 135.0, 129.7, 127.9, 126.4, 121.8, 121.7, 119.3, 118.3, 54.9, 36.8. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 325.24; found  $[\text{M}+\text{H}]^+$ : 325.06.

**Example 101: N-(4-(cyclopentyloxy)-3-fluorophenyl)-2-(methylamino)acetamide**

15 **[0290]**

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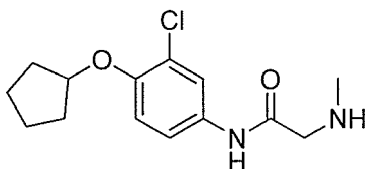
25 **[0291]** Red oil, Yield: 100 mg (38%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.24 (s, 1H), 7.51 (dd,  $J = 12.8$ , 2.4, 1H), 7.15 (d,  $J = 8.7$ , 1H), 6.93 - 6.86 (m, 1H), 3.33 (s, 2H), 2.45 (d,  $J = 23.2$ , 3H), 2.16 - 2.05 (m, 1H), 1.92 - 1.76 (m, 6H), 1.67 - 1.54 (m, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  169.6, 153.1, 142.5, 131.3, 117.2, 115.1, 108.6, 81.6, 54.8, 36.7, 32.7, 23.8. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 267.32; found  $[\text{M}+\text{H}]^+$ : 267.27.

**Example 102: N-(3-chloro-4-(cyclopentyloxy)phenyl)-2-(methylamino)acetamide**

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**[0292]**

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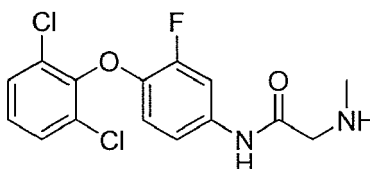


40 **[0293]** Brown oil, Yield: 292 mg (65%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.32 (s, 1H), 7.67 (d,  $J = 2.6$ , 1H), 7.36 (dd,  $J = 8.8$ , 2.5, 1H), 6.85 (d,  $J = 8.9$ , 1H), 4.73 (s, 1H), 3.30 (s, 2H), 2.50 (s, 1H), 2.44 (s, 3H), 1.90 - 1.76 (m, 6H), 1.66 - 1.55 (m, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  169.8, 150.2, 131.2, 123.6, 121.9, 119.0, 115.4, 81.2, 54.7, 36.6, 32.7, 23.8. Mass: MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 283.77; found  $[\text{M}+\text{H}]^+$ : 283.06.

**Example 103: N-(4-(2,6-dichlorophenoxy)-3-fluorophenyl)-2-(methylamino)acetamide**

**[0294]**

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**[0295]** Light brown oil, Yield: 514 mg (90%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.26 (s, 1H), 7.69 - 7.65 (m, 1H), 7.39 (d,  $J = 8.1$ , 2H), 7.15 (t,  $J = 8.1$ , 1H), 7.11 - 7.07 (m, 1H), 6.50 (td,  $J = 8.9$ , 2.7, 1H), 3.34 (s, 2H), 2.49 (s, 3H), 1.63 (s, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  169.6, 151.7, 140.9, 133.2, 129.7, 129.3, 126.6, 121.6, 115.7, 114.8, 109.0, 54.9, 36.9.

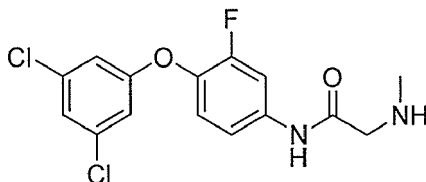
### EP 3 666 769 A1

Mass: MS (ESI) m/z calculated [M+H]<sup>+</sup>: 343,03; found [M+H]<sup>+</sup>: 343,19.

#### Example 104: N-(4-(3,5-dichlorophenoxy)-3-fluorophenyl)-2-(methylamino)acetamide

5 [0296]

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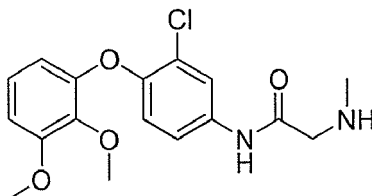
[0297] Brown oil, Yield: 256 mg (75%); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.44 (s, 1H), 7.76 (dd, *J* = 12.2, 2.4, 1H), 7.28-7.24 (m, 1H), 7.09 (t, *J* = 8.7, 1H), 7.05 (t, *J* = 1.7, 1H), 6.81 (d, *J* = 1.7, 2H), 3.38 (s, 2H), 2.52 (s, 3H), 1.81 (s, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 169.9, 159.1, 154.4, 137.5, 136.1, 135.6, 123.2, 123.0, 115.5, 115.1, 109.0, 54.9, 36.9. Mass: MS (ESI) m/z calculated [M+H]<sup>+</sup>: 343,03; found [M+H]<sup>+</sup>: 343,19.

#### Example 105: N-(3-chloro-4-(2,3-dimethoxyphenoxy)phenyl)-2-(methylamino)acetamide

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[0298]

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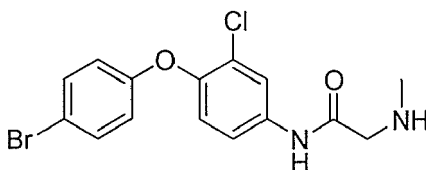
[0299] Transparent oil, Yield: 199 mg (51%); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.33 (s, 1H), 7.85 (d, *J* = 2.5, 1H), 7.36 (dd, *J* = 8.8, 2.5, 1H), 6.97 - 6.92 (m, 1H), 6.87 (d, *J* = 8.8, 1H), 6.71 (dd, *J* = 8.4, 1.1, 1H), 6.43 (dd, *J* = 8.3, 1.1, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.32 (s, 2H), 2.47 (s, 3H), 1.88 (s, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 169.9, 154.1, 150.1, 148.8, 139.8, 134.1, 125.1, 123.7, 121.6, 119.9, 119.0, 111.3, 107.8, 61.1, 56.1, 54.9, 36.8. Mass: MS (ESI) m/z calculated [M-H]<sup>-</sup>: 349,80; found [M-H]<sup>-</sup>: 349,04.

#### Example 106: N-(4-(4-bromophenoxy)-3-chlorophenyl)-2-(methylamino)acetamide

[0300]

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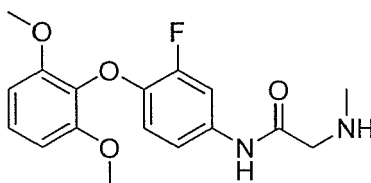
[0301] Transparent oil, Yield: 260mg (27%); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.39 (s, 1H), 7.85 (dd, *J* = 4.3, 2.6, 1H), 7.42 (ddd, *J* = 11.2, 8.9, 2.5, 1H), 7.32 - 7.27 (m, 2H), 6.97 (dd, *J* = 8.8, 5.5, 1H), 6.91 (d, *J* = 8.1, 2H), 3.33 (s, 2H), 2.47 (s, 3H), 2.15 (s, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 170.0, 157.3, 148.2, 134.6, 132.6, 129.8, 123.1, 121.6, 119.2, 118.7, 117.3, 54.9, 36.8. Mass: MS (ESI) m/z calculated [M-H]<sup>-</sup>: 368.64; found [M-H]<sup>-</sup>: 368.20.

#### Example 107: N-(4-(2,6-dimethoxyphenoxy)-3-fluorophenyl)-2-(methylamino)acetamide

55 [0302]

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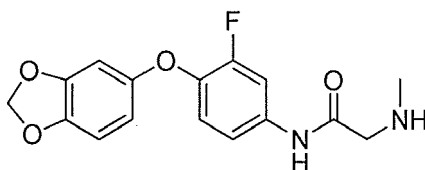


10 **[0303]** White solid, Yield: 362 mg (72%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.20 (s, 1H), 7.61 - 7.55 (m, 1H), 7.13 (t,  $J = 8.4$ , 1H), 7.03 (d,  $J = 8.8$ , 1H), 6.64 (d,  $J = 8.4$ , 2H), 6.55 (t,  $J = 9.0$ , 1H), 3.76 (s, 6H), 3.30 (s, 2H), 2.46 (s, 3H), 1.78 (s, 1H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  169.6, 153.4, 151.7, 142.8, 132.3, 132.0, 125.7, 116.1, 115.6, 114.8, 108.6, 105.4, 56.2, 54.9, 36.8. Mass: MS (ESI)  $m/z$  calculated  $[\text{M-H}]^-$ : 333.35; found  $[\text{M-H}]^-$ : 333.05.

**Example 108: N-(4-(benzo[d][1,3]dioxol-5-yloxy)-3-fluorophenyl)-2-(methylamino)acetamide**

15 **[0304]**

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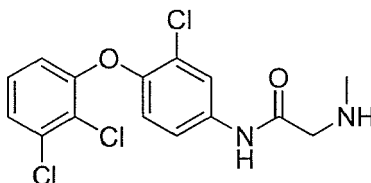


25 **[0305]** Light brown oil, Yield: 113 mg (64%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.34 (s, 1H), 7.68 (dd,  $J = 12.4$ , 2.4, 1H), 7.19 - 7.15 (m, 1H), 6.97 (t,  $J = 8.8$ , 1H), 6.71 (d,  $J = 8.4$ , 1H), 6.54 (d,  $J = 2.4$ , 1H), 6.41 (dd,  $J = 8.4$ , 2.4, 1H), 5.95 (s, 2H), 3.35 (s, 2H), 2.50 (s, 3H), 1.93 (s, 1H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  189.0, 169.7, 153.8, 152.4, 148.4, 143.4, 140.4, 134.4, 121.5, 115.3, 109.5, 108.9, 108.1, 101.5, 100.3, 54.9, 36.8. Mass: MS (ESI)  $m/z$  calculated  $[\text{M-H}]^-$ : 317.30; found  $[\text{M-H}]^-$ : 317.26.

30 **Example 109: N-(3-chloro-4-(2,3-dichlorophenoxy)phenyl)-2-(methylamino)acetamide**

**[0306]**

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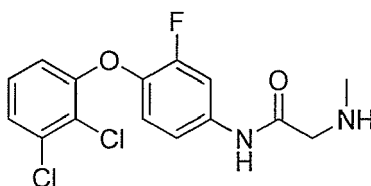
**[0307]** Light brown oil, Yield: 115 mg (58%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.38 (s, 1H), 7.86 (d,  $J = 2.5$ , 1H), 7.49 - 7.44 (m, 1H), 7.20 (d,  $J = 8.1$ , 1H), 7.09 (t,  $J = 8.3$ , 1H), 6.96 (d,  $J = 8.8$ , 1H), 6.64 (d,  $J = 8.3$ , 1H), 3.35 (s, 2H), 2.50 (s, 3H), 1.77 (s, 1H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  169.9, 154.3, 147.3, 135.3, 134.3, 127.4, 124.8, 121.7, 121.4, 121.2, 119.3, 119.1, 115.7, 54.9, 36.9. MS (ESI)  $m/z$  calculated  $[\text{M-H}]^-$ : 358.63; found  $[\text{M-H}]^-$ : 358.93.

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**Example 110: N-(4-(2,3-dichlorophenoxy)-3-fluorophenyl)-2-(methylamino)acetamide**

**[0308]**

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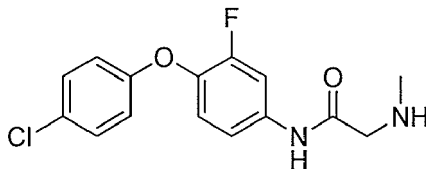
**[0309]** Dark brown oil, Yield: 752 mg (84%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.54 (s, 1H), 7.81 (dd,  $J = 12.4$ , 2.4, 1H), 7.21 (dd,  $J = 8.8$ , 1.1, 1H), 7.17 (dd,  $J = 8.1$ , 1.1, 1H), 7.08 (t,  $J = 8.2$ , 1H), 7.00 (t,  $J = 8.8$ , 1H), 6.69 (d,  $J = 8.3$ , 1H),

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3.35 (s, 2H), 2.47 (s, 3H), 2.12 (s, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.2, 154.5, 153.6, 138.3, 135.7, 134.0, 127.5, 124.6, 122.7, 122.0, 115.5, 115.1, 108.8, 54.9, 36.7. MS (ESI)  $m/z$  calculated  $[\text{M-H}]^-$ : 342.18; found  $[\text{M-H}]^-$ : 342.93

### Example 111: N-(4-(4-chlorophenoxy)-3-fluorophenyl)-2-(methylamino)acetamide

[0310]

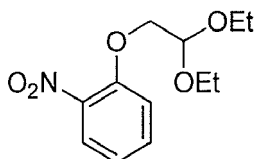


[0311] Dark brown oil, Yield: 827 mg (64%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.48 (s, 1H), 7.69 (dt,  $J = 12.5, 2.9$ , 1H), 7.13 - 7.06 (m, 3H), 6.89 (t,  $J = 8.9$ , 1H), 6.77 - 6.70 (m, 2H), 3.24 (s, 2H), 2.33 (s, 3H), 2.08 (s, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.3, 156.4, 153.9, 138.6, 135.4, 129.5, 127.6, 122.4, 117.8, 115.7, 108.9, 54.8, 36.5. MS (ESI)  $m/z$  calculated  $[\text{M+H}]^+$ : 309.74; found  $[\text{M+H}]^+$ : 309.07.

Following examples were synthesized by using Method 5: Method for 2-bromo-1,1-diethoxyethane coupling reaction

### Example 112: 1-(2,2-diethoxyethoxy)-2-nitrobenzene

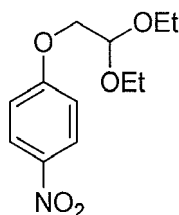
[0312]



[0313] Yellow solid, Yield: 980 mg (77 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.83 (dd,  $J = 8.1, 1.6$ , 1H), 7.57 - 7.46 (m, 1H), 7.10 (d,  $J = 8.5$ , 1H), 7.07 - 7.00 (m, 1H), 4.85 (t,  $J = 5.2$ , 1H), 4.12 (d,  $J = 5.2$ , 2H), 3.87 - 3.76 (m, 2H), 3.71 - 3.64 (m, 2H), 1.24 (t,  $J = 7.0$ , 6H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  152.1, 134.1, 125.6, 120.7, 114.9, 100.7, 70.7, 63.9, 15.3 ppm.

### Example 113: 1-(2,2-diethoxyethoxy)-4-nitrobenzene

[0314]



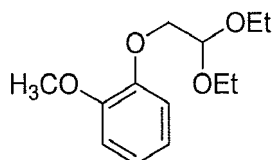
[0315] Yellow solid, Yield: 870 mg (68 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.20 (d,  $J = 9.2$ , 2H), 6.99 (d,  $J = 9.2$ , 2H), 4.85 (t,  $J = 5.1$ , 1H), 4.09 (d,  $J = 5.1$ , 2H), 3.78 (dq,  $J = 9.2, 7.1$ , 2H), 3.65 (dq,  $J = 9.3, 7.1$ , 2H), 1.25 (t,  $J = 7.0$ , 6H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  163.59, 141.74, 125.86, 114.66, 100.23, 69.13, 63.03, 15.32 ppm.

### Example 114: 1-(2,2-diethoxyethoxy)-2-methoxybenzene

[0316]



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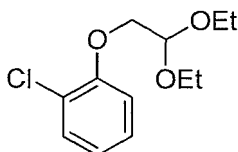
[0317] Colorless liquid, Yield: 1040 mg (87 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.98 - 6.93 (m, 1H), 6.91 - 6.84 (m, 3H), 4.85 (t,  $J = 5.2$ , 1H), 4.05 (d,  $J = 5.1$ , 2H), 3.84 (s, 3H), 3.81 - 3.71 (m, 2H), 3.70 - 3.58 (m, 2H), 1.22 (t,  $J = 7.0$ , 6H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  150.3, 148.9, 121.8, 121.1, 115.5, 113.2, 100.9, 70.7, 62.6, 56.2, 15.2 ppm.

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**Example 115: 1-chloro-2-(2,2-diethoxyethoxy)benzene**

[0318]

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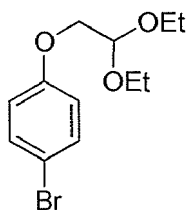
[0319] Colorless liquid, Yield: 2.04 gm (87 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31 (d,  $J = 8.0$ , 2H), 7.18 (t,  $J = 7.8$ , 2H), 7.02 (d,  $J = 8.1$ , 2H), 6.87 (t,  $J = 7.7$ , 2H), 5.62 (s, 2H), 4.67 (t,  $J = 5.4$ , 1H), 3.71 (dq,  $J = 9.0$ , 7.0, 2H), 3.59 (dq,  $J = 9.1$ , 7.0, 2H), 3.37 (d,  $J = 5.6$ , 2H), 1.24 (t,  $J = 7.1$ , 6H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  151.4, 129.0, 128.4, 121.3, 116.3, 101.5, 62.5, 31.9, 15.2 ppm.

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**Example 116: 1-bromo-4-(2,2-diethoxyethoxy)benzene**

[0320]

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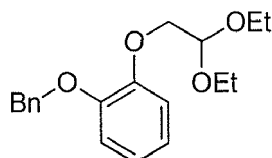
[0321] White liquid, Yield: 1040 mg (72 %); MS (ESI)  $m/z$  calculated  $[\text{M}+\text{Na}]^+$ : 311; found  $[\text{M}+\text{Na}]^+$ : 311.14

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**Example 117: 1-(benzyloxy)-2-(2,2-diethoxyethoxy)benzene**

[0322]

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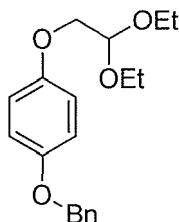
50

[0323] Colorless Liquid, Yield: 470 mg (30 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.50 - 7.47 (m, 2H), 7.39 (M, 2H), 7.33 (M, 1H), 7.05 - 6.85 (m, 4H), 5.14 (s, 2H), 4.90 (t,  $J = 5.2$ , 1H), 4.09 (d,  $J = 5.3$ , 2H), 3.79 (dq,  $J = 9.3$ , 7.1, 2H), 3.66 (dq,  $J = 9.3$ , 7.0, 2H), 1.25 (t,  $J = 7.1$ , 6H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  149.1, 137.4, 128.5, 128.4, 127.8, 127.4, 127.3, 121.7, 121.7, 121.6, 115.3, 115.2, 114.8, 100.8, 71.3, 71.2, 70.2, 62.9, 15.3 ppm.

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**Example 118: 1-(benzyloxy)-4-(2,2-diethoxyethoxy)benzene****[0324]**

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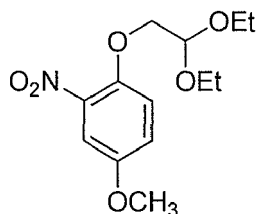
10

**[0325]** Colorless Liquid, Yield: 890 mg (47 %);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42 (M, 2H), 7.38 (t,  $J = 7.5$ , 2H), 7.31 (M, 1H), 6.94 - 6.81 (m, 4H), 5.01 (s, 2H), 4.81 (t,  $J = 5.2$ , 1H), 3.96 (d,  $J = 5.2$ , 2H), 3.76 (dq,  $J = 9.3$ , 7.1, 2H), 3.63 (dq,  $J = 9.3$ , 7.1, 2H), 1.24 (t,  $J = 7.1$ , 6H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  153.2, 153.0, 137.3, 128.5, 127.9, 127.5, 115.8, 115.7, 100.6, 70.7, 69.2, 62.5, 15.4 ppm.

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**Example 119: 1-(2,2-diethoxyethoxy)-4-methoxy-2-nitrobenzene**

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**[0326]**

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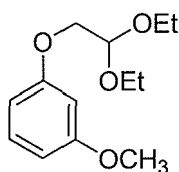
30

**[0327]** Brown solid, Yield: 1000 mg (88 %);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37 (d,  $J = 2.8$ , 1H), 7.14 - 7.00 (m, 2H), 4.83 (t,  $J = 5.2$ , 1H), 4.07 (d,  $J = 5.2$ , 2H), 3.82 (s, 3H), 3.81 - 3.73 (m, 2H), 3.72 - 3.61 (m, 2H), 1.24 (t,  $J = 6.9$ , 6H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  162.5, 153.3, 146.4, 120.8, 117.2, 109.7, 100.8, 71.6, 63.7, 56.0, 15.3 ppm.

35

**Example 120: 1-(2,2-diethoxyethoxy)-3-methoxybenzene****[0328]**

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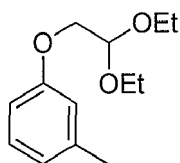
Brown solid, Yield: 730 mg (76 %);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.17 (t,  $J = 8.1$ , 1H), 6.60 - 6.44 (m, 3H), 4.83 (t,  $J = 5.2$ , 1H), 3.99 (d,  $J = 5.2$ , 2H), 3.80 - 3.71 (m, 5H), 3.64 (dq,  $J = 9.3$ , 7.0, 2H), 1.25 (t,  $J = 7.1$ , 6H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  160.8, 159.9, 129.9, 106.8, 106.7, 101.1, 100.4, 68.5, 62.5, 55.3, 15.3 ppm.

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**Example 121: 1-(2,2-diethoxyethoxy)-3-methylbenzene****[0329]**

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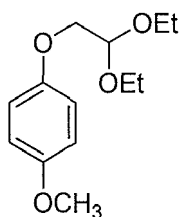
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Brown solid, Yield: 640 mg (72 %); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.15 (t, *J* = 7.8, 1H), 6.82 - 6.68 (m, 3H), 4.83 (t, *J* = 5.2, 1H), 4.00 (d, *J* = 5.2, 2H), 3.76 (dq, *J* = 9.3, 7.1, 2H), 3.64 (dq, *J* = 9.3, 7.0, 2H), 2.32 (s, 3H), 1.25 (t, *J* = 7.1, 6H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 158.6, 139.5, 129.2, 121.8, 115.5, 111.5, 100.5, 68.5, 62.5, 21.5, 15.4 ppm.

10 **Example 122: 1-(2,2-diethoxyethoxy)-4-methoxybenzene**

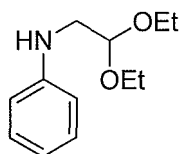
15 **[0330]**



25 **[0331]** White solid, Yield: 912 mg (95 %); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.91 - 6.84 (m, 2H), 6.84 - 6.78 (m, 2H), 4.82 (t, *J* = 5.2, 1H), 3.96 (d, *J* = 5.2, 2H), 3.82 - 3.71 (m, 5H), 3.63 (dq, *J* = 9.3, 7.1, 2H), 1.25 (t, *J* = 7.1, 6H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 154.0, 152.8, 115.7, 114.6, 100.6, 69.3, 62.5, 55.7, 15.4 ppm.

30 **Example 123: N-(2,2-diethoxyethyl)aniline**

35 **[0332]**

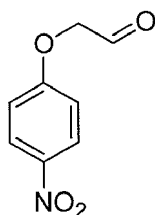


45 **[0333]** Colorless liquid, Yield: 600 mg (72 %); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.18 (t, *J* = 7.8, 2H), 6.71 (td, *J* = 7.4, 0.7, 1H), 6.64 (d, *J* = 8.4, 2H), 4.68 (t, *J* = 5.6, 1H), 3.88 (s, 1H), 3.78 - 3.67 (m, 2H), 3.62 - 3.53 (m, 2H), 3.25 (d, *J* = 5.5, 2H), 1.24 (t, *J* = 7.1, 6H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 147.9, 129.3, 117.7, 113.1, 100.9, 63.1, 62.4, 46.4, 15.5, 15.4 ppm.

50 **Following examples were synthesized by using Method 6: Method for hydrolysis reaction**

55 **Example 124: 2-(4-nitrophenoxy)acetaldehyde**

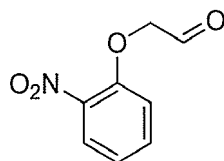
**[0334]**



**[0335]** Colorless liquid, Yield: 540 mg (74 %); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.87 (d, *J* = 0.5, 1H), 8.24 (d, *J* = 9.3, 2H), 6.99 (d, *J* = 9.2, 2H), 4.72 (s, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 197.6, 134.3, 126.1, 122.0, 115.1, 73.8 ppm.

**Example 125: 2-(2-nitrophenoxy)acetaldehyde****[0336]**

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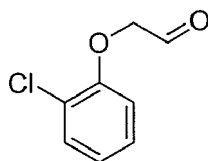
10

**[0337]** Colorless viscous liquid, Yield: 530 mg (77 %);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.88 (s, 1H), 7.90 (dd,  $J = 8.1$ , 1.5, 1H), 7.61 - 7.48 (m, 1H), 7.14 (t,  $J = 7.8$ , 1H), 6.97 (d,  $J = 8.3$ , 1H), 4.71 (s, 2H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  197.6, 150.9, 134.3, 126.1, 122.0, 121.2, 115.1, 73.8 ppm.

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**Example 126: 2-(2-chlorophenoxy)acetaldehyde****[0338]**

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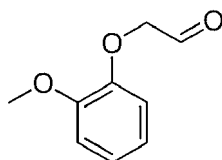
25

**[0339]** Colorless liquid, Yield: 750 mg (88 %);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.91 (s, 1H), 7.42 (d,  $J = 7.9$ , 1H), 7.22 (d,  $J = 8.0$ , 1H), 6.99 (t,  $J = 7.7$ , 1H), 6.82 (d,  $J = 8.2$ , 1H), 4.63 (s, 2H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  198.93, 130.83, 127.88, 122.90, 113.91, 73.58 ppm.

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**Example 127: 2-(2-methoxyphenoxy)acetaldehyde****[0340]**

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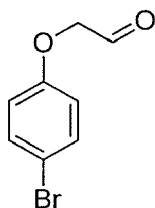
40

**[0341]** Colorless liquid, Yield: 550 mg (79 %);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.91 (d,  $J = 0.9$ , 1H), 7.02 (td,  $J = 8.1$ , 1.3, 1H), 6.94 (d,  $J = 6.8$ , 1H), 6.91 - 6.89 (m, 1H), 6.84 (d,  $J = 7.9$ , 1H), 4.60 (s, 2H), 3.90 (s, 3H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  200.3, 123.0, 122.6, 120.9, 116.0, 114.9, 112.2, 74.2, 55.8 ppm.

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**Example 128: 2-(4-bromophenoxy)acetaldehyde****[0342]**

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**[0343]** Colorless liquid, Yield: 530 mg (73 %);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.84 (d,  $J = 0.7$ , 1H), 7.41 (d,  $J = 8.8$ , 2H),

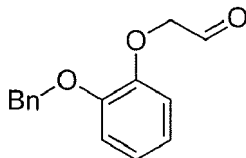
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6.79 (d,  $J = 8.9$ , 2H), 4.56 (s, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  198.5, 132.6, 116.4, 72.8 ppm.

### Example 129: 2-(2-(benzyloxy)phenoxy)acetaldehyde

5 [0344]

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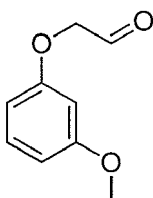
[0345] Colorless liquid, Yield: 140 mg (58 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.79 (s, 1H), 7.41 (d,  $J = 7.3$ , 2H), 7.34 (t,  $J = 7.4$ , 2H), 7.30 - 7.24 (m, 1H), 6.97 - 6.79 (m, 6H), 5.09 (s, 2H), 4.53 (s, 2H) ppm.

### Example 130: 2-(3-methoxyphenoxy)acetaldehyde

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[0346]

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[0347] Colorless liquid, Yield: 430 mg (99 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.85 (d,  $J = 0.8$ , 1H), 7.19 (m, 2H), 6.61 - 6.56 (m, 1H), 6.55 (d,  $J = 2.3$ , 1H), 4.56 (s, 2H), 3.52 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  199.3, 160.8, 159.6, 129.9, 107.1, 106.7, 101.3, 70.2, 55.4 ppm.

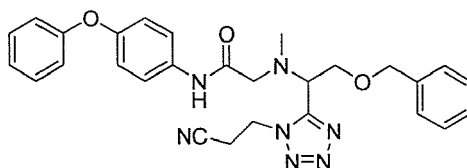
### Following examples were synthesized by using Method 7: Method for Ugi reaction

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### Example 131: 2-((2-(benzyloxy)-1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(4-phenoxyphenyl)acetamide

[0348]

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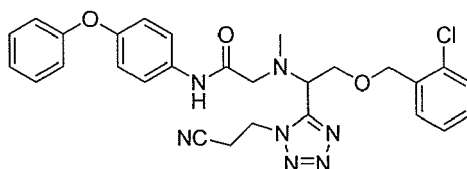
[0349] White Solid, Yield: 440 mg (43 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.53 (s, 1H), 7.44 - 7.39 (m, 2H), 7.37 - 7.30 (m, 6H), 7.26 - 7.23 (m, 1H), 7.09 (t,  $J = 7.4$ , 1H), 7.00 - 6.92 (m, 4H), 4.78 (dt,  $J = 13.6$ , 6.7, 1H), 4.73 - 4.65 (m, 1H), 4.58 - 4.49 (m, 2H), 4.48 - 4.42 (m, 1H), 4.23 (dd,  $J = 9.7$ , 7.4, 1H), 3.91 (dd,  $J = 9.7$ , 6.2, 1H), 3.59 (d,  $J = 16.3$ , 1H), 3.40 (d,  $J = 16.2$ , 1H), 3.12 - 2.92 (m, 2H), 2.48 (s, 3H). MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 459,51; found  $[\text{M}+\text{H}]^+$ : 459,21.

### Example 132: 2-((2-((2-chlorobenzyl)oxy)-1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)ethyl)-(methyl)amino)-N-(4-phenoxyphenyl)acetamide

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[0350]

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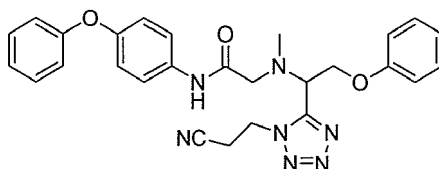
**[0351]** White Solid, Yield: 200 mg (27 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.59 (s, 1H), 7.43 - 7.30 (m, 8H), 7.29 - 7.25 (m, 6H), 7.25 - 7.20 (m, 2H), 7.10 (t,  $J = 7.4$ , 1H), 6.96 (d,  $J = 7.8$ , 2H), 6.92 - 6.84 (m, 2H), 5.30 (s, 1H), 4.74 (d,  $J = 3.0$ , 2H), 4.48 (dd,  $J = 9.0$ , 4.6, 1H), 4.25 - 4.16 (m, 1H), 3.94 (dd,  $J = 10.3$ , 4.7, 1H), 3.47 (s, 2H), 2.44 (s, 3H), 2.17 (s, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  177.1, 132.4, 130.4, 129.8, 129.8, 127.1, 123.2, 121.9, 119.5, 118.5, 71.2, 68.2, 58.2, 57.7, 38.9; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 493.95; found  $[\text{M}+\text{H}]^+$ : 493.17.

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**Example 133: 2-((1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)-2-phenoxyethyl)(methylamino)-N-(4-phenoxyphenyl)acetamide**

**[0352]**

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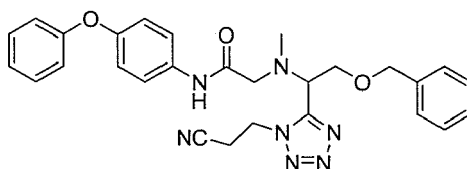
**[0353]** White Solid, Yield: 588 mg (25 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.23 (s, 1H), 7.49 (d,  $J = 8.9$ , 2H), 7.35 - 7.27 (m, 4H), 7.09 (t,  $J = 7.4$ , 1H), 7.04 - 6.97 (m, 5H), 6.92 (d,  $J = 8.2$ , 2H), 4.93 (t,  $J = 6.3$ , 2H), 4.80 - 4.71 (m, 2H), 4.51 (q,  $J = 9.1$ , 1H), 3.75 (d,  $J = 16.2$ , 1H), 3.52 (d,  $J = 16.2$ , 1H), 3.25 - 3.06 (m, 2H), 2.53 (s, 3H), 1.54 (s, 3H); MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 497.5; found  $[\text{M}+\text{H}]^+$ : 497.5.

30

**Example 134: 2-((2-(2-chlorophenoxy)-1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)ethyl)(methylamino)-N-(4-phenoxyphenyl)acetamide**

**[0354]**

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**[0355]** White Solid, Yield: 630 mg (27 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.22 (s, 1H), 7.51 (d,  $J = 8.8$ , 2H), 7.39 (d,  $J = 7.9$ , 1H), 7.32 (t,  $J = 7.8$ , 2H), 7.27 (d,  $J = 5.9$ , 2H), 7.13 - 7.03 (m, 2H), 7.03 - 6.91 (m, 5H), 5.09 (t,  $J = 6.4$ , 2H), 4.90 - 4.76 (m, 2H), 4.64 - 4.52 (m, 1H), 4.00 (d,  $J = 15.6$ , 1H), 3.64 (d,  $J = 15.6$ , 1H), 3.24 - 3.06 (m, 2H), 2.47 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  168.01, 157.37, 153.88, 153.26, 152.93, 132.65, 130.48, 129.74, 128.37, 123.19, 122.73, 122.04, 121.79, 119.60, 118.51, 116.33, 113.49, 77.27, 77.02, 76.77, 66.62, 59.72, 55.51, 43.26, 38.05, 18.98; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 532.18; found  $[\text{M}+\text{H}]^+$ : 532.25.

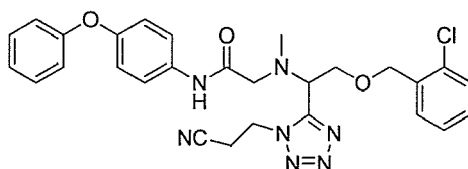
45

**Example 135: 2-((2-((2-chlorobenzyl)oxy)-1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)ethyl)(methylamino)-N-(4-phenoxyphenyl)acetamide**

**[0356]**

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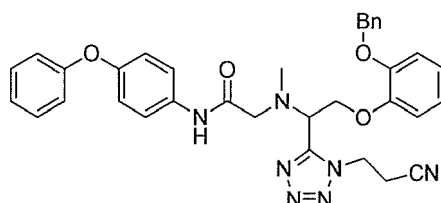
**[0357]** White Solid, Yield: 200 mg (27 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.59 (s, 1H), 7.43 - 7.30 (m, 8H), 7.29 - 7.25 (m, 6H), 7.25 - 7.20 (m, 2H), 7.10 (t,  $J = 7.4$ , 1H), 6.96 (d,  $J = 7.8$ , 2H), 6.92 - 6.84 (m, 2H), 5.30 (s, 1H), 4.74 (d,  $J = 3.0$ , 2H), 4.48 (dd,  $J = 9.0$ , 4.6, 1H), 4.25 - 4.16 (m, 1H), 3.94 (dd,  $J = 10.3$ , 4.7, 1H), 3.47 (s, 2H), 2.44 (s, 3H), 2.17 (s, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  177.1, 132.4, 130.4, 129.8, 129.8, 127.1, 123.2, 121.9, 119.5, 118.5, 71.2, 68.2, 58.2, 57.7, 38.9; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 493.95; found  $[\text{M}+\text{H}]^+$ : 493.17.

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**Example 136: 2-((2-(2-(benzyloxy)phenoxy)-1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)ethyl)-(methyl)amino)-N-(4-phenoxyphenyl)acetamide**

**[0358]**

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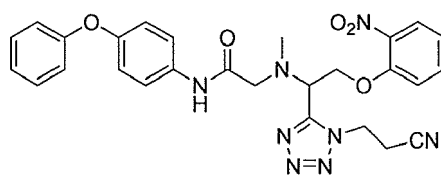
**[0359]** Colorless Solid, Yield: 17 mg (28 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.39 (s, 1H), 7.43 - 7.37 (m, 2H), 7.35 - 7.29 (m, 7H), 7.11 - 7.05 (m, 2H), 7.02 - 6.99 (m, 3H), 6.97 (d,  $J = 8.3$ , 2H), 6.94 (d,  $J = 8.9$ , 2H), 5.07 (s, 2H), 4.96 - 4.86 (m, 1H), 4.78 - 4.63 (m, 3H), 4.54 (dd,  $J = 9.3$ , 5.0, 1H), 3.75 - 3.67 (m, 1H), 3.64 - 3.58 (m, 1H), 3.43 (d,  $J = 14.2$ , 1H), 2.96 - 2.84 (m, 1H), 2.78 (dt,  $J = 17.1$ , 6.3, 1H), 2.37 (s, 3H).

35

**Example 137: 2-((1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)-2-(2-nitrophenoxy)ethyl)-(methyl)amino)-N-(4-phenoxyphenyl)acetamide**

**[0360]**

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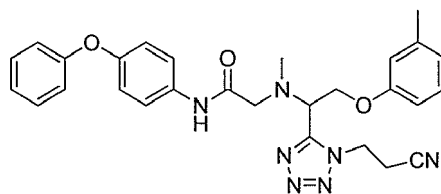
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**[0361]** Colorless Solid, Yield: 17 mg (28 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.31 (s, 1H), 7.87 (dd,  $J = 8.1$ , 1.6, 1H), 7.63 - 7.59 (m, 1H), 7.58 (d,  $J = 8.9$ , 2H), 7.34 - 7.29 (m, 2H), 7.27 (d,  $J = 7.3$ , 1H), 7.12 (t,  $J = 7.5$ , 1H), 7.08 (t,  $J = 7.4$ , 1H), 7.00 - 6.96 (m, 4H), 5.20 (td,  $J = 6.6$ , 2.5, 2H), 4.97 (t,  $J = 9.5$ , 1H), 4.86 (dd,  $J = 9.1$ , 4.2, 1H), 4.67 (dd,  $J = 9.9$ , 4.2, 1H), 4.04 (d,  $J = 15.6$ , 1H), 3.61 (d,  $J = 15.5$ , 1H), 3.23 - 3.09 (m, 2H), 2.44 - 2.36 (m, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  168.1, 157.4, 153.7, 152.8, 151.4, 139.5, 135.0, 133.0, 129.7, 125.9, 123.1, 121.8, 121.6, 119.6, 118.5, 116.6, 114.4, 66.6, 59.4, 54.8, 43.2, 37.4, 19.0 ppm. MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 543.20; found  $[\text{M}+\text{H}]^+$ : 543.27.

**Example 138: 2-((1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)-2-(m-tolyloxy)ethyl)(methyl)amino)-N-(4-phenoxyphenyl)acetamide**

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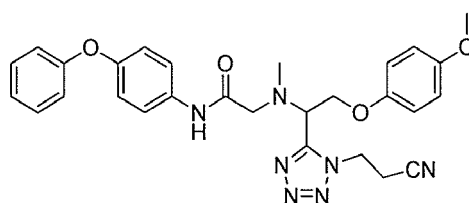
**[0362]**



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[0363] Brown Solid, Yield: 40 mg (39 %);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.48 (s, 1H), 7.49 (d,  $J = 8.9$ , 2H), 7.35 - 7.28 (m, 4H), 7.16 (t,  $J = 7.8$ , 1H), 7.13 - 7.04 (m, 2H), 7.00 - 6.93 (m, 6H), 6.81 (d,  $J = 7.5$ , 1H), 6.75 - 6.69 (m, 2H), 6.63 - 6.55 (m, 1H), 4.92 (t,  $J = 6.6$ , 2H), 4.76 - 4.67 (m, 2H), 4.46 (dd,  $J = 9.6$ , 4.9, 1H), 3.74 (d,  $J = 16.4$ , 1H), 3.52 (d,  $J = 16.3$ , 1H), 3.20 - 3.06 (m, 2H), 2.50 (s, 3H), 2.31 (s, 3H).

15  
Example 139: N-(3-chloro-4-(3-chlorophenoxy)phenyl)-2-((2-(2-chlorophenoxy)-1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)ethyl)(methyl)amino)acetamide

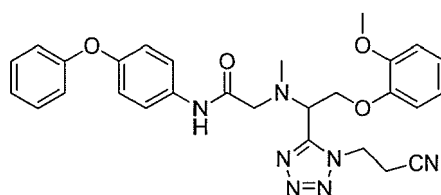
20  
[0364]



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[0365] Colorless Solid, Yield: 50 mg (32 %);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.77 (s, 1H), 7.49 (d,  $J = 8.9$ , 2H), 7.32 (t,  $J = 7.9$ , 2H), 7.09 (t,  $J = 7.4$ , 1H), 6.97 (d,  $J = 8.8$ , 4H), 6.87 - 6.78 (m, 4H), 4.88 (td,  $J = 6.5$ , 2.0, 2H), 4.73 (dd,  $J = 7.5$ , 5.8, 1H), 4.64 (dd,  $J = 9.7$ , 7.8, 1H), 4.40 (dd,  $J = 9.8$ , 5.7, 1H), 3.74 (s, 3H), 3.71 - 3.65 (m, 1H), 3.51 (d,  $J = 16.5$ , 1H), 3.15 (dd,  $J = 12.0$ , 6.4, 2H), 2.77 (t,  $J = 6.6$ , 1H), 2.51 (s, 3H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  168.7, 157.3, 154.7, 153.8, 153.3, 151.7, 132.7, 129.8, 123.3, 122.0, 119.5, 118.5, 117.3, 116.7, 115.8, 114.9, 66.8, 58.9, 56.7, 55.8, 41.7, 39.1, 19.1 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{Na}]^+$ : 550.22; found  $[\text{M}+\text{Na}]^+$ : 550.36.

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Example 140: 2-((1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)-2-(2-methoxyphenoxy)ethyl)(methyl)amino)-N-(4-phenoxyphenyl)acetamide

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[0366]



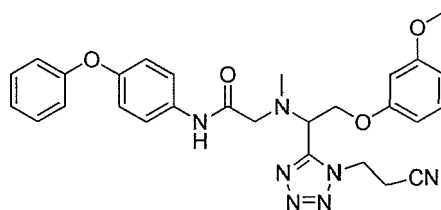
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[0367] Colorless Solid, Yield: 50 mg (32 %);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.20 (s, 1H), 7.53 (d,  $J = 8.9$ , 2H), 7.30 (dd,  $J = 8.4$ , 7.6, 2H), 7.07 (t,  $J = 7.4$ , 1H), 7.01 - 6.92 (m, 8H), 5.02 (dt,  $J = 13.4$ , 6.5, 1H), 4.90 (dt,  $J = 13.8$ , 6.7, 1H), 4.79 (t,  $J = 9.3$ , 1H), 4.71 (dd,  $J = 8.8$ , 4.1, 1H), 4.54 (dd,  $J = 9.7$ , 4.1, 1H), 3.94 (d,  $J = 13.6$ , 1H), 3.87 (s, 3H), 3.55 (d,  $J = 13.5$ , 1H), 3.14 (t,  $J = 6.6$ , 2H), 2.35 (s, 3H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  168.4, 157.4, 153.8, 153.1, 148.4, 147.1, 133.1, 129.8, 123.2, 122.2, 121.8, 121.6, 119.6, 118.5, 116.4, 112.9, 111.7, 66.1, 60.7, 55.7, 54.4, 43.1, 37.6, 18.7 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{Na}]^+$ : 550.22; found  $[\text{M}+\text{Na}]^+$ : 550.39.

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Example 141: 2-((1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)-2-(3-methoxyphenoxy)ethyl)(methyl)amino)-N-(4-phenoxyphenyl)acetamide

[0368]



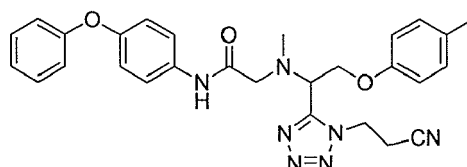
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**[0369]** Brown Solid, Yield: 90 mg (27 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.72 (s, 1H), 7.49 (d,  $J$  = 8.9, 2H), 7.30 (t,  $J$  = 8.0, 2H), 7.16 (t,  $J$  = 8.2, 1H), 7.07 (t,  $J$  = 7.4, 1H), 7.01 - 6.93 (m, 4H), 6.51 (ddd,  $J$  = 13.3, 8.2, 2.2, 2H), 6.46 (t,  $J$  = 2.3, 1H), 4.88 (t,  $J$  = 6.5, 2H), 4.74 (dd,  $J$  = 7.7, 5.6, 1H), 4.71 - 4.62 (m, 1H), 4.43 (dd,  $J$  = 9.9, 5.5, 1H), 3.78 - 3.67 (m, 4H), 3.51 (d,  $J$  = 16.4, 1H), 3.18 - 3.09 (m, 2H), 2.48 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  168.5, 161.0, 158.8, 157.4, 153.8, 153.2, 132.8, 130.3, 129.8, 123.2, 121.9, 119.6, 118.5, 116.7, 107.3, 106.7, 101.3, 65.9, 58.9, 56.6, 55.4, 43.3, 38.9, 18.8 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{Na}]^+$ : 550.22; found  $[\text{M}+\text{Na}]^+$ : 550.36.

**Example 142: 2-((1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)-2-(p-tolyloxy)ethyl)(methyl)amino)-N-(4-phenoxyphenyl)acetamide**

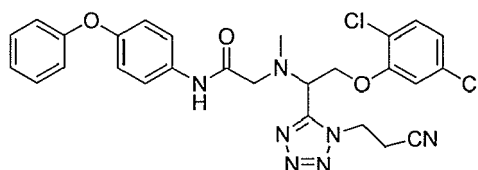
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**[0370]**



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**[0371]** Brown Solid, Yield: 26 mg (26 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.64 (s, 1H), 7.48 (d,  $J$  = 8.8, 2H), 7.31 (t,  $J$  = 7.8, 2H), 7.13 - 7.05 (m, 3H), 6.97 (d,  $J$  = 8.7, 4H), 6.80 (d,  $J$  = 8.4, 2H), 4.89 (t,  $J$  = 6.5, 2H), 4.74 (dd,  $J$  = 7.4, 5.7, 1H), 4.70 - 4.63 (m, 1H), 4.42 (dd,  $J$  = 9.8, 5.5, 1H), 3.72 (d,  $J$  = 16.4, 1H), 3.51 (d,  $J$  = 16.4, 1H), 3.19 - 3.02 (m, 2H), 2.50 (s, 3H), 2.26 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  168.4, 157.4, 155.5, 153.8, 153.2, 132.8, 131.4, 130.3, 129.8, 123.2, 121.9, 119.6, 118.5, 116.5, 114.4, 66.1, 59.1, 56.7, 43.3, 39.0, 20.5, 18.9 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{Na}]^+$ : 534.22; found  $[\text{M}+\text{Na}]^+$ : 534.36.

**Example 143: 2-((1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)-2-(2,5-dichlorophenoxy)ethyl)(methyl)amino)-N-(4-phenoxyphenyl)acetamide**

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**[0372]**

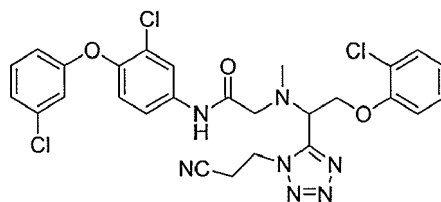


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**[0373]** Brown Solid, Yield: 33 mg (35 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.31 (s, 1H), 7.50 (d,  $J$  = 8.9, 2H), 7.35 - 7.27 (m, 3H), 7.07 (dd,  $J$  = 12.1, 4.8, 2H), 7.01 - 6.92 (m, 5H), 5.14 - 4.99 (m, 2H), 4.88 (dd,  $J$  = 8.5, 4.9, 1H), 4.80 (t,  $J$  = 9.1, 1H), 3.93 (d,  $J$  = 15.9, 1H), 3.62 (d,  $J$  = 15.9, 1H), 3.23 - 3.04 (m, 2H), 2.47 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  168.1, 157.3, 153.9, 153.8, 152.8, 133.7, 132.7, 130.9, 129.8, 123.2, 122.6, 121.9, 120.6, 119.6, 118.5, 116.5, 114.1, 66.8, 59.5, 55.8, 43.3, 38.1, 18.9 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{Na}]^+$ : 588.13; found  $[\text{M}+\text{Na}]^+$ : 588.32.

**Example 144: N-(3-chloro-4-(3-chlorophenoxy)phenyl)-2-((1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)ethyl)(methyl)amino)acetamide**

**[0374]**

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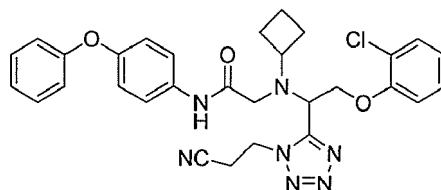
[0375] Colorless Solid, Yield: 77 mg (42 %); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.60 (s, 1H), 7.82 (d, *J* = 2.5, 1H), 7.43 (dd, *J* = 8.8, 2.5, 1H), 7.36 (dd, *J* = 7.9, 1.5, 1H), 7.26 - 7.18 (m, 2H), 7.07 - 6.98 (m, 3H), 6.96 (td, *J* = 7.8, 1.2, 1H), 6.87 (t, *J* = 2.1, 1H), 6.79 (dd, *J* = 8.2, 2.0, 1H), 5.05 (td, *J* = 6.6, 1.3, 2H), 4.86 (dd, *J* = 8.2, 5.1, 1H), 4.83 - 4.75 (m, 1H), 4.53 (dd, *J* = 9.7, 5.1, 1H), 3.95 (d, *J* = 16.1, 1H), 3.68 (d, *J* = 16.0, 1H), 3.26 - 3.09 (m, 2H), 2.51 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 168.5, 158.1, 153.2, 153.1, 147.7, 135.1, 134.9, 130.5, 130.5, 128.4, 126.8, 123.2, 122.8, 122.4, 122.2, 122.2, 119.8, 117.3, 116.5, 115.3, 113.7, 66.8, 59.24, 56.1, 43.3, 38.7, 19.0 ppm; MS (ESI) *m/z* calculated [M+Na]<sup>+</sup>: 622.10; found [M+Na]<sup>+</sup>: 622.24.

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**Example 145: 2-((2-(2-chlorophenoxy)-1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)ethyl)-(cyclobutyl)amino)-N-(4-phenoxyphenyl)acetamide**

[0376]

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[0377] Yellow Solid, Yield: 40 mg (36%); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.52 - 8.42 (m, 1H), 7.48 (d, *J* = 8.9, 2H), 7.37 (dd, *J* = 7.9, 1.4, 1H), 7.32 (d, *J* = 8.3, 2H), 7.25 - 7.21 (m, 1H), 7.09 - 7.06 (m, 1H), 7.03 - 7.00 (m, 1H), 6.96 (dd, *J* = 8.6, 1.9, 5H), 5.10 (dt, *J* = 13.9, 6.9, 1H), 5.02 - 4.91 (m, 1H), 4.82 (dd, *J* = 8.7, 5.1, 1H), 4.72 (t, *J* = 9.2, 1H), 4.53 (dd, *J* = 9.7, 5.1, 1H), 4.02 (d, *J* = 16.2, 1H), 3.64 (d, *J* = 16.1, 1H), 3.51 - 3.46 (m, 1H), 3.17 (t, *J* = 6.9, 2H), 2.08 - 1.96 (m, 2H), 1.76 (dt, *J* = 19.7, 9.9, 2H).

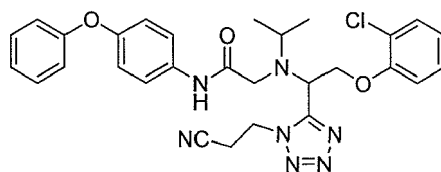
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**Example 146: 2-((2-(2-chlorophenoxy)-1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)ethyl)-(isopropyl)amino)-N-(4-phenoxyphenyl)acetamide**

[0378]

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[0379] Yellow Solid, Yield: 201 mg (36%); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.92 (s, 1H), 7.56 - 7.50 (m, 2H), 7.35 (dd, *J* = 7.8, 1.5, 1H), 7.33 - 7.27 (m, 2H), 7.25 - 7.18 (m, 1H), 7.08 (t, *J* = 7.4, 1H), 6.96 (dd, *J* = 6.9, 5.0, 5H), 5.18 - 5.07 (m, 1H), 4.93 - 4.82 (m, 2H), 4.72 - 4.62 (m, 1H), 4.43 (dd, *J* = 9.5, 6.0, 1H), 4.00 (d, *J* = 16.7, 1H), 3.61 (d, *J* = 16.7, 1H), 3.22 - 3.08 (m, 3H), 1.14 (d, *J* = 6.6, 3H), 0.99 (d, *J* = 6.5, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 169.8, 157.5, 154.5, 153.6, 153.1, 133.0, 130.5, 129.7, 128.4, 123.1, 123.0, 122.2, 121.6, 119.6, 118.4, 116.2, 114.0, 68.9, 53.6, 50.9, 50.5, 43.3, 20.4, 20.3, 19.0 ppm; MS (ESI) *m/z* calculated [M+Na]<sup>+</sup>: 582.20; found [M+Na]<sup>+</sup>: 582.27.

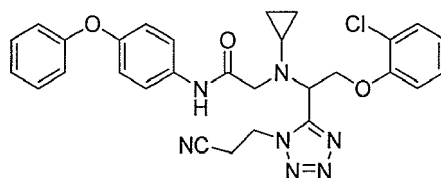
50

**Example 147: 2-((2-(2-chlorophenoxy)-1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)ethyl)-(cyclopropyl)amino)-N-(4-phenoxyphenyl)acetamide**

[0380]

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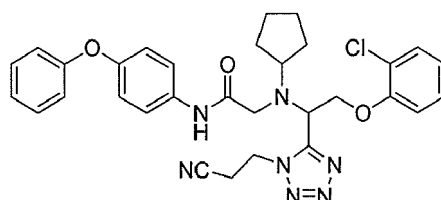
EP 3 666 769 A1



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[0381] Yellow Solid, Yield: 277 mg (50 %); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.45 (s, 1H), 7.43 (d, *J* = 8.9, 2H), 7.35 (dd, *J* = 7.9, 1.4, 1H), 7.31 (t, *J* = 7.9, 2H), 7.24 (td, *J* = 8.3, 1.4, 1H), 7.08 (t, *J* = 7.4, 1H), 7.02 (d, *J* = 8.3, 1H), 6.99 - 6.90 (m, 5H), 5.03 - 4.95 (m, 1H), 4.94 - 4.91 (m, 1H), 4.50 (dd, *J* = 9.1, 4.5, 1H), 4.08 (d, *J* = 16.4, 1H), 3.57 (d, *J* = 16.4, 1H), 3.33 (t, *J* = 6.5, 1H), 3.14 (t, *J* = 6.6, 2H), 2.65 (t, *J* = 6.5, 1H), 2.42 - 2.30 (m, 1H), 0.70 - 0.51 (m, 3H), 0.28 (td, *J* = 10.3, 4.9, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 169.0, 157.4, 153.8, 153.2, 152.9, 132.6, 130.4, 129.8, 128.4, 123.2, 122.7, 122.2, 122.0, 119.5, 118.5, 116.3, 113.7, 67.3, 57.4, 55.3, 43.2, 41.9, 34.7, 19.1, 18.9, 7.4, 7.2 ppm; MS (ESI) *m/z* calculated [M+Na]<sup>+</sup>: 580.18; found [M+Na]<sup>+</sup>: 580.26.

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Example 148: 2-((2-(2-chlorophenoxy)-1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)ethyl)-(cyclopentyl)amino)-N-(4-phenoxyphenyl)acetamide

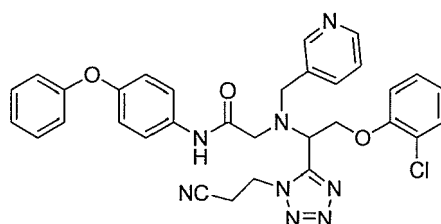
[0382]



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[0383] White Solid, Yield: 230 mg (39 %); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.64 (s, 1H), 7.48 (d, *J* = 8.9, 2H), 7.35 (dd, *J* = 7.9, 1.5, 1H), 7.33 - 7.27 (m, 2H), 7.26 - 7.19 (m, 1H), 7.07 (t, *J* = 7.4, 1H), 7.00 (d, *J* = 8.3, 1H), 6.98 - 6.91 (m, 5H), 5.20 - 5.06 (m, *J* = 13.8, 6.8, 1H), 4.96 - 4.85 (m, 2H), 4.72 (t, *J* = 9.0, 1H), 4.50 (dd, *J* = 9.7, 5.4, 1H), 4.08 (d, *J* = 16.7, 1H), 3.62 (d, *J* = 16.7, 1H), 3.27 (p, *J* = 7.8, 1H), 3.16 (t, *J* = 6.7, 2H), 1.81 - 1.70 (m, 2H), 1.69 - 1.58 (m, 2H), 1.58 - 1.49 (m, 2H), 1.48 - 1.36 (m, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 169.7, 157.5, 153.7, 153.6, 153.2, 133.0, 130.4, 129.7, 128.4, 123.1, 122.8, 122.2, 121.7, 119.6, 118.4, 116.4, 113.8, 68.5, 62.2, 54.9, 52.5, 43.3, 30.9, 29.5, 24.1, 23.6, 18.9 ppm; MS (ESI) *m/z* calculated [M+Na]<sup>+</sup>: 608.22; found [M+Na]<sup>+</sup>: 608.30.

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Example 149: 2-((2-(2-chlorophenoxy)-1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)ethyl)-(pyridin-3-ylmethyl)amino)-N-(4-phenoxyphenyl)acetamide

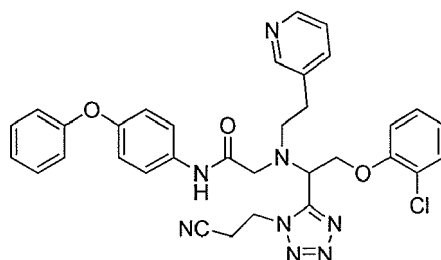
[0384]



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[0385] Yellow Solid, Yield: 183 mg (30 %); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.84 (s, 1H), 8.57 (s, 1H), 8.51 (d, *J* = 4.8, 1H), 8.43 (s, 1H), 7.68 (d, *J* = 7.8, 1H), 7.45 - 7.36 (m, 3H), 7.33 - 7.28 (m, *J* = 11.7, 4.3, 2H), 7.28 - 7.26 (m, 1H), 7.11 - 7.04 (m, 2H), 7.00 - 6.91 (m, 5H), 5.15 - 5.01 (m, *J* = 12.5, 11.5, 5.8, 2H), 4.93 (t, *J* = 9.6, 1H), 4.74 (t, *J* = 6.5, 1H), 4.58 (dd, *J* = 10.0, 4.6, 1H), 3.98 (d, *J* = 15.9, 1H), 3.89 (d, *J* = 13.7, 1H), 3.51 (d, *J* = 16.0, 1H), 3.10 (t, *J* = 6.7, 2H), 3.06 (td, *J* = 6.6, 1.1, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 168.3, 157.4, 154.0, 153.3, 152.8, 150.4, 149.5, 143.1, 137.0, 132.9, 132.7, 130.6, 129.8, 128.5, 124.0, 123.3, 122.9, 122.0, 119.6, 118.6, 116.4, 113.6, 67.3, 55.4, 53.5, 52.4, 43.2, 19.0 ppm; MS (ESI) *m/z* calculated [M+H]<sup>+</sup>: 609.21; found [M+H]<sup>+</sup>: 609.27.

**Example 150: 2-((2-(2-chlorophenoxy)-1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)ethyl)(2-(pyridin-3-yl)ethyl)amino)-N-(4-phenoxyphenyl)acetamide**

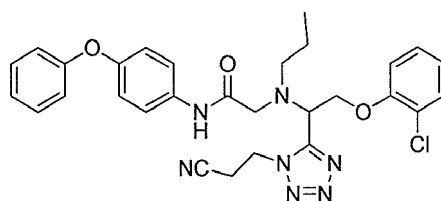
[0386]



[0387] Yellow Solid, Yield: 380 mg (38 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.74 (s, 1H), 8.41 (d,  $J = 4.7$ , 1H), 7.60 (td,  $J = 7.7$ , 1.7, 1H), 7.52 (d,  $J = 8.9$ , 2H), 7.35 - 7.28 (m, 3H), 7.19 (td,  $J = 8.2$ , 1.5, 1H), 7.14 (t,  $J = 7.2$ , 2H), 7.08 (t,  $J = 7.4$ , 1H), 7.01 - 6.95 (m, 4H), 6.93 (td,  $J = 7.7$ , 1.1, 1H), 6.88 (dd,  $J = 8.2$ , 0.9, 1H), 4.79 (dd,  $J = 7.6$ , 6.0, 1H), 4.74 - 4.67 (m, 1H), 4.61 - 4.55 (m, 1H), 4.48 (dt,  $J = 14.0$ , 6.5, 1H), 4.38 (dd,  $J = 9.6$ , 5.9, 1H), 3.98 (d,  $J = 16.6$ , 1H), 3.61 (d,  $J = 16.6$ , 1H), 3.37 - 3.23 (m, 2H), 3.09 - 2.96 (m, 2H), 2.99 - 2.87 (m, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  169.4, 159.5, 157.4, 153.7, 153.22, 152.9, 148.6, 137.1, 133.3, 130.4, 129.8, 128.1, 123.8, 123.2, 122.6, 122.3, 122.1, 121.9, 119.5, 118.5, 116.1, 113.5, 67.4, 57.3, 54.6, 51.4, 42.6, 36.1, 18.7 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 623.22; found  $[\text{M}+\text{H}]^+$ : 623.27.

**Example 151: 2-((2-(2-chlorophenoxy)-1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)ethyl)-(propyl)amino)-N-(4-phenoxyphenyl)acetamide**

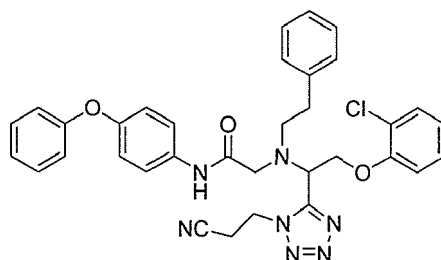
[0388]



[0389] Colorless Solid, Yield: 75 mg (14 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.54 (s, 1H), 7.50 (d,  $J = 8.8$ , 2H), 7.36 (d,  $J = 7.9$ , 1H), 7.31 (t,  $J = 7.8$ , 2H), 7.27 - 7.22 (m, 1H), 7.08 (t,  $J = 7.4$ , 1H), 7.02 (d,  $J = 8.3$ , 1H), 6.98 - 6.94 (m, 5H), 5.17 (dt,  $J = 13.9$ , 6.9, 1H), 4.95 - 4.86 (m, 2H), 4.78 (t,  $J = 9.1$ , 1H), 4.50 (dd,  $J = 9.8$ , 5.1, 1H), 3.98 (d,  $J = 16.2$ , 1H), 3.58 (d,  $J = 16.2$ , 1H), 3.15 (t,  $J = 6.6$ , 2H), 2.81 - 2.69 (m, 1H), 2.63 - 2.51 (m, 1H), 1.58 - 1.43 (m, 2H), 0.84 (t,  $J = 7.3$ , 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  169.0, 157.4, 153.7, 153.3, 153.2, 132.9, 130.5, 129.8, 128.3, 123.2, 122.7, 121.7, 119.6, 118.5, 116.3, 113.7, 67.5, 56.5, 54.8, 53.4, 43.2, 21.3, 19.0, 11.6 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 582.20; found  $[\text{M}+\text{H}]^+$ : 582.35.

**Example 152: 2-((2-(2-chlorophenoxy)-1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)ethyl)-(phenethyl)amino)-N-(4-phenoxyphenyl)acetamide**

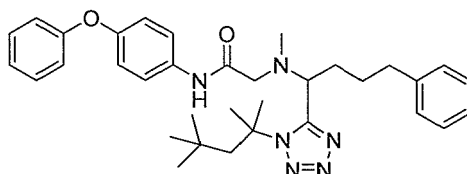
[0390]



**[0391]** Yellow viscous liquid, Yield: 480 mg (52 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.28 (s, 1H), 7.44 (d,  $J = 8.9$ , 2H), 7.36 (dd,  $J = 7.9$ , 1.3, 1H), 7.31 (t,  $J = 8.0$ , 2H), 7.26 - 7.19 (m, 4H), 7.08 (t,  $J = 7.4$ , 1H), 7.03 - 6.99 (m, 3H), 6.98 - 6.93 (m, 5H), 4.90 - 4.74 (m, 3H), 4.50 (dd,  $J = 9.8$ , 4.7, 1H), 4.27 - 4.17 (m, 1H), 4.06 (d,  $J = 15.8$ , 1H), 3.69 (d,  $J = 15.8$ , 1H), 3.11 (dt,  $J = 11.8$ , 5.8, 1H), 3.06 - 2.97 (m, 1H), 2.85 (t,  $J = 6.7$ , 2H), 2.78 (t,  $J = 6.6$ , 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  168.6, 157.4, 153.8, 153.3, 152.7, 139.1, 132.8, 130.5, 129.8, 128.8, 128.6, 128.4, 126.6, 123.2, 122.7, 122.0, 121.7, 119.6, 118.6, 116.4, 113.5, 67.4, 56.5, 54.4, 51.7, 42.6, 34.0, 18.7 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{Na}]^+$ : 644.22; found  $[\text{M}+\text{Na}]^+$ : 644.32.

**Example 153: 2-(methyl(4-phenyl-1-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)butyl)amino)-N-(4-phenoxyphenyl)acetamide**

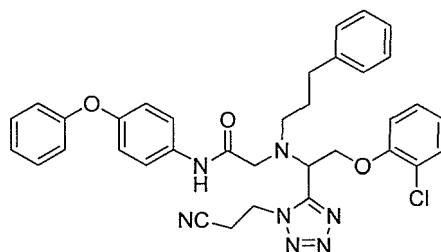
**[0392]**



**[0393]** Yellow viscous liquid, Yield: 568 mg (65 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.57 (s, 1H), 7.42 (d,  $J = 8.8$ , 2H), 7.31 (t,  $J = 7.7$ , 2H), 7.25 (d,  $J = 7.5$ , 2H), 7.18 (t,  $J = 7.0$ , 1H), 7.13 (d,  $J = 7.6$ , 2H), 7.11 - 7.05 (m, 1H), 6.97 (dd,  $J = 8.8$ , 2.3, 4H), 4.35 (t,  $J = 7.2$ , 1H), 3.58 (d,  $J = 16.7$ , 1H), 3.36 (d,  $J = 16.7$ , 1H), 2.68 (t,  $J = 7.5$ , 2H), 2.52 (s, 3H), 2.04 (s, 2H), 1.85 (s, 3H), 1.83 (s, 3H), 1.74 - 1.65 (m, 2H), 1.65 - 1.53 (m, 2H), 0.82 (s, 9H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  171.1, 153.4, 133.0, 129.7, 128.4, 128.3, 128.3, 128.2, 126.1, 123.0, 121.1, 119.6, 118.3, 100.0, 99.0, 62.8, 60.3, 59.7, 57.2, 54.1, 40.3, 35.5, 31.5, 30.8, 30.5, 30.4, 29.7, 29.6.

**Example 154: 2-((2-(2-chlorophenoxy)-1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)ethyl)(3-phenylpropyl)amino)-N-(4-phenoxyphenyl)acetamide**

**[0394]**

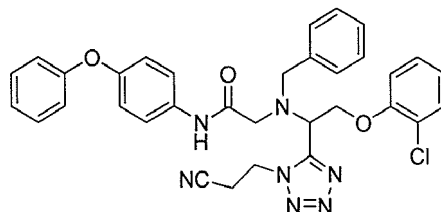


**[0395]** Purple viscous liquid, Yield: 230 mg (36 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.54 (s, 1H), 7.52 - 7.46 (m, 2H), 7.35 (dd,  $J = 7.9$ , 1.5, 1H), 7.33 - 7.29 (m, 2H), 7.23 (dd,  $J = 11.4$ , 4.3, 3H), 7.18 - 7.14 (m, 2H), 7.08 (d,  $J = 7.3$ , 3H), 6.98 - 6.95 (m, 5H), 5.02 (dt,  $J = 14.0$ , 6.9, 1H), 4.86 (dd,  $J = 8.5$ , 5.0, 1H), 4.82 - 4.71 (m, 2H), 4.50 - 4.42 (m, 1H), 3.97 (d,  $J = 16.2$ , 1H), 3.52 (d,  $J = 16.2$ , 1H), 3.07 (t,  $J = 6.6$ , 2H), 2.89 - 2.79 (m, 2H), 2.72 - 2.60 (m, 2H), 1.92 - 1.84 (m, 1H), 1.83 - 1.75 (m, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  168.9, 157.4, 153.8, 153.2, 152.9, 141.1, 132.8, 130.5, 129.8, 128.8, 128.7, 128.5, 128.4, 128.3, 128.1, 126.1, 123.2, 122.8, 121.8, 119.6, 118.5, 116.3, 113.7, 67.4, 56.4, 54.7, 51.1,

43.1, 33.1, 29.8, 19.0 ppm; MS (ESI) m/z calculated  $[M+Na]^+$ : 658.23; found  $[M+Na]^+$ : 658.32

**Example 155: 2-(benzyl(2-(2-chlorophenoxy)-1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)ethyl)amino)-N-(4-phenoxyphenyl)acetamide**

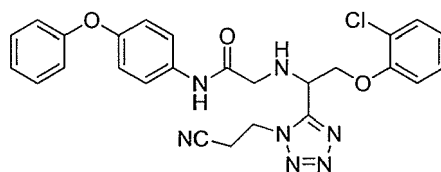
[0396]



[0397] White solid, Yield: 400 mg (55 %);  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  8.37 (s, 1H), 7.43 - 7.40 (m, 2H), 7.39 - 7.34 (m, 5H), 7.32 - 7.27 (m, 3H), 7.25 - 7.21 (m, 1H), 7.07 (t,  $J = 7.4$ , 1H), 7.03 (dd,  $J = 8.2$ , 0.9, 1H), 6.97 - 6.91 (m, 5H), 4.94 (dd,  $J = 8.7$ , 4.7, 1H), 4.88 (t,  $J = 9.2$ , 1H), 4.74 (dt,  $J = 14.0$ , 7.0, 1H), 4.55 - 4.46 (m, 2H), 4.12 (d,  $J = 14.3$ , 1H), 3.90 (d,  $J = 16.1$ , 1H), 3.81 (d,  $J = 13.3$ , 1H), 3.57 (d,  $J = 16.1$ , 1H), 3.06 - 2.91 (m, 2H).  $^{13}C$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  168.4, 157.4, 153.8, 153.3, 152.8, 137.0, 132.7, 130.5, 129.8, 129.4, 129.1, 128.3, 128.3, 123.2, 122.8, 121.9, 119.5, 118.5, 116.2, 113.6, 67.3, 55.9, 55.1, 52.5, 42.9, 18.7 ppm; MS (ESI) m/z calculated  $[M+Na]^+$ : 630.20; found  $[M+Na]^+$ : 630.29.

**Example 156: 2-((2-(2-chlorophenoxy)-1-(1-(2-cyanoethyl)-1H-tetrazol-5-yl)ethyl)-(methyl)amino)-N-(4-phenoxyphenyl)acetamide (A)**

[0398]

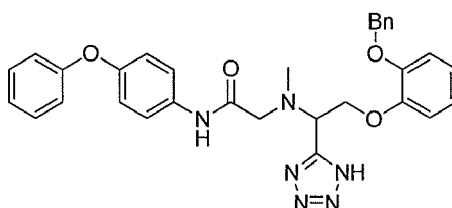


[0399] Brown liquid, Yield: 178 mg (17 %);  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  8.38 (s, 1H), 7.48 (d,  $J = 8.9$ , 2H), 7.36 - 7.30 (m, 3H), 7.23 (td,  $J = 8.0$ , 1.6, 1H), 7.09 (t,  $J = 7.4$ , 1H), 7.01 - 6.96 (m, 4H), 6.96 - 6.88 (m, 2H), 5.13 - 5.00 (m, 1H), 4.97 - 4.87 (m, 1H), 4.74 (s, 1H), 4.55 - 4.48 (m, 1H), 4.41 - 4.30 (m, 1H), 3.64 (d,  $J = 16.5$ , 1H), 3.45 (d,  $J = 17.7$ , 1H), 3.16 (t,  $J = 6.6$ , 2H), 2.81 (s, 1H).  $^{13}C$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  168.28, 154.95, 153.77, 152.98, 132.67, 130.58, 129.74, 128.21, 123.16, 123.13, 121.64, 119.59, 118.50, 116.34, 114.19, 70.99, 53.07, 51.08, 43.55, 18.95 ppm. MS (ESI) m/z calculated  $[M+Na]^+$ : 540.15; found  $[M+Na]^+$ : 540.21.

#### Method 8: Isocyanide deprotection of Ugi-product

**Example 157: 2-((2-(2-(benzyloxy)phenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(4-phenoxyphenyl)acetamide**

[0400]

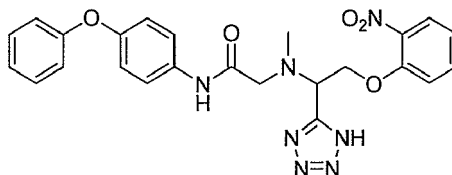


[0401] White solid, Yield: 10 mg (63 %);  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  8.40 (s, 1H), 7.40 (dd,  $J = 6.5$ , 2.9, 2H), 7.37 -

7.29 (m, 7H), 7.08 (dd,  $J = 14.1, 6.7, 2\text{H}$ ), 7.04 - 6.99 (m, 3H), 6.99 - 6.91 (m, 4H), 5.07 (s, 2H), 4.95 - 4.87 (m, 1H), 4.73 (m, 1H), 4.54 (dd,  $J = 9.3, 5.0, 1\text{H}$ ), 3.83 (d,  $J = 14.2, 1\text{H}$ ), 3.43 (d,  $J = 14.2, 1\text{H}$ ), 2.37 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  168.0, 157.5, 153.7, 153.3, 147.9, 147.3, 135.8, 132.8, 129.7, 128.9, 128.9, 128.9, 123.1, 122.2, 122.0, 121.8, 119.5, 118.4, 116.4, 112.9, 112.8, 71.3, 66.5, 60.3, 54.8, 43.1 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}-\text{H}]^-$ : 549.61; found  $[\text{M}+\text{H}]^+$ : 549.11.

**Example 158: 2-(methyl(2-(2-nitrophenoxy)-1-(1H-tetrazol-5-yl)ethyl)amino)-N-(4-phenoxyphenyl)acetamide**

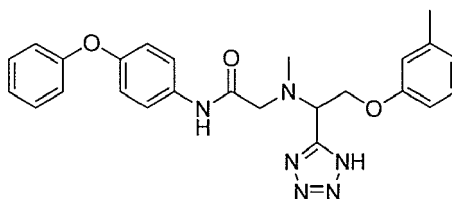
[0402]



[0403] White solid, Yield: 30 mg (88 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.28 (s, 1H), 7.86 (d,  $J = 8.0, 1\text{H}$ ), 7.56 (t,  $J = 7.6, 1\text{H}$ ), 7.49 (d,  $J = 8.1, 2\text{H}$ ), 7.30 (t,  $J = 7.8, 2\text{H}$ ), 7.20 (d,  $J = 8.2, 1\text{H}$ ), 7.07 (t,  $J = 7.2, 2\text{H}$ ), 6.98 - 6.87 (m, 4H), 4.79 (s, 1H), 4.72 (t,  $J = 8.9, 1\text{H}$ ), 4.63 (d,  $J = 6.4, 1\text{H}$ ), 3.63 (d,  $J = 16.8, 1\text{H}$ ), 3.52 (d,  $J = 18.4, 1\text{H}$ ), 2.50 (s, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  169.9, 157.3, 154.1, 151.5, 139.5, 135.0, 132.3, 129.7, 126.1, 123.2, 122.3, 121.6, 119.4, 118.5, 114.8, 67.2, 58.7, 58.0, 39.2 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 490.48; found  $[\text{M}+\text{H}]^+$ : 490.30.

**Example 159: 2-((1-(1H-tetrazol-5-yl)-2-(m-tolylloxy)ethyl)(methyl)amino)-N-(4-phenoxyphenyl)acetamide**

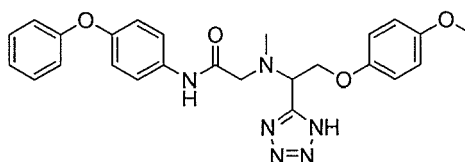
[0404]



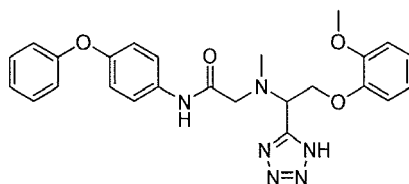
[0405] White solid, Yield: 30 mg (93 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.73 (s, 1H), 7.49 (d,  $J = 8.8, 2\text{H}$ ), 7.30 (t,  $J = 7.9, 3\text{H}$ ), 7.14 (t,  $J = 7.8, 1\text{H}$ ), 7.08 (t,  $J = 7.3, 1\text{H}$ ), 7.00 - 6.88 (m, 4H), 6.83 - 6.68 (m, 3H), 4.70 (dd,  $J = 9.6, 3.7, 1\text{H}$ ), 4.62 (t,  $J = 10.0, 1\text{H}$ ), 4.39 (dd,  $J = 10.2, 3.8, 1\text{H}$ ), 3.58 (s, 2H), 2.47 (s, 3H), 2.27 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.4, 157.9, 157.2, 154.4, 139.9, 132.1, 129.9, 129.8, 129.5, 123.3, 122.7, 122.5, 119.5, 119.2, 118.6, 115.6, 111.6, 65.7, 58.3, 58.1, 38.9, 21.6 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 459.51; found  $[\text{M}+\text{H}]^+$ : 459.36.

**Example 160: 2-((2-(4-methoxyphenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(4-phenoxyphenyl)acetamide**

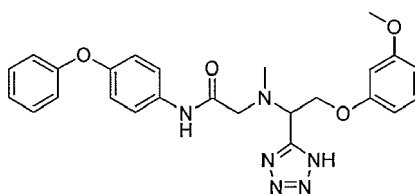
[0406]



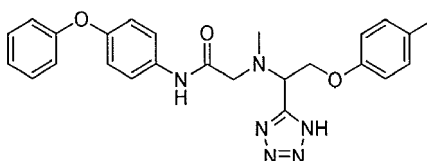
[0407] White solid, Yield: 40 mg (94 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.76 (s, 1H), 7.47 (d,  $J = 8.8, 2\text{H}$ ), 7.30 (dd,  $J = 8.3, 7.6, 2\text{H}$ ), 7.08 (t,  $J = 7.4, 1\text{H}$ ), 6.98 - 6.90 (m, 4H), 6.86 (d,  $J = 9.1, 2\text{H}$ ), 6.78 (d,  $J = 9.1, 2\text{H}$ ), 4.70 (dd,  $J = 9.6, 4.0, 1\text{H}$ ), 4.58 (t,  $J = 10.0, 1\text{H}$ ), 4.35 (dd,  $J = 10.4, 4.1, 1\text{H}$ ), 3.72 (s, 3H), 3.58 (d,  $J = 5.1, 2\text{H}$ ), 2.48 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.3, 157.1, 154.7, 154.4, 151.9, 132.0, 129.8, 123.4, 122.4, 119.4, 118.7, 115.9, 114.9, 66.8, 58.2, 58.0, 55.7, 39.1 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 475.51; found  $[\text{M}+\text{H}]^+$ : 475.22.

**Example 161: 2-((2-(2-methoxyphenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methylamino)-N-(4-phenoxyphenyl)acetamide****[0408]**

**[0409]** White solid, Yield: 40 mg (93 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.83 (s, 1H), 7.52 (d,  $J = 8.8$ , 2H), 7.30 (t,  $J = 7.9$ , 2H), 7.07 (t,  $J = 7.4$ , 1H), 7.04 - 6.98 (m, 2H), 6.92 (dd,  $J = 16.7$ , 7.7, 5H), 4.70 (dd,  $J = 7.8$ , 5.1, 1H), 4.65 - 4.56 (m, 1H), 4.40 (dd,  $J = 10.1$ , 5.0, 1H), 3.78 (s, 3H), 3.61 - 3.48 (m, 2H), 2.50 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  169.8, 157.4, 153.9, 149.4, 147.1, 132.8, 129.8, 123.2, 122.4, 121.5, 119.4, 118.5, 115.5, 111.8, 67.8, 58.5, 57.8, 55.7, 39.3 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 475.51; found  $[\text{M}+\text{H}]^+$ : 475.28.

**Example 162: 2-((2-(3-methoxyphenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methylamino)-N-(4-phenoxyphenyl)acetamide****[0410]**

**[0411]** White solid, Yield: 80 mg (99 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.74 (s, 1H), 7.48 (d,  $J = 8.8$ , 2H), 7.29 (t,  $J = 7.9$ , 2H), 7.13 (t,  $J = 8.2$ , 1H), 7.07 (t,  $J = 7.4$ , 1H), 6.92 (t,  $J = 8.6$ , 4H), 6.56 - 6.42 (m, 3H), 4.72 (dd,  $J = 9.4$ , 4.0, 1H), 4.62 (t,  $J = 10.0$ , 1H), 4.40 (dd,  $J = 10.3$ , 3.9, 1H), 3.68 (s, 3H), 3.60 (d,  $J = 6.1$ , 2H), 2.47 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.3, 161.0, 159.0, 157.2, 154.4, 132.0, 130.3, 129.8, 123.4, 122.5, 119.5, 118.6, 107.5, 106.7, 101.3, 65.8, 58.3, 58.1, 55.3, 39.0 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 475.51; found  $[\text{M}+\text{H}]^+$ : 475.41.

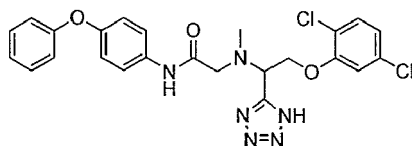
**Example 163: 2-((1-(1H-tetrazol-5-yl)-2-(p-tolyloxy)ethyl)(methylamino)-N-(4-phenoxyphenyl)acetamide****[0412]**

**[0413]** White solid, Yield: 20 mg (89 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.74 (s, 1H), 7.48 (d,  $J = 8.8$ , 2H), 7.31 (t,  $J = 8.0$ , 2H), 7.09 (t,  $J = 7.4$ , 1H), 7.06 (d,  $J = 8.4$ , 2H), 6.95 (t,  $J = 8.2$ , 4H), 6.83 (d,  $J = 8.5$ , 2H), 4.69 (dd,  $J = 9.8$ , 3.9, 1H), 4.61 (t,  $J = 10.1$ , 1H), 4.36 (dd,  $J = 10.3$ , 3.9, 1H), 3.57 (d,  $J = 3.2$ , 2H), 2.48 (s, 3H), 2.26 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.5, 157.1, 155.8, 154.5, 131.9, 131.3, 130.2, 129.8, 123.4, 122.5, 119.5, 118.7, 114.7, 66.1, 58.1, 57.9, 39.0, 20.5 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 459.51; found  $[\text{M}+\text{H}]^+$ : 459.23.

**Example 164: 2-((2-(2,5-dichlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methylamino)-N-(4-phenoxyphenyl)acetamide****[0414]**



EP 3 666 769 A1



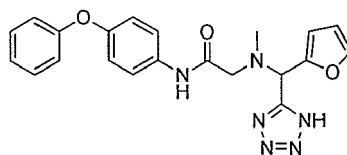
5

**[0415]** White solid, Yield: 30 mg (83 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.49 (s, 1H), 7.47 (d,  $J = 8.6$ , 2H), 7.30 (t,  $J = 7.9$ , 2H), 7.24 (d,  $J = 8.5$ , 1H), 7.08 (t,  $J = 7.4$ , 1H), 7.04 (d,  $J = 1.7$ , 1H), 6.99 - 6.87 (m, 5H), 4.78 (d,  $J = 5.6$ , 1H), 4.65 (t,  $J = 9.9$ , 1H), 4.49 (dd,  $J = 10.0$ , 3.7, 1H), 3.67 (d,  $J = 17.1$ , 1H), 3.58 (d,  $J = 17.1$ , 1H), 2.50 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  157.2, 154.4, 154.0, 133.5, 131.9, 130.9, 129.8, 123.3, 122.6, 122.6, 121.3, 119.4, 118.6, 114.6, 67.1, 58.6, 58.2, 38.9 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 514.38; found  $[\text{M}+\text{H}]^+$ : 514.18.

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**Example 165: 2-((furan-2-yl)(1H-tetrazol-5-yl)methyl)(methyl)amino)-N-(4-phenoxyphenyl)acetamide**

15 **[0416]**



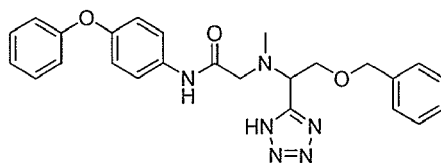
20

**[0417]** White solid, Yield: 100 mg (95 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41 (d,  $J = 1.3$ , 1H), 7.34 - 7.30 (m, 2H), 7.22 - 7.18 (m, 2H), 7.10 (t,  $J = 7.4$ , 1H), 7.04 - 6.95 (m, 3H), 6.94 - 6.89 (m, 2H), 6.40 (d,  $J = 3.2$ , 1H), 6.32 (dd,  $J = 3.2$ , 1.8, 1H), 5.41 (s, 1H), 3.81 (dd,  $J = 14.6$ , 1.0, 1H), 3.41 (dd,  $J = 14.6$ , 1.0, 1H), 2.43 (s, 3H) ppm.

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**Example 166: 2-((2-(benzyloxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(4-phenoxyphenyl)acetamide**

30 **[0418]**



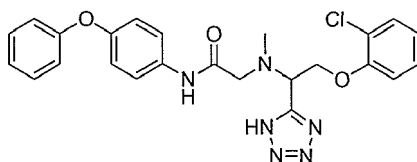
35

**[0419]** White Solid, Yield: 246 mg (89 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.59 (s, 1H), 7.43 - 7.30 (m, 8H), 7.29 - 7.25 (m, 6H), 7.25 - 7.20 (m, 2H), 7.10 (t,  $J = 7.4$ , 1H), 6.96 (d,  $J = 7.8$ , 2H), 6.92 - 6.84 (m, 2H), 5.30 (s, 1H), 4.74 (d,  $J = 3.0$ , 2H), 4.48 (dd,  $J = 9.0$ , 4.6, 1H), 4.25 - 4.16 (m, 1H), 3.94 (dd,  $J = 10.3$ , 4.7, 1H), 3.47 (s, 2H), 2.44 (s, 3H), 2.17 (s, 1H). MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 459,51; found  $[\text{M}+\text{H}]^+$ : 459,21.

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**Example 167: 2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(4-phenoxyphenyl)acetamide**

45 **[0420]**



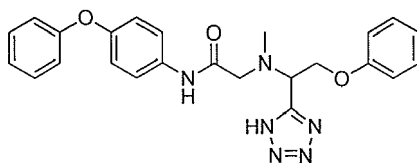
50

**[0421]** White solid, Yield: 94 mg (98 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.42 (s, 1H), 7.51 (d,  $J = 8.9$ , 2H), 7.37 (dd,  $J = 7.9$ , 1.4, 1H), 7.35 - 7.29 (m, 2H), 7.25 - 7.19 (m, 1H), 7.09 (t,  $J = 7.4$ , 1H), 7.05 (d,  $J = 8.2$ , 1H), 7.01 - 6.92 (m, 5H), 4.76 (dd,  $J = 9.4$ , 4.3, 1H), 4.65 (t,  $J = 9.9$ , 1H), 4.52 (dd,  $J = 10.3$ , 4.3, 1H), 3.71 - 3.53 (m, 2H), 2.54 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.5, 157.2, 154.4, 153.5, 132.0, 130.5, 129.8, 128.2, 123.3, 122.9, 122.6, 119.4, 118.7, 114.4, 77.3, 77.0, 76.8, 67.1, 58.4, 58.0, 39.1 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 479.13; found  $[\text{M}+\text{H}]^+$ : 479.26.

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**Example 168: 2-(methyl(2-phenoxy-1-(1H-tetrazol-5-yl)ethyl)amino)-N-(4-phenoxy-phenyl)acetamide****[0422]**

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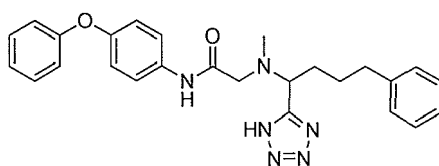
**[0423]** White Solid, Yield: 150 mg (94 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.66 (s, 1H), 7.50 (d,  $J = 8.9$ , 2H), 7.36 - 7.26 (m, 4H), 7.10 (t,  $J = 7.4$ , 1H), 7.01 - 6.92 (m, 7H), 4.70 (dd,  $J = 9.8$ , 3.7, 1H), 4.65 (t,  $J = 9.9$ , 1H), 4.41 (dd,  $J = 10.0$ , 3.7, 1H), 3.57 (d,  $J = 4.9$ , 2H), 2.49 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.5, 157.9, 157.1, 154.5, 131.9, 129.8, 129.8, 123.4, 122.5, 121.9, 119.5, 118.7, 114.8, 68.1, 65.9, 58.1, 57.9, 39.1. MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 445.49; found  $[\text{M}+\text{H}]^+$ : 445.29.

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**Example 169: 2-(methyl(4-phenyl-1-(1H-tetrazol-5-yl)butyl)amino)-N-(4-phenoxy-phenyl)acetamide**

**[0424]** Procedure: 2-(methyl(4-phenyl-1-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)butyl)amino)-N-(4-phenoxy-phenyl)acetamide (269 mg, 0.47 mmol) was added to 5 ml 4 M HCl in Dioxane in a 25 ml RBF and refluxed for overnight. Then solvent was removed under reduced pressure and residue was dissolved in water and extracted in DCM. The solvent was removed under reduced pressure, the residue was purified by flash column chromatography on silica gel and eluted with methanol:DCM to afford product.

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**[0425]** White solid, Yield: 100 mg (47 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.16 (s, 1H), 7.50 (d,  $J = 8.8$ , 2H), 7.33 (t,  $J = 7.7$ , 2H), 7.23 (d,  $J = 7.5$ , 2H), 7.20 - 7.12 (m, 4H), 7.10 (t,  $J = 7.8$ , 1H), 7.04 - 6.93 (m, 4H), 4.26 (t,  $J = 7.6$ , 1H), 3.38 (d,  $J = 16.8$ , 1H), 3.28 (d,  $J = 16.8$ , 1H), 2.76 - 2.60 (m, 3H), 2.39 (s, 3H), 2.23 - 2.02 (m, 3H), 1.87 - 1.63 (m, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  153.9, 140.5, 129.8, 128.5, 128.3, 126.1, 123.2, 121.6, 119.6, 118.5, 72.3, 71.1, 61.7, 42.89, 30.6, 29.9 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 457.23; found  $[\text{M}+\text{H}]^+$ : 457.23.

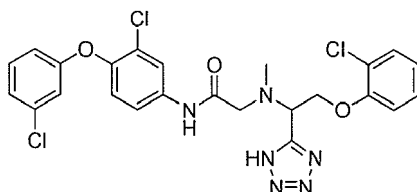
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**Example 170: N-(3-chloro-4-(3-chlorophenoxy)phenyl)-2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)acetamide**

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**[0426]**

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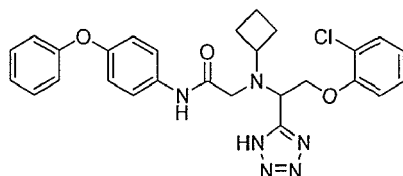
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**[0427]** White Solid, Yield: 46 mg (65 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.74 (s, 1H), 7.77 (d,  $J = 2.1$ , 1H), 7.42 (dd,  $J = 8.8$ , 2.1, 1H), 7.33 (dd,  $J = 7.9$ , 1.2, 1H), 7.20 (t,  $J = 8.2$ , 2H), 7.07 - 7.00 (m, 2H), 6.97 - 6.90 (m, 2H), 6.85 (t,  $J = 2.1$ , 1H), 6.76 (dd,  $J = 8.2$ , 2.1, 1H), 4.83 (dd,  $J = 9.0$ , 4.0, 1H), 4.66 (t,  $J = 9.8$ , 1H), 4.54 (dd,  $J = 10.3$ , 4.0, 1H), 3.75 (d,  $J = 17.2$ , 1H), 3.64 (d,  $J = 17.2$ , 1H), 2.55 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.6, 157.9, 153.4, 148.2, 135.1, 134.2, 130.5, 130.5, 128.2, 126.6, 123.3, 122.9, 122.9, 122.0, 120.4, 117.4, 115.4, 114.3, 66.9, 58.6, 58.4, 39.2 ppm. MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 547.07; found  $[\text{M}+\text{H}]^+$ : 547.22.

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**Example 171: 2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(cyclobutyl)amino)-N-(4-phenoxyphenyl)acetamide****[0428]**

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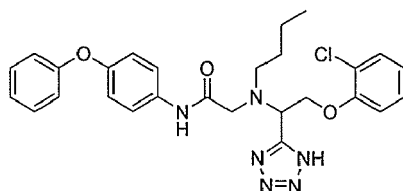
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**[0429]** White solid, Yield: 30 mg (88 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.69 (s, 1H), 7.45 (d,  $J = 8.9$ , 2H), 7.38 - 7.28 (m, 4H), 7.17 (t,  $J = 7.1$ , 1H), 7.08 (t,  $J = 7.4$ , 1H), 6.98 - 6.91 (m, 4H), 6.90 (d,  $J = 8.8$ , 2H), 4.81 (dd,  $J = 9.8$ , 4.0, 1H), 4.55 (t,  $J = 10.1$ , 1H), 4.42 (dd,  $J = 10.3$ , 4.1, 1H), 3.69 (d,  $J = 17.9$ , 1H), 3.65 - 3.55 (m, 1H), 3.42 (d,  $J = 17.8$ , 1H), 2.14 - 1.90 (m, 4H), 1.77 - 1.65 (m, 1H), 1.64 - 1.52 (m, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  172.0, 157.3, 154.1, 153.4, 132.2, 130.5, 129.7, 128.1, 123.2, 122.9, 122.6, 122.4, 119.4, 118.5, 114.0, 67.2, 56.5, 54.9, 51.4, 28.5, 28.2, 14.4 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 519.99; found  $[\text{M}+\text{H}]^+$ : 519.42.

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**Example 172: 2-(butyl(2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)amino)-N-(4-phenoxyphenyl)acetamide****[0430]**

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**[0431]** White solid, Yield: 40 mg (85 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.75 (s, 1H), 7.46 (d,  $J = 8.9$ , 2H), 7.36 - 7.28 (m, 3H), 7.19 (t,  $J = 7.2$ , 1H), 7.08 (t,  $J = 7.4$ , 1H), 7.00 (d,  $J = 8.0$ , 1H), 6.97 - 6.88 (m, 5H), 4.87 (dd,  $J = 9.9$ , 3.9, 1H), 4.64 (t,  $J = 10.2$ , 1H), 4.43 (dd,  $J = 10.4$ , 4.0, 1H), 3.74 (d,  $J = 17.8$ , 1H), 3.44 (d,  $J = 17.8$ , 1H), 2.91 - 2.79 (m, 1H), 2.75 - 2.57 (m, 1H), 1.69 - 1.49 (m, 2H), 1.49 - 1.38 (m, 1H), 1.38 - 1.29 (m, 1H), 0.88 (t,  $J = 7.3$ , 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  171.5, 157.2, 156.6, 154.3, 153.5, 132.1, 130.5, 129.8, 128.1, 123.3, 122.9, 122.7, 122.7, 119.4, 118.6, 114.2, 67.2, 56.4, 55.5, 52.8, 30.4, 20.2, 13.9 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 507.18; found  $[\text{M}+\text{H}]^+$ : 507.39.

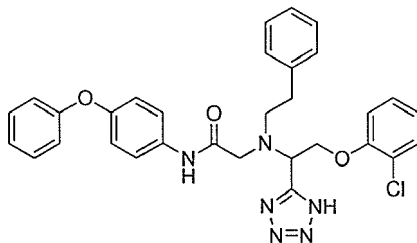
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**Example 173: 2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(phenethyl)amino)-N-(4-phenoxyphenyl)acetamide**

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**[0432]**

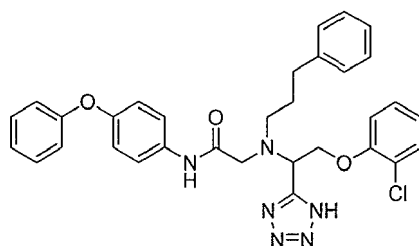
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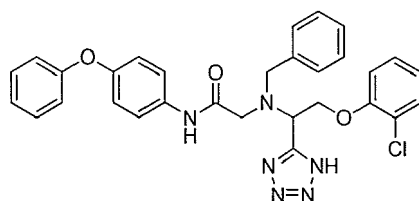
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**[0433]** White solid, Yield: 386 mg (88 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.29 (d,  $J = 21.2$ , 1H), 7.35 - 7.28 (m, 5H), 7.23 - 7.18 (m, 3H), 7.17 - 7.13 (m, 3H), 7.10 - 7.06 (m, 1H), 6.98 - 6.91 (m, 4H), 6.90 - 6.87 (m, 2H), 4.88 (dd,  $J = 9.5$ , 4.2, 1H), 4.57 (t,  $J = 10.0$ , 1H), 4.39 (dd,  $J = 10.4$ , 4.2, 1H), 3.77 (d,  $J = 17.8$ , 1H), 3.53 (d,  $J = 17.8$ , 1H), 3.16 (dt,  $J = 14.3$ , 7.3, 1H), 3.02 - 2.92 (m, 1H), 2.88 (t,  $J = 6.9$ , 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  171.2, 157.2, 154.3, 153.4, 138.8, 131.8, 130.4, 129.8, 128.7, 128.6, 128.1, 126.5, 123.3, 123.0, 122.8, 119.3, 118.6, 114.3, 67.5, 56.5, 55.5, 54.1, 34.7 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 568.20; found  $[\text{M}+\text{H}]^+$ : 568.27.

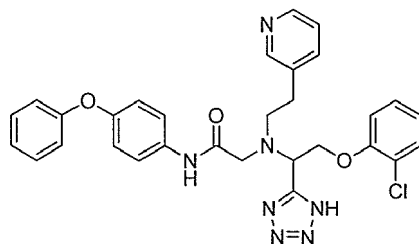
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**Example 174: 2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(3-phenylpropyl)-amino)-N-(4-phenoxyphenyl)acetamide****[0434]**

**[0435]** White solid, Yield: 130 mg (62 %);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  11.08 (s, 1H), 9.72 (s, 1H), 7.43 (d,  $J = 8.9$ , 2H), 7.33 - 7.27 (m, 3H), 7.20 - 7.15 (m, 3H), 7.12 (d,  $J = 7.2$ , 1H), 7.10 - 7.06 (m, 3H), 6.96 (d,  $J = 8.3$ , 1H), 6.94 - 6.90 (m, 3H), 6.88 (d,  $J = 8.8$ , 2H), 4.84 (dd,  $J = 9.9$ , 3.8, 1H), 4.60 (t,  $J = 10.2$ , 1H), 4.40 (dd,  $J = 10.4$ , 3.8, 1H), 3.71 (d,  $J = 17.8$ , 1H), 3.43 (d,  $J = 17.7$ , 1H), 2.88 (dt,  $J = 14.6$ , 7.5, 1H), 2.75 - 2.59 (m, 3H), 1.95 - 1.82 (m, 2H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  171.4, 157.3, 156.6, 154.3, 153.5, 141.3, 132.1, 130.5, 129.8, 128.5, 128.3, 128.1, 126.0, 123.3, 122.8, 122.7, 119.4, 118.6, 114.2, 67.2, 56.6, 55.6, 52.5, 33.2, 29.9 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 583.21; found  $[\text{M}+\text{H}]^+$ : 583.36.

**Example 175: 2-(benzyl(2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)amino)-N-(4-phenoxyphenyl)acetamide****[0436]**

**[0437]** White solid, Yield: 300 mg (82 %);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.55 (s, 1H), 7.45 (d,  $J = 7.3$ , 2H), 7.37 - 7.32 (m, 4H), 7.31 - 7.28 (m, 3H), 7.26 - 7.22 (m, 1H), 7.21 - 7.15 (m, 1H), 7.09 (t,  $J = 7.4$ , 1H), 7.00 - 6.96 (m, 1H), 6.95 - 6.92 (m, 3H), 6.91 - 6.88 (m, 2H), 4.89 (dd,  $J = 10.2$ , 4.1, 1H), 4.70 (t,  $J = 10.4$ , 1H), 4.45 (dd,  $J = 10.5$ , 4.1, 1H), 4.10 (d,  $J = 13.3$ , 1H), 3.78 - 3.63 (m, 2H), 3.47 (d,  $J = 17.5$ , 1H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  171.2, 157.2, 154.3, 153.4, 138.9, 131.8, 130.5, 129.8, 128.7, 128.6, 128.1, 126.5, 123.3, 122.8, 119.3, 118.6, 114.3, 67.5, 56.5, 55.5, 34.7 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 555.18; found  $[\text{M}+\text{H}]^+$ : 555.34.

**Example 176: 2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(2-(pyridin-3-yl)ethyl)-amino)-N-(4-phenoxyphenyl)acetamide****[0438]**

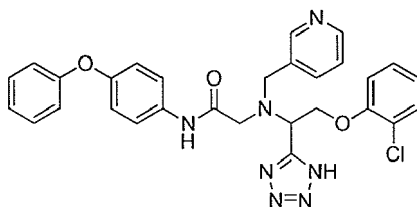
**[0439]** Yellow solid, Yield: 240 mg (69 %);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.29 (s, 1H), 8.67 (d,  $J = 4.6$ , 1H), 7.71 (t,  $J = 7.4$ , 1H), 7.35 - 7.25 (m, 5H), 7.23 - 7.13 (m, 3H), 7.06 (t,  $J = 7.4$ , 1H), 6.96 (d,  $J = 8.1$ , 1H), 6.93 - 6.87 (m, 3H), 6.82 (d,  $J = 8.8$ , 2H), 4.92 (d,  $J = 6.2$ , 1H), 4.63 (dd,  $J = 10.0$ , 3.1, 1H), 4.53 (t,  $J = 9.9$ , 1H), 3.93 (d,  $J = 17.7$ , 1H), 3.69 (d,  $J$

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= 17.6, 1H), 3.40 (t,  $J = 5.3$ , 2H), 3.31 - 3.10 (m, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  169.9, 158.1, 157.5, 156.0, 153.5, 153.4, 146.4, 139.5, 132.7, 130.4, 129.7, 128.1, 125.3, 123.1, 122.8, 122.6, 122.4, 121.6, 119.3, 118.4, 113.5, 67.3, 58.3, 57.7, 34.4 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 570.19; found  $[\text{M}+\text{H}]^+$ : 570.35.

5 **Example 177: 2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(pyridin-3-ylmethyl)-amino)-N-(4-phenoxyphenyl)acetamide**

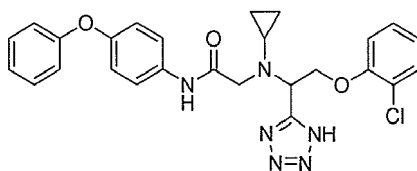
[0440]



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[0441] Yellow solid, Yield: 70 mg (46 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  10.00 (s, 1H), 9.62 (s, 1H), 8.81 (s, 1H), 8.56 (d,  $J = 4.1$ , 1H), 8.02 (d,  $J = 7.8$ , 1H), 7.43 - 7.39 (m, 2H), 7.35 (dd,  $J = 7.9$ , 1.4, 1H), 7.33 - 7.28 (m, 2H), 7.24 - 7.16 (m, 1H), 7.08 (t,  $J = 7.4$ , 1H), 7.00 (d,  $J = 8.2$ , 1H), 6.96 - 6.91 (m, 3H), 6.87 (d,  $J = 8.9$ , 2H), 4.87 (dd,  $J = 10.1$ , 3.8, 1H), 4.72 (t,  $J = 10.4$ , 1H), 4.57 (dd,  $J = 10.4$ , 3.8, 1H), 4.17 (d,  $J = 13.9$ , 1H), 3.91 (d,  $J = 13.9$ , 1H), 3.83 (d,  $J = 17.3$ , 1H), 3.46 (d,  $J = 17.2$ , 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.0, 157.8, 157.3, 154.0, 153.3, 149.1, 147.8, 138.6, 134.2, 132.3, 130.5, 129.7, 128.2, 124.4, 123.2, 122.6, 122.4, 122.3, 119.4, 118.5, 113.6, 66.9, 55.7, 55.1, 54.0 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 556.18; found  $[\text{M}+\text{H}]^+$ : 556.33.

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**Example 178: 2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(cyclopropyl)amino)-N-(4-phenoxyphenyl)acetamide**

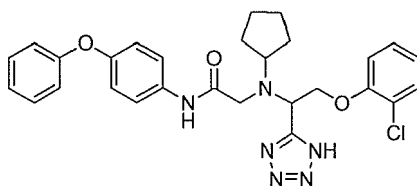
[0442]



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[0443] Yellow solid, Yield: 180 mg (72 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.48 (s, 1H), 7.42 - 7.37 (m, 2H), 7.32 - 7.27 (m, 3H), 7.17 (td,  $J = 8.3$ , 1.5, 1H), 7.07 (t,  $J = 7.4$ , 1H), 6.98 (d,  $J = 8.3$ , 1H), 6.92 (d,  $J = 8.3$ , 2H), 6.90 - 6.84 (m, 3H), 4.91 (dd,  $J = 10.2$ , 4.0, 1H), 4.71 (t,  $J = 10.2$ , 1H), 4.49 (dd,  $J = 10.2$ , 4.0, 1H), 3.83 (d,  $J = 17.7$ , 1H), 3.68 (d,  $J = 17.6$ , 1H), 2.50 - 2.36 (m, 1H), 0.78 - 0.68 (m, 1H), 0.66 - 0.50 (m, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  172.1, 157.2, 154.5, 153.3, 131.8, 130.1, 129.8, 128.2, 123.3, 123.1, 122.6, 122.5, 119.3, 118.6, 113.7, 66.6, 57.6, 56.5, 35.4, 7.9, 6.6 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 505.17; found  $[\text{M}+\text{H}]^+$ : 505.32.

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**Example 179: 2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(cyclopentyl)amino)-N-(4-phenoxyphenyl)acetamide**

[0444]



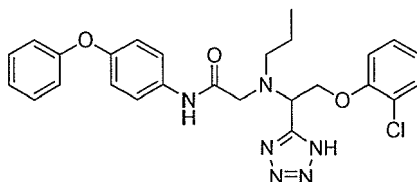
[0445] Yellow solid, Yield: 160 mg (77 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.76 (s, 1H), 7.47 (d,  $J = 8.9$ , 2H), 7.37 (dd,  $J = 7.9$ , 1.5, 1H), 7.36 - 7.31 (m, 2H), 7.25 - 7.20 (m, 1H), 7.11 (t,  $J = 7.4$ , 1H), 7.05 - 7.00 (m, 1H), 6.99 - 6.96 (m, 3H),

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6.94 (d,  $J = 8.9$ , 2H), 5.01 (dd,  $J = 9.5$ , 3.6, 1H), 4.62 (t,  $J = 10.1$ , 1H), 4.47 (dd,  $J = 10.4$ , 4.1, 1H), 3.81 (d,  $J = 18.2$ , 1H), 3.53 (d,  $J = 18.1$ , 1H), 3.49 - 3.37 (m, 1H), 2.01 - 1.82 (m, 2H), 1.79 - 1.65 (m, 2H), 1.64 - 1.39 (m, 4H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  172.6, 157.3, 154.2, 153.4, 132.0, 130.5, 129.8, 128.2, 123.2, 122.7, 122.5, 119.4, 118.6, 114.2, 67.5, 56.4, 53.4, 52.4, 30.8, 30.7, 23.6, 23.5 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 533.20; found  $[\text{M}+\text{H}]^+$ : 533.33.

**Example 180: 2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(propyl)amino)-N-(4-phenoxyphenyl)acetamide**

[0446]

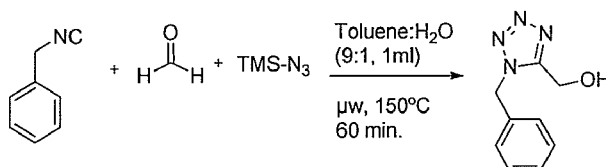


**[0447]** White solid, Yield: 40 mg (60 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.72 (s, 1H), 7.49 (d,  $J = 8.8$ , 2H), 7.37 - 7.31 (m, 3H), 7.24 - 7.19 (m, 1H), 7.10 (t,  $J = 7.4$ , 1H), 7.03 (d,  $J = 8.3$ , 1H), 6.98 - 6.92 (m, 5H), 4.89 (dd,  $J = 9.6$ , 3.5, 1H), 4.66 (t,  $J = 10.1$ , 1H), 4.46 (dd,  $J = 10.3$ , 3.8, 1H), 3.75 (d,  $J = 17.7$ , 1H), 3.45 (d,  $J = 17.7$ , 1H), 2.88 - 2.76 (m, 1H), 2.71 - 2.63 (m, 1H), 1.68 - 1.58 (m, 2H), 0.97 (t,  $J = 7.3$ , 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  171.4, 157.3, 154.2, 153.5, 132.2, 130.5, 129.7, 128.1, 123.2, 122.6, 122.5, 119.4, 118.6, 114.1, 67.2, 56.4, 55.6, 55.0, 21.5, 11.6 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 507.18; found  $[\text{M}+\text{H}]^+$ : 507.33.

**Tetrazole as building blocks:**

**Method 9: General procedure for tetrazole synthesis by using Isocyanide, paraformaldehyde and TMS-N<sub>3</sub>**

[0448]

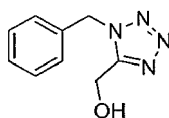


**[0449]** A 5 ml microwave vial equipped with a magnetic stir bar was charged with a benzylisocyanide (117  $\mu\text{l}$ , 1.0 mmol) and paraformaldehyde (60 mg, 2.0 mmol) in toluene: $\text{H}_2\text{O}$  (9:1, 1 ml) and trimethylsilyl azide (131  $\mu\text{l}$ , 1.0 mmol) was added slowly at room temperature. Vial was sealed with cap containing a septum and subjected to microwave heating at 150  $^\circ\text{C}$  for 60 min [attention: during irradiation, pressure develops]. The solvent was removed under reduced pressure and residue was purified by silica gel flash chromatography using EtOAc-hexane as eluent on to afford the titled product.

**Following examples were synthesized by using Method 9: Method for tetrazole synthesis by using Isocyanide, paraformaldehyde and TMS-N<sub>3</sub>**

**Example 181: (1-benzyl-1H-tetrazol-5-yl)methanol**

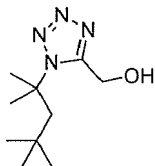
[0450]



**[0451]** White Solid, Yield: 103 mg (54 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39 - 7.33 (m, 3H), 7.32 - 7.27 (m, 2H), 5.65 (s, 2H), 4.83 (d,  $J = 6.0$ , 2H), 4.10 (s, 1H). MS (ESI)  $m/z$  calculated  $[\text{M}-\text{H}]^-$ : 189.09; found  $[\text{M}-\text{H}]^-$ : 189.09.

**Example 182: (1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)methanol****[0452]**

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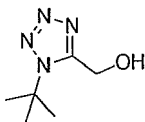
10

**[0453]** White Solid, Yield: 158 mg (74 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.06 (d,  $J = 6.3$ , 2H), 4.15 (t,  $J = 6.6$ , 1H), 2.02 (s, 2H), 1.83 (s, 6H), 0.78 (s, 9H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  154.0, 65.1, 55.4, 53.5, 31.7, 30.6, 29.9.

15

**Example 183: (1-(tert-butyl)-1H-tetrazol-5-yl)methanol****[0454]**

20

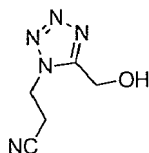


25

**[0455]** White Solid, Yield: 81 mg (52 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.05 (d,  $J = 6.6$ , 2H), 4.08 - 3.93 (m, 1H), 1.77 (s, 9H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  153.5, 61.8, 55.0, 29.6.

**Example 184: 3-(5-(hydroxymethyl)-1H-tetrazol-1-yl)propanenitrile****[0456]**

35

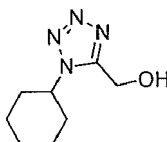


40

**[0457]** White Solid, Yield: 190 mg (62 %);  $^1\text{H}$  NMR (500 MHz, MeOD)  $\delta$  4.01 (t,  $J = 2.8$ , 2H), 3.58 - 3.46 (m, 2H), 2.70 (td,  $J = 6.6$ , 2.9, 2H).  $^{13}\text{C}$  NMR (126 MHz, MeOD)  $\delta$  175.7, 119.3, 62.5, 36.0, 18.5. MS (ESI)  $m/z$  calculated  $[\text{M}+\text{H}]^+$ : 154.07; found  $[\text{M}+\text{H}]^+$ : 154.06.

**Example 185: (1-cyclohexyl-1H-tetrazol-5-yl)methanol****[0458]**

45



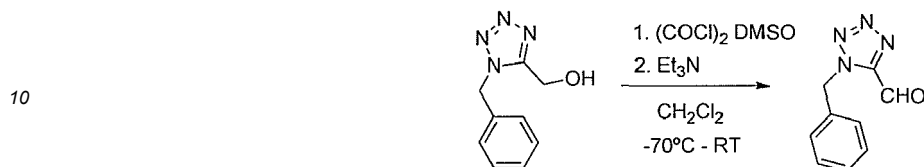
50

**[0459]** White Solid, Yield: 139 mg (77 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.96 (d,  $J = 6.7$ , 2H), 4.45 (tt,  $J = 11.4$ , 4.1, 1H), 3.48 (t,  $J = 6.6$ , 1H), 2.20 - 1.94 (m, 6H), 1.86 - 1.76 (m, 1H), 1.55 - 1.19 (m, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  176.0, 58.5, 53.6, 32.9, 25.2, 24.8.

55

**Method 10: General procedure for Swern oxidation**Reference: [http://www.ochemonline.com/Swern\\_oxidation](http://www.ochemonline.com/Swern_oxidation)

5 [0460]



15 [0461] To a solution of oxalyl chloride (5 mmol) and 3 Å MS in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) at -78 °C under N<sub>2</sub> was added dropwise a solution of DMSO (10 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL). After 15 min a solution of the alcohol in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was slowly added dropwise. After 30 min, Et<sub>3</sub>N (15 mmol) was added dropwise. The reaction was stirred 30 min at -78 °C then slowly allowed to warm to rt. Water was added and stirred for few min to separate organic layer and extracted with DCM. The organic fraction was dried under reduced pressure and residue was purified by silica gel flash chromatography using EtOAc-hexane (40 %) as eluent on to afford the titled product.

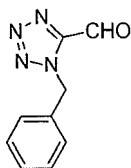
20

Following examples were synthesized by using Method 10: Method for Swern oxidation

**Example 186: 1-benzyl-1H-tetrazole-5-carbaldehyde**

25 [0462]

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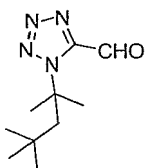


35 [0463] Colorless liquid, Yield: 76 mg (82 %); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 10.25 (s, 1H), 7.42 - 7.32 (m, 6H), 5.87 (s, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 179.5, 148.7, 132.9, 129.3, 129.1, 129.0, 128.6, 52.7 ppm. MS (ESI) m/z calculated [M+H]<sup>+</sup>: 189.07; found [M+H]<sup>+</sup>: 189.14.

**Example 187: 1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazole-5-carbaldehyde**

40 [0464]

45



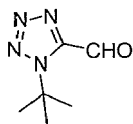
50 [0465] Colorless liquid, Yield: 540 mg (86 %); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 10.30 (s, 1H), 0.81 (s, 2H), 0.78 (s, 4H), 0.72 (s, 9H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 179.2, 140.6, 54.3, 51.2, 30.6, 29.9, 29.5 ppm.

**Example 188: 1-(tert-butyl)-1H-tetrazole-5-carbaldehyde**

55 [0466]



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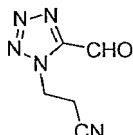


5

**[0467]** Pale yellow liquid, Yield: 600 mg (80 %); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 10.30 (s, 1H), 1.78 (s, 9H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 179.1, 150.6, 64.1, 28.7 ppm.

### 10 **Example 189: 1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazole-5-carbaldehyde**

**[0468]**



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**[0469]** Colorless liquid, Yield: 45 mg (47 %); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.86 (s, 1H), 4.80 (t, *J* = 6.5, 2H), 3.13 (t, *J* = 6.5, 2H).

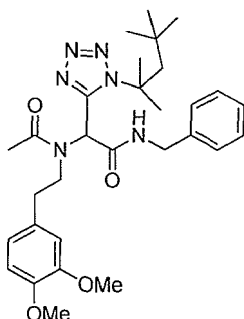
20

### **Tetrazole-5-carbaldehydes as aldehyde component in Ugi and Passerini reaction**

25 **Following examples were synthesized by using Method 7: Method for Ugi reaction**

**Example 190: N-benzyl-2-(N-(3,4-dimethoxyphenethyl)acetamido)-2-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)acetamide**

30 **[0470]**



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**[0471]** Yellowish solid, Yield: 115 mg (56 %); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.29 (d, *J* = 7.4, 2H), 7.26 - 7.21 (m, 3H), 7.15 (s, 1H), 6.77 (d, *J* = 8.1, 1H), 6.68 (s, 1H), 6.64 (d, *J* = 8.1, 1H), 6.46 (s, 1H), 4.48 (d, *J* = 5.7, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 3.83 - 3.76 (m, 1H), 3.76 - 3.66 (m, 1H), 2.67 (td, *J* = 12.3, 5.2, 1H), 2.26 (s, 3H), 2.15 (td, *J* = 12.3, 5.3, 1H), 2.03 (d, *J* = 2.4, 2H), 1.88 (s, 3H), 1.80 (s, 3H), 0.79 (s, 9H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 171.9, 165.5, 161.1, 150.5, 149.2, 148.0, 137.2, 130.1, 128.8, 128.7, 127.8, 127.8, 127.7, 127.6, 120.6, 112.0, 111.5, 66.3, 56.0, 55.9, 53.6, 52.1, 48.9, 44.2, 35.8, 31.6, 30.7, 30.2, 30.0, 21.5 ppm; MS (ESI) *m/z* calculated [M+Na]<sup>+</sup>: 573.32; found [M+Na]<sup>+</sup>: 573.40.

45

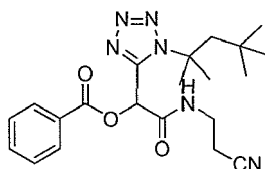
50

**Example 191: 2-((2-cyanoethyl)amino)-2-oxo-1-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)ethyl benzoate**

**[0472]**

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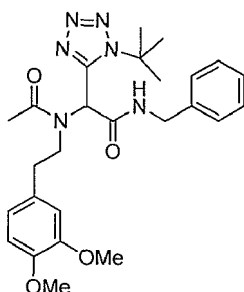
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[0473] White solid, Yield: 110 mg (567%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.12 - 8.05 (m, 2H), 7.64 (t,  $J = 7.5$ , 1H), 7.47 (t,  $J = 7.8$ , 2H), 7.33 (t,  $J = 6.0$ , 1H), 6.95 (s, 1H), 3.71 - 3.61 (m, 1H), 3.59 - 3.47 (m, 1H), 2.74 - 2.54 (m, 2H), 2.14 (q,  $J = 15.3$ , 2H), 1.96 (s, 3H), 1.91 (s, 3H), 0.80 (s, 9H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  165.5, 164.5, 150.4, 134.6, 130.2, 128.9, 127.5, 117.4, 66.8, 66.5, 54.4, 35.8, 31.7, 30.5, 30.4, 30.3, 18.0 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}-\text{H}]^-$ : 411.22; found  $[\text{M}-\text{H}]^-$ : 411.29.

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Example 192: N-benzyl-2-(N-(3,4-dimethoxyphenethyl)acetamido)-2-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)acetamide

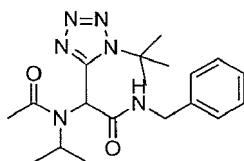
[0474]



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[0475] White solid, Yield: 140 mg (57 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37 - 7.19 (m, 6H), 6.81 - 6.72 (m, 2H), 6.61 (s, 1H), 6.59 (s, 1H), 5.29 (s, 1H), 4.47 (dd,  $J = 7.7$ , 6.1, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 3.81 - 3.75 (m, 1H), 3.75 - 3.65 (m, 1H), 2.64 (td,  $J = 12.4$ , 5.2, 1H), 2.22 (s, 3H), 2.10 - 2.04 (m, 1H), 1.75 (s, 9H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  172.0, 165.5, 150.4, 149.1, 147.9, 137.3, 129.9, 128.7, 127.8, 127.7, 120.5, 111.9, 111.4, 62.6, 55.9, 55.9, 52.2, 48.9, 44.2, 35.8, 29.8, 29.7, 21.5 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{Na}]^+$ : 517.25; found  $[\text{M}+\text{Na}]^+$ : 517.37.

Example 193: N-benzyl-2-(1-(tert-butyl)-1H-tetrazol-5-yl)-2-(N-isopropylacetamido)acetamide

[0476]

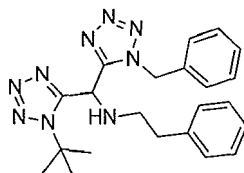


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[0477] White solid, Yield: 84 mg (48 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35 - 7.31 (m, 2H), 7.30 - 7.27 (m, 3H), 5.30 (s, 2H), 4.51 - 4.44 (m, 2H), 2.24 (s, 3H), 1.80 (s, 2H), 1.74 (s, 9H), 1.30 (d,  $J = 7.0$ , 3H), 1.26 (br s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  165.9, 165.8, 150.6, 128.8, 128.1, 127.8, 66.1, 53.4, 44.3, 43.9, 30.0, 29.9, 29.7 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{Na}]^+$ : 395.22; found  $[\text{M}+\text{Na}]^+$ : 395.31.

Example 194: N-((1-benzyl-1H-tetrazol-5-yl)(1-(tert-butyl)-1H-tetrazol-5-yl)methyl)-2-phenylethanamine

[0478]

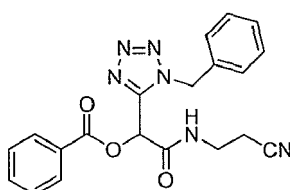
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[0479] Brown solid, Yield: 162 mg (39 %);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38 - 7.33 (m, 3H), 7.32 - 7.27 (m, 2H), 7.22 (t,  $J = 7.4$ , 1H), 7.14 (d,  $J = 7.1$ , 2H), 7.03 (dd,  $J = 7.1$ , 1.9, 2H), 5.78 - 5.65 (m, 2H), 5.16 (s, 1H), 2.88 - 2.77 (m, 1H), 2.72 - 2.59 (m, 2H), 2.57 - 2.43 (m, 1H), 2.26 (s, 1H), 1.39 (s, 9H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  179.1, 152.5, 151.5, 139.2, 133.2, 129.3, 129.1, 128.8, 128.6, 127.9, 126.6, 62.1, 51.9, 50.8, 49.7, 36.2, 29.5 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{Na}]^+$ : 440.23; found  $[\text{M}+\text{Na}]^+$ : 440.30.

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Example 195: 1-(1-benzyl-1H-tetrazol-5-yl)-2-((2-cyanoethyl)amino)-2-oxoethyl benzoate

[0480]



25  
[0481] White viscous liquid, Yield: 120 mg (58 %);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.03 (t,  $J = 6.1$ , 1H), 7.75 (d,  $J = 7.3$ , 2H), 7.49 (t,  $J = 7.5$ , 1H), 7.35 - 7.27 (m, 5H), 7.23 (dd,  $J = 7.2$ , 1.7, 2H), 6.67 (s, 1H), 5.90 (d,  $J = 15.5$ , 1H), 5.81 (d,  $J = 15.6$ , 1H), 3.66 - 3.42 (m, 2H), 2.58 (t,  $J = 6.6$ , 2H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  179.6, 164.8, 164.6, 150.6, 134.2, 133.2, 130.1, 129.1, 128.8, 128.6, 127.7, 127.4, 117.9, 65.9, 52.0, 35.8, 17.9 ppm; MS (ESI)  $m/z$  calculated  $[\text{M}+\text{Na}]^+$ : 413.13; found  $[\text{M}+\text{Na}]^+$ : 413.21.

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[0482] The following further examples have been synthesized:

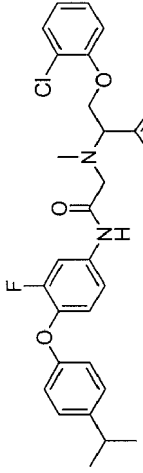
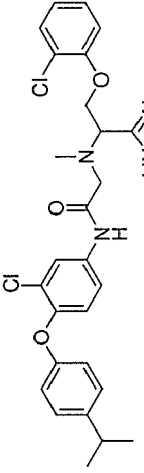
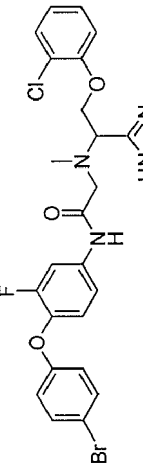
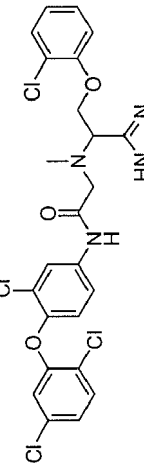
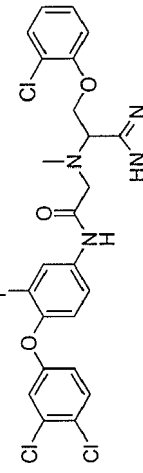
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No.	Structure	Name	Chemical formula	Mass [M+Na] <sup>+</sup>
196		N-(3-chloro-4-(4-isopropylphenoxy)phenyl)-2-((2-(2-chlorophenoxy)phenyl)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)acetamide	C <sub>27</sub> H <sub>28</sub> Cl FN <sub>6</sub> O <sub>3</sub>	561.18
197		N-(4-(4-bromophenoxy)-3-fluorophenyl)-2-((2-(2-chlorophenoxy)phenyl)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)acetamide	C <sub>27</sub> H <sub>28</sub> Cl BrF <sub>2</sub> N <sub>6</sub> O <sub>3</sub>	577.15
198		N-(3-chloro-4-(2,5-dichlorophenoxy)phenyl)-2-((2-(2-chlorophenoxy)phenyl)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)acetamide	C <sub>24</sub> H <sub>21</sub> Br Cl <sub>3</sub> FN <sub>6</sub> O <sub>3</sub>	597.04
199		N-(4-(3,4-dichlorophenoxy)-3-fluorophenyl)-2-((2-(2-chlorophenoxy)phenyl)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)acetamide	C <sub>24</sub> H <sub>20</sub> Cl F <sub>2</sub> N <sub>6</sub> O <sub>3</sub>	603.02
200		N-(3-chloro-4-(4-isopropylphenoxy)phenyl)-2-((2-(2-chlorophenoxy)phenyl)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)acetamide	C <sub>27</sub> H <sub>28</sub> Cl FN <sub>6</sub> O <sub>3</sub>	561.18

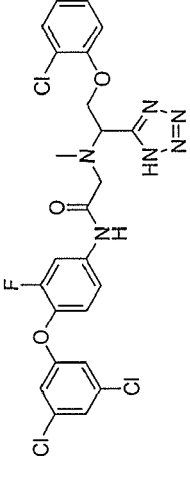
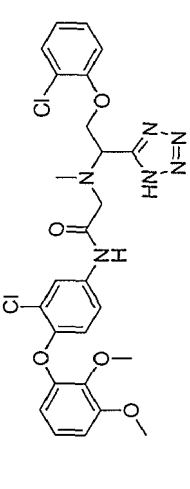
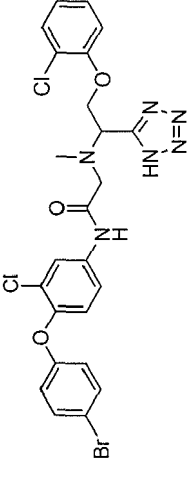
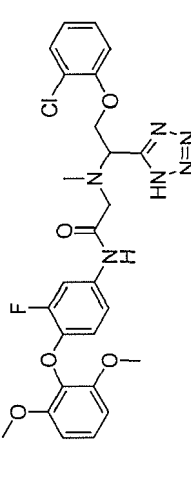
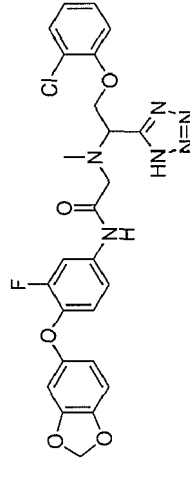
(continued)

No.	Structure	Name	Chemical formula	Mass [M+Na] <sup>+</sup>
201		2-((2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(4-(cyclopentylmethoxy)-3-fluorophenyl)acetamide	C <sub>24</sub> H <sub>28</sub> ClFN <sub>6</sub> O <sub>3</sub>	525.18
202		N-(3-chloro-4-(cyclopentylmethoxy)phenyl)-2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)acetamide	C <sub>24</sub> H <sub>28</sub> Cl <sub>2</sub> N <sub>6</sub> O <sub>3</sub>	541.15
203		2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(4-(3,5-dimethoxyphenoxy)-3-fluorophenyl)acetamide	C <sub>26</sub> H <sub>26</sub> ClFN <sub>6</sub> O <sub>5</sub>	579.15
204		2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(4-(2,3-dimethoxyphenoxy)-3-fluorophenyl)acetamide	C <sub>26</sub> H <sub>26</sub> ClFN <sub>6</sub> O <sub>5</sub>	579.15
205		2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(4-(3-chlorophenoxy)-3-fluorophenyl)acetamide	C <sub>24</sub> H <sub>21</sub> Cl <sub>2</sub> FN <sub>6</sub> O <sub>3</sub>	553.09

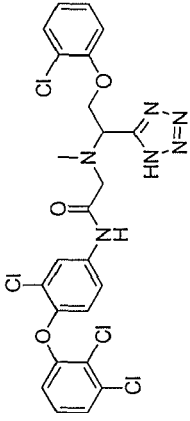
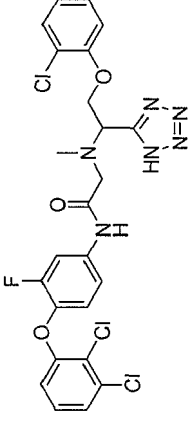
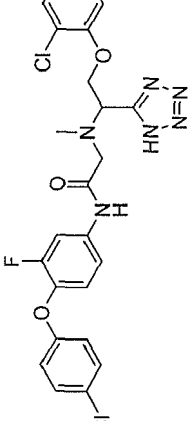
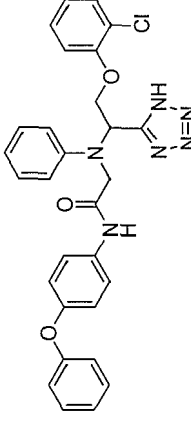
(continued)

No.	Structure	Name	Chemical formula	Mass [M+Na] <sup>+</sup>
206		2-((2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(3-fluoro-4-((3,4,5-trimethoxybenzyloxy)phenyl)acetamide	C <sub>28</sub> H <sub>30</sub> Cl FN <sub>6</sub> O <sub>6</sub>	623.18
207		N-(3-chloro-4-(4-chlorophenoxy)phenyl)-2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)acetamide	C <sub>24</sub> H <sub>21</sub> Cl <sub>3</sub> N <sub>6</sub> O <sub>3</sub>	569.06
208		2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(4-(cyclopentyloxy)-3-fluorophenyl)acetamide	C <sub>23</sub> H <sub>26</sub> Cl FN <sub>6</sub> O <sub>3</sub>	511.16
209		N-(3-chloro-4-(cyclopentyloxy)phenyl)-2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)acetamide	C <sub>23</sub> H <sub>26</sub> Cl <sub>2</sub> N <sub>6</sub> O <sub>3</sub>	527.13
210		2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(4-(2,6-dichlorophenoxy)-3-fluorophenyl)acetamide	C <sub>24</sub> H <sub>20</sub> Cl <sub>3</sub> FN <sub>6</sub> O <sub>3</sub>	587.05

(continued)

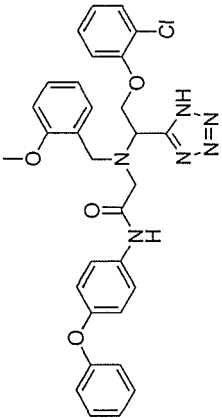
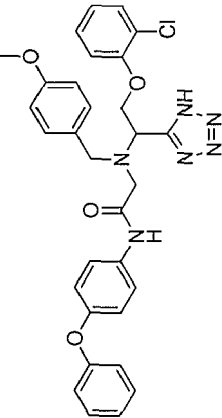
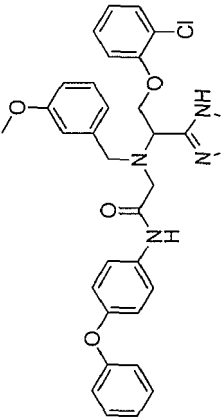
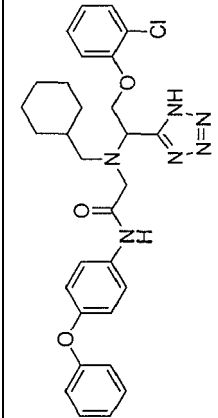
No.	Structure	Name	Chemical formula	Mass [M+Na] <sup>+</sup>
211		2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(4-(3,5-dichlorophenoxy)-3-fluorophenyl)acetamide	C <sub>24</sub> H <sub>20</sub> Cl <sub>3</sub> FN <sub>6</sub> O <sub>3</sub>	587.05
212		N-(3-chloro-4-(2,3-dimethoxyphenoxy)phenyl)-2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)acetamide	C <sub>26</sub> H <sub>26</sub> Cl <sub>2</sub> N <sub>6</sub> O <sub>5</sub>	595.12
213		N-(4-(4-bromophenoxy)-3-chlorophenyl)-2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)acetamide	C <sub>24</sub> H <sub>21</sub> BrCl <sub>2</sub> N <sub>6</sub> O <sub>3</sub>	613.01
214		2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(4-(2,6-dimethoxyphenoxy)-3-fluorophenyl)acetamide	C <sub>26</sub> H <sub>26</sub> ClFN <sub>6</sub> O <sub>5</sub>	579.15
215		N-(4-(benzo[d][1,3]dioxol-5-yloxy)-3-fluorophenyl)-2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)acetamide	C <sub>25</sub> H <sub>22</sub> ClFN <sub>6</sub> O <sub>5</sub>	563.12

(continued)

No.	Structure	Name	Chemical formula	Mass [M+Na] <sup>+</sup>
216		N-(3-chloro-4-(2,3-dichlorophenoxy)phenyl)-2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)acetamide	C <sub>24</sub> H <sub>20</sub> Cl <sub>4</sub> N <sub>6</sub> O <sub>3</sub>	603.02
217		2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(4-(2,3-dichlorophenoxy)-3-fluorophenyl)acetamide	C <sub>24</sub> H <sub>20</sub> Cl <sub>3</sub> FN <sub>6</sub> O <sub>3</sub>	587.05
218		2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(4-(4-chlorophenoxy)-3-fluorophenyl)acetamide	C <sub>24</sub> H <sub>21</sub> Cl <sub>2</sub> FN <sub>6</sub> O <sub>3</sub>	553.09
219		2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(phenyl)amino)-N-(4-phenoxyphenyl)acetamide	C <sub>29</sub> H <sub>25</sub> ClN <sub>6</sub> O <sub>3</sub>	563.16



(continued)

No.	Structure	Name	Chemical formula	Mass [M+Na] <sup>+</sup>
220		2-((2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(2-methoxybenzyl)amino)-N-(4-phenoxyphenyl)acetamide	C <sub>31</sub> H <sub>29</sub> Cl N <sub>6</sub> O <sub>4</sub>	607.18
221		2-((2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(4-methoxybenzyl)amino)-N-(4-phenoxyphenyl)acetamide	C <sub>31</sub> H <sub>29</sub> Cl N <sub>6</sub> O <sub>4</sub>	607.18
222		2-((2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(3-methoxybenzyl)amino)-N-(4-phenoxyphenyl)acetamide	C <sub>31</sub> H <sub>29</sub> Cl N <sub>6</sub> O <sub>4</sub>	607.18
223		2-((2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(cyclohexylmethyl)amino)-N-(4-phenoxyphenyl)acetamide	C <sub>30</sub> H <sub>33</sub> Cl N <sub>6</sub> O <sub>3</sub>	583.22

(continued)

No.	Structure	Name	Chemical formula	Mass [M+Na] <sup>+</sup>
224		2-((2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(cyclohexyl)amino)-N-(4-phenoxyphenyl)acetamide	C <sub>29</sub> H <sub>31</sub> Cl N <sub>6</sub> O <sub>3</sub>	569.20
225		2-((2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(cyclopropylmethyl)amino)-N-(4-phenoxyphenyl)acetamide	C <sub>27</sub> H <sub>27</sub> Cl N <sub>6</sub> O <sub>3</sub>	541.17
226		2-allyl(2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)amino)-N-(4-phenoxyphenyl)acetamide	C <sub>26</sub> H <sub>25</sub> Cl N <sub>6</sub> O <sub>3</sub>	527.16
227		2-((2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(isobutyl)amino)-N-(4-phenoxyphenyl)acetamide	C <sub>27</sub> H <sub>29</sub> Cl N <sub>6</sub> O <sub>3</sub>	543.19

(continued)

No.	Structure	Name	Chemical formula	Mass [M+Na] <sup>+</sup>
228		2-((2-(2-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(2-morpholinoethyl)amino)-N-(4-phenoxyphenyl)acetamide	C <sub>29</sub> H <sub>32</sub> ClN <sub>7</sub> O <sub>4</sub>	600.21
229		2-((2-(2-hydroxyphenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(4-phenoxyphenyl)acetamide	C <sub>24</sub> H <sub>24</sub> N <sub>6</sub> O <sub>4</sub>	483.18
230		2-((2-(2-aminophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(4-phenoxyphenyl)acetamide	C <sub>24</sub> H <sub>25</sub> N <sub>7</sub> O <sub>3</sub>	482.19
231		2-((2-(4-hydroxyphenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(4-phenoxyphenyl)acetamide	C <sub>24</sub> H <sub>24</sub> N <sub>6</sub> O <sub>4</sub>	483.18
232		2-((2-(4-(benzyloxy)phenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(4-phenoxyphenyl)acetamide	C <sub>31</sub> H <sub>30</sub> N <sub>6</sub> O <sub>4</sub>	573.22

(continued)

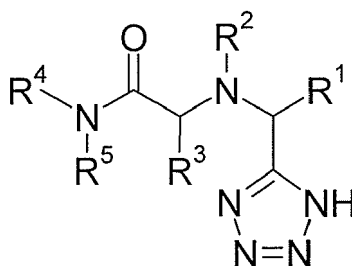
No.	Structure	Name	Chemical formula	Mass [M+Na] <sup>+</sup>
233		2-((2-(4-bromophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(4-phenoxyphenyl)acetamide	C <sub>24</sub> H <sub>23</sub> Br N <sub>6</sub> O <sub>3</sub>	545.09
234		2-((2-(4-chlorophenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(4-phenoxyphenyl)acetamide	C <sub>24</sub> H <sub>23</sub> Cl N <sub>6</sub> O <sub>3</sub>	501.14
235		2-((2-(2,3-dimethoxyphenoxy)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(4-phenoxyphenyl)acetamide	C <sub>26</sub> H <sub>28</sub> N <sub>6</sub> O <sub>5</sub>	527.20
236		2-((2-((2-hydroxyphenyl)amino)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(4-phenoxyphenyl)acetamide	C <sub>24</sub> H <sub>25</sub> N <sub>7</sub> O <sub>3</sub>	482.19
237		2-((2-((2-chlorophenyl)amino)-1-(1H-tetrazol-5-yl)ethyl)(methyl)amino)-N-(4-phenoxyphenyl)acetamide	C <sub>24</sub> H <sub>24</sub> Cl N <sub>7</sub> O <sub>2</sub>	500.16

(continued)

No.	Structure	Name	Chemica 1 formula	Mass [M+Na] <sup>+</sup>
238		2-(2-(4-chlorophenyl)amino)-1-(1H-tetrazol-5-yl)ethyl(methyl)amino)-N-(4-phenoxyphenyl)acetamide	C <sub>24</sub> H <sub>24</sub> ClN <sub>7</sub> O <sub>2</sub>	500.16
239		2-(2-(2,5-dichlorophenyl)amino)-1-(1H-tetrazol-5-yl)ethyl(methyl)amino)-N-(4-phenoxyphenyl)acetamide	C <sub>24</sub> H <sub>23</sub> Cl <sub>2</sub> N <sub>7</sub> O <sub>2</sub>	534.12
240		2-(2-(2-chlorophenyl)thio)-1-(1H-tetrazol-5-yl)ethyl(methyl)amino)-N-(4-phenoxyphenyl)acetamide	C <sub>24</sub> H <sub>23</sub> ClN <sub>6</sub> O <sub>2</sub> S	517.12
241		2-(methyl(2-(phenylthio)-1-(1H-tetrazol-5-yl)ethyl)amino)-N-(4-phenoxyphenyl)acetamide	C <sub>24</sub> H <sub>24</sub> N <sub>6</sub> O <sub>2</sub> S	483.16

## Claims

1. A compound of formula (I):



(I)

wherein

R<sup>1</sup> is a hydrogen atom or an alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl group, all of which groups may optionally be substituted;

R<sup>2</sup> is a hydrogen atom or an alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl group, all of which groups may optionally be substituted;

R<sup>3</sup> is a hydrogen atom or an alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl group, all of which groups may optionally be substituted;

R<sup>4</sup> is a hydrogen atom or an alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl group, all of which groups may optionally be substituted; and

R<sup>5</sup> is a hydrogen atom or an alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl group, all of which groups may optionally be substituted;

or a pharmaceutically acceptable salt, ester, solvate or hydrate or a pharmaceutically acceptable formulation thereof.

2. A compound according to claim 1, wherein R<sup>3</sup> is hydrogen.

3. A compound according to claim 1 or 2, wherein R<sup>4</sup> is hydrogen.

4. A compound according to any one of the preceding claims, wherein R<sup>1</sup> is alkylcycloalkyl containing 4 to 16 carbon atoms; heteroalkylcycloalkyl containing 4 to 16 atoms selected from C, O, S and N; aralkyl containing 7 to 16 carbon atoms; or heteroaralkyl containing 6 to 16 atoms selected from C, O, S and N; wherein all these groups may optionally be substituted.

5. A compound according to any one of the preceding claims 1 to 3, wherein R<sup>1</sup> is a group of formula -CH<sub>2</sub>-X-R<sup>10</sup> wherein X is O, S or NH and R<sup>10</sup> is a cycloalkyl, heterocycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl group, all of which groups may optionally be substituted..

6. A compound according to claim 5, wherein R<sup>10</sup> is phenyl, naphthyl or a heteroaryl group containing one or two rings and 5 to 10 ring atoms selected from C, O, S and N, wherein all these groups may optionally be substituted by halogen, OH, NO<sub>2</sub>, OMe, Me, NH<sub>2</sub>, NHMe or NMe<sub>2</sub> or a group of formula -O-CH<sub>2</sub>CH<sub>2</sub>-O- or -O-CH<sub>2</sub>-O-.

7. A compound according to any one of the preceding claims, wherein R<sup>2</sup> is C<sub>1-6</sub> alkyl; C<sub>2-6</sub> alkenyl; C<sub>1-6</sub> alkynyl; heteroalkyl containing 1 to 6 carbon atoms and 1 to 4 heteroatoms selected from O, S and N; C<sub>3-7</sub> cycloalkyl; C<sub>4-10</sub> alkylcycloalkyl; heterocycloalkyl containing 3 to 7 ring atoms selected from C, O, S and N; heteroalkylcycloalkyl containing 4 to 10 atoms selected from C, O, S and N; phenyl; heteroaryl containing 5 or 6 ring atoms selected from C, O, S and N; aralkyl containing 7 to 12 carbon atoms; or heteroaralkyl containing 6 to 12 atoms selected from C,

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O, S and N; wherein all these groups may optionally be substituted by halogen, OH, NO<sub>2</sub>, OMe, Me, =O, NH<sub>2</sub>, NHMe or NMe<sub>2</sub>.

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8. A compound according to any one of the preceding claims 1 to 6, wherein R<sup>2</sup> is methyl.
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9. A compound according to any one of the preceding claims, wherein R<sup>5</sup> is an aryl, heteroaryl, aralkyl or heteroaralkyl group, all of which groups may optionally be substituted.
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10. A compound according to any one of the preceding claims 1 to 8, wherein R<sup>5</sup> is a group of formula -Ar-L-Cy, wherein Ar is an arylene, heteroarylene, aralkylene or heteroaralkylene group, all of which groups may optionally be substituted; L is a bond, -O-, -NH-, -S- or a C<sub>1-4</sub> alkyl group or a heteroalkyl group containing 1 to 6 atoms selected from C, O, S and N; and Cy is a cycloalkyl, heterocycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl group, all of which groups may optionally be substituted.
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11. A compound according to claim 10, wherein Ar is an optionally substituted phenylene group or an optionally substituted heteroarylene group containing 5 or 6 ring atoms selected from C, O, S and N.
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12. A compound according to claim 10 or 11, wherein L is -O-, -CH<sub>2</sub>O- or -OCH<sub>2</sub>-.
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13. A compound according to claim 10, 11 or 12, wherein Cy is cycloalkyl containing one or two rings and 3 to 10 carbon atoms; heterocycloalkyl containing one or two rings and 3 to 10 ring atoms selected from C, O, S and N; phenyl; naphthyl; or heteroaryl containing one or two rings and 5 to 10 ring atoms selected from C, O, S and N; all of which groups may optionally be substituted.
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14. A pharmaceutical composition comprising a compound according to anyone of the preceding claims or a pharmaceutically acceptable ester, prodrug, hydrate, solvate or salt thereof, optionally in combination with a pharmaceutically acceptable carrier.
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15. A compound or a pharmaceutical composition according to anyone of the preceding claims for use in the treatment of cancer and infectious diseases.
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Place of search Munich		Date of completion of the search 13 February 2019	Examiner Jeanjean, Fabien
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