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(71) Applicant: PROSETTA BIOSCIENCES, INC. [US/US];  
670 5th St., San Francisco, California 94107 (US).

(72) Inventors: PAULVANNAN, Kumarapandian; 6974  
Blue Hill Drive, San Jose, California 95129 (US). SO-  
LAS, Dennis; 22 Sequoia Way, San Francisco, California  
94127-1827 (US). KITAYGORODSKYY, Anatoliy; 350  
26th Avenue, Apt. 3, San Francisco, California 94121 (US).  
LINGAPPA, Vishwanath; 626 Pacheco St., San Francis-  
co, California 94116 (US).

(74) Agent: SINGH, Sunil, K.; 3001 West Big Beaver Road,  
Suite 624, Troy, Michigan 48084-3107 (US).

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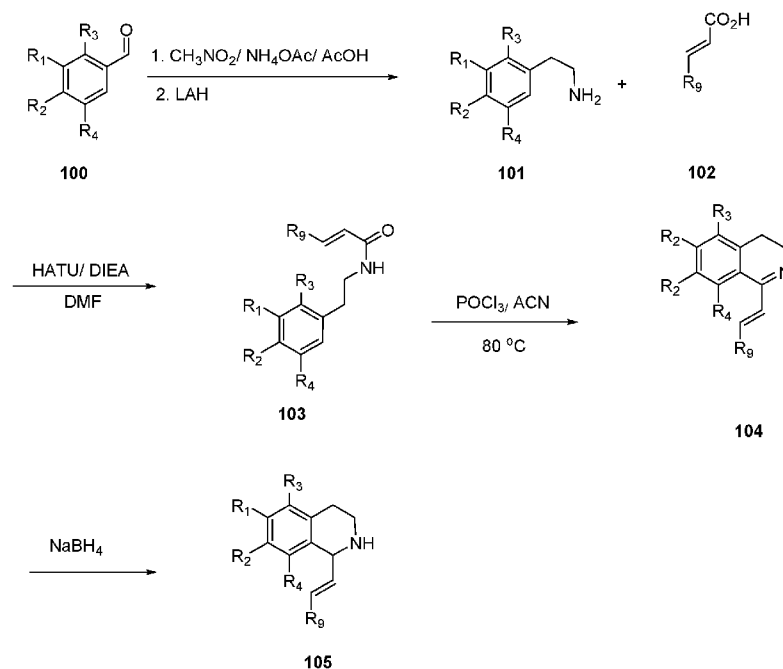


Fig. 1

(57) Abstract: Described herein are compounds, pharmaceutical compositions and methods of using these compounds and pharmaceu-  
tical compositions for treating and/or preventing conditions such as amyotrophic lateral sclerosis. These compounds and pharmaceutical  
compositions are also useful as antivirals and antimicrobial agents.



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# ISOQUINOLINE DERIVATIVES, METHODS OF SYNTHESIS AND USES THEREOF

## CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. § 119 (e) from United States Provisional Application Serial No. 63/046,219, filed June 30, 2020.

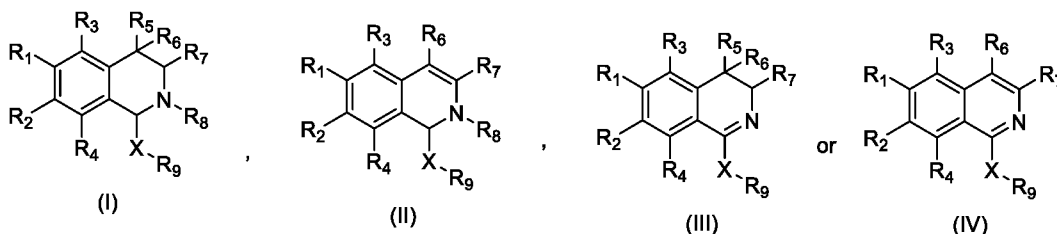
## BACKGROUND

[0002] There is a need for compounds useful as antivirals, antimicrobial and useful in the treatment and prevention of diseases such as amyotrophic lateral sclerosis (ALS).

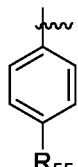
[0003] It has now been discovered that certain compounds described herein are effective against diseases such as ALS and are also useful as antiviral and antimicrobial compounds. These and other uses of these compounds are described herein.

## SUMMARY

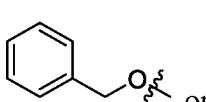
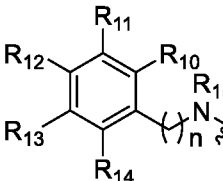
[0004] In one aspect, a compound of structural Formula (I), (II), (III) or (IV):



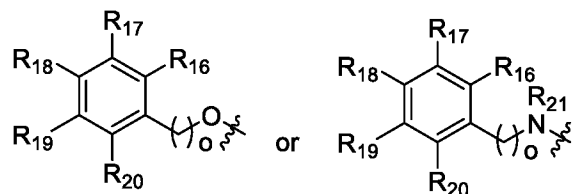
or a solvate, hydrate or salt thereof is provided wherein:  $X$  is absent,  $-\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}_2\text{NR}_{56}\text{R}_{57}$ ,  $-\text{C}=\text{C}-$ , cycloheteroalkyl, cycloheteroalkenyl, substituted cycloheteroalkyl,



substituted cycloheteroalkyl or  $\text{R}_{55}$ ;  $R_1$  is hydrogen,  $-\text{OR}_{22}$ , alkyl, alkenyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl,  $-\text{NR}_{43}\text{R}_{44}$ ,  $-\text{OPh}$ , where

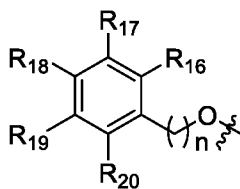
Ph is optionally substituted phenyl,  or ;  $R_2$  is hydrogen,  $-\text{OR}_{23}$ ,

-CF<sub>3</sub>, alkyl, alkenyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, heteroaryl, substituted heteroaryl, -NR<sub>45</sub>R<sub>46</sub>,



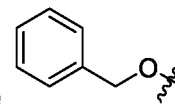
; or R<sub>1</sub> and R<sub>2</sub> along with the carbon atoms to which

they are attached form an aryl, substituted aryl, heteroaryl or substituted heteroaryl ring; n is 0, 1, 2 or 3; o is 0, 1, 2 or 3; R<sub>3</sub> and R<sub>4</sub> are independently hydrogen, halo, alkyl, alkenyl, -OR<sub>24</sub> or -NR<sub>25</sub>R<sub>26</sub>; R<sub>5</sub> is hydrogen, fluoro, alkyl or alkenyl; R<sub>6</sub> is hydrogen, fluoro, alkyl, alkenyl, -OR<sub>27</sub> or -NR<sub>28</sub>R<sub>29</sub>; R<sub>7</sub> is hydrogen, alkyl, alkenyl, -CO<sub>2</sub>R<sub>30</sub>, -CONR<sub>31</sub>R<sub>32</sub>, -CH<sub>2</sub>NR<sub>33</sub>R<sub>34</sub>, -CH<sub>2</sub>R<sub>42</sub> or -CH<sub>2</sub>OR<sub>35</sub>; R<sub>8</sub> is hydrogen, -SO<sub>2</sub>R<sub>47</sub>, -OR<sub>48</sub>, -SO<sub>2</sub>NR<sub>69</sub>R<sub>70</sub>, -CONR<sub>71</sub>R<sub>72</sub>, -COR<sub>73</sub>, -CO<sub>2</sub>R<sub>74</sub>, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl; R<sub>9</sub> is aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloheteroalkyl, cycloheteroalkenyl, substituted cycloheteroalkyl or substituted cycloheteroalkenyl; R<sub>10</sub>-R<sub>14</sub> and R<sub>16</sub>-R<sub>20</sub> are independently hydrogen, alkyl, alkenyl, halo, -CH<sub>2</sub>OR<sub>36</sub>, -CO<sub>2</sub>R<sub>37</sub>, -CONR<sub>38</sub>R<sub>39</sub> - NR<sub>40</sub>R<sub>41</sub>, cycloheteroalkyl, cycloheteroalkenyl, substituted cycloheteroalkyl or substituted cycloheteroalkenyl; R<sub>15</sub> and R<sub>21</sub> are independently hydrogen, alkyl or alkenyl; R<sub>22</sub> and R<sub>23</sub> are independently alkyl, alkenyl, halo substituted alkyl, substituted alkenyl, heteroaryl or substituted heteroaryl; R<sub>24</sub>, R<sub>27</sub>, R<sub>35</sub> and R<sub>36</sub> are independently alkyl, alkenyl, halo substituted alkyl or halo substituted alkenyl; R<sub>28</sub>, R<sub>29</sub>, R<sub>30</sub>-R<sub>33</sub>, R<sub>38</sub>-R<sub>41</sub>, R<sub>63</sub>-R<sub>74</sub>, R<sub>75</sub>, R<sub>77</sub> and R<sub>79</sub>-R<sub>83</sub> are independently hydrogen, alkyl or alkenyl; R<sub>25</sub> and R<sub>26</sub> are independently hydrogen, alkyl, alkenyl or together with the nitrogen atom to which they are attached form an aryl or substituted aryl group; R<sub>34</sub> hydrogen, -SO<sub>2</sub>R<sub>63</sub>, -SO<sub>2</sub>NR<sub>64</sub>R<sub>65</sub>, -CONR<sub>66</sub>R<sub>67</sub> or -COR<sub>68</sub>; R<sub>76</sub> and R<sub>78</sub> are independently hydrogen, -SO<sub>2</sub>R<sub>79</sub>, -SO<sub>2</sub>NR<sub>80</sub>R<sub>81</sub>, -CONR<sub>82</sub>R<sub>83</sub> or -COR<sub>84</sub>; R<sub>42</sub> is cycloheteroalkenyl, substituted cycloheteroalkyl or substituted cycloheteroalkenyl; R<sub>43</sub>-R<sub>46</sub> are independently hydrogen, alkyl, alkenyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl; R<sub>47</sub> is alkyl, alkenyl, aryl or heteroaryl; R<sub>48</sub> is hydrogen, alkyl, alkenyl, substituted alkyl, substituted alkenyl, or aryl; R<sub>55</sub> is heteroarylalkyl, substituted heteroarylalkyl, heteroarylalkenyl, substituted heteroarylalkenyl, -NR<sub>75</sub>R<sub>76</sub> or -CH<sub>2</sub>R<sub>77</sub>R<sub>78</sub>; R<sub>56</sub> is hydrogen, alkyl or alkenyl; R<sub>57</sub> is substituted aryl, heteroaryl or substituted heteroaryl; provided that when R<sub>1</sub> is hydrogen or -OR<sub>22</sub>, R<sub>22</sub> is alkyl and X is -C=C-



, that  $R_2$  is not hydrogen,  $-OR_{23}$ ,  $-CF_3$  or

where  $R_{23}$  is alkyl,  $n$  is 1 and  $R_{16}$ -



$R_{20}$  are hydrogen in the compound of Formula (I); provided that when  $R_1$  is that at least one of  $R_3$ - $R_7$  are not hydrogen in the compound of Formula (I) when  $X$  is  $-C=C-$ , or if each of  $R_3$ - $R_7$  are hydrogen that  $R_8$  is not hydrogen,  $-CONR_{71}R_{72}$ ,  $-COR_{73}$  or  $-CO_2R_{74}$  in the compound of Formula (I) when  $X$  is  $-C=C-$ ; and provided that both  $R_1$  and  $R_2$  are not both alkyl.

**[0005]** Also provided are derivatives, including salts, esters, enol ethers, enol esters, solvates, hydrates, metabolites and prodrugs of the compounds described herein. Further provided are pharmaceutical compositions which include the compounds provided herein and a pharmaceutically acceptable vehicle.

**[0006]** Methods of treating, preventing, or ameliorating symptoms of medical disorders such as, for example, amyotrophic lateral sclerosis or Alzheimer's disease are provided herein. Also provided herein are methods for treating viral and microbial infections.

### BRIEF DESCRIPTION OF THE DRAWINGS

**[0007]** Fig. 1 illustrates preparation of compounds of Formula (I) and Formula (II) where  $R_3$  and  $R_4$  are not hydrogen.

**[0008]** Fig. 2 illustrates preparation of compounds of Formula (I) where  $R_3$  and  $R_4$  are not hydrogen.

**[0009]** Fig. 3 illustrates preparation of compounds of Formula (I) where  $R_3$  and  $R_4$  are not hydrogen.

**[0010]** Fig. 4 illustrates preparation of compounds of Formula (I) where  $R_3$  and  $R_4$  are not hydrogen and  $X$  is  $-CH_2-$ .

**[0011]** Fig. 5 illustrates preparation of compounds of Formula (I) where  $R_3$  and  $R_4$  are not hydrogen and  $X$  is absent.

**[0012]** Fig. 6 illustrates preparation of compounds of Formula (I) and (II) where  $R_6$  is not hydrogen.

- [0013] Fig. 7 illustrates preparation of compounds of Formula (I) and (II) where R<sub>6</sub> is fluorine.
- [0014] Fig. 8 illustrates preparation of compounds of Formula (I) and (II) where R<sub>6</sub> and R<sub>7</sub> are fluorine.
- [0015] Fig. 9 illustrates preparation of compounds of Formula (I) and (II) where R<sub>6</sub> is a hydroxyl or ether derivative.
- [0016] Fig. 10 illustrates preparation of compounds of Formula (I) and (II) where R<sub>8</sub> is alkyl.
- [0017] Fig. 11 illustrates preparation of compounds of Formula (I) and (II) where R<sub>8</sub> is an ester.
- [0018] Fig. 12 illustrates preparation of compounds of Formula (I) where R<sub>9</sub> is a benzyl derivative.
- [0019] Fig. 13 illustrates preparation of compounds of Formula (I) where R<sub>9</sub> is an amine derivative.
- [0020] Fig. 14 illustrates preparation of compounds of Formula (I) where R<sub>3</sub> an amine derivative.

## DETAILED DESCRIPTION

### Definitions

[0021] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this invention belongs. If a plurality of definitions for a term exist herein, those in this section prevail unless stated otherwise.

[0022] As used herein, and unless otherwise specified, the terms "about" and "approximately," when used in connection with a property with a numeric value or range of values indicate that the value or range of values may deviate to an extent deemed reasonable to one of ordinary skill in the art while still describing the particular property. Specifically, the terms "about" and "approximately," when used in this context, indicate that the numeric value or range of values may vary by 5%, 4%, 3%, 2%, 1%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2% or 0.1% of the recited value or range of values.

**[0023]** “Alkyl,” by itself or as part of another substituent, refers to a saturated or unsaturated, branched, straight-chain or cyclic monovalent hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. Typical alkyl groups include, but are not limited to, methyl; ethyl; propyls such as propan-1-yl, propan-2-yl, *etc.*; butyls such as butan-1-yl, butan-2-yl, 2-methyl-propan-1-yl, 2-methyl-propan-2-yl, *etc.*; and the like. In some embodiments, an alkyl group comprises from 1 to 20 carbon atoms (C<sub>1</sub>-C<sub>20</sub> alkyl). In other embodiments, an alkyl group comprises from 1 to 10 carbon atoms (C<sub>1</sub>-C<sub>10</sub> alkyl). In still other embodiments, an alkyl group comprises from 1 to 6 carbon atoms (C<sub>1</sub>-C<sub>6</sub> alkyl).

**[0024]** “Alkenyl,” by itself or as part of another substituent, refers to an unsaturated branched, straight-chain or cyclic alkyl radical having at least one carbon-carbon double bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkene. The group may be in either the *cis* or *trans* conformation about the double bond(s). Typical alkenyl groups include, but are not limited to, ethenyl; propenyls such as prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl (allyl), prop-2-en-2-yl, cycloprop-1-en-1-yl; cycloprop-2-en-1-yl; butenyls such as but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, *etc.*; and the like.

**[0025]** “Alkynyl,” by itself or as part of another substituent refers to an unsaturated branched, straight-chain or cyclic alkyl radical having at least one carbon-carbon triple bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkyne. Typical alkynyl groups include, but are not limited to, ethynyl; propynyls such as prop-1-yn-1-yl, prop-2-yn-1-yl, *etc.*; butynyls such as but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl, *etc.*; and the like.

**[0026]** “Aryl,” by itself or as part of another substituent, refers to a monovalent aromatic hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system, as defined herein. Typical aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene,

pleiadene, pyrene, pyranthrene, rubicene, triphenylene, trinaphthalene and the like. In some embodiments, an aryl group comprises from 6 to 20 carbon atoms (C<sub>6</sub>-C<sub>20</sub> aryl). In other embodiments, an aryl group comprises from 6 to 15 carbon atoms (C<sub>6</sub>-C<sub>15</sub> aryl). In still other embodiments, an aryl group comprises from 6 to 10 carbon atoms (C<sub>6</sub>-C<sub>10</sub> aryl).

**[0027]** “Arylalkyl,” by itself or as part of another substituent, refers to an acyclic alkyl group in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or *sp*<sup>3</sup> carbon atom, is replaced with an aryl group as, as defined herein. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 2-phenylethen-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, 2-naphthylethen-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. In some embodiments, an arylalkyl group is (C<sub>6</sub>-C<sub>30</sub>) arylalkyl, *e.g.*, the alkyl moiety of the arylalkyl group is (C<sub>1</sub>-C<sub>10</sub>) alkyl and the aryl moiety is (C<sub>6</sub>-C<sub>20</sub>) aryl. In other embodiments, an arylalkyl group is (C<sub>6</sub>-C<sub>20</sub>) arylalkyl, *e.g.*, the alkyl moiety of the arylalkyl group is (C<sub>1</sub>-C<sub>8</sub>) alkyl and the aryl moiety is (C<sub>6</sub>-C<sub>12</sub>) aryl. In still other embodiments, an arylalkyl group is (C<sub>6</sub>-C<sub>15</sub>) arylalkyl, *e.g.*, the alkyl moiety of the arylalkyl group is (C<sub>1</sub>-C<sub>5</sub>) alkyl and the aryl moiety is (C<sub>6</sub>-C<sub>10</sub>) aryl.

**[0028]** “Arylalkenyl,” by itself or as part of another substituent, refers to an acyclic alkenyl group in which one of the hydrogen atoms bonded to a carbon atom, is replaced with an aryl group as, as defined herein.

**[0029]** “Cycloalkyl,” by itself or as part of another substituent, refers to a saturated cyclic monovalent hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent cycloalkane. Typical cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl cycopentenyl; *etc.*; and the like. In some embodiments, a cycloalkyl group comprises from 3 to 20 carbon atoms (C<sub>1</sub>-C<sub>15</sub> alkyl). In other embodiments, a cycloalkyl group comprises from 3 to 10 carbon atoms (C<sub>1</sub>-C<sub>10</sub> alkyl). In still other embodiments, a cycloalkyl group comprises from 3 to 8 carbon atoms (C<sub>1</sub>-C<sub>8</sub> alkyl). The term ‘cyclic monovalent hydrocarbon radical’ also includes multicyclic hydrocarbon ring systems having a single radical and between 3 and 12 carbon atoms. Exemplary multicyclic cycloalkyl rings include, for example, norbornyl, pinyl, and adamantyl.

**[0030]** “Cycloalkenyl,” by itself or as part of another substituent, refers to an unsaturated cyclic monovalent hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent cycloalkene. Typical cycloalkenyl groups include, but are not

limited to, cyclopropene, cyclobutene cyclopentene; *etc.*; and the like. In some embodiments, a cycloalkenyl group comprises from 3 to 20 carbon atoms (C<sub>1</sub>-C<sub>20</sub> alkenyl). In other embodiments, a cycloalkenyl group comprises from 3 to 10 carbon atoms (C<sub>1</sub>-C<sub>10</sub> alkenyl). In still other embodiments, a cycloalkenyl group comprises from 3 to 8 carbon atoms (C<sub>1</sub>-C<sub>8</sub> alkenyl). The term ‘cyclic monovalent hydrocarbon radical’ also includes multicyclic hydrocarbon ring systems having a single radical and between 3 and 12 carbon atoms with an alkenyl group

**[0031]** “Cycloheteroalkyl,” by itself or as part of another substituent, refers to a cycloalkyl group as defined herein in which one or more one or more of the carbon atoms (and optionally any associated hydrogen atoms), are each, independently of one another, replaced with the same or different heteroatoms or heteroatomic groups as defined in “heteroalkyl” below.

**[0032]** “Cycloheteroalkenyl,” by itself or as part of another substituent, refers to a cycloalkenyl group as defined herein in which one or more one or more of the carbon atoms (and optionally any associated hydrogen atoms), are each, independently of one another, replaced with the same or different heteroatoms or heteroatomic groups as defined in “heteroalkenyl” below.

**[0033]** “Compounds,” refers to compounds encompassed by structural formulae disclosed herein and includes any specific compounds within these formulae whose structure is disclosed herein. Compounds may be identified either by their chemical structure and/or chemical name. The chemical structure is determinative of the identity of the compound. The compounds described herein may contain one or more chiral centers and/or double bonds and therefore, may exist as stereoisomers, such as double-bond isomers (i.e., geometric isomers), enantiomers or diastereomers. Accordingly, the chemical structures depicted herein encompass the stereoisomerically pure form depicted in the structure (e.g., geometrically pure, enantiomerically pure or diastereomerically pure). The chemical structures depicted herein also encompass the enantiomeric and stereoisomeric derivatives of the compound depicted. Enantiomeric and stereoisomeric mixtures can be resolved into their component enantiomers or stereoisomers using separation techniques or chiral synthesis techniques well known to the skilled artisan. The compounds may also exist in several tautomeric forms including the enol form, the keto form and mixtures thereof. Accordingly, the chemical structures depicted herein encompass all possible tautomeric forms of the illustrated compounds. The compounds

described also include isotopically labeled compounds where one or more atoms have an atomic mass different from the atomic mass conventionally found in nature. Examples of isotopes that may be incorporated into the compounds disclosed herein include, but are not limited to,  $^2\text{H}$ ,  $^3\text{H}$ ,  $^{11}\text{C}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{18}\text{O}$ ,  $^{17}\text{O}$ , etc. Compounds may exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, compounds may be hydrated or solvated. Certain compounds may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated herein and are intended to be within the scope of the present disclosure. Further, it should be understood, when partial structures of the compounds are illustrated, that brackets indicate the point of attachment of the partial structure to the rest of the molecule.

**[0034]** “Halo,” by itself or as part of another substituent refers to a radical -F, -Cl, -Br or -I.

**[0035]** “Heteroalkyl,” refer to an alkyl group, in which one or more of the carbon atoms (and optionally any associated hydrogen atoms), are each, independently of one another, replaced with the same or different heteroatoms or heteroatomic groups. Typical heteroatoms or heteroatomic groups which can replace the carbon atoms include, but are not limited to, -O-, -S-, -N-, -Si-, -NH-, -S(O)-, -S(O)<sub>2</sub>-, -S(O)NH-, -S(O)<sub>2</sub>NH- and the like and combinations thereof. The heteroatoms or heteroatomic groups may be placed at any interior position of the alkyl group. Typical heteroatomic groups which can be included in these groups include, but are not limited to, -O-, -S-, -O-O-, -S-S-, -O-S-, -NR<sup>501</sup>R<sup>502</sup>, =N-N=, -N=N-, -N=N-NR<sup>503</sup>R<sup>404</sup>, -PR<sup>505</sup>-, -P(O)<sub>2</sub>-, -POR<sup>506</sup>-, -O-P(O)<sub>2</sub>-, -SO-, -SO<sub>2</sub>-, -SnR<sup>507</sup>R<sup>508</sup> and the like, where R<sup>501</sup>, R<sup>502</sup>, R<sup>503</sup>, R<sup>504</sup>, R<sup>505</sup>, R<sup>506</sup>, R<sup>507</sup> and R<sup>508</sup> are independently hydrogen, alkyl, aryl, substituted aryl, heteroalkyl, heteroaryl or substituted heteroaryl.

**[0036]** “Heteroalkenyl,” refers to an alkenyl group in which one or more of the carbon atoms (and optionally any associated hydrogen atoms), are each, independently of one another, replaced with the same or different heteroatoms or heteroatomic groups. Typical heteroatoms or heteroatomic groups which can replace the carbon atoms include, but are not limited to, -O-, -S-, -N-, -Si-, -NH-, -S(O)-, -S(O)<sub>2</sub>-, -S(O)NH-, -S(O)<sub>2</sub>NH- and the like and combinations thereof. The heteroatoms or heteroatomic groups may be placed at any interior position of the alkenyl group. Typical heteroatomic groups which can be included in these groups include, but are not limited to, -O-, -S-, -O-O-, -S-S-, -O-S-, -NR<sup>501</sup>R<sup>502</sup>,

=N-N=, -N=N-, -N=N-NR<sup>503</sup>R<sup>404</sup>, -PR<sup>505</sup>-, -P(O)<sub>2</sub>-, -POR<sup>506</sup>-, -O-P(O)<sub>2</sub>-, -SO-, -SO<sub>2</sub>-, -SnR<sup>507</sup>R<sup>508</sup> and the like, where R<sup>501</sup>, R<sup>502</sup>, R<sup>503</sup>, R<sup>504</sup>, R<sup>505</sup>, R<sup>506</sup>, R<sup>507</sup> and R<sup>508</sup> are independently hydrogen, alkyl, aryl, substituted aryl, heteroalkyl, heteroaryl or substituted heteroaryl.

**[0037]** “Heteroalkynyl,” refers to an alkynyl group in which one or more of the carbon atoms (and optionally any associated hydrogen atoms), are each, independently of one another, replaced with the same or different heteroatoms or heteroatomic groups. Typical heteroatoms or heteroatomic groups which can replace the carbon atoms include, but are not limited to, -O-, -S-, -N-, -Si-, -NH-, -S(O)-, -S(O)<sub>2</sub>-, -S(O)NH-, -S(O)<sub>2</sub>NH- and the like and combinations thereof. The heteroatoms or heteroatomic groups may be placed at any interior position of the alkynyl group. Typical heteroatomic groups which can be included in these groups include, but are not limited to, -O-, -S-, -O-O-, -S-S-, -O-S-, -NR<sup>501</sup>R<sup>502</sup>, =N-N=, -N=N-, -N=N-NR<sup>503</sup>R<sup>404</sup>, -PR<sup>505</sup>-, -P(O)<sub>2</sub>-, -POR<sup>506</sup>-, -O-P(O)<sub>2</sub>-, -SO-, -SO<sub>2</sub>-, -SnR<sup>507</sup>R<sup>508</sup> and the like, where R<sup>501</sup>, R<sup>502</sup>, R<sup>503</sup>, R<sup>504</sup>, R<sup>505</sup>, R<sup>506</sup>, R<sup>507</sup> and R<sup>508</sup> are independently hydrogen, alkyl, aryl, substituted aryl, heteroalkyl, heteroaryl or substituted heteroaryl.

**[0038]** “Heteroaryl,” by itself or as part of another substituent, refers to a monovalent heteroaromatic radical derived by the removal of one hydrogen atom from a single atom of a parent heteroaromatic ring systems, as defined herein. Typical heteroaryl groups include, but are not limited to, groups derived from acridine,  $\beta$ -carboline, chromane, chromene, cinnoline, furan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene, and the like. In some embodiments, the heteroaryl group comprises from 5 to 20 ring atoms (5-20 membered heteroaryl). In other embodiments, the heteroaryl group comprises from 5 to 10 ring atoms (5-10 membered heteroaryl). Exemplary heteroaryl groups include those derived from furan, thiophene, pyrrole, benzothiophene, benzofuran, benzimidazole, indole, pyridine, pyrazole, quinoline, imidazole, oxazole, isoxazole and pyrazine.

**[0039]** “Heteroarylalkyl,” by itself or as part of another substituent refers to an acyclic alkyl group in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or *sp*<sup>3</sup> carbon atom, is replaced with a heteroaryl group. In some embodiments, the heteroarylalkyl

group is a 6-21 membered heteroarylalkyl, *e.g.*, the alkyl moiety of the heteroarylalkyl is (C<sub>1</sub>-C<sub>6</sub>) alkyl and the heteroaryl moiety is a 5-15-membered heteroaryl. In other embodiments, the heteroarylalkyl is a 6-13 membered heteroarylalkyl, *e.g.*, the alkyl moiety is (C<sub>1</sub>-C<sub>3</sub>) alkyl and the heteroaryl moiety is a 5-10 membered heteroaryl.

**[0040]** “Heteroarylalkenyl,” by itself or as part of another substituent refers to an acyclic alkenyl group in which one of the hydrogen atoms bonded to a carbon atom, is replaced with a heteroaryl group.

**[0041]** “Heteroarylalkynyl,” by itself or as part of another substituent refers to an acyclic alkynyl group in which one of the hydrogen atoms bonded to a carbon atom, is replaced with a heteroaryl group.

**[0042]** “Hydrates,” refers to incorporation of water into to the crystal lattice of a compound described herein, in stoichiometric proportions, resulting in the formation of an adduct. Methods of making hydrates include, but are not limited to, storage in an atmosphere containing water vapor, dosage forms that include water, or routine pharmaceutical processing steps such as, for example, crystallization (*i.e.*, from water or mixed aqueous solvents), lyophilization, wet granulation, aqueous film coating, or spray drying. Hydrates may also be formed, under certain circumstances, from crystalline solvates upon exposure to water vapor, or upon suspension of the anhydrous material in water. Hydrates may also crystallize in more than one form resulting in hydrate polymorphism. See *e.g.*, (Guillory, K., Chapter 5, pp. 202205 in *Polymorphism in Pharmaceutical Solids*, (Brittain, H. ed.), Marcel Dekker, Inc., New York, NY, 1999). The above methods for preparing hydrates are well within the ambit of those of skill in the art, are completely conventional and do not require any experimentation beyond what is typical in the art. Hydrates may be characterized and/or analyzed by methods well known to those of skill in the art such as, for example, single crystal X-ray diffraction, X-ray powder diffraction, polarizing optical microscopy, thermal microscopy, thermogravimetry, differential thermal analysis, differential scanning calorimetry, IR spectroscopy, Raman spectroscopy and NMR spectroscopy. (Brittain, H., Chapter 6, pp. 205208 in *Polymorphism in Pharmaceutical Solids*, (Brittain, H. ed.), Marcel Dekker, Inc. New York, 1999). In addition, many commercial companies routinely offer services that include preparation and/or characterization of hydrates such as, for example, HOLODIAG, Pharmaparc II, Voie de l'Innovation, 27 100 Val de Reuil, France (<http://www.holodiag.com>).

**[0043]** “Parent Aromatic Ring System,” refers to an unsaturated cyclic or polycyclic ring system having a conjugated  $\pi$  electron system. Specifically included within the definition of “parent aromatic ring system” are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, such as, for example, fluorene, indane, indene, phenalene, *etc.* Typical parent aromatic ring systems include, but are not limited to, aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, trinaphthalene and the like.

**[0044]** “Parent Heteroaromatic Ring System,” refers to a parent aromatic ring system in which one or more carbon atoms (and optionally any associated hydrogen atoms) are each independently replaced with the same or different heteroatom. Typical heteroatoms to replace the carbon atoms include, but are not limited to, N, P, O, S, Si, *etc.* Specifically included within the definition of “parent heteroaromatic ring system” are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, such as, for example, benzodioxan, benzofuran, chromane, chromene, indole, indoline, xanthene, *etc.* Typical parent heteroaromatic ring systems include, but are not limited to, arindole, carbazole,  $\beta$ -carboline, chromane, chromene, cinnoline, furan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene and the like.

**[0045]** “Pharmaceutically acceptable salt,” refers to a salt of a compound, which possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid,

methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like.

**[0046]** “Preventing,” or “prevention,” refers to a reduction in risk of acquiring a disease or disorder (*i.e.*, causing at least one of the clinical symptoms of the disease not to develop in a patient that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease). The application of a therapeutic for preventing or prevention of a disease or disorder is known as ‘prophylaxis.’ In some embodiments, the compounds provided herein provide superior prophylaxis because of lower long term side effects over long time periods.

**[0047]** “Protecting group,” refers to a grouping of atoms that when attached to a reactive functional group in a molecule masks, reduces or prevents reactivity of the functional group during chemical synthesis. Examples of protecting groups can be found in Green *et al.*, “Protective Groups in Organic Chemistry”, (Wiley, 2<sup>nd</sup> ed. 1991) and Harrison *et al.*, “Compendium of Synthetic Organic Methods”, Vols. 1-8 (John Wiley and Sons, 1971-1996). Representative amino protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl (“CBZ”), *tert*-butoxycarbonyl (“Boc”), trimethylsilyl (“TMS”), 2-trimethylsilyl-ethanesulfonyl (“SES”), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl (“Fmoc”), nitro-veratryloxycarbonyl (“NVOC”) and the like. Representative hydroxy protecting groups include, but are not limited to, those where the hydroxy group is either acylated or alkylated such as benzyl, and trityl ethers as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers and allyl ethers.

**[0048]** “Solvates,” refers to incorporation of solvents into to the crystal lattice of a compound described herein, in stoichiometric proportions, resulting in the formation of an adduct. Methods of making solvates include, but are not limited to, storage in an atmosphere

containing a solvent, dosage forms that include the solvent, or routine pharmaceutical processing steps such as, for example, crystallization (*i.e.*, from solvent or mixed solvents) vapor diffusion, *etc.* Solvates may also be formed, under certain circumstances, from other crystalline solvates or hydrates upon exposure to the solvent or upon suspension material in solvent. Solvates may crystallize in more than one form resulting in solvate polymorphism. See *e.g.*, (Guillory, K., Chapter 5, pp. 205208 in *Polymorphism in Pharmaceutical Solids*, (Brittain, H. ed.), Marcel Dekker, Inc., New York, NY, 1999)). The above methods for preparing solvates are well within the ambit of those of skill in the art, are completely conventional do not require any experimentation beyond what is typical in the art. Solvates may be characterized and/or analyzed by methods well known to those of skill in the art such as, for example, single crystal X-ray diffraction, X-ray powder diffraction, polarizing optical microscopy, thermal microscopy, thermogravimetry, differential thermal analysis, differential scanning calorimetry, IR spectroscopy, Raman spectroscopy and NMR spectroscopy. (Brittain, H., Chapter 6, pp. 205208 in *Polymorphism in Pharmaceutical Solids*, (Brittain, H. ed.), Marcel Dekker, Inc. New York, 1999). In addition, many commercial companies routine offer services that include preparation and/or characterization of solvates such as, for example, HOLODIAG, Pharmaparc II, Voie de l'Innovation, 27 100 Val de Reuil, France (<http://www.holodiag.com>).

**[0049]** “Substituted,” when used to modify a specified group or radical, means that one or more hydrogen atoms of the specified group or radical are each, independently of one another, replaced with the same or different substituent(s). Substituent groups useful for substituting saturated carbon atoms in the specified group or radical include  $-R^a$ , halo,  $-O^{\cdot}$ ,  $=O$ ,  $-OR^b$ ,  $-SR^b$ ,  $-S^{\cdot}$ ,  $=S$ ,  $-NR^cR^c$ ,  $=NR^b$ ,  $=N-OR^b$ , trihalomethyl,  $-CF_3$ ,  $-CN$ ,  $-OCN$ ,  $-SCN$ ,  $-NO$ ,  $-NO_2$ ,  $-N-OR^b$ ,  $-N-NR^cR^c$ ,  $-NR^bS(O)_2R^b$ ,  $=N_2$ ,  $-N_3$ ,  $-S(O)_2R^b$ ,  $-S(O)_2NR^bR^b$ ,  $-S(O)_2O^{\cdot}$ ,  $-S(O)_2OR^b$ ,  $-OS(O)_2R^b$ ,  $-OS(O)_2O^{\cdot}$ ,  $-OS(O)_2OR^b$ ,  $-OS(O)_2NR^cR^c$ ,  $-P(O)(O^{\cdot})_2$ ,  $-P(O)(OR^b)(O^{\cdot})$ ,  $-P(O)(OR^b)(OR^b)$ ,  $-C(O)R^b$ ,  $-C(O)NR^b-OR^b$ ,  $-C(S)R^b$ ,  $-C(NR^b)R^b$ ,  $-C(O)O^{\cdot}$ ,  $-C(O)OR^b$ ,  $-C(S)OR^b$ ,  $-C(O)NR^cR^c$ ,  $-C(NR^b)NR^cR^c$ ,  $-OC(O)R^b$ ,  $-OC(S)R^b$ ,  $-OC(O)O^{\cdot}$ ,  $-OC(O)OR^b$ ,  $-OC(O)NR^cR^c$ ,  $-OC(NCN)NR^cR^c$ ,  $-OC(S)OR^b$ ,  $-NR^bC(O)R^b$ ,  $-NR^bC(S)R^b$ ,  $-NR^bC(O)O^{\cdot}$ ,  $-NR^bC(O)OR^b$ ,  $-NR^bC(NCN)OR^b$ ,  $-NR^bS(O)_2NR^cR^c$ ,  $-NR^bC(S)OR^b$ ,  $-NR^bC(O)NR^cR^c$ ,  $-NR^bC(S)NR^cR^c$ ,  $-NR^bC(S)NR^bC(O)R^a$ ,  $-NR^bS(O)_2OR^b$ ,  $-NR^bS(O)_2R^b$ ,  $-NR^bC(NCN)NR^cR^c$ ,  $-NR^bC(NR^b)R^b$  and  $-NR^bC(NR^b)NR^cR^c$ , where each  $R^a$  is independently, substituted alkyl, aryl, substituted aryl, heteroalkyl, substituted heteroalkyl, heteroaryl or substituted

heteroaryl; each  $R^b$  is independently hydrogen, alkyl, heteroalkyl, substituted heteroalkyl, arylalkyl, substituted arylalkyl, heteroarylalkyl or substituted heteroarylalkyl; and each  $R^c$  is independently  $R^b$  or alternatively, the two  $R^c$ s taken together with the nitrogen atom to which they are bonded form a 4-, 5-, 6- or 7 membered- cycloheteroalkyl, substituted cycloheteroalkyl or a cycloheteroalkyl fused with an aryl group which may optionally include from 1 to 4 of the same or different additional heteroatoms selected from the group consisting of O, N and S. As specific examples,  $-NR^cR^c$  is meant to include  $-NH_2$ ,  $-NH$ -alkyl, N-pyrrolidinyl and N-morpholinyl. In other embodiments, substituent groups useful for substituting saturated carbon atoms in the specified group or radical include  $R^a$ , halo,  $-OR^b$ ,  $-NR^cR^c$ , trihalomethyl,  $-CN$ ,  $-NR^bS(O)_2R^b$ ,  $-C(O)R^b$ ,  $-C(O)NR^b-OR^b$ ,  $-C(O)OR^b$ ,  $-C(O)NR^cR^c$ ,  $-OC(O)R^b$ ,  $-OC(O)OR^b$ ,  $-OS(O)_2NR^cNR^c$ ,  $-OC(O)NR^cR^c$ , and  $-NR^bC(O)OR^b$ , where each  $R^a$  is independently alkyl, aryl, heteroaryl, each  $R^b$  is independently hydrogen,  $R^a$ , heteroalkyl, arylalkyl, heteroarylalkyl; and each  $R^c$  is independently  $R^b$  or alternatively, the two  $R^c$ s taken together with the nitrogen atom to which they are bonded form a 4-, 5-, 6 or -7 membered- cycloheteroalkyl ring.

**[0050]** Substituent groups useful for substituting unsaturated carbon atoms in the specified group or radical include  $-R^a$ , halo,  $-O^-$ ,  $-OR^b$ ,  $-SR^b$ ,  $-S^-$ ,  $-NR^cR^c$ , trihalomethyl,  $-CF_3$ ,  $-CN$ ,  $-OCN$ ,  $-SCN$ ,  $-NO$ ,  $-NO_2$ ,  $-N_3$ ,  $-S(O)_2O^-$ ,  $-S(O)_2OR^b$ ,  $-OS(O)_2R^b$ ,  $-OS(O)_2OR^b$ ,  $-OS(O)_2O^-$ ,  $-P(O)(O^-)_2$ ,  $-P(O)(OR^b)(O^-)$ ,  $-P(O)(OR^b)(OR^b)$ ,  $-C(O)R^b$ ,  $-C(S)R^b$ ,  $-C(NR^b)R^b$ ,  $-C(O)O^-$ ,  $-C(O)OR^b$ ,  $-C(S)OR^b$ ,  $-C(O)NR^cR^c$ ,  $-C(NR^b)NR^cR^c$ ,  $-OC(O)R^b$ ,  $-OC(S)R^b$ ,  $-OC(O)O^-$ ,  $-OC(O)OR^b$ ,  $-OC(S)OR^b$ ,  $-OC(O)NR^cR^c$ ,  $-OS(O)_2NR^cNR^c$ ,  $-NR^bC(O)R^b$ ,  $-NR^bC(S)R^b$ ,  $-NR^bC(O)O^-$ ,  $-NR^bC(O)OR^b$ ,  $-NR^bS(O)_2OR^a$ ,  $-NR^bS(O)_2R^a$ ,  $-NR^bC(S)OR^b$ ,  $-NR^bC(O)NR^cR^c$ ,  $-NR^bC(NR^b)R^b$  and  $-NR^bC(NR^b)NR^cR^c$ , where  $R^a$ ,  $R^b$  and  $R^c$  are as previously defined. In other embodiments, substituent groups useful for substituting unsaturated carbon atoms in the specified group or radical include  $-R^a$ , halo,  $-OR^b$ ,  $-SR^b$ ,  $-NR^cR^c$ , trihalomethyl,  $-CN$ ,  $-S(O)_2OR^b$ ,  $-C(O)R^b$ ,  $-C(O)OR^b$ ,  $-C(O)NR^cR^c$ ,  $-OC(O)R^b$ ,  $-OC(O)OR^b$ ,  $-OS(O)_2NR^cNR^c$ ,  $-NR^bC(O)R^b$  and  $-NR^bC(O)OR^b$ , where  $R^a$ ,  $R^b$  and  $R^c$  are as previously defined.

**[0051]** Substituent groups useful for substituting nitrogen atoms in heteroalkyl and cycloheteroalkyl groups include, but are not limited to,  $-R^a$ ,  $-O^-$ ,  $-OR^b$ ,  $-SR^b$ ,  $-S^-$ ,  $-NR^cR^c$ , trihalomethyl,  $-CF_3$ ,  $-CN$ ,  $-NO$ ,  $-NO_2$ ,  $-S(O)_2R^b$ ,  $-S(O)_2O^-$ ,  $-S(O)_2OR^b$ ,  $-OS(O)_2R^b$ ,  $-OS(O)_2O^-$ ,  $-OS(O)_2OR^b$ ,  $-P(O)(O^-)_2$ ,  $-P(O)(OR^b)(O^-)$ ,  $-P(O)(OR^b)(OR^b)$ ,  $-C(O)R^b$ ,  $-C(S)R^b$ ,  $-C(NR^b)R^b$ ,  $-C(O)$

)OR<sup>b</sup>, -C(S)OR<sup>b</sup>, -C(O)NR<sup>c</sup>R<sup>c</sup>, -C(NR<sup>b</sup>)NR<sup>c</sup>R<sup>c</sup>, -OC(O)R<sup>b</sup>, -OC(S)R<sup>b</sup>, -OC(O)OR<sup>b</sup>, -OC(S)OR<sup>b</sup>, -NR<sup>b</sup>C(O)R<sup>b</sup>, -NR<sup>b</sup>C(S)R<sup>b</sup>, -NR<sup>b</sup>C(O)OR<sup>b</sup>, -NR<sup>b</sup>C(S)OR<sup>b</sup>, -NR<sup>b</sup>C(O)NR<sup>c</sup>R<sup>c</sup>, -NR<sup>b</sup>C(NR<sup>b</sup>)R<sup>b</sup> and -NR<sup>b</sup>C(NR<sup>b</sup>)NR<sup>c</sup>R<sup>c</sup>, where R<sup>a</sup>, R<sup>b</sup> and R<sup>c</sup> are as previously defined. In some embodiments, substituent groups useful for substituting nitrogen atoms in heteroalkyl and cycloheteroalkyl groups include, R<sup>a</sup>, halo, -OR<sup>b</sup>, -NR<sup>c</sup>R<sup>c</sup>, trihalomethyl, -CN, -S(O)<sub>2</sub>OR<sup>b</sup>, -OS(O)<sub>2</sub>R<sup>b</sup>, -OS(O)<sub>2</sub>OR<sup>b</sup>, -C(O)R<sup>b</sup>, -C(NR<sup>b</sup>)R<sup>b</sup>, -C(O)OR<sup>b</sup>, -C(O)NR<sup>c</sup>R<sup>c</sup>, -OC(O)R<sup>b</sup>, -OC(O)OR<sup>b</sup>, -OS(O)<sub>2</sub>NR<sup>c</sup>NR<sup>c</sup>, -NR<sup>b</sup>C(O)R<sup>b</sup> and -NR<sup>b</sup>C(O)OR<sup>b</sup>, where R<sup>a</sup>, R<sup>b</sup> and R<sup>c</sup> are as previously defined.

**[0052]** Substituent groups from the above lists useful for substituting other specified groups or atoms will be apparent to those of skill in the art.

**[0053]** The substituents used to substitute a specified group can be further substituted, typically with one or more of the same or different groups selected from the various groups specified above.

**[0054]** “Subject,” “individual,” or “patient,” is used interchangeably herein and refers to a vertebrate, preferably a mammal. Mammals include, but are not limited to, murines, rodents, simians, humans, farm animals, sport animals and pets.

**[0055]** “Treating,” or “treatment,” of any disease or disorder refers, in some embodiments, to ameliorating the disease or disorder (*i.e.*, arresting or reducing the development of the disease or at least one of the clinical symptoms thereof,). Treatment may also be considered to include preemptive or prophylactic administration to ameliorate, arrest or prevent the development of the disease or at least one of the clinical symptoms. In a further feature the treatment rendered has lower potential for long-term side effects over multiple years. In other embodiments “treating” or “treatment” refers to ameliorating at least one physical parameter, which may not be discernible by the patient. In yet other embodiments, “treating” or “treatment” refers to inhibiting the disease or disorder, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter) or both. In yet other embodiments, “treating” or “treatment” refers to delaying the onset of the disease or disorder.

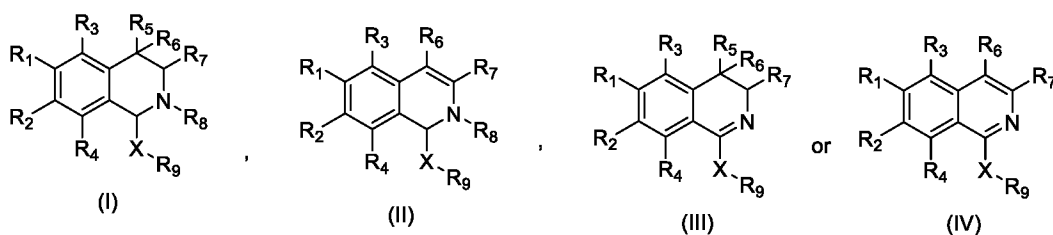
**[0056]** “Therapeutically effective amount,” means the amount of a compound that, when administered to a patient for treating a disease, is sufficient to treat the disease. The “therapeutically effective amount” will vary depending on the compound, the disease and its

severity and the age, weight, adsorption, distribution, metabolism and excretion *etc.*, of the patient to be treated.

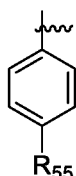
[0057] “Vehicle,” refers to a diluent, excipient or carrier with which a compound is administered to a subject. In some embodiments, the vehicle is pharmaceutically acceptable.

### Compounds

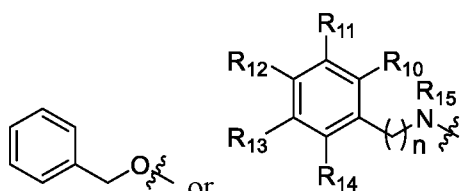
[0058] Provided herein are compounds structural Formula (I), (II), (III) or (IV):



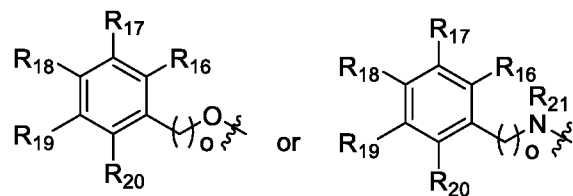
or a solvate, hydrate or salt thereof wherein: X is absent, -CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>NR<sub>56</sub>R<sub>57</sub>, -C=C-, cycloheteroalkyl, cycloheteroalkenyl, substituted cycloheteroalkyl, substituted



cycloheteroalkyl or R<sub>55</sub>; R<sub>1</sub> is hydrogen, -OR<sub>22</sub>, alkyl, alkenyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, -NR<sub>43</sub>R<sub>44</sub>, -OPh, where Ph is optionally

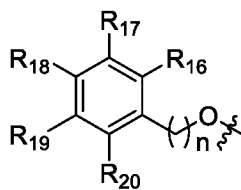


substituted phenyl, or R<sub>55</sub>; R<sub>2</sub> is hydrogen, -OR<sub>23</sub>, -CF<sub>3</sub>, alkyl, alkenyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, heteroaryl, substituted heteroaryl, -NR<sub>45</sub>R<sub>46</sub>,



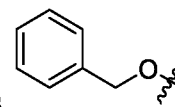
; or R<sub>1</sub> and R<sub>2</sub> along with the carbon atoms to which they are attached form an aryl, substituted aryl, heteroaryl or substituted heteroaryl ring; n is 0, 1, 2 or 3; o is 0, 1, 2 or 3; R<sub>3</sub> and R<sub>4</sub> are independently hydrogen, halo, alkyl, alkenyl, -OR<sub>24</sub> or -NR<sub>25</sub>R<sub>26</sub>; R<sub>5</sub> is hydrogen, fluoro, alkyl or alkenyl; R<sub>6</sub> is hydrogen, fluoro, alkyl, alkenyl, -OR<sub>27</sub> or

-NR<sub>28</sub>R<sub>29</sub>; R<sub>7</sub> is hydrogen, alkyl, alkenyl, -CO<sub>2</sub>R<sub>30</sub>, -CONR<sub>31</sub>R<sub>32</sub>, -CH<sub>2</sub>NR<sub>33</sub>R<sub>34</sub>, -CH<sub>2</sub>R<sub>42</sub> or -CH<sub>2</sub>OR<sub>35</sub>; R<sub>8</sub> is hydrogen, -SO<sub>2</sub>R<sub>47</sub>, -OR<sub>48</sub>, -SO<sub>2</sub>NR<sub>69</sub>R<sub>70</sub>, -CONR<sub>71</sub>R<sub>72</sub>, -COR<sub>73</sub>, -CO<sub>2</sub>R<sub>74</sub>, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl; R<sub>9</sub> is aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloheteroalkyl, cycloheteroalkenyl, substituted cycloheteroalkyl or substituted cycloheteroalkenyl; R<sub>10</sub>-R<sub>14</sub> and R<sub>16</sub>-R<sub>20</sub> are independently hydrogen, alkyl, alkenyl, halo, -CH<sub>2</sub>OR<sub>36</sub>, -CO<sub>2</sub>R<sub>37</sub>, -CONR<sub>38</sub>R<sub>39</sub> - NR<sub>40</sub>R<sub>41</sub>, cycloheteroalkyl, cycloheteroalkenyl, substituted cycloheteroalkyl or substituted cycloheteroalkenyl; R<sub>15</sub> and R<sub>21</sub> are independently hydrogen, alkyl or alkenyl; R<sub>22</sub> and R<sub>23</sub> are independently alkyl, alkenyl, halo substituted alkyl, substituted alkenyl, heteroaryl or substituted heteroaryl; R<sub>24</sub>, R<sub>27</sub>, R<sub>35</sub> and R<sub>36</sub> are independently alkyl, alkenyl, halo substituted alkyl or halo substituted alkenyl; R<sub>28</sub>, R<sub>29</sub>, R<sub>30</sub>-R<sub>33</sub>, R<sub>38</sub>-R<sub>41</sub>, R<sub>63</sub>-R<sub>74</sub>, R<sub>75</sub>, R<sub>77</sub> and R<sub>79</sub>-R<sub>83</sub> are independently hydrogen, alkyl or alkenyl; R<sub>25</sub> and R<sub>26</sub> are independently hydrogen, alkyl, alkenyl or together with the nitrogen atom to which they are attached form an aryl or substituted aryl group; R<sub>34</sub> is hydrogen, -SO<sub>2</sub>R<sub>63</sub>, -SO<sub>2</sub>NR<sub>64</sub>R<sub>65</sub>, -CONR<sub>66</sub>R<sub>67</sub> or -COR<sub>68</sub>; R<sub>76</sub> and R<sub>78</sub> are independently hydrogen, -SO<sub>2</sub>R<sub>79</sub>, -SO<sub>2</sub>NR<sub>80</sub>R<sub>81</sub>, -CONR<sub>82</sub>R<sub>83</sub> or -COR<sub>84</sub>; R<sub>42</sub> is cycloheteroalkenyl, substituted cycloheteroalkyl or substituted cycloheteroalkenyl; R<sub>43</sub>-R<sub>46</sub> are independently hydrogen, alkyl, alkenyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl; R<sub>47</sub> is alkyl, alkenyl, aryl or heteroaryl; R<sub>48</sub> is hydrogen, alkyl, alkenyl, substituted alkyl, substituted alkenyl, or aryl; R<sub>55</sub> is heteroarylalkyl, substituted heteroarylalkyl, heteroarylalkenyl, substituted heteroarylalkenyl, -NR<sub>75</sub>R<sub>76</sub> or -CH<sub>2</sub>R<sub>77</sub>R<sub>78</sub>; R<sub>56</sub> is hydrogen, alkyl or alkenyl; R<sub>57</sub> is substituted aryl, heteroaryl or substituted heteroaryl; provided that when R<sub>1</sub> is hydrogen or -OR<sub>22</sub>, R<sub>22</sub> is alkyl and X is -C=C-



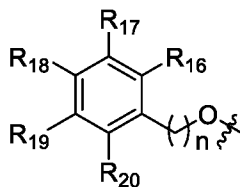
, that R<sub>2</sub> is not hydrogen, -OR<sub>23</sub>, -CF<sub>3</sub> or

where R<sub>23</sub> is alkyl, n is 1 and R<sub>16</sub>-



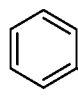
R<sub>20</sub> are hydrogen in the compound of Formula (I); provided that when R<sub>1</sub> is that at least one of R<sub>3</sub>-R<sub>7</sub> are not hydrogen in the compound of Formula (I) when X is -C=C-, or if each of R<sub>3</sub>-R<sub>7</sub> are hydrogen that R<sub>8</sub> is not hydrogen, -CONR<sub>71</sub>R<sub>72</sub>, -COR<sub>73</sub> or -CO<sub>2</sub>R<sub>74</sub> in the compound of Formula (I) when X is -C=C-; and provided that both R<sub>1</sub> and R<sub>2</sub> are not both alkyl.

[0059] In some embodiments, when  $R_1$  is hydrogen or  $-OR_{22}$  and  $R_{22}$  is alkyl that  $R_2$  is



not hydrogen,  $-OR_{23}$ ,  $-CF_3$  or

where  $R_{23}$  is alkyl or  $n$  is 1 and  $R_{16}$ - $R_{20}$  are

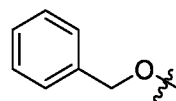


hydrogen; when  $R_1$  is

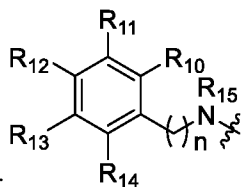
that at least one of  $R_3$ - $R_8$  are not hydrogen in the compounds of Formulae (II)-(IV) and both  $R_1$  and  $R_2$  are not both alkyl.

[0060]

In some embodiments,  $R_1$  is hydrogen,  $-OR_{22}$ ,



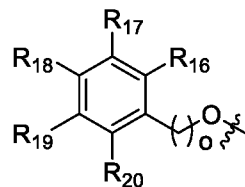
, arylalkyl,



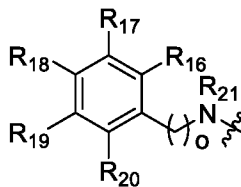
substituted arylalkyl or

. In other embodiments,  $R_2$  is hydrogen,  $-OR_{23}$ ,  $-CF_3$ ,

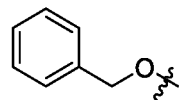
arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl,



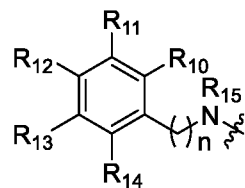
or



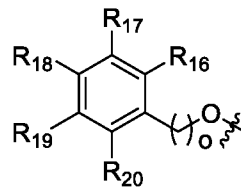
. In still other embodiments,  $R_1$  is hydrogen,  $-OR_{22}$ ,



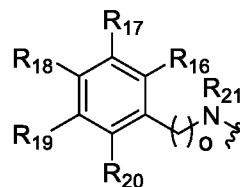
, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl,



and  $R_2$  is hydrogen,  $-OR_{23}$ ,  $-CF_3$ , arylalkyl, substituted arylalkyl, arylalkenyl,



or



substituted arylalkenyl,

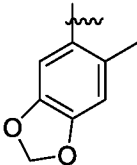
. In still other embodiments,

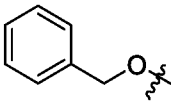
R<sub>1</sub> and R<sub>2</sub> along with the carbon atoms to which they are attached form an aryl, substituted aryl, heteroaryl or substituted heteroaryl ring.

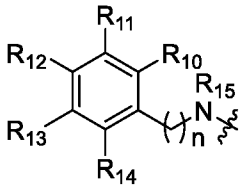
**[0061]** In some embodiments, R<sub>3</sub> and R<sub>4</sub> are hydrogen. In other embodiments, R<sub>3</sub>, R<sub>4</sub> and R<sub>8</sub> are hydrogen. In still other embodiments, R<sub>5</sub>-R<sub>7</sub> are hydrogen. In still other embodiments, R<sub>5</sub>-R<sub>8</sub> are hydrogen. In still other embodiments, R<sub>3</sub>-R<sub>8</sub> are hydrogen.

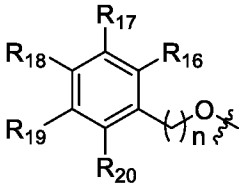
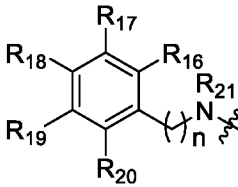
**[0062]** In some embodiments, R<sub>22</sub> and R<sub>23</sub> are pyridyl or substituted pyridyl.

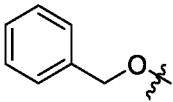
**[0063]** In some embodiments, R<sub>9</sub> is phenyl, substituted phenyl, imidazopyridine, substituted imidazopyridine, imidazopyrimidine, substituted imidazopyrimidine, imidazopyrazine, substituted imidazopyrazine, imidazopyridazine, substituted imidazopyridazine, indole, substituted indole, azaindole, substituted azaindole, pyrrolopyrazine, substituted pyrrolopyrazine, benzofuran, substituted benzofuran, benzothiophene, substituted benzothiophene, furopyrimidine, substituted furopyrimidine, thienopyrimidine, substituted thienopyrimidine, pyrazolopyrindine, substituted pyrazolopyrindine, pyrazolopyrimidine, substituted pyrazolopyrimidine, pyrazolopyrazine, substituted pyrazolopyrazine,

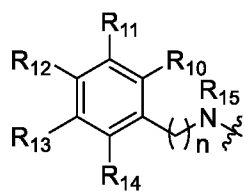
pyrazolopyradazine, substituted pyrazolopyradazine or . In some of the above

embodiments, R<sub>1</sub> is hydrogen, -OR<sub>22</sub>, , arylalkyl, substituted arylalkyl, arylalkenyl,

substituted arylalkenyl . In still other of the above embodiments, R<sub>2</sub> is hydrogen, -OR<sub>23</sub>, -CF<sub>3</sub>, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl,

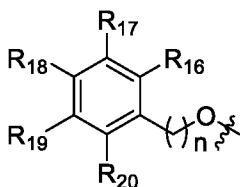
 or . In still other of the above embodiments, R<sub>1</sub> is

hydrogen, -OR<sub>22</sub>, , arylalkyl, substituted arylalkyl, arylalkenyl, substituted

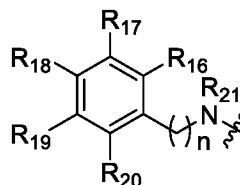


arylalkenyl,

and R<sub>2</sub> is hydrogen, -OR<sub>23</sub>, -CF<sub>3</sub>, arylalkyl, substituted arylalkyl,



or

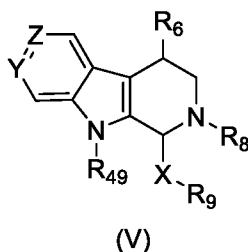


arylalkenyl, substituted arylalkenyl,

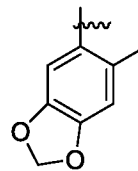
. In still other of

the above embodiments, R<sub>1</sub> and R<sub>2</sub> along with the carbon atoms to which they are attached form an aryl, substituted aryl, heteroaryl or substituted heteroaryl ring. In still other of the above embodiments, R<sub>3</sub> and R<sub>4</sub> are hydrogen. In still other of the above embodiments, R<sub>3</sub>, R<sub>4</sub> and R<sub>8</sub> are hydrogen. In still other of the above embodiments, R<sub>5</sub>-R<sub>7</sub> are hydrogen. In still other of the above embodiments, R<sub>5</sub>-R<sub>8</sub> are hydrogen. In still other of the above embodiments, R<sub>3</sub>-R<sub>8</sub> are hydrogen. In still other of the above embodiments, R<sub>22</sub> and R<sub>23</sub> are pyridyl or substituted pyridyl.

**[0064]** In some embodiments, a compound of structural formula (V) is provided:

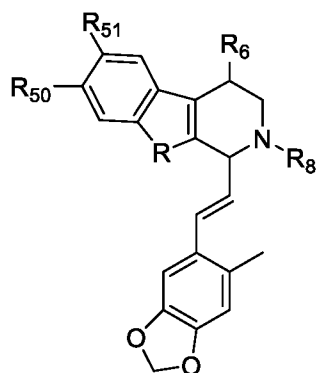


**[0065]** wherein R<sub>49</sub> is hydrogen or alkyl; Y is -CR<sub>50</sub>- or -N-; Z is -CR<sub>51</sub>- or -N-; R<sub>50</sub> and R<sub>51</sub> are independently, hydrogen, halo, alkyl, -OR<sub>52</sub> or -NR<sub>53</sub>R<sub>54</sub>; R<sub>52</sub> is alkyl; and R<sub>53</sub> and R<sub>54</sub> are



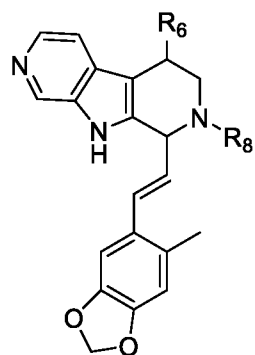
independently hydrogen or alkyl. In other embodiments, R<sub>9</sub> is

**[0066]** In some embodiments, a compound of structural formula (VI) is provided:



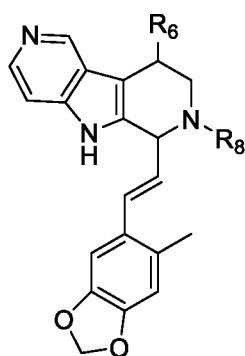
(VI)

. In other embodiments, a compound of structural formula (VII) is provided:



(VII)

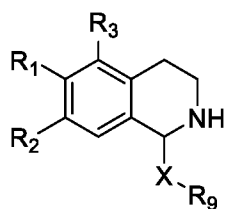
. In still other embodiments, a compound of structural formula (VIII) is provided:



(VIII)

[0067]

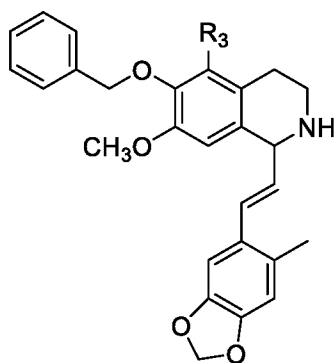
In some embodiments, a compound of structural formula (IX) is provided:



(IX)

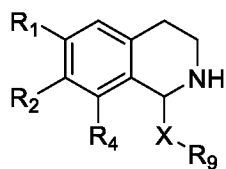
where R<sub>3</sub> is F, Cl, Br, -CH<sub>3</sub>, alkyl, alkenyl, -CF<sub>3</sub>, -OCR<sub>24</sub> or -NR<sub>25</sub>R<sub>26</sub>.

[0068] In some embodiments, a compound of structural formula (X) is provided:



(X)

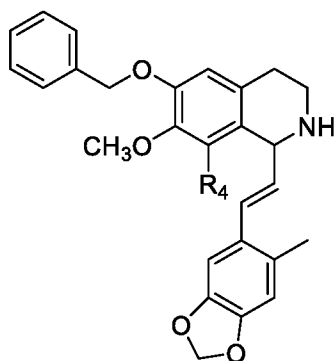
[0069] In some embodiments, a compound of structural formula (XI) is provided:



(XI)

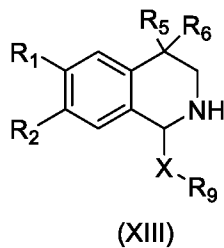
where R<sub>4</sub> is F, Cl, Br, -CH<sub>3</sub>, alkyl, alkenyl, -CF<sub>3</sub>, -OCR<sub>24</sub> or -NR<sub>25</sub>R<sub>26</sub>.

[0070] In some embodiments, a compound of structural formula (XII) is provided:



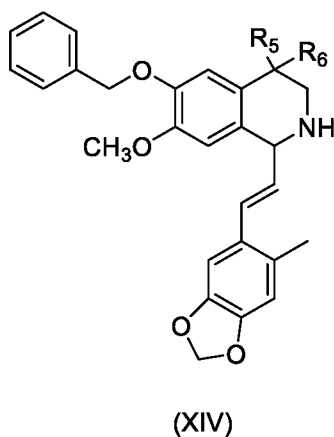
(XII)

[0071] In some embodiments, a compound of structural formula (XIII) is provided:

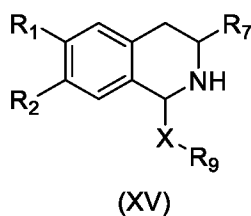


where R<sub>5</sub> is hydrogen or fluorine and R<sub>6</sub> is alkyl, methyl, alkenyl, fluorine, -OR<sub>27</sub> or -NR<sub>28</sub>R<sub>29</sub>.

[0072] In some embodiments, a compound of structural formula (XIV) is provided:

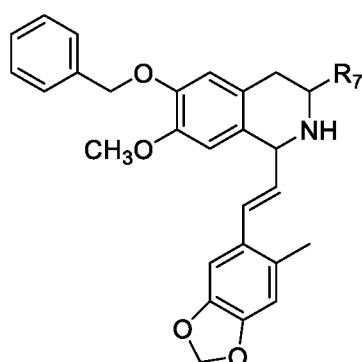


[0073] In some embodiments, a compound of structural formula (XV) is provided:



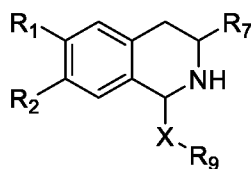
where R<sub>7</sub> is alkyl, alkenyl, -CO<sub>2</sub>R<sub>30</sub>, -CONR<sub>31</sub>R<sub>32</sub>, -CH<sub>2</sub>NR<sub>33</sub>R<sub>34</sub>, -CH<sub>2</sub>R<sub>42</sub> or -CH<sub>2</sub>OR<sub>35</sub>

[0074] In some embodiments, a compound of structural formula (XVI) is provided:



(XVI)

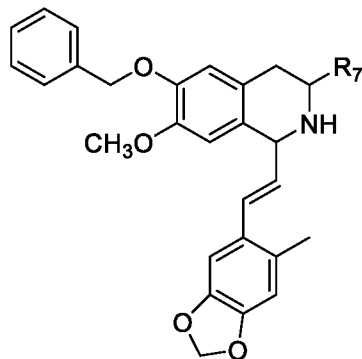
[0075] In some embodiments, a compound of structural formula (XVII) is provided:



(XVII)

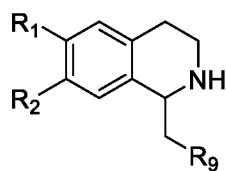
where R<sub>7</sub> is alkyl, alkenyl, -CO<sub>2</sub>R<sub>30</sub>, -CONR<sub>31</sub>R<sub>32</sub>, -CH<sub>2</sub>NR<sub>33</sub>R<sub>34</sub>, -CH<sub>2</sub>R<sub>42</sub> or -CH<sub>2</sub>OR<sub>35</sub>

[0076] In some embodiments, a compound of structural formula (XVIII) is provided:



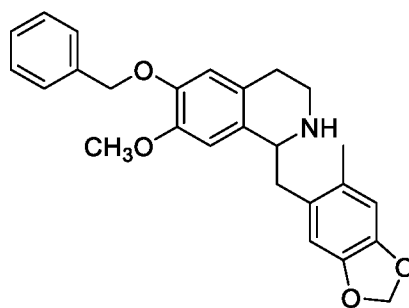
(XVIII)

[0077] In some embodiments, a compound of structural formula (XIX) is provided:



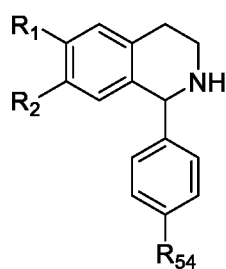
(XIX)

[0078] In some embodiments, a compound of structural formula (XX) is provided:



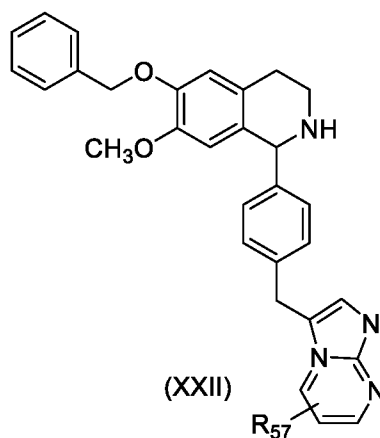
(XX)

[0079] In some embodiments, a compound of structural formula (XXI) is provided:



(XXI)

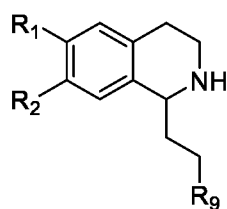
[0080] In some embodiments, a compound of structural formula (XXII) is provided:



(XXII)

where  $R_{58}$  is hydrogen, alkyl, alkenyl,  $-\text{CO}_2R_{59}$ ,  $-\text{CONR}_{60}R_{61}$ , or  $-\text{CH}_2\text{OR}_{62}$ ;  $R_{59}$  is hydrogen, alkyl or alkenyl;  $R_{60}$  and  $R_{61}$  are independently hydrogen, alkyl or alkenyl; and  $R_{62}$  is alkyl or alkenyl.

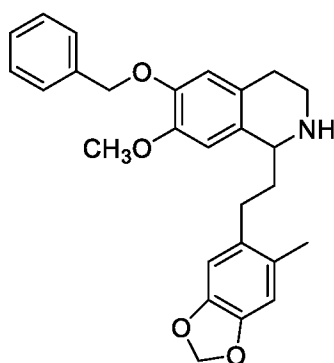
[0081] In some embodiments, a compound of structural formula (XXIII) is provided:



(XXIII)

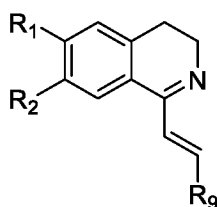
where R<sub>7</sub> is alkyl, alkenyl, -CO<sub>2</sub>R<sub>30</sub>, -CONR<sub>31</sub>R<sub>32</sub>, -CH<sub>2</sub>NR<sub>33</sub>R<sub>34</sub>, -CH<sub>2</sub>R<sub>42</sub> or -CH<sub>2</sub>OR<sub>35</sub>

[0082] In some embodiments, a compound of structural formula (XXIV) is provided:



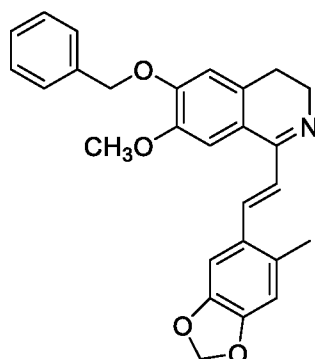
(XXIV)

[0083] In some embodiments, a compound of structural formula (XXV) is provided:



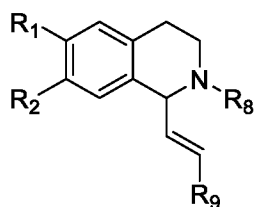
(XXV)

[0084] In some embodiments, a compound of structural formula (XXVI) is provided:



(XXVI)

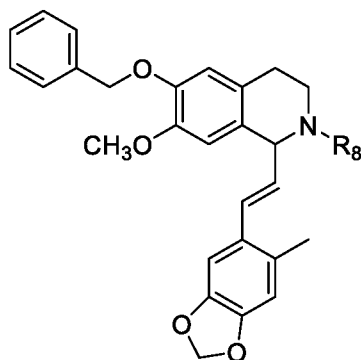
[0085] In some embodiments, a compound of structural formula (XXVII) is provided:



(XXVII)

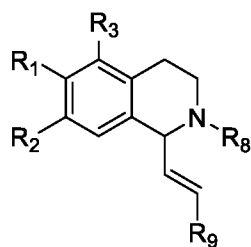
where  $R_8$  is hydrogen,  $-SO_2R_{47}$ ,  $-OR_{48}$ ,  $-SO_2NR_{69}R_{70}$ ,  $-CONR_{71}R_{72}$  or  $-COR_{73}$ , alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl.

[0086] In some embodiments, a compound of structural formula (XXVIII) is provided:



(XXVIII)

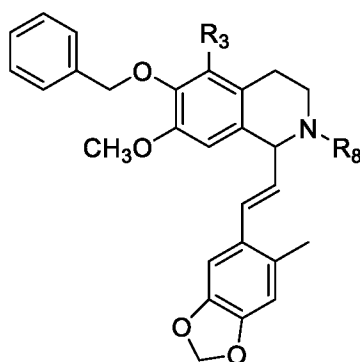
[0087] In some embodiments, a compound of structural formula (XXIX) is provided:



(XXIX)

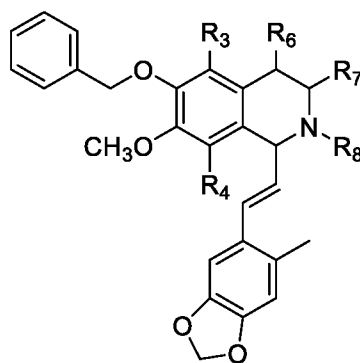
where  $R_3$  is F, Cl, Br,  $-\text{CH}_3$ , alkyl,  $-\text{CF}_3$ ,  $-\text{OCR}_{24}$  or  $-\text{NR}_{25}\text{R}_{26}$  and  $R_8$  is hydrogen,  $-\text{SO}_2\text{R}_{47}$ ,  $-\text{OR}_{48}$ ,  $-\text{SO}_2\text{NR}_{69}\text{R}_{70}$ ,  $-\text{CONR}_{71}\text{R}_{72}$  or  $-\text{COR}_{73}$ , alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl.

**[0088]** In some embodiments, a compound of structural formula (XXX) is provided:



(XXX)

**[0089]** In some embodiments, a compound of structural formula (XXXI) is provided:



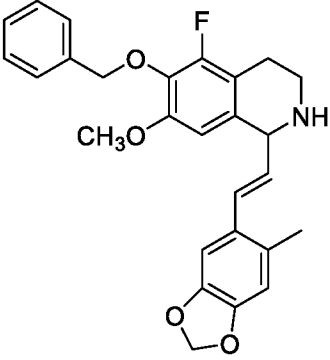
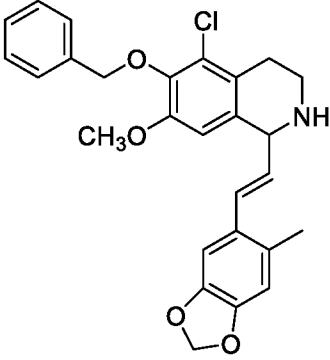
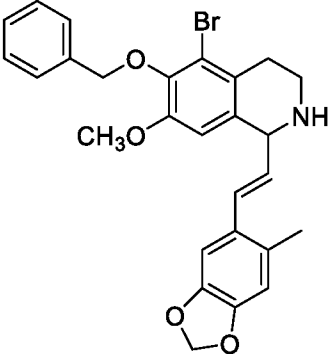
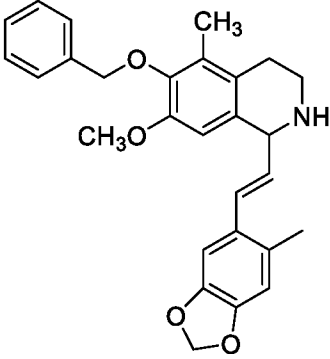
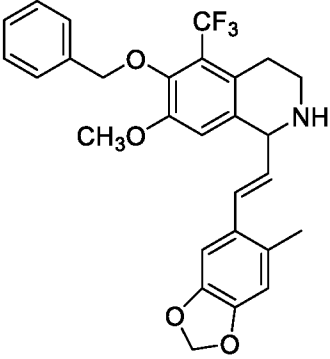
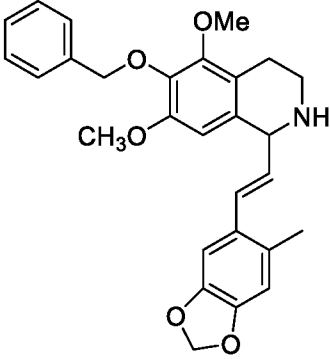
(XXXI)

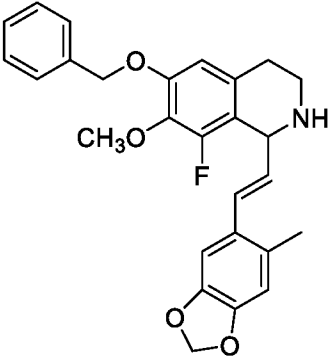
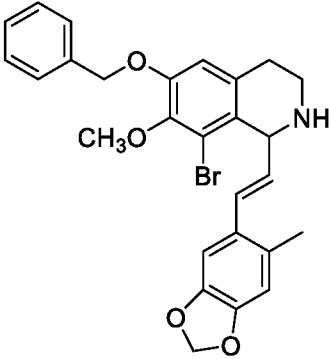
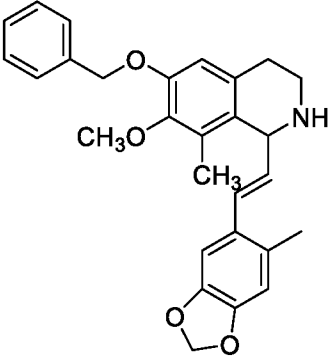
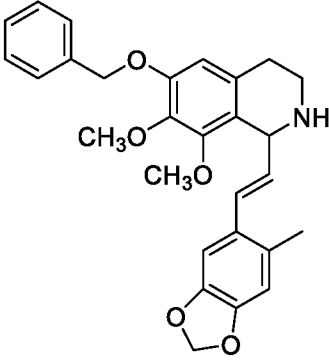
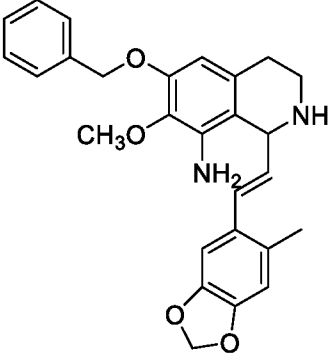
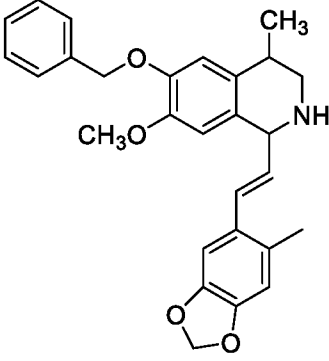
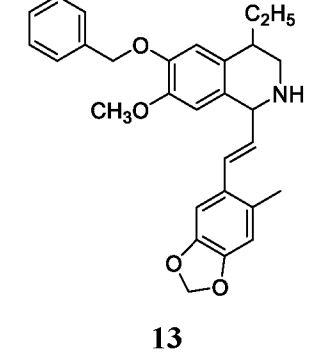
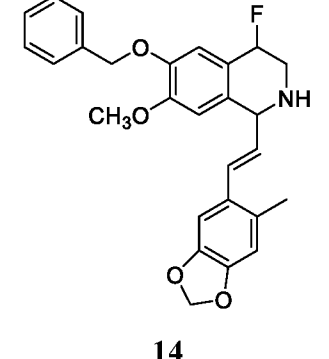
**[0090]** In some embodiments,  $R_3$  is  $-\text{CH}_3$ ,  $R_4$  is  $-\text{CH}_3$ ,  $R_6$  is H,  $-\text{CH}_3$ ,  $-\text{C}_2\text{H}_5$ ,  $-\text{OR}_{27}$ ,  $-\text{NR}_{28}\text{R}_{29}$  and  $R_7$  is H,  $-\text{CH}_3$  or  $-\text{C}_2\text{H}_5$ . In other embodiments,  $R_3$  is  $-\text{OCH}_3$ ,  $R_4$  is  $-\text{OCH}_3$ ,  $R_6$  is H,  $-\text{CH}_3$ ,  $-\text{C}_2\text{H}_5$ ,  $-\text{OR}_{27}$ ,  $-\text{NR}_{28}\text{R}_{29}$  and  $R_7$  is H,  $-\text{CH}_3$  or  $-\text{C}_2\text{H}_5$ . In still other embodiments,  $R_3$  is  $-\text{F}_3$ ,

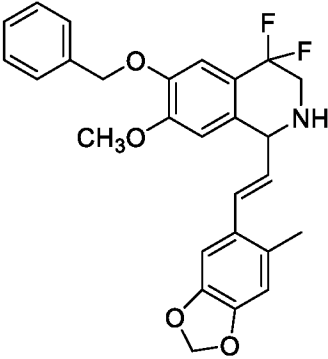
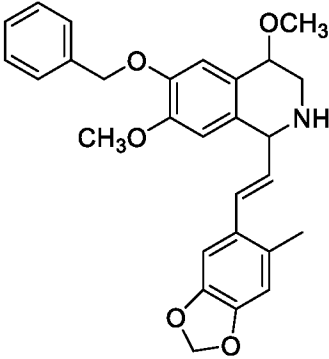
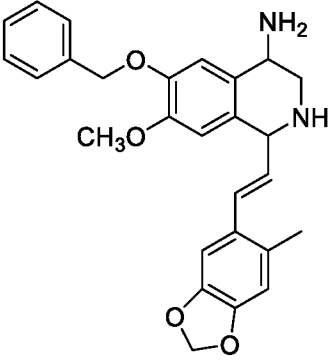
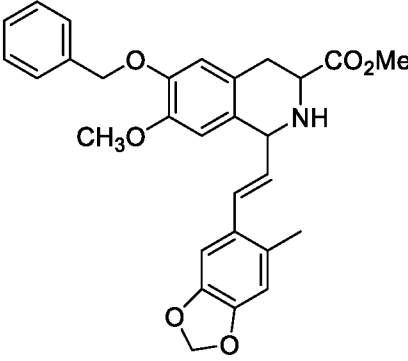
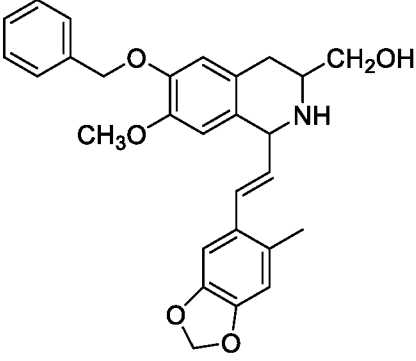
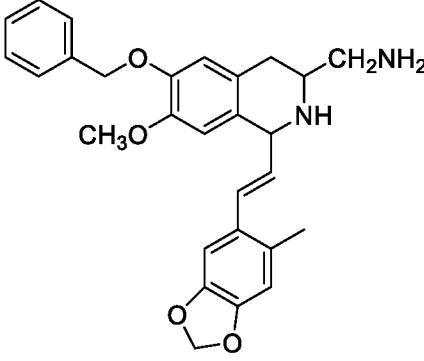
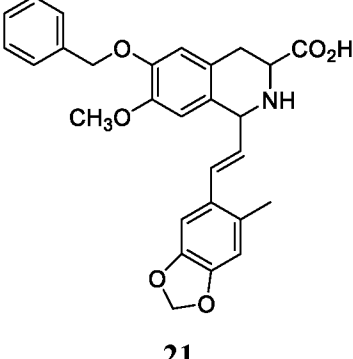
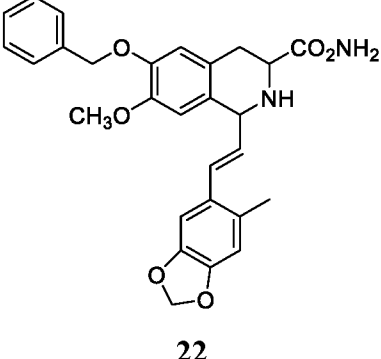
R<sub>4</sub> is -F, R<sub>6</sub> is H, -CH<sub>3</sub>, -C<sub>2</sub>H<sub>5</sub>, -OR<sub>27</sub>, -NR<sub>28</sub>R<sub>29</sub> and R<sub>7</sub> is H, -CH<sub>3</sub> or -C<sub>2</sub>H<sub>5</sub>. In still other embodiments, R<sub>3</sub> is -Cl, R<sub>4</sub> is -Cl, R<sub>6</sub> is H, -CH<sub>3</sub>, -C<sub>2</sub>H<sub>5</sub>, -OR<sub>27</sub>, -NR<sub>28</sub>R<sub>29</sub> and R<sub>7</sub> is H, -CH<sub>3</sub> or -C<sub>2</sub>H<sub>5</sub>. In other embodiments, R<sub>3</sub> is -Br, R<sub>4</sub> is -Br, R<sub>6</sub> is H, -CH<sub>3</sub>, -C<sub>2</sub>H<sub>5</sub>, -OR<sub>27</sub>, -NR<sub>28</sub>R<sub>29</sub> and R<sub>7</sub> is H, -CH<sub>3</sub> or -C<sub>2</sub>H<sub>5</sub>.

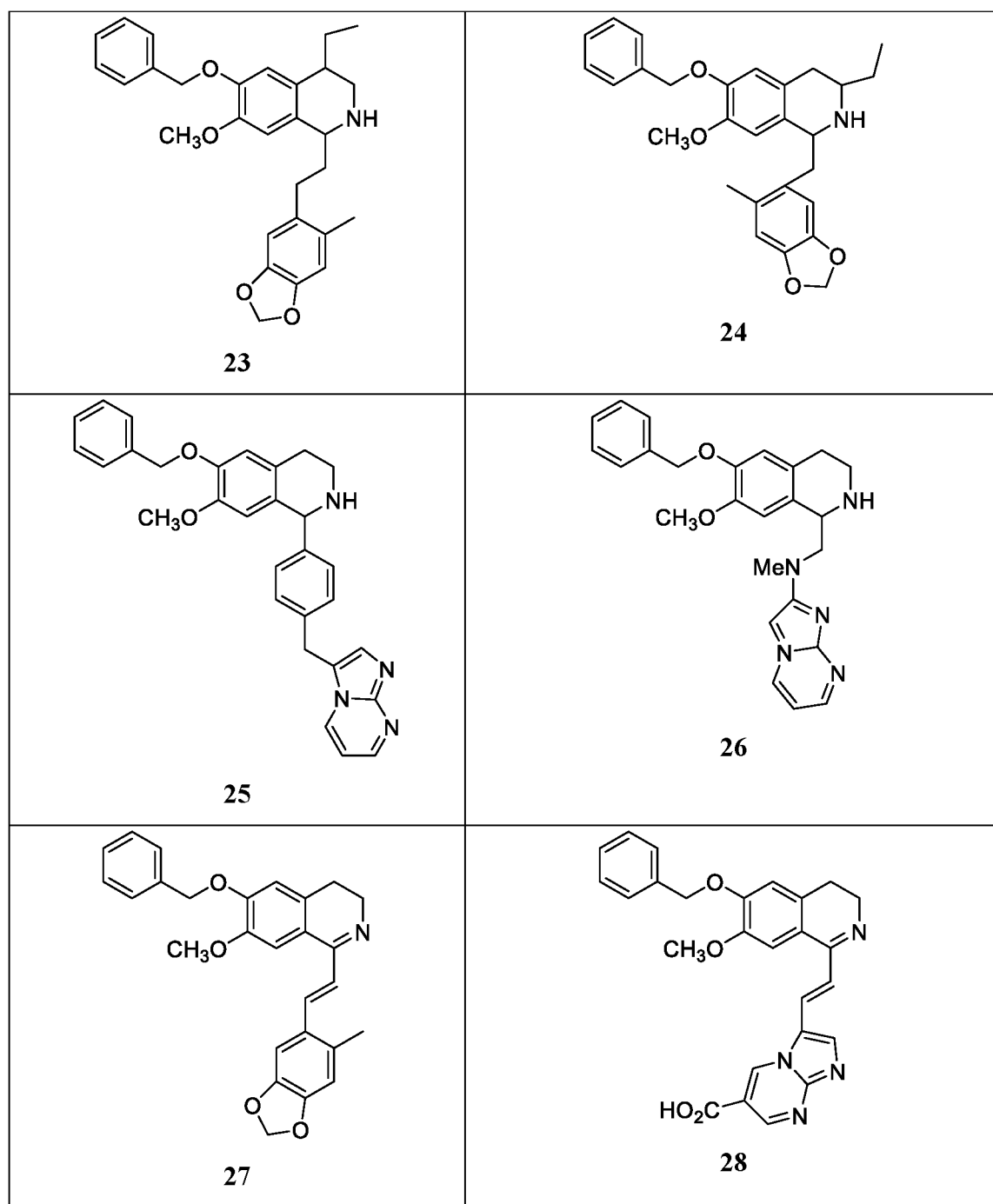
[0091] Specific compounds are disclosed in Table 1, below.

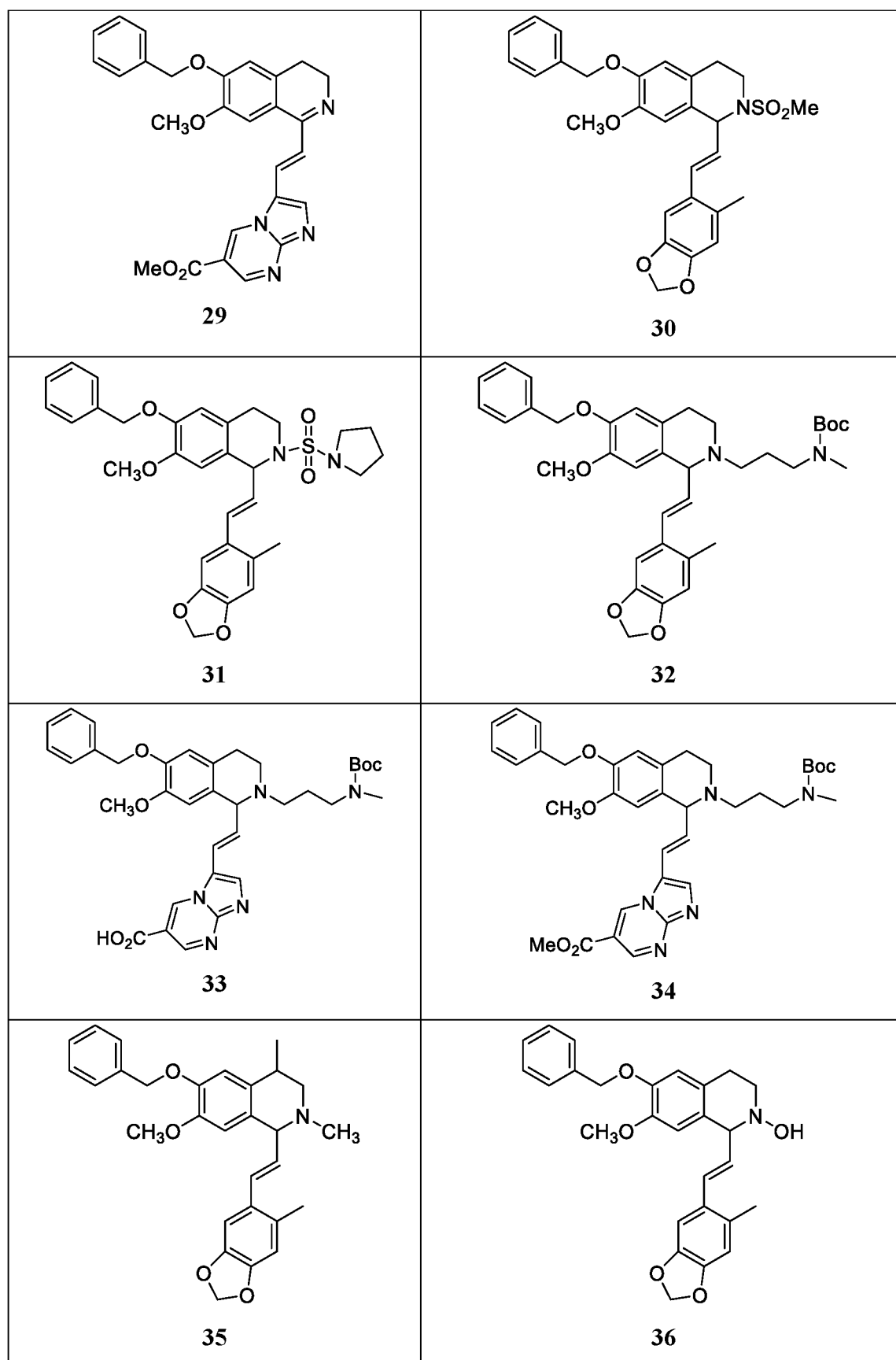
Table 1

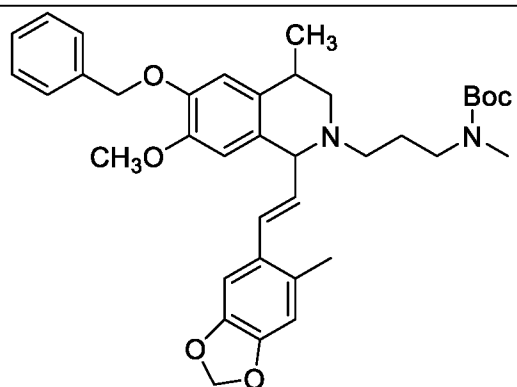
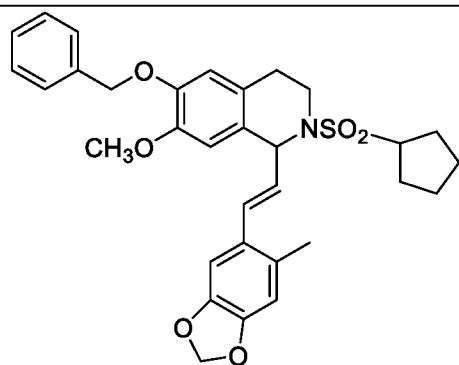
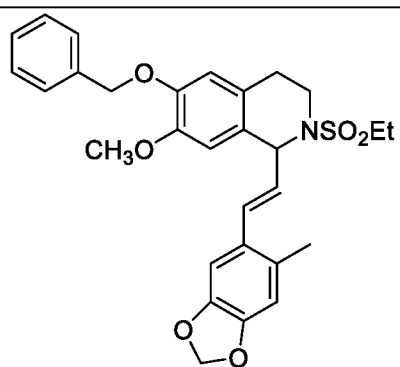
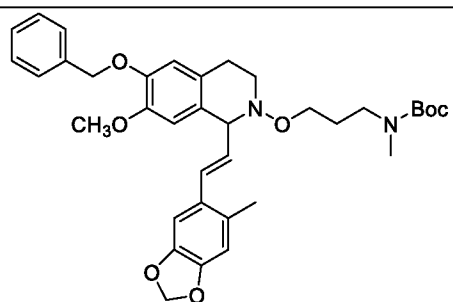
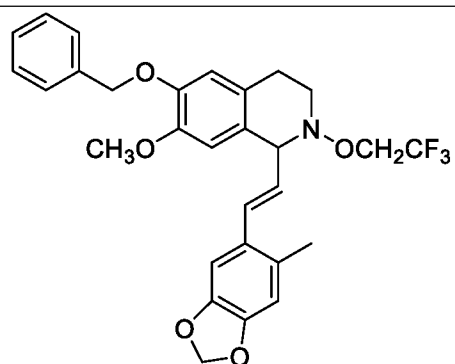
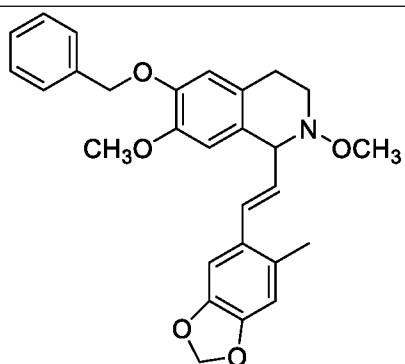
|                                                                                                                                 |                                                                                                                                  |
|---------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
|  <p style="text-align: center;"><b>1</b></p>   |  <p style="text-align: center;"><b>2</b></p>   |
|  <p style="text-align: center;"><b>3</b></p> |  <p style="text-align: center;"><b>4</b></p> |
|  <p style="text-align: center;"><b>5</b></p> |  <p style="text-align: center;"><b>6</b></p> |

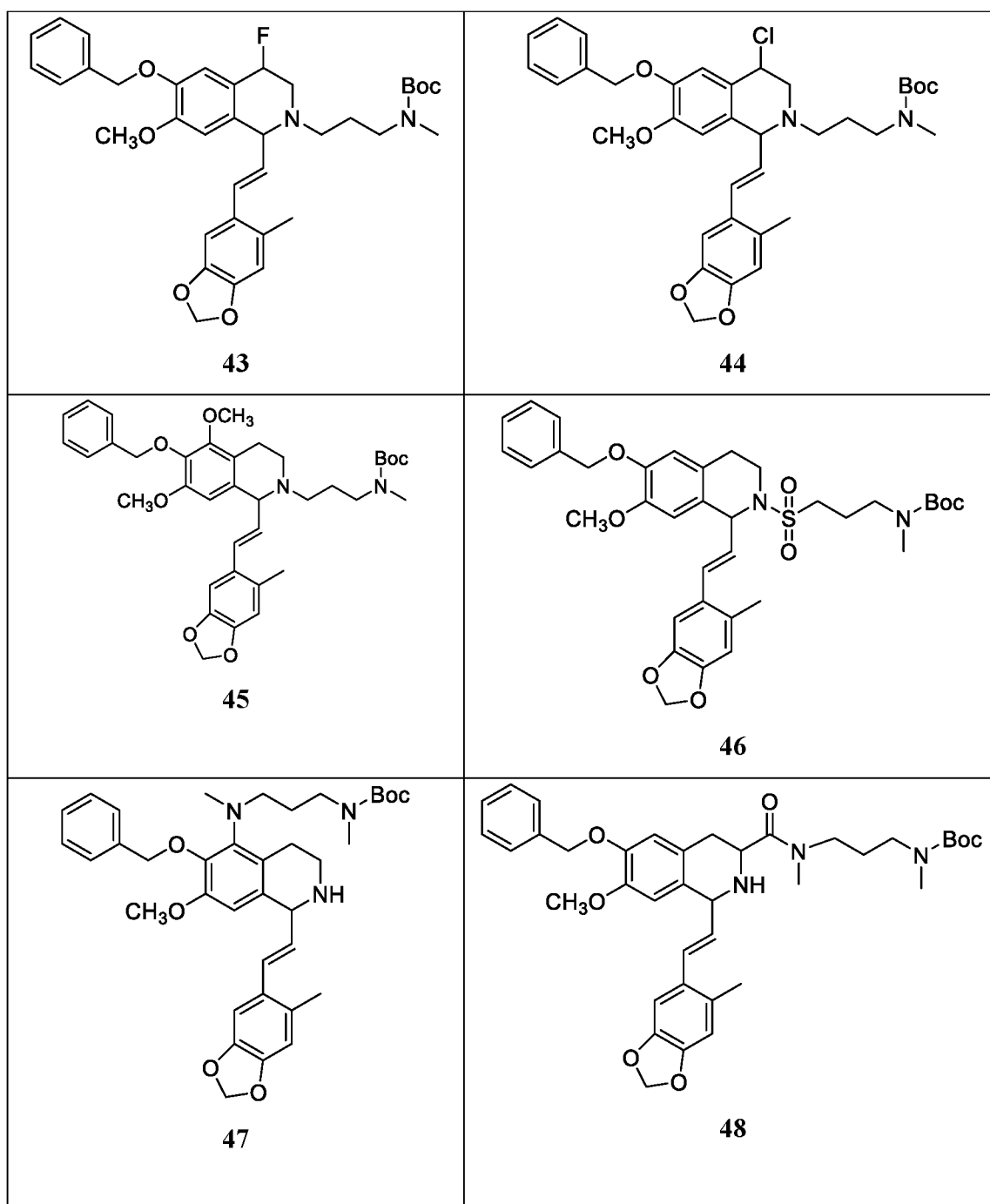
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|-----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
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|  <p>9</p>   |  <p>10</p>  |
|  <p>11</p> |  <p>12</p> |
|  <p>13</p> |  <p>14</p> |

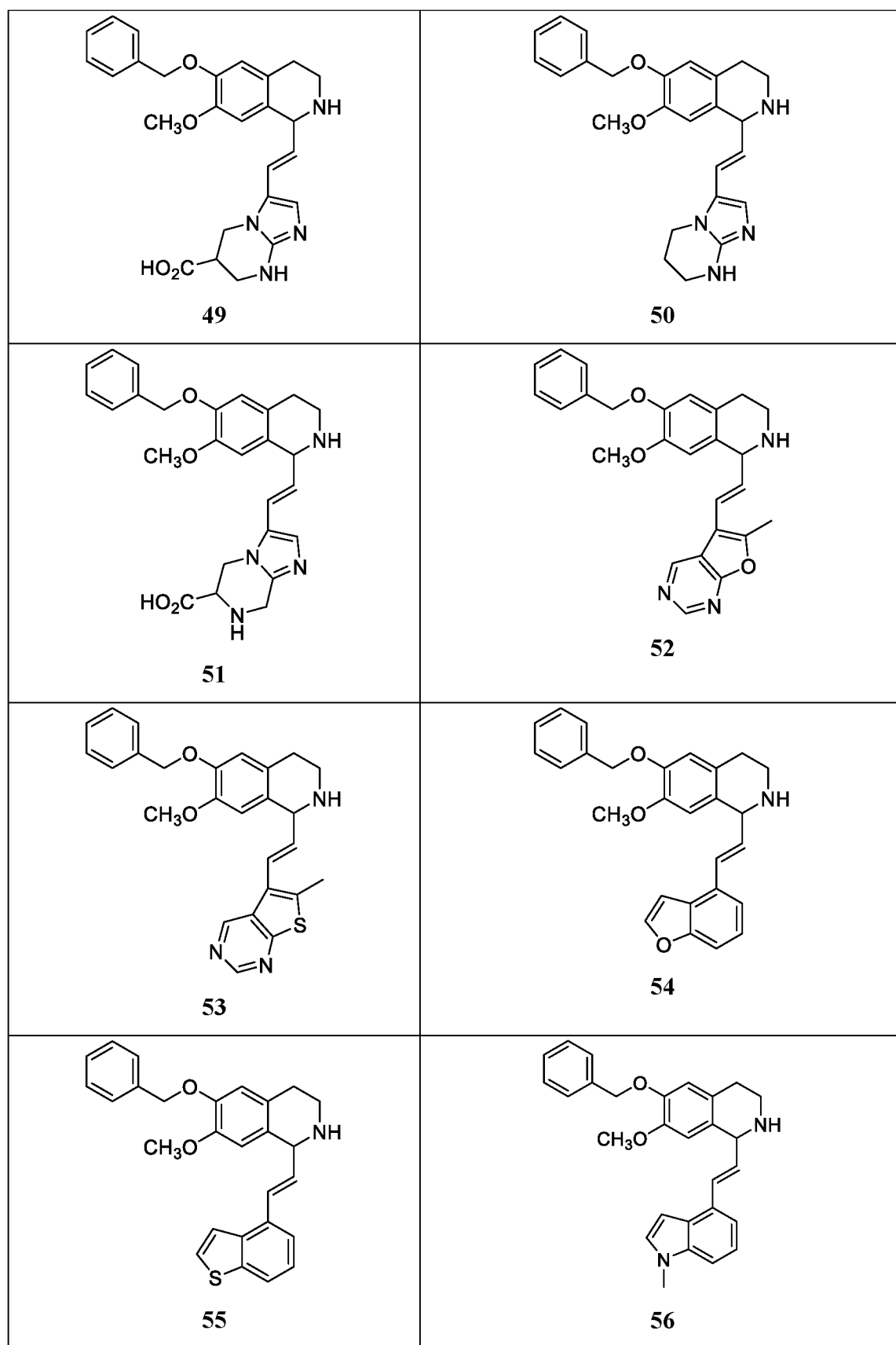
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|-----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
|  <p>15</p>   |  <p>16</p>   |
|  <p>17</p>  |  <p>18</p>  |
|  <p>19</p> |  <p>20</p> |
|  <p>21</p> |  <p>22</p> |

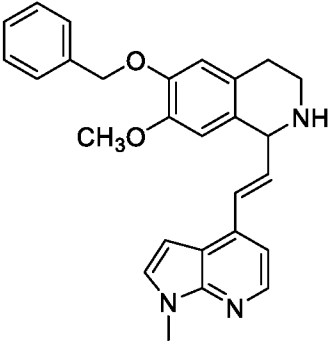
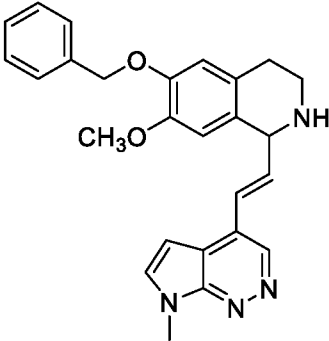
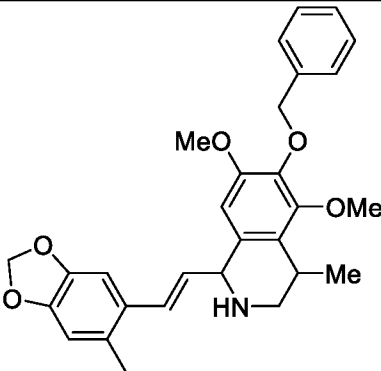
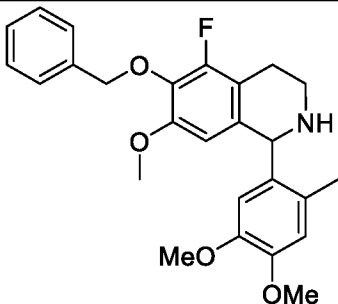
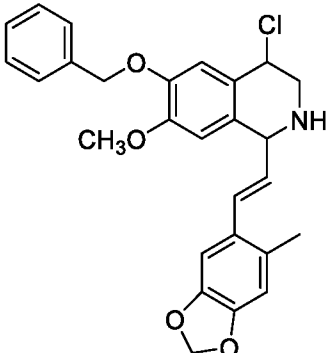
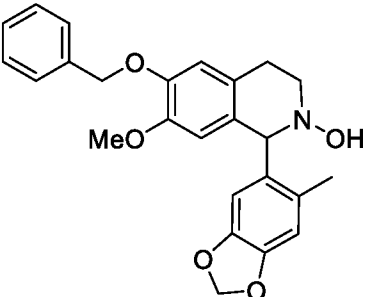
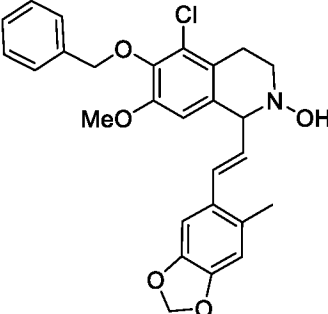










|                                                                                               |                                                                                                |
|-----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
|  <p>57</p>   |  <p>58</p>   |
|  <p>59</p>  |  <p>60</p>   |
|  <p>61</p> |  <p>62</p> |
|  <p>63</p> |                                                                                                |

## Methods of Synthesis

**[0092]** Referring now to Fig. 1, aldehyde **100** undergoes aldol condensation with nitromethane and is reduced with lithium aluminum hydride to yield amine **101**. Reaction with carboxylic acid **102** provides amide **103** which is cyclized to yield imine **104**, which is a compound of Formula (II). Reduction of imine **104** yields compound **105** which is a compound of Formula (I). It should be noted that use of multicyclic aryl and heteroaryl aldehydes allows for preparation of multicyclic aryl and heteroaryl derivatives of compounds of Formula (I) and (II).

**[0093]** Fig. 2 illustrates preparation of compounds of Formula (I) where  $R_3$  and  $R_4$  are not hydrogen. Reaction of amine **100** with thiol **106** provided protected amine **107** which condenses with unsaturated aldehyde **109** to yield tetrahydroisoquinoline **110** which is then deprotected to provide amine **105**.

**[0094]** Fig. 3 illustrates preparation of compounds of Formula (I) where  $R_3$  and  $R_4$  are not hydrogen. Amine **100** is reacted with acid **102** to provide **112** which was then cyclized to imine **113** and then reduced to yield alkene **114**. Protection of the amine provides **115** and Heck reaction with aryl bromide **116** to yield functionalized compound **117** which is then deprotected to provide amine salt **118**.

**[0095]** Fig. 4 illustrates preparation of compounds of Formula (I) where  $R_3$  and  $R_4$  are not hydrogen and X is  $-\text{CH}_2-$ . Protected amine **107** is condensed with aldehyde **119** to provide protected tetrahydroisoquinoline **120**, which is deprotected to yield amine salt **121**.

**[0096]** Fig. 5 illustrates preparation of compounds of Formula (I) where  $R_3$  and  $R_4$  are not hydrogen and X is absent. Protected amine **107** is condensed with aldehyde **122** to provide protected tetrahydroisoquinoline **123**, which is deprotected to yield the amine salt **124**.

**[0097]** Fig. 6 illustrates preparation of compounds of Formula (I) and (II) where  $R_6$  is not hydrogen. Aldehyde **100** is reacted with an alkyl Grignard reagent to yield an alcohol which is then oxidized to ketone **125**. Aldol condensation with nitromethane and followed by reduction of the nitro group provides amine **126**, which is then reacted with acid **102** to form an amide, which is then cyclized to provide an imine (i.e. a compound of Formula (II)) that is then reduced to yield the tetrahydroisoquinoline **127** of Formula (I).

**[0098]** Fig. 7 illustrates preparation of compounds of Formula (I) and (II) where  $R_6$  is fluorine. Condensation of aldehyde **100** with trimethylsilyl chloride in the presence of zinc

iodide and diethylamino sulfur trifluoride provides cyano fluoride **128**, which is reduced to yield fluoroamine **129**. Fluoroamine **129** is reacted with acid **102** to form an amide, which is then cyclized to provide an imine (i.e. a compound of Formula (II)) that is then reduced to yield the tetrahydroisoquinoline **130** of Formula (I).

**[0099]** Fig. 8 illustrates preparation of compounds of Formula (I) and (II) where  $R_6$  and  $R_7$  are fluorine. Bromination of ketone **131** provides bromoketone **132**, which is converted to difluoroazide **133**. Reduction of the azide provides difluoroamine **134** which is then reacted with acid **102** to form an amide, which is then cyclized to provide an imine (i.e. a compound of Formula (II)) which is then reduced to yield the tetrahydroisoquinoline **135** of Formula (I).

**[00100]** Fig. 9 illustrates preparation of compounds of Formula (I) and (II) where  $R_6$  is a hydroxyl or ether derivative. Reduction of ketoazide **136** to the alcohol and protection of the alcohol yield the protected azide **137**, which is then reduced the amine **138**. Amine **138** is then reacted with acid **102** to form an amide, that is then cyclized to provide an imine (i.e. a compound of Formula (II)) which is then reduced to yield the tetrahydroisoquinoline **139** of Formula (I). Deprotection can provide the alcohol directly. Dihydroisoquinolines (i.e. a compound of Formula (III)) may be prepared by dehydration of the alcohol. Alternatively, amino derivatives may be prepared from the alcohol by oxidation and reductive amination. Ether derivatives may be prepared by protecting the free nitrogen and deprotection of the alcohol to yield **140**, which then alkylated and deprotected to yield the tetrahydroisoquinoline **141** of Formula (I).

**[00101]** Fig. 10 illustrates preparation of compounds of Formula (I) and (II) where  $R_8$  is an alkyl group. Aldol condensation of aldehyde **100** with an alkyl nitro compound followed by reduction of the nitro group yields amine **142**. Amine **142** is reacted with acid **102** to form an amide, which is then cyclized to provide an imine (i.e. a compound of Formula (II)) that is then reduced to yield the tetrahydroisoquinoline **143** of Formula (I).

**[00102]** Fig. 11 illustrates preparation of compounds of Formula (I) and (II) where  $R_8$  is an ester. Conversion of aldehyde **100** to bromide **144** is accomplished through conventional means. Bromide is converted to the protected amino acid **145** by standard procedures and after deprotection of the amino group is reacted with acid **102** to form an amide, which is then cyclized to provide an imine (i.e. a compound of Formula (II)) that is then reduced to yield the tetrahydroisoquinoline **146** of Formula (I). Those of skill in the art will appreciate the ester

group can be converted to a wide variety of functionalized derivatives that fall within the ambit of compounds of Formula (I).

**[00103]** Fig. 12 illustrates preparation of compounds of Formula (I) where R<sub>9</sub> is a benzyl derivative. Aryl bromide **116** is converted to the aldehyde **147** through Suzuki coupling, alcohol deprotection and oxidation. Condensation with amine **148** and deprotection yields the tetrahydroisoquinoline **149** of Formula (I).

**[00104]** Fig. 13 illustrates preparation of compounds of Formula (I) where R<sub>9</sub> is an amine derivative. Alkyl bromide **150** is converted to the aldehyde **151** through conventional procedures. Condensation with amine **107** and deprotection of **152** yields the tetrahydroisoquinoline **153** of Formula (I).

**[00105]** Fig. 14 illustrates preparation of compounds of Formula (I) where R<sub>3</sub> is an amine derivative. Condensation of amine **239** with unsaturated aldehyde **242** provided key intermediate **154**. The unsaturated imine **154** is converted to sulfonamide **155**, sulfamide **156**, urea **157**, or carbamate **158** upon treatment with the appropriate chloro derivative.

**[00106]** Although functionalization of the tetrahydroisoquinoline nitrogen has not been described many such procedures are conventional and are well known to the skilled artisan.

### Compositions and Methods of Administration

**[00107]** The compositions provided herein contain therapeutically effective amounts of one or more of the compounds provided herein that are useful in the prevention, treatment, or amelioration of one or more of the symptoms of diseases or disorders described herein and a vehicle. Vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration. In addition, the compounds may be formulated as the sole active ingredient in the composition or may be combined with other active ingredients.

**[00108]** The compositions contain one or more compounds provided herein. The compounds are, in some embodiments, formulated into suitable preparations such as solutions, suspensions, tablets, dispersible tablets, pills, capsules, powders, sustained release formulations or elixirs, for oral administration or in sterile solutions or suspensions for parenteral administration, as well as topical administration, transdermal administration and oral inhalation via nebulizers, pressurized metered dose inhalers and dry powder inhalers. In some

embodiments, the compounds described above are formulated into compositions using techniques and procedures well known in the art (see, *e.g.*, Ansel, Introduction to Pharmaceutical Dosage Forms, Seventh Edition (1999)).

**[00109]** In the compositions, effective concentrations of one or more compounds or derivatives thereof is (are) mixed with a suitable vehicle. The compounds may be derivatized as the corresponding salts, esters, enol ethers or esters, acetals, ketals, orthoesters, hemiacetals, hemiketals, acids, bases, solvates, ion-pairs, hydrates or prodrugs prior to formulation, as described above. The concentrations of the compounds in the compositions are effective for delivery of an amount, upon administration that treats, leads to prevention, or amelioration of one or more of the symptoms of diseases or disorders described herein. In some embodiments, the compositions are formulated for single dosage administration. To formulate a composition, the weight fraction of a compound is dissolved, suspended, dispersed or otherwise mixed in a selected vehicle at an effective concentration such that the treated condition is relieved, prevented, or one or more symptoms are ameliorated.

**[00110]** The active compound is included in the vehicle in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration may be predicted empirically by testing the compounds in *in vitro* and *in vivo* systems well known to those of skill in the art and then extrapolated therefrom for dosages for humans. Human doses are then typically fine-tuned in clinical trials and titrated to response.

**[00111]** The concentration of active compound in the composition will depend on absorption, inactivation and excretion rates of the active compound, the physicochemical characteristics of the compound, the dosage schedule, and amount administered as well as other factors known to those of skill in the art. For example, the amount that is delivered is sufficient to ameliorate one or more of the symptoms of diseases or disorders as described herein.

**[00112]** In instances in which the compounds exhibit insufficient solubility, methods for solubilizing compounds may be used such as use of liposomes, prodrugs, complexation/chelation, nanoparticles, or emulsions or tertiary templating. Such methods are known to those of skill in this art, and include, but are not limited to, using co-solvents, such as dimethylsulfoxide (DMSO), using surfactants or surface modifiers, such as TWEEN<sup>®</sup>, complexing agents such as cyclodextrin or dissolution by enhanced ionization (*i.e.* dissolving in

aqueous sodium bicarbonate). Derivatives of the compounds, such as prodrugs of the compounds may also be used in formulating effective compositions.

**[00113]** Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected vehicle. The effective concentration is sufficient for ameliorating the symptoms of the disease, disorder or condition treated and may be empirically determined.

**[00114]** The compositions are provided for administration to humans and animals in indication appropriate dosage forms, such as dry powder inhalers (DPIs), pressurized metered dose inhalers (pMDIs), nebulizers, tablets, capsules, pills, sublingual tapes/bioerodible strips, tablets or capsules, powders, granules, lozenges, lotions, salves, suppositories, fast melts, transdermal patches or other transdermal application devices/preparations, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil-water emulsions containing suitable quantities of the compounds or derivatives thereof. The therapeutically active compounds and derivatives thereof are, in some embodiments, formulated and administered in unit-dosage forms or multiple-dosage forms. Unit-dose forms as used herein refer to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the therapeutically active compound sufficient to produce the desired therapeutic effect, in association with the required vehicle. Examples of unit-dose forms include ampoules and syringes and individually packaged tablets or capsules. Unit-dose forms may be administered in fractions or multiples thereof. A multiple-dose form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dose form. Examples of multiple-dose forms include vials, bottles of tablets or capsules or bottles of pints or gallons. Hence, multiple dose form is a multiple of unit-doses which are not segregated in packaging.

**[00115]** Liquid compositions can, for example, be prepared by dissolving, dispersing, or otherwise mixing an active compound as defined above and optional adjuvants in a vehicle, such as, for example, water, saline, aqueous dextrose, glycerol, glycols, ethanol, and the like, to thereby form a solution or suspension, colloidal dispersion, emulsion or liposomal formulation. If desired, the composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting agents, emulsifying agents, solubilizing agents, pH

buffering agents and the like, for example, acetate, sodium citrate, cyclodextrin derivatives, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, and other such agents.

**[00116]** Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 15th Edition, 1975 or later editions thereof.

**[00117]** Dosage forms or compositions containing active ingredient in the range of 0.005% to 100% with the balance made up from vehicle or carrier may be prepared. Methods for preparation of these compositions are known to those skilled in the art. The contemplated compositions may contain 0.001%-100% active ingredient, in one embodiment 0.1-95%, in another embodiment 0.4-10%.

**[00118]** In certain embodiments, the compositions are lactose-free compositions containing excipients that are well known in the art and are listed, for example, in the *U.S. Pharmacopeia* (USP) 25-NF20 (2002). In general, lactose-free compositions contain active ingredients, a binder/filler, and a lubricant in compatible amounts. Particular lactose-free dosage forms contain active ingredients, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

**[00119]** Further provided are anhydrous compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (*e.g.*, 5%) is widely accepted as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. *See, e.g.*, Jens T. Carstensen, *Drug Stability: Principles & Practice*, 2d. Ed., Marcel Dekker, NY, NY, 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

**[00120]** Anhydrous compositions and dosage forms provided herein can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions.

**[00121]** An anhydrous composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are generally packaged using materials known to prevent exposure to water such that they can be included in suitable

formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (*e.g.*, vials), blister packs, and strip packs.

**[00122]** Oral dosage forms are either solid, gel or liquid. The solid dosage forms are tablets, capsules, granules, and bulk powders. Types of oral tablets include compressed, chewable lozenges and tablets which may be enteric-coated, sugar-coated or film-coated. Capsules may be hard or soft gelatin capsules, while granules and powders may be provided in non-effervescent or effervescent form with the combination of other ingredients known to those skilled in the art.

**[00123]** In certain embodiments, the formulations are solid dosage forms such as for example, capsules or tablets. The tablets, pills, capsules, troches and the like can contain one or more of the following ingredients, or compounds of a similar nature: a binder; a lubricant; a diluent; a glidant; a disintegrating agent; a coloring agent; a sweetening agent; a flavoring agent; a wetting agent; an enteric coating; a film coating agent and modified release agent. Examples of binders include microcrystalline cellulose, methyl paraben, polyalkyleneoxides, gum tragacanth, glucose solution, acacia mucilage, gelatin solution, molasses, polyvinylpyrrolidone, povidone, crospovidones, sucrose and starch and starch derivatives. Lubricants include talc, starch, magnesium/calcium stearate, lycopodium and stearic acid. Diluents include, for example, lactose, sucrose, trehalose, lysine, leucine, lecithin, starch, kaolin, salt, mannitol and dicalcium phosphate. Glidants include, but are not limited to, colloidal silicon dioxide. Disintegrating agents include crosscarmellose sodium, sodium starch glycolate, alginic acid, corn starch, potato starch, bentonite, methylcellulose, agar and carboxymethylcellulose. Coloring agents include, for example, any of the approved certified water soluble FD and C dyes, mixtures thereof; and water insoluble FD and C dyes suspended on alumina hydrate and advanced coloring or anti-forgery color/opalescent additives known to those skilled in the art. Sweetening agents include sucrose, lactose, mannitol and artificial sweetening agents such as saccharin and any number of spray dried flavors. Flavoring agents include natural flavors extracted from plants such as fruits and synthetic blends of compounds which produce a pleasant sensation or mask unpleasant taste, such as, but not limited to peppermint and methyl salicylate. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether. Enteric-coatings include fatty acids, fats, waxes, shellac, ammoniated shellac and cellulose acetate phthalates. Film coatings include

hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose acetate phthalate. Modified release agents include polymers such as the Eudragit<sup>®</sup> series and cellulose esters.

**[00124]** The compound, or derivative thereof, can be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

**[00125]** When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, sprinkle, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

**[00126]** The active materials can also be mixed with other active materials which do not impair the desired action, or with materials that supplement the desired action, such as antacids, H<sub>2</sub> blockers, and diuretics. The active ingredient is a compound or derivative thereof as described herein. Higher concentrations, up to about 98% by weight of the active ingredient may be included.

**[00127]** In all embodiments, tablets and capsules formulations may be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient. Thus, for example, they may be coated with a conventional enterically digestible coating, such as phenylsalicylate, waxes and cellulose acetate phthalate.

**[00128]** Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Aqueous solutions include, for example, elixirs and syrups. Emulsions are either oil-in-water or water-in-oil.

**[00129]** Elixirs are clear, sweetened, hydroalcoholic preparations. Vehicles used in elixirs include solvents. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may contain a preservative. An emulsion is a two-phase system in which one liquid is

dispersed in the form of small globules throughout another liquid. Carriers used in emulsions are non-aqueous liquids, emulsifying agents and preservatives. Suspensions use suspending agents and preservatives. Acceptable substances used in non-effervescent granules, to be reconstituted into a liquid oral dosage form, include diluents, sweeteners and wetting agents. Acceptable substances used in effervescent granules, to be reconstituted into a liquid oral dosage form, include organic acids and a source of carbon dioxide. Coloring and flavoring agents are used in all of the above dosage forms.

**[00130]** Solvents include glycerin, sorbitol, ethyl alcohol and syrup. Examples of preservatives include glycerin, methyl and propylparaben, benzoic acid, sodium benzoate and alcohol. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Examples of emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate. Suspending agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum and acacia. Sweetening agents include sucrose, syrups, glycerin and artificial sweetening agents such as saccharin. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether. Organic acids include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate. Coloring agents include any of the approved certified water soluble FD and C dyes, and mixtures thereof. Flavoring agents include natural flavors extracted from plants such fruits, and synthetic blends of compounds which produce a pleasant taste sensation.

**[00131]** For a solid dosage form, the solution or suspension, in for example, propylene carbonate, vegetable oils or triglycerides, is in some embodiments encapsulated in a gelatin capsule. Such solutions, and the preparation and encapsulation thereof, are disclosed in U.S. Patent Nos. 4,328,245; 4,409,239; and 4,410,545. For a liquid dosage form, the solution, *e.g.*, for example, in a polyethylene glycol, may be diluted with a sufficient quantity of a liquid vehicle, *e.g.*, water, to be easily measured for administration.

**[00132]** Alternatively, liquid or semi-solid oral formulations may be prepared by dissolving or dispersing the active compound or salt in vegetable oils, glycols, triglycerides, propylene glycol esters (*e.g.*, propylene carbonate) and other such carriers, and encapsulating these solutions or suspensions in hard or soft gelatin capsule shells. Other useful formulations include those set forth in U.S. Patent Nos. RE28,819 and 4,358,603. Briefly, such formulations

include, but are not limited to, those containing a compound provided herein, a dialkylated mono- or polyalkylene glycol, including, but not limited to, 1,2-dimethoxyethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether wherein 350, 550 and 750 refer to the approximate average molecular weight of the polyethylene glycol, and one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, thiodipropionic acid and its esters, and dithiocarbamates.

**[00133]** Other formulations include, but are not limited to, aqueous alcoholic solutions including an acetal. Alcohols used in these formulations are any water-miscible solvents having one or more hydroxyl groups, including, but not limited to, propylene glycol and ethanol. Acetals include, but are not limited to, di(lower alkyl) acetals of lower alkyl aldehydes such as acetaldehyde diethyl acetal.

**[00134]** Parenteral administration, in some embodiments characterized by injection, either subcutaneously, intramuscularly or intravenously is also contemplated herein. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. The injectables, solutions and emulsions also contain one or more excipients. Suitable excipients are, for example, water, saline, dextrose, glycerol or ethanol. In addition, if desired, the compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate and cyclodextrins.

**[00135]** Implantation of a slow-release or sustained-release system, such that a constant level of dosage is maintained (see, *e.g.*, U.S. Patent No. 3,710,795) is also contemplated herein. Briefly, a compound provided herein is dispersed in a solid inner matrix, *e.g.*, polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and

cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, *e.g.*, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The compound diffuses through the outer polymeric membrane in a release rate controlling step. The percentage of active compound contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject.

**[00136]** Parenteral administration of the compositions includes intravenous, subcutaneous and intramuscular administrations. Preparations for parenteral administration include sterile solutions ready for injection, sterile dry soluble products, such as lyophilized powders, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions may be either aqueous or nonaqueous.

**[00137]** If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

**[00138]** Vehicles used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other substances.

**[00139]** Examples of aqueous vehicles include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to parenteral preparations packaged in multiple-dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride.

Isotonic agents include sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcellulose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Emulsifying agents include Polysorbate 80 (Tween<sup>®</sup> 80). A sequestering or chelating agent of metal ions includes EDTA. Carriers also include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles; and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

**[00140]** The concentration of compound is adjusted so that an injection provides an effective amount to produce the desired pharmacological effect. The exact dose depends on the age, weight, body surface area and condition of the patient or animal as is known in the art.

**[00141]** The unit-dose parenteral preparations are packaged in an ampoule, a vial or a syringe with a needle. All preparations for parenteral administration must be sterile, as is known and practiced in the art.

**[00142]** Illustratively, intravenous or intraarterial infusion of a sterile aqueous solution containing an active compound is an effective mode of administration. Another embodiment is a sterile aqueous or oily solution or suspension containing an active material injected as necessary to produce the desired pharmacological effect.

**[00143]** Injectables are designed for local and systemic administration. In some embodiments, a therapeutically effective dosage is formulated to contain a concentration of at least about 0.01% w/w up to about 90% w/w or more, in certain embodiments more than 0.1% w/w of the active compound to the treated tissue(s).

**[00144]** The compound may be suspended in micronized or other suitable form or may be derivatized to produce a more soluble active product or to produce a prodrug. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the condition and may be empirically determined.

**[00145]** Active ingredients provided herein can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543;

5,639,476; 5,354,556; 5,639,480; 5,733,566; 5,739,108; 5,891,474; 5,922,356; 5,972,891; 5,980,945; 5,993,855; 6,045,830; 6,087,324; 6,113,943; 6,197,350; 6,248,363; 6,264,970; 6,267,981; 6,376,461; 6,419,961; 6,589,548; 6,613,358; 6,699,500 and 6,740,634. Such dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydroxypropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients provided herein.

**[00146]** All controlled-release products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (*e.g.*, adverse) effects.

**[00147]** Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

**[00148]** In certain embodiments, the agent may be administered using intravenous infusion, an implantable osmotic pump, a transdermal patch, liposomes, or other modes of administration. In some embodiments, a pump may be used (*see*, Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald *et al.*, *Surgery* 88:507 (1980); Saudek *et al.*, *N. Engl. J. Med.* 321:574 (1989)). In other embodiments, polymeric materials can be used. In other embodiments, a controlled release system can be placed in proximity of the therapeutic target, *i.e.*, thus

requiring only a fraction of the systemic dose (*see, e.g., Goodson, Medical Applications of Controlled Release*, vol. 2, pp. 115-138 (1984)). In some embodiments, a controlled release device is introduced into a subject in proximity of the site of inappropriate immune activation or a tumor. Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)). The active ingredient can be dispersed in a solid inner matrix, *e.g.*, polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, *e.g.*, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The active ingredient then diffuses through the outer polymeric membrane in a release rate controlling step. The percentage of active ingredient contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the needs of the subject.

**[00149]** Of interest herein are also lyophilized powders, which can be reconstituted for administration as solutions, emulsions and other mixtures. They may also be reconstituted and formulated as solids or gels.

**[00150]** The sterile, lyophilized powder is prepared by dissolving a compound provided herein, or a derivative thereof, in a suitable solvent. The solvent may contain an excipient which improves the stability or other pharmacological component of the powder or reconstituted solution, prepared from the powder. Excipients that may be used include, but are not limited to, an antioxidant, a buffer and a bulking agent. In some embodiments, the excipient is selected from dextrose, sorbitol, fructose, corn syrup, xylitol, glycerin, glucose, sucrose and other suitable agent. The solvent may contain a buffer, such as citrate, sodium or potassium phosphate or other

such buffer known to those of skill in the art at, at about neutral pH. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. In some embodiments, the resulting solution will be apportioned into vials for lyophilization. Each vial will contain a single dosage or multiple dosages of the compound. The lyophilized powder can be stored under appropriate conditions, such as at about 4 °C to room temperature.

**[00151]** Reconstitution of this lyophilized powder with water for injection provides a formulation for use in parenteral administration. For reconstitution, the lyophilized powder is added to sterile water or other suitable carriers. The precise amount depends upon the selected compound. Such amount can be empirically determined.

**[00152]** Topical mixtures are prepared as described for the local and systemic administration. The resulting mixture may be a solution, suspension, emulsions or the like and are formulated as creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, dermal patches or any other formulations suitable for topical administration.

**[00153]** The compounds or derivatives thereof may be formulated as aerosols for topical application, such as by inhalation (see, *e.g.*, U.S. Patent Nos. 4,044,126, 4,414,209, and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment of inflammatory diseases, particularly asthma). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will, in some embodiments, have mass median geometric diameters of less than 5 microns, in other embodiments less than 10 microns.

**[00154]** Oral inhalation formulations of the compounds or derivatives suitable for inhalation include metered dose inhalers, dry powder inhalers and liquid preparations for administration from a nebulizer or metered dose liquid dispensing system. For both metered dose inhalers and dry powder inhalers, a crystalline form of the compounds or derivatives is the preferred physical form of the drug to confer longer product stability.

**[00155]** In addition to particle size reduction methods known to those skilled in the art, crystalline particles of the compounds or derivatives can be generated using supercritical fluid processing which offers significant advantages in the production of such particles for inhalation

delivery by producing respirable particles of the desired size in a single step. (*e.g.*, International Publication No. WO2005/025506). A controlled particle size for the microcrystals can be selected to ensure that a significant fraction of the compounds or derivatives is deposited in the lung. In some embodiments, these particles have a mass median aerodynamic diameter of about 0.1 to about 10 microns, in other embodiments, about 1 to about 5 microns and still other embodiments, about 1.2 to about 3 microns.

**[00156]** Inert and non-flammable HFA propellants are selected from HFA 134a (1,1,1,2-tetrafluoroethane) and HFA 227e (1,1,1,2,3,3,3-heptafluoropropane) and provided either alone or as a ratio to match the density of crystal particles of the compounds or derivatives. A ratio is also selected to ensure that the product suspension avoids detrimental sedimentation or cream (which can precipitate irreversible agglomeration) and instead promote a loosely flocculated system, which is easily dispersed when shaken. Loosely fluctuated systems are well regarded to provide optimal stability for pMDI canisters. As a result of the formulation's properties, the formulation contained no ethanol and no surfactants/stabilizing agents.

**[00157]** The compounds may be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the active compound alone or in combination with other excipients can also be administered.

**[00158]** For nasal administration, the preparation may contain an esterified phosphonate compound dissolved or suspended in a liquid carrier, in particular, an aqueous carrier, for aerosol application. The carrier may contain solubilizing or suspending agents such as propylene glycol, surfactants, absorption enhancers such as lecithin or cyclodextrin, or preservatives.

**[00159]** Solutions, particularly those intended for ophthalmic use, may be formulated as 0.01% - 10% isotonic solutions, pH about 5-7.4, with appropriate salts.

**[00160]** Other routes of administration, such as transdermal patches, including iontophoretic and electrophoretic devices, and rectal administration, are also contemplated herein.

**[00161]** Transdermal patches, including iontophoretic and electrophoretic devices, are well known to those of skill in the art. For example, such patches are disclosed in U.S. Patent

Nos. 6,267,983, 6,261,595, 6,256,533, 6,167,301, 6,024,975, 6,010,715, 5,985,317, 5,983,134, 5,948,433 and 5,860,957.

**[00162]** For example, dosage forms for rectal administration are rectal suppositories, capsules and tablets for systemic effect. Rectal suppositories are used herein mean solid bodies for insertion into the rectum which melt or soften at body temperature releasing one or more pharmacologically or therapeutically active ingredients. Substances utilized in rectal suppositories are bases or vehicles and agents to raise the melting point. Examples of bases include cocoa butter (theobroma oil), glycerin-gelatin, carbowax (polyoxyethylene glycol) and appropriate mixtures of mono-, di- and triglycerides of fatty acids. Combinations of the various bases may be used. Agents to raise the melting point of suppositories include spermaceti and wax. Rectal suppositories may be prepared either by the compressed method or by molding. The weight of a rectal suppository, in one embodiment, is about 2 to 3 gm. Tablets and capsules for rectal administration are manufactured using the same substance and by the same methods as for formulations for oral administration.

**[00163]** The compounds provided herein, or derivatives thereof, may also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated. Many such targeting methods are well known to those of skill in the art. All such targeting methods are contemplated herein for use in the instant compositions. For non-limiting examples of targeting methods, see, *e.g.*, U.S. Patent Nos. 6,316,652, 6,274,552, 6,271,359, 6,253,872, 6,139,865, 6,131,570, 6,120,751, 6,071,495, 6,060,082, 6,048,736, 6,039,975, 6,004,534, 5,985,307, 5,972,366, 5,900,252, 5,840,674, 5,759,542 and 5,709,874.

**[00164]** In some embodiments, liposomal suspensions, including tissue-targeted liposomes, such as tumor-targeted liposomes, may also be suitable as carriers. These may be prepared according to methods known to those skilled in the art. For example, liposome formulations may be prepared as described in U.S. Patent No. 4,522,811. Briefly, liposomes such as multilamellar vesicles (MLV's) may be formed by drying down phosphatidyl choline and phosphatidyl serine (7:3 molar ratio) on the inside of a flask. A solution of a compound provided herein in phosphate buffered saline lacking divalent cations (PBS) is added and the flask shaken until the lipid film is dispersed. The resulting vesicles are washed to remove unencapsulated compound, pelleted by centrifugation, and then resuspended in PBS.

**[00165]** The compounds or derivatives may be packaged as articles of manufacture containing packaging material, a compound or derivative thereof provided herein, which is effective for treatment, prevention or amelioration of one or more symptoms of the diseases or disorders, *supra*, within the packaging material, and a label that indicates that the compound or composition or derivative thereof, is used for the treatment, prevention or amelioration of one or more symptoms of the diseases or disorders, *supra*.

**[00166]** The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging products are well known to those of skill in the art. See, *e.g.*, U.S. Patent Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. A wide array of formulations of the compounds and compositions provided herein are contemplated as are a variety of treatments for any disease or disorder described herein.

### **Dosages**

**[00167]** For use to treat or prevent infectious disease, the compounds described herein, or pharmaceutical compositions thereof, are administered or applied in a therapeutically effective amount. In human therapeutics, the physician will determine the dosage regimen that is most appropriate according to a preventive or curative treatment and according to the age, weight, stage of the disease and other factors specific to the subject to be treated. The amount of active ingredient in the formulations provided herein, which will be effective in the prevention or treatment of an infectious disease will vary with the nature and severity of the disease or condition, and the route by which the active ingredient is administered. The frequency and dosage will also vary according to factors specific for each subject depending on the specific therapy (*e.g.*, therapeutic or prophylactic agents) administered, the severity of the infection, the route of administration, as well as age, body, weight, response, and the past medical history of the subject.

**[00168]** Exemplary doses of a formulation include milligram or microgram amounts of the active compound per kilogram of subject (*e.g.*, from about 1 microgram per kilogram to about 50 milligrams per kilogram, from about 10 micrograms per kilogram to about 30 milligrams per

kilogram, from about 100 micrograms per kilogram to about 10 milligrams per kilogram, or from about 100 micrograms per kilogram to about 5 milligrams per kilogram).

**[00169]** In some embodiments, a therapeutically effective dosage should produce a serum concentration of active ingredient of from about 0.001 ng/ml to about 50-200 µg/ml. The compositions, in other embodiments, should provide a dosage of from about 0.0001 mg to about 70 mg of compound per kilogram of body weight per day. Dosage unit forms are prepared to provide from about 0.01 mg, 0.1 mg or 1 mg to about 500 mg, 1000 mg or 5000 mg, and in some embodiments from about 10 mg to about 500 mg of the active ingredient or a combination of essential ingredients per dosage unit form.

**[00170]** The active ingredient may be administered at once or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data or subsequent clinical testing. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

**[00171]** It may be necessary to use dosages of the active ingredient outside the ranges disclosed herein in some cases, as will be apparent to those of ordinary skill in the art. Furthermore, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with subject response.

**[00172]** For systemic administration, a therapeutically effective dose can be estimated initially from *in vitro* assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the IC<sub>50</sub> as determined in cell culture (*i.e.*, the concentration of test compound that is lethal to 50% of a cell culture), or the IC<sub>100</sub> as determined in cell culture (*i.e.*, the concentration of compound that is lethal to 100% of a cell culture). Such information can be used to more accurately determine useful doses in humans.

[00173] Initial dosages can also be estimated from *in vivo* data (*e.g.*, animal models) using techniques that are well known in the art. One of ordinary skill in the art can readily optimize administration to humans based on animal data.

[00174] Alternatively, initial dosages can be determined from the dosages administered of known agents by comparing the IC<sub>50</sub>, MIC and/or I<sub>100</sub> of the specific compound disclosed herein with that of a known agent and adjusting the initial dosages accordingly. The optimal dosage may be obtained from these initial values by routine optimization

[00175] In cases of local administration or selective uptake, the effective local concentration compound used may not be related to plasma concentration. One of skill in the art will be able to optimize therapeutically effective local dosages without undue experimentation.

[00176] Ideally, a therapeutically effective dose of the compounds described herein will provide therapeutic benefit without causing substantial toxicity. Toxicity of compounds can be determined using standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, by determining the LD<sub>50</sub> (the dose lethal to 50% of the population) or the LD<sub>100</sub> (the dose lethal to 100% of the population). The dose ratio between toxic and therapeutic effect is the therapeutic index. Compounds which exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a dosage range that is not toxic for use in subjects. The dosage of the compounds described herein lies preferably within a range of circulating concentrations that include the effective dose with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition (See, *e.g.*, Fingl *et al.*, 1975, *In: The Pharmacological Basis of Therapeutics*, Ch.1, p.1).

[00177] The therapy may be repeated intermittently. In certain embodiments, administration of the same formulation provided herein may be repeated and the administrations may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months.

### Methods of Use of the Compounds and Compositions

**[00178]** Methods of treating, preventing, or ameliorating symptoms of medical disorders such as, for example, amyotrophic lateral sclerosis or Alzheimer's disease in a patient with the disclosed compounds and pharmaceutical compositions are described herein. Also described herein are methods of using the disclosed compounds and pharmaceutical compositions as antivirals and antimicrobial agents. In some embodiments, the disclosed compounds and pharmaceutical compositions are used to treat a patient with HIV. In other embodiments, the disclosed compounds and pharmaceutical compositions are used to treat a patient with a staphylococcus A infection. In practicing the methods, therapeutically effective amounts of the compounds or compositions, described herein, *supra*, are administered to the patient with the disorder or condition.

### **Combination Therapy**

**[00179]** The compounds and compositions disclosed herein may also be used in combination with one or more other active ingredients. In certain embodiments, the compounds may be administered in combination, or sequentially, with another therapeutic agent. Such other therapeutic agents include those known for treatment, prevention, or amelioration of one or more symptoms associated with amyotrophic lateral sclerosis or Alzheimer's disease. Other therapeutic agents include those known for treatment, prevention, or amelioration of one or more symptoms of viral or bacterial infection, particularly of HIV or staphylococcus A infection .

**[00180]** It should be understood that any suitable combination of the compounds and compositions provided herein with one or more of the above therapeutic agents and optionally one or more further pharmacologically active substances are considered to be within the scope of the present disclosure. In some embodiments, the compounds and compositions provided herein are administered prior to or subsequent to the one or more additional active ingredients.

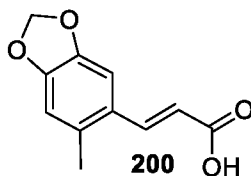
**[00181]** Finally, it should be noted that there are alternative ways of implementing the present invention. Accordingly, the present embodiments are to be considered as illustrative and not restrictive, and the invention is not to be limited to the details given herein, but may be modified within the scope and equivalents of the appended claims.

**[00182]** All publications and patents cited herein are incorporated by reference in their entirety.

[00183] The following examples are provided for illustrative purposes only and are not intended to limit the scope of the invention.

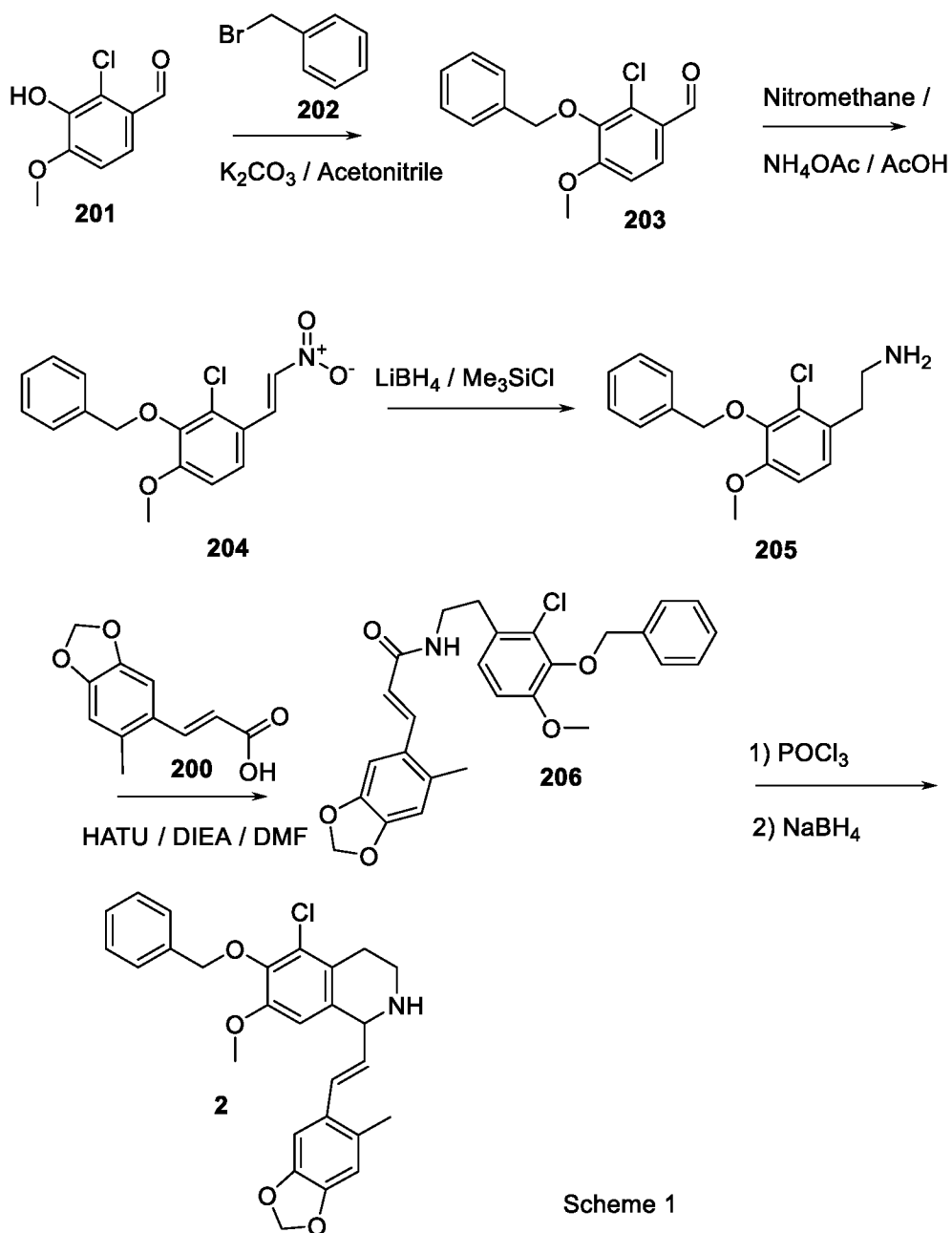
### EXAMPLES

#### General Procedure for Preparing $\alpha,\beta$ Unsaturated Carboxylic Acids: (E)-3-(6-methyl-1,3-benzodioxol-5-yl)prop-2-enoic acid (**200**)

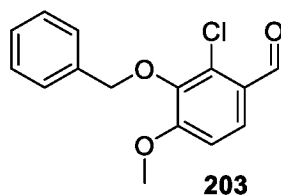


[00184] A suspension of 6-methyl-1,3-benzodioxole-5-carbaldehyde (2 g, 12.2 mmol), malonic acid (5 g, 48.8 mM), pyridine (15 mL), and piperidine (0.104 g, 0.120 mL, 1.22 mmol) was heated at 80–85 °C for 1 h and then at reflux (110–115 °C) for 3 h. The reaction mixture was poured into water and acidified with concentrated HCl. The solution was filtered, and solid was washed with cold water (2x). The residue was dissolved in aqueous NaOH and then acidified using aq HCl. The solid was filtered and then washed with cold water. The product, (E)-3-(6-methyl-1,3-benzodioxol-5-yl)prop-2-enoic acid (**200**), was used without further purification. MS (m/z): 193 [M+H].

[00185] Scheme 1 illustrates the preparation of compound **2**.



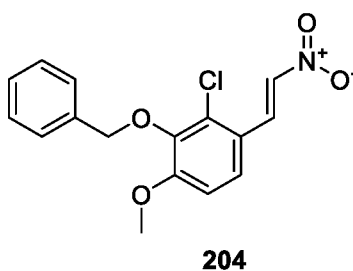
### 3-Benzyloxy-2-chloro-4-methoxy-benzaldehyde (203)



**[00186]** A mixture of 2-chloro-3-hydroxy-4-methoxybenzaldehyde (**201**) (1 g, 5.4 mmol), benzyl bromide (**202**) (1 g, 6 mmol), and anhydrous  $\text{K}_2\text{CO}_3$  (1.5 g, 10.8 mmol) in acetonitrile

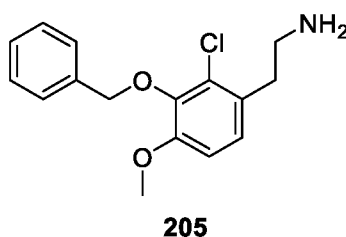
(100 mL) was stirred at 40<sup>0</sup> C for 12 h. The reaction mixture was filtered and the filtrate concentrated to dryness and redissolved in 100 mL of CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with brine (2x50 mL) and H<sub>2</sub>O (2x50 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, and evaporated to afford an off white solid of 3-benzyloxy-2-chloro-4-methoxy-benzaldehyde (**203**) (1.5g, 99%). MS (m/z): 277 [M<sup>+</sup>H].

**2-benzyloxy-3-chloro-1-methoxy-4-[(E)-2-nitrovinyl]benzene (204)**



**[00187]** A mixture of 3-benzyloxy-2-chloro-4-methoxy-benzaldehyde (**203**) (1.5 g, 5.4 mmol), nitromethane (3 g, 2.7 mL, 50 mmol), and NH<sub>4</sub>OAc (1 g, 13 mmol) in AcOH (11 mL) was refluxed for 4 h. After cooling, the mixture was diluted with H<sub>2</sub>O (100 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x30 mL). The organic solution was washed with brine (2x50 mL) and H<sub>2</sub>O (2x30 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness to afford the corresponding 2-benzyloxy-3-chloro-1-methoxy-4-[(E)-2-nitrovinyl]benzene (**204**) (1 g, 81%). MS (m/z): 320 [M<sup>+</sup>H].

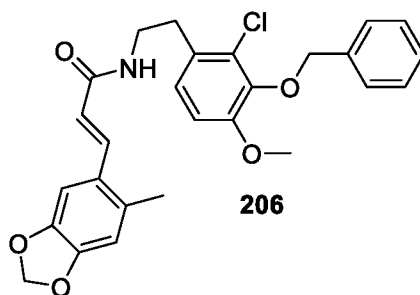
**2-(3-benzyloxy-2-chloro-4-methoxy-phenyl)ethanamine (205)**



**[00188]** To a solution of 1M LiBH<sub>4</sub>/THF (3.7ml, 3.7mmol) at room temperature and under an argon atmosphere was added dropwise Me<sub>3</sub>SiCl (906ul, 7.1mmol). After addition was complete a solution of 2-benzyloxy-3-chloro-1-methoxy-4-[(E)-2-nitrovinyl]benzene (**204**) (600 g, 1.8 mmol) in 3 mL of anhydrous THF was added dropwise. After the solution had stirred for 24h, methanol (3 ml) was added and the reaction mixture was evaporated to dryness. The residue was treated with 20% KOH (10ml) and then extracted three times with dichloromethane

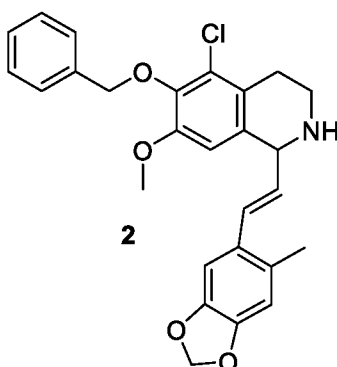
(10 ml). The combined organic extracts were dried with anhydrous  $\text{Na}_2\text{SO}_4$ , and evaporated to dryness to afford the desired 2-(3-benzyloxy-2-chloro-4-methoxy-phenyl)ethanamine (**205**) (300mg) as a crude oil which was used without further purification. MS (m/z): 292 [ $\text{M}^+\text{H}$ ].

**(E)-N-[2-(3-benzyloxy-2-chloro-4-methoxy-phenyl)ethyl]-3-(6-methyl-1,3-benzodioxol-5-yl)prop-2-enamide (**206**)**



**[00189]** To a stirred solution of (E)-3-(6-methyl-1,3-benzodioxol-5-yl)prop-2-enoic acid (**200**) (140mg, 0.68 mmol) and 2-(3-benzyloxy-2-chloro-4-methoxy-phenyl)ethanamine (**205**) (200mg, 0.68 mmol) in DMF (2 mL) was added HATU (310 g, 0.82 mmol) followed by diisopropylethylamine (351mg, 0.473 mL, 15.0 mmol). The reaction mixture was stirred at room temperature for 1 h, diluted with EtOAc (50 mL), washed with 10% citric acid, saturated aqueous solution of  $\text{NaHCO}_3$ , dried ( $\text{Na}_2\text{SO}_4$ ) filtered and purified by flash chromatography (ethyl acetate/hexanes) to provide compound **206**. Yield 114mg (35% overall yield from nitrostyrene). MS (m/z): 480 [ $\text{M}^+\text{H}$ ].

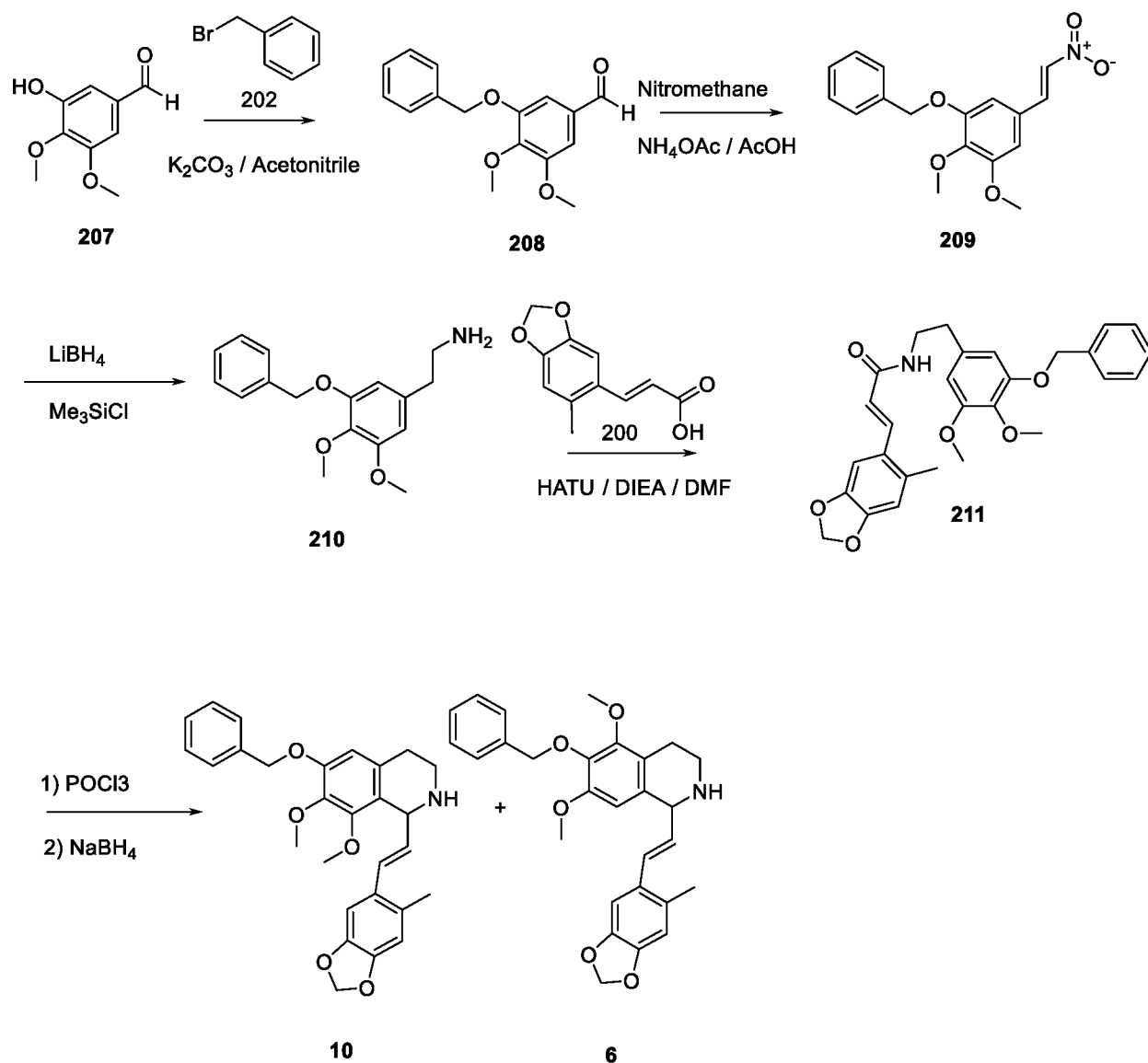
**Example 1: 6-benzyloxy-5-chloro-7-methoxy-1-[(E)-2-(6-methyl-1,3-benzodioxol-5-yl)vinyl]-1,2,3,4-tetrahydroisoquinoline (**2**)**



**[00190]** A suspension of (E)-N-[2-(3-benzyloxy-2-chloro-4-methoxy-phenyl)ethyl]-3-(6-methyl-1,3-benzodioxol-5-yl)prop-2-enamide (**206**) (114 mg, 0.24 mmol) in dry acetonitrile (10

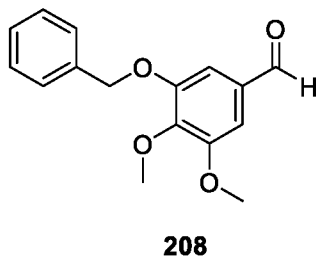
mL) was stirred and heated to reflux. Then phosphorus oxychloride (400 mg, 0.24 mL, 2.6 mmol) was added drop wise. Heating at reflux was continued for another 1h. The solution was evaporated thoroughly to dryness under high vacuum to remove excess POCl<sub>3</sub>. The residue was dissolved in chloroform (10 mL), shaken with 2M KOH (10mL) and ether (20mL). The separated upper layer was washed with water (2x10mL) and evaporated in vacuo to give an oil which was dissolved in ethanol (8mL). Then sodium borohydride (9.8mg, 0.26 mmol) was added and the mixture stirred at room temperature for 30 min. Excess reagent was destroyed by dropwise addition of 2M HCl and the reaction mixture was basified with 2M NaOH. Most of the ethanol was removed in vacuo. The residue was partitioned between water (10mL) and chloroform (10mL). The organic layer was washed with water (2x10mL). The solvent was removed in vacuo and the residue purified by column chromatography (dichloromethane/methanol) to give 6-benzyloxy-5-chloro-7-methoxy-1-[(E)-2-(6-methyl-1,3-benzodioxol-5-yl)vinyl]-1,2,3,4-tetrahydroisoquinoline (**2**) (10mg, 10%). MS(m/z): 464 [M+H].

**[00191]** Scheme 2 illustrates the synthesis of compounds **6** and **10**.



Scheme 2

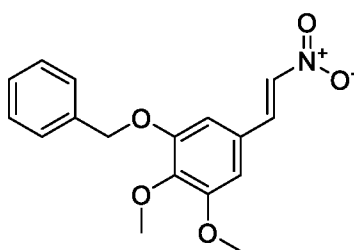
### 3-Benzyloxy-4,5-dimethoxybenzaldehyde (208)



**[00192]** A mixture of 3-hydroxy-4,5-dimethoxybenzaldehyde (**207**) (1 g, 5.5 mmol), benzyl bromide (**202**) (1 g, 6 mmol), and anhydrous  $\text{K}_2\text{CO}_3$  (1.5 g, 10.8 mmol) in acetonitrile

(100 mL) was stirred at 40<sup>0</sup> C for 12 h. The reaction mixture was filtered and the filtrate was concentrated to dryness and redissolved in 100 mL of CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with brine (2x50 mL) and H<sub>2</sub>O (2x50 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, and evaporated to afford an off white solid of 3-benzyloxy-4,5-dimethoxy-benzaldehyde (**208**) (1.2g, 80%). MS(m/z): 273 [M<sup>+</sup>H].

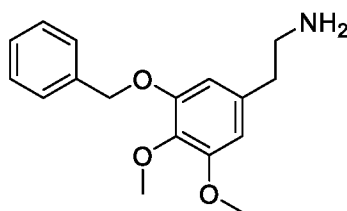
### 1-Benzyloxy-2,3-dimethoxy-5-[(E)-2-nitrovinyl]benzene (**209**)



**209**

**[00193]** A mixture of 3-benzyloxy-4,5-dimethoxybenzaldehyde (**208**) (1.2 g, 4.4 mmol), nitromethane (3 g, 2.7 mL, 50 mmol), and NH<sub>4</sub>OAc (800mg, 10 mmol) in AcOH (11 mL) was refluxed for 4 h. After cooling, the mixture was diluted with H<sub>2</sub>O (100 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x30 mL). The organic solution was washed with brine (2x50 mL) and H<sub>2</sub>O (2x30 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness to afford the corresponding 1-benzyloxy-2,3-dimethoxy-5-[(E)-2-nitrovinyl]benzene (**209**) (1.1 g, 81%). MS (m/z): 316 [M<sup>+</sup>H].

### 2-(3-benzyloxy-4,5-dimethoxy-phenyl)ethanamine (**210**)

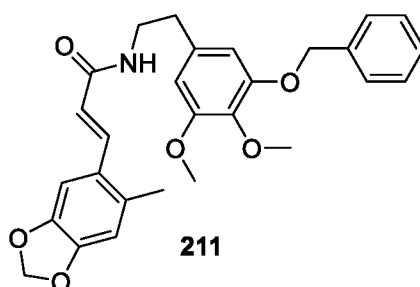


**210**

**[00194]** To a solution of 1M LiBH<sub>4</sub>/THF (5.8ml, 5.8mmol) at room temperature and under an argon atmosphere was added dropwise Me<sub>3</sub>SiCl (1.4 ml, 11 mmol). After addition was complete a solution of 1-benzyloxy-2,3-dimethoxy-5-[(E)-2-nitrovinyl]benzene (**209**) (900 g, 2.8 mmol) in 4 mL of anhydrous THF was added dropwise. After the solution had stirred for 24h, methanol (5 ml) was added and the reaction mixture was evaporated to dryness. The residue was

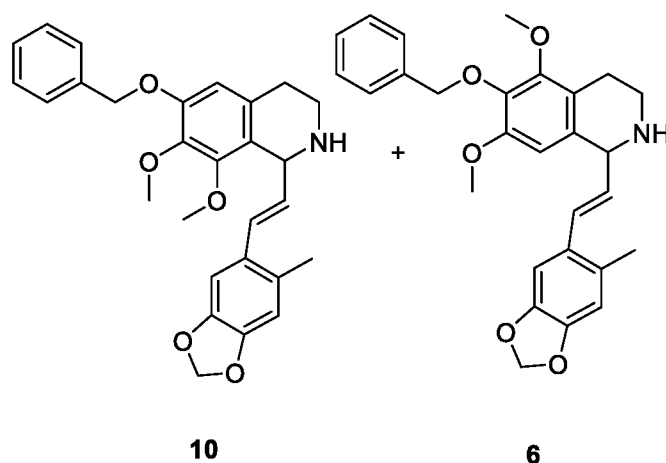
treated with 20% KOH (10ml) and then extracted three times with dichloromethane (10 ml). The combined organic extracts were dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, and evaporated to dryness to afford (3-benzyloxy-2-chloro-4-methoxy-phenyl)ethanamine (**210**) (200mg) as a crude oil which was used without further purification. MS (m/z): 288 [M<sup>+</sup>H].

**(E)-N-[2-(3-benzyloxy-4,5-dimethoxy-phenyl)ethyl]-3-(6-methyl-1,3-benzodioxol-5-yl)prop-2-enamide (**211**)**



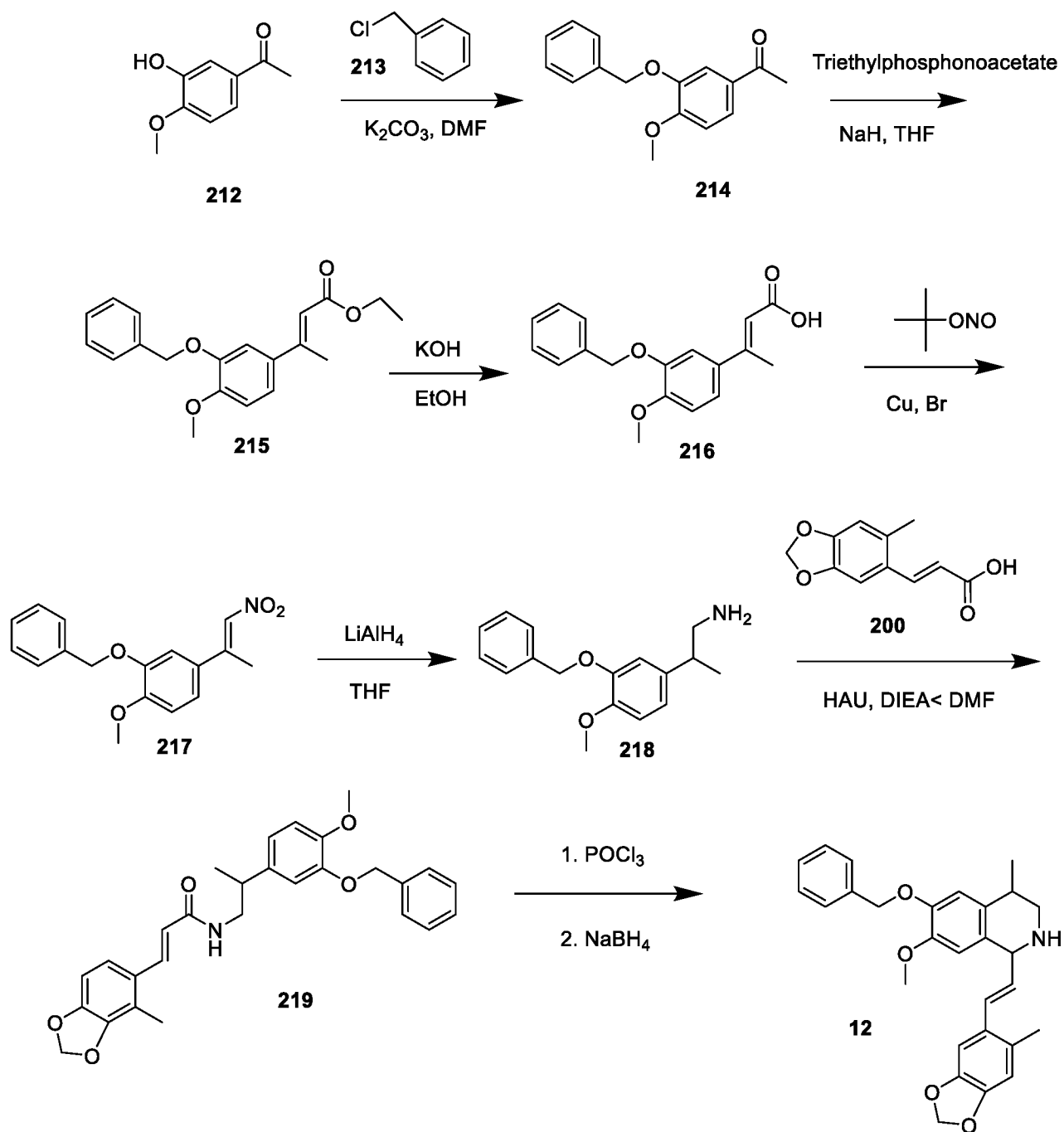
**[00195]** To a stirred solution of the (E)-3-(6-methyl-1,3-benzodioxol-5-yl)prop-2-enoic acid (143mg, 0.68 mmol) (**200**) and 2-(3-benzyloxy-4,5-dimethoxy-phenyl)ethanamine (**210**) (200mg, 0.68 mmol) in DMF (2 mL) was added HATU (310 g, 0.82 mmol) followed by diisopropylethylamine (351mg, 0.473 mL, 15.0 mmol). The reaction mixture was stirred at room temperature for 1 h, diluted with EtOAc (50 mL), washed with 10% citric acid, saturated aqueous solution of NaHCO<sub>3</sub>, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and purified by flash chromatography (ethyl acetate/hexanes) to provide compound **211**. Yield (30% overall yield from nitrostyrene). MS (m/z): 476 [M<sup>+</sup>H].

**Example 2: 6-benzyloxy-7,8-dimethoxy-1-[(E)-2-(6-methyl-1,3-benzodioxol-5-yl)vinyl]-1,2,3,4-tetrahydroisoquinoline (**10**) and 6-benzyloxy-5,7-dimethoxy-1-[(E)-2-(6-methyl-1,3-benzodioxol-5-yl)vinyl]-1,2,3,4-tetrahydroisoquinoline (**6**)**



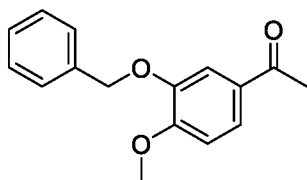
**[00196]** A suspension of (E)-N-[2-(3-benzyloxy-4,5-dimethoxy-phenyl)ethyl]-3-(6-methyl-1,3-benzodioxol-5-yl)prop-2-enamide (**211**) (90mg, 0.189 mmol) in dry acetonitrile (10 mL) was stirred and heated to reflux. Then phosphorus oxychloride (400 mg, 0.24 mL, 2.6 mmol) was added drop wise and heating at reflux was continued for a further 1h. The solution was evaporated thoroughly to dryness under high vacuum to remove excess POCl<sub>3</sub>. The residue was dissolved in chloroform (10 mL), shaken with 2M KOH (10mL) and ether (20mL). The separated upper layer was washed with water (2x10mL) and evaporated in vacuo to give an oil which was dissolved in ethanol (8mL). Then sodium borohydride (4 mg, 0.11 mmol) was added and the mixture was stirred at room temperature for 30 min. Excess reagent was destroyed by dropwise addition of 2M HCl and the reaction mixture was basified with 2M NaOH. Most of the ethanol was removed in vacuo and residue was partitioned between water (10mL) and chloroform (10mL). The organic layer was washed with water (2x10mL) and solvent was removed in vacuo. The residue was purified by RP chromatography (acetonitrile 0.1% TFA / Water 0.1% TFA) to give 10mg (11%) of 6-benzyloxy-7,8-dimethoxy-1-[(E)-2-(6-methyl-1,3-benzodioxol-5-yl)vinyl]-1,2,3,4-tetrahydroisoquinoline (**10**) and 3mg (3%) of 6-benzyloxy-5,7-dimethoxy-1-[(E)-2-(6-methyl-1,3-benzodioxol-5-yl)vinyl]-1,2,3,4-tetrahydroisoquinoline (**6**). MS(m/z): 460 [M<sup>+</sup>H] for both isomers. The structures were confirmed by making an authentic sample of 6-benzyloxy-5,7-dimethoxy-1-[(E)-2-(6-methyl-1,3-benzodioxol-5-yl)vinyl]-1,2,3,4-tetrahydroisoquinoline (**6**) using the amine 2-(3-benzyloxy-2,4-dimethoxy-phenyl)ethanamine following the same procedure outlined above.

**[00197]** Scheme 3 illustrates the preparation of compound **12**.



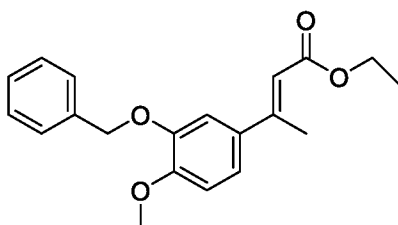
Scheme 4

**3-Benzyloxy-4-methoxy-acetophenone (214)**

**214**

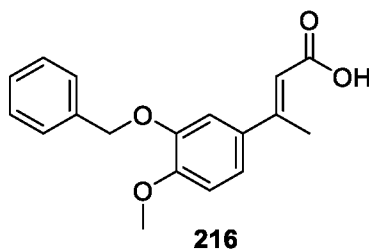
**[00198]** A mixture of 3-hydroxy-4-methoxyacetophenone (**213**) (16.6 g, 100 mmol), benzyl chloride (**214**) (13.8 mL, 120 mmol), and anhydrous  $K_2CO_3$  (20.7 g, 150 mmol) in DMF (100 mL) was heated at reflux for 5 h. The reaction mixture was concentrated to dryness, the residue was redissolved in EtOAc (100 mL) and then washed with 5% aqueous NaOH (3x30 mL). The organic layer was washed with brine (2x10 mL) and  $H_2O$  (2x30 mL), dried ( $Na_2SO_4$ ) and evaporated to a residue, which was purified by flash chromatography to provide (**214**) (22.9 g, 90%). MS (m/z): 257 [ $M^+H$ ].

#### Ethyl 3-(3-Benzyloxy-4-methoxyphenyl)-2-butenate (**215**)

**215**

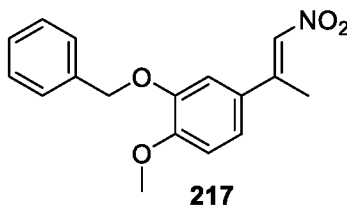
**[00199]** NaH (60 wt% in mineral oil, 1.95 g, 48.5 mmol) was suspended in THF (100 mL) and cooled to 0°C. Triethylphosphonoacetate (9.6 mL, 48.5 mmol) was added dropwise and the reaction mixture was stirred at 0°C for 30 min. Then 3-benzyloxy-4-methoxyacetophenone (**214**) (6.2 g, 24.2 mmol) was dissolved in THF (0.1 mL/mmol) and added to the reaction mixture. The cooling bath was removed and the mixture was stirred at 50°C until full conversion was detected (TLC). The reaction mixture was quenched by slow addition of  $H_2O$  (2 mL/mmol ketone), extracted with t-butyl methyl ether (3 x 3 mL/mmol) and the combined organic layers were dried ( $Na_2SO_4$ ) and evaporated to give a residue, which was purified by flash column chromatography to provide compound **215** (6.4 g, 81%). MS (m/z): 327 [ $M^+H$ ].

#### 3-(3-Benzyloxy-4-methoxyphenyl)-2-butenic acid (**216**)



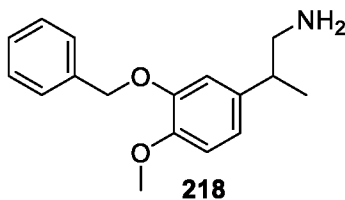
**[00200]** A mixture of ethyl ester (**215**) (6.4 g, 19.5 mmol) and alcoholic potassium hydroxide (4.0 g, 71 mmol KOH / 100 mL EtOH) was stirred at room temperature for 12h. The solution was then concentrated to give a residue, which was purified by flash column chromatography on silica gel to provide **216** (5.6 g, 96%). MS (m/z): 299 [ $M^+H$ ].

### 3-(3-Benzyloxy-4-methoxyphenyl)-1-nitro-2-butene (**217**)



**[00201]** A suspension of 3-(3-benzyloxy-4-methoxyphenyl)-2-butenic acid (**216**) (5.6 g, 18.8 mmol), CuBr (270 mg, 1.9 mmol) and tertiary butyl nitrite (8.9 mL, 37.6 mmol) in acetonitrile (50 mL) was stirred at 80 °C for 18 h. Reaction completion was monitored by TLC. After completion, the reaction mixture was cooled to room temperature, solvent was removed under reduced pressure and the crude product was purified by flash chromatography to yield compound **217** (3.9 g, 70%). MS (m/z): 300 [ $M^+H$ ].

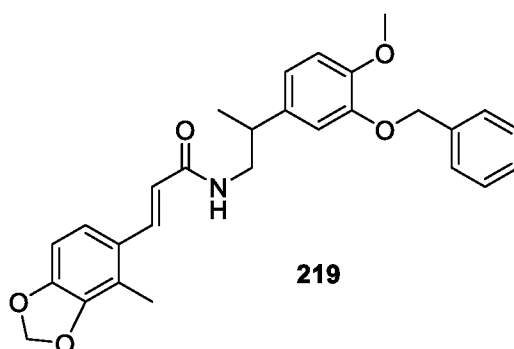
### 2-Methyl-2-(3-benzyloxy-4-methoxyphenyl)-1-aminoethane (**218**)



**[00202]** To a solution of 3-(3-benzyloxy-4-methoxyphenyl)-1-nitro-2-butene (**217**) (3.9 g, 13.2 mmol) in 40 mL of anhydrous THF under argon was slowly added a 2.0 M solution of  $LiAlH_4$  in THF (40 mL, 80 mmol) and the reaction mixture was heated at reflux for 2 h. The reaction mixture was cooled and excess reagent was quenched by dropwise addition of  $H_2O$  and 15% aqueous NaOH. The reaction mixture was extracted with  $CH_2Cl_2$  (3x30 mL) and the

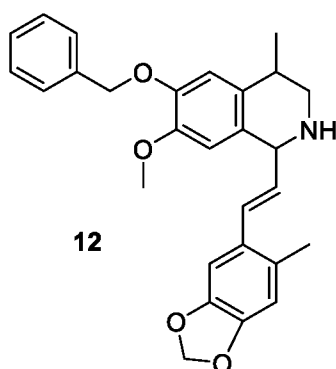
combined organic layers were treated with 5% aqueous HCl. The aqueous acid layer was then basified (5% aqueous NH<sub>4</sub>OH, pH 9) and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic solution was washed with brine (2x30 mL) and H<sub>2</sub>O (2x30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give compound **218** (2.3 g, 63%). MS (m/z): 272 [M<sup>+</sup>H].

**(E)-N-[2-(3-benzyloxy-4-methoxy-phenyl)propyl]-3-(6-methyl-1,3-benzodioxol-5-yl)prop-2-enamide (219)**



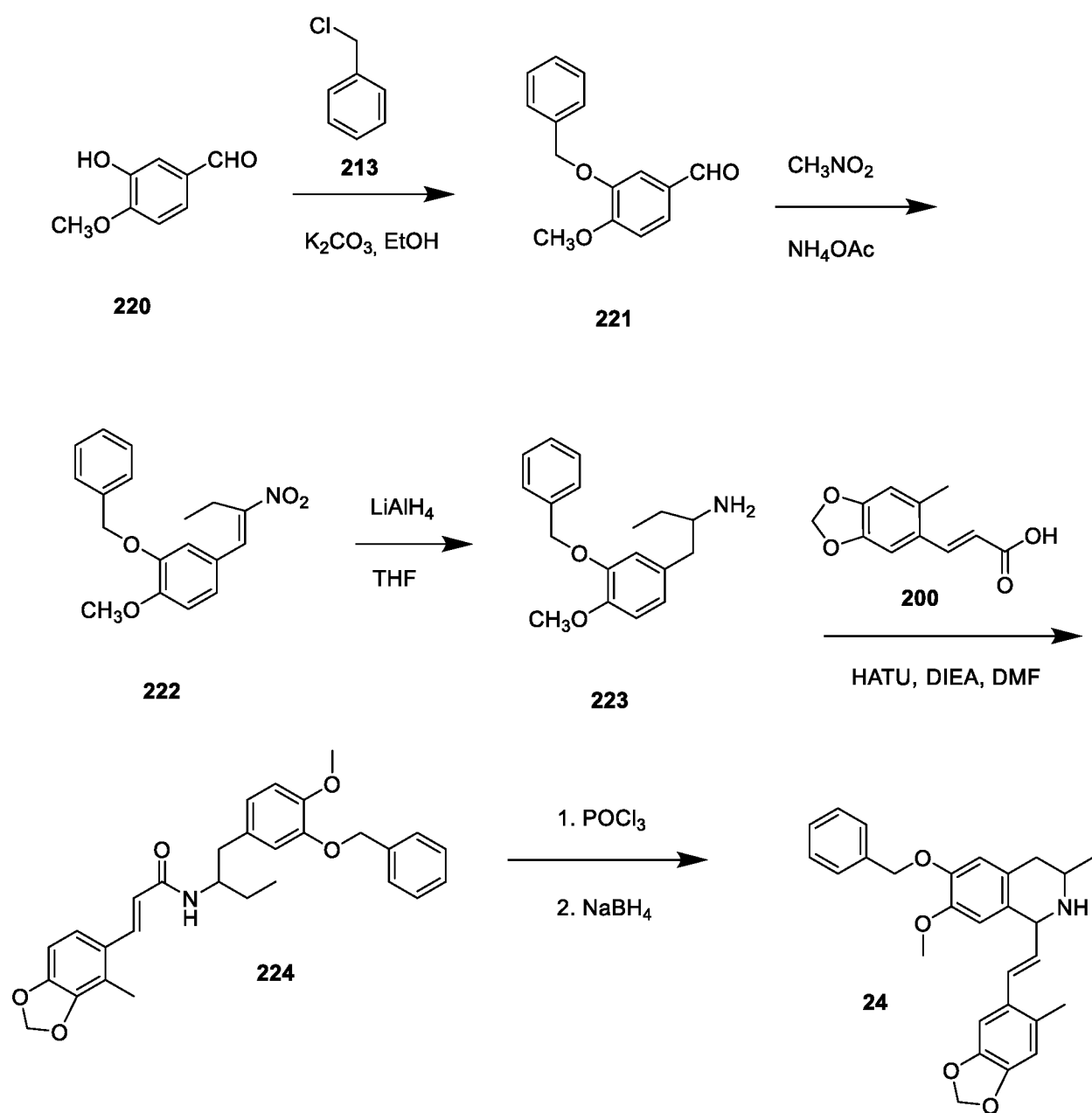
**[00203]** To the stirred solution of (E)-3-(6-methyl-1,3-benzodioxol-5-yl)prop-2-enoic acid (**200**) (140mg, 0.68 mmol) and 2-(3-benzyloxy-4-methoxy-phenyl)propylamine (**218**) (185mg, 0.68 mmol) in DMF (2 mL) was added HATU (310 g, 0.82 mmol) and diisopropylethylamine (351mg, 0.473 mL, 15.0 mmol). The reaction mixture was stirred at room temperature for 1 h, diluted with EtOAc (50 mL), washed with 10% citric acid, saturated aqueous solution of NaHCO<sub>3</sub>, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated to give a residue, which was purified by flash chromatography (ethyl acetate/hexanes) to provide compound **219**. Yield 11.4mg (35% overall yield from nitrostyrene). MS (m/z): 460 [M<sup>+</sup>H].

**Example 3: 6-Benzyloxy-7-methoxy-4-methyl-1-[(E)-2-(6-methyl-1,3-benzodioxol-5-yl)vinyl]-1,2,3,4-tetrahydroisoquinoline (12)**



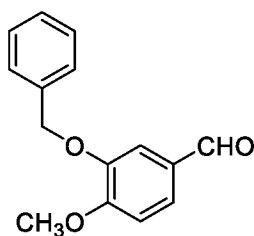
**[00204]** A suspension of (E)-N-[2-(3-benzyloxy-4-methoxy-phenyl)propyl]-3-(6-methyl-1,3-benzodioxol-5-yl)prop-2-enamide (**219**) (110 mg, 0.24 mmol) in dry acetonitrile (10 mL) was heated at reflux. Then phosphorus oxychloride (400 mg, 0.24 mL, 2.6 mmol) was added drop wise and the reaction mixture was heated at reflux for an additional 1h. The solvent and reagent were evaporated under vacuum, the organic layer was washed with water (2x10mL). and evaporated in vacuo to give an oil, which was then was dissolved in ethanol (8mL) and sodium borohydride (9.8mg, 0.26 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and excess reagent was destroyed by dropwise addition of 2M HCl. The reaction mixture was basified with 2M NaOH and ethanol was removed in vacuo to give a residue, which was partitioned between water (10mL) and chloroform (10mL). The organic layer was washed with water (2x10mL), dried and evaporated to give a residue, which was purified by column chromatography (dichloromethane/methanol) to give 6-nenzyloxy-7-methoxy-4-methyl-1-[(E)-2-(6-methyl-1,3-benzodioxol-5-yl)vinyl]-1,2,3,4-tetrahydroisoquinoline (**12**) (10mg, 10%). MS (m/z): 444 [M<sup>+</sup>H].

**[00205]** Scheme 4 illustrates the preparation of compound **24**.



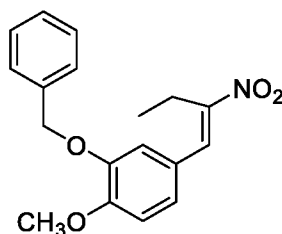
Scheme 4

**3-Benzyloxy-4-methoxybenzaldehyde (221)**

**221**

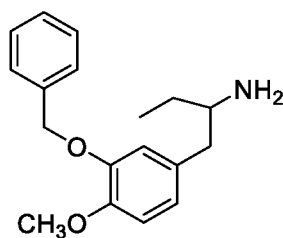
**[00206]** A mixture of isovanillin (**220**) (10.0 g, 65.7 mmol), benzyl chloride (**213**) (11.3 mL, 98.6 mmol), and anhydrous  $K_2CO_3$  (18.1 g, 131 mmol) in EtOH (100 mL) was refluxed for 5 h. After being stirred, the reaction mixture was concentrated to dryness and redissolved in 60 mL of  $CH_2Cl_2$  and then 5% aqueous NaOH (3x20 mL) was added. The organic layer was washed with brine (2x30 mL) and  $H_2O$  (2x30 mL), dried with anhydrous  $Na_2SO_4$ , and evaporated to dryness. Needles were obtained after crystallization from MeOH/ $CH_2Cl_2$  corresponding to O-benzylisovanillin(3-benzyloxy-4-methoxybenzaldehyde) (**221**) (13.5 g, 85%); mp 61-63 °C (lit. 61-64 °C). MS (m/z): 243 [M+H].

### 3-Benzyloxy-4-methoxy- $\beta$ -ethyl- $\beta$ -nitrostyrene (**222**)

**222**

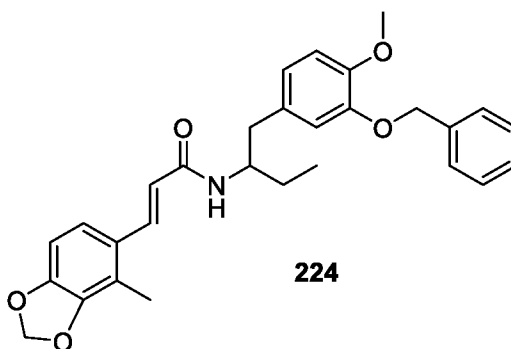
**[00207]** 3-Benzyloxy-4-methoxybenzaldehyde (2.42 g, 10 mmol) (**221**) and ammonium acetate (770mg, 10 mmol) were mixed with 1-nitropropane (9.0 mL, 100 mmol) and heated at 160°C for 22 h. The reaction mixture was then cooled to room temperature and excess 1-nitropropane was removed in vacuo. The residue was dissolved in ethyl acetate (30 mL), washed with water (10 mL), brine (10 mL), dried ( $MgSO_4$ ), filtered, concentrated in vacuo and recrystallized from ethanol (20 mL). The solid was dried in vacuo to give compound **222** as yellow powder (2.0 g, 65%). MS (m/z): 314 [M<sup>+</sup>H].

### **[00208]** 2-Amino-1-(3-benzyloxy-4-methoxyphenyl)butane (**223**)

**223**

**[00209]** To a solution of 3-benzyloxy-4-methoxy- $\beta$ -ethyl- $\beta$ -nitrostyrene (**222**) (3.1 g, 10.0 mmol) in 20 mL of anhydrous THF, a 2.0 M solution of  $\text{LiAlH}_4$  in THF (20 mL, 40 mmol) was added under argon and was refluxed for 2 h. After the solution was cooled, excess reagent was destroyed by dropwise addition of  $\text{H}_2\text{O}$  and 15% aqueous  $\text{NaOH}$ . After partial evaporation of the filtered portion, the aqueous solution was extracted with  $\text{CH}_2\text{Cl}_2$  (3x30 mL) and the organic layers were treated with 5% aqueous  $\text{HCl}$ . The resulting aqueous acid layer was made basic (5% aqueous  $\text{NH}_4\text{OH}$ , pH 9) and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic solution was washed with brine (2x30 mL) and  $\text{H}_2\text{O}$  (2x30 mL), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , and evaporated to dryness to provide 2-amino-1-(3-benzyloxy-4-methoxyphenyl)butane (**223**) (1.7 g, 60%). MS (m/z): 286  $[\text{M}^+\text{H}]$ .

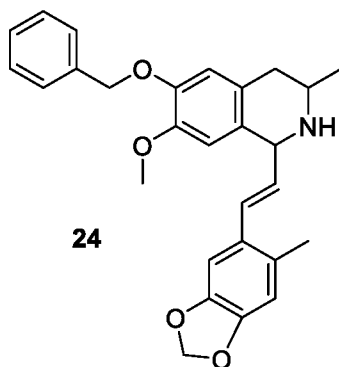
**(E)-N-[2-(3-Benzyloxy-4-methoxyphenyl)butyl]-3-(6-methyl-1,3-benzodioxol-5-yl)prop-2-enamide (224)**

**224**

**[00210]** To a stirred solution of (E)-3-(6-methyl-1,3-benzodioxol-5-yl)prop-2-enoic acid (**200**) (159 mg, 0.77 mmol) and 2-amino-1-(3-benzyloxy-4-methoxyphenyl)butane (**223**) (220mg, 0.77 mmol) in DMF (2 mL) was added HATU (351mg, 0.92 mmol) followed by diisopropylethylamine (397mg, 0.5 mL, 3.1 mmol). The reaction mixture was stirred at room temperature for 1 h. The solution was diluted with EtOAc (50 mL), washed with 10% citric acid,

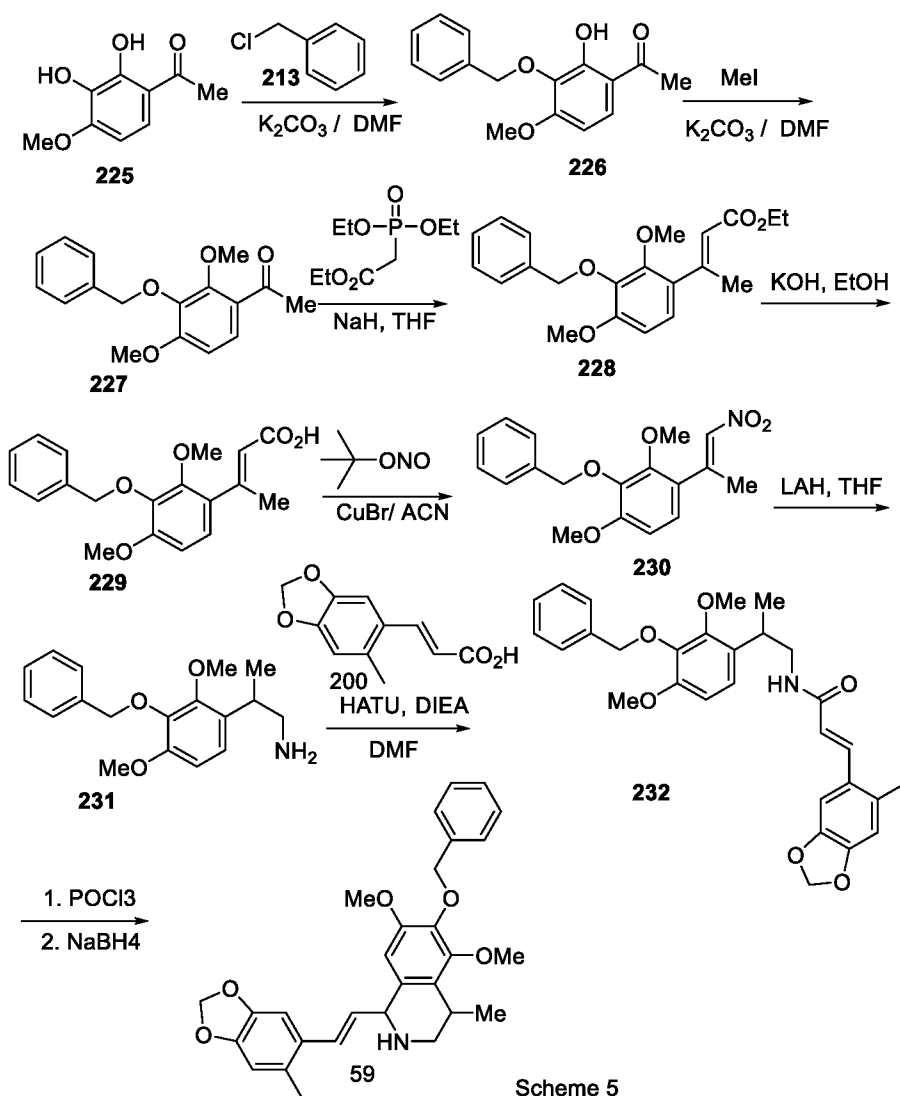
saturated aqueous solution of  $\text{NaHCO}_3$ , dried ( $\text{Na}_2\text{SO}_4$ ), filtered and purified by flash chromatography (ethyl acetate/hexanes) to give compound **224**. Yield 90mg (30% overall yield from nitrostyrene). MS (m/z): 474 [ $\text{M}^+\text{H}$ ].

**Example 4: 6-Benzyloxy-7-methoxy-3-ethyl-1-[(E)-2-(6-methyl-1,3-benzodioxol-5-yl)vinyl]-1,2,3,4-tetrahydroisoquinoline (24)**

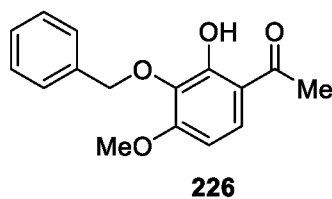


**[00211]** A suspension of (E)-N-[2-(3-benzyloxy-4-methoxy-phenyl)butyl]-3-(6-methyl-1,3-benzodioxol-5-yl)prop-2-enamide (**224**) (100mg, 0.21 mmol) in dry acetonitrile (10 mL) was stirred and heated to reflux. Then phosphorus oxychloride (223 mg, 0.14 mL, 1.5 mmol) was added drop wise and heating at reflux was continued for 1h. The solution was evaporated to dryness under high vacuum to remove excess  $\text{POCl}_3$ . The residue was dissolved in chloroform (10 mL), shaken with 2M KOH (10mL) and ether (20mL). The separated upper layer was washed with water (2x10mL). and evaporated in vacuo to give an oil which was dissolved in ethanol (8mL). Then sodium borohydride (5.6mg, 0.15 mmol) was added and the mixture stirred at room temperature for 30 min. Excess reagent was destroyed by dropwise addition of 2M HCl. The reaction mixture was then basified with 2M NaOH and most of the ethanol removed in vacuo. The residue was partitioned between water (10mL) and chloroform (10mL). The organic layer was washed with water (2x10mL) and the solvent was removed in vacuo. The residue was purified by RP chromatography (acetonitrile 0.1% TFA/water 0.1% TFA) to give 10mg (11%) of 6-benzyloxy-7-methoxy-3-ethyl-1-[(E)-2-(6-methyl-1,3-benzodioxol-5-yl)vinyl]-1,2,3,4-tetrahydroisoquinoline (**24**). MS (m/z): 458 [ $\text{M}^+\text{H}$ ].

**[00212]** Scheme 5 illustrates the preparation of compound **59**.



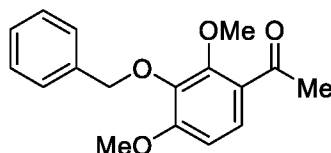
### Preparation of Benzyl Ether of 2,3-dihydroxy-4-methoxyacetophenone (226)



**[00213]** A mixture of 2,3-dihydroxy-4-methoxyacetophenone (**225**) (9.1 g, 50 mmol), benzyl chloride (**213**) (7.6 g, 60 mmol), and anhydrous  $K_2CO_3$  (10.35 g, 75 mmol) in DMF (50 mL) was refluxed for 5 h. The reaction mixture was concentrated to dryness and redissolved in 100 mL of EtOAc and then 5% aqueous NaOH (3x30 mL) was added. The organic layer was

washed with brine (2x30 mL) and H<sub>2</sub>O (2x30 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, evaporated to dryness and purified by flash chromatography to provide compound **226**. MS (m/z): 273<sup>+</sup>[H].

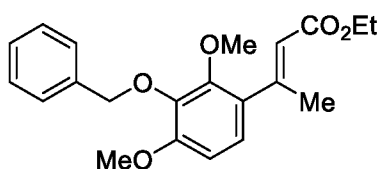
**Preparation of Methyl Ether of Benzyl Ether of 2,3-dihydroxy-4-methoxyacetophenone (227)**



**227**

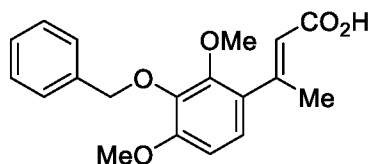
**[00214]** A mixture of hydroxyl acetophenone (**226**) (6.8 g, 25 mmol), methyl iodide (7.05 g, 50 mmol), and anhydrous K<sub>2</sub>CO<sub>3</sub> (1.43 g, 37.5 mmol) in DMF (50 mL) was stirred for 12 h at room temperature. The reaction mixture was concentrated to dryness, redissolved in 100 mL of EtOAc and 5% aqueous NaOH (3x30 mL) was added. The organic layer was washed with brine (2x30 mL) and H<sub>2</sub>O (2x30 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, evaporated to dryness and purified with flash chromatography to provide compound **227**. MS (m/z): 287 (M<sup>+</sup>H).

**Preparation of unsaturated ester (228)**

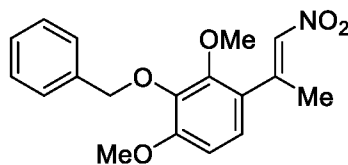


**228**

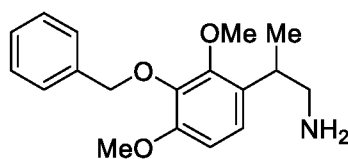
**[00215]** NaH (60 wt% in mineral oil, 1.95 g, 48.5 mmol) was suspended in THF (100 mL) and cooled to 0°C. Triethylphosphonoacetate (9.6 mL, 48.5 mmol) was added dropwise and the reaction mixture was stirred at 0°C for 30 min. A solution of acetophenone (6.92 g, 24.2 mmol) in THF was added slowly to the reaction mixture. The cooling bath was removed and the mixture was stirred at 50°C until full conversion was detected (TLC). After quenching the reaction by addition of H<sub>2</sub>O (2 ml/mmol of ketone), the aqueous phase was extracted with t-butyl methyl ether (3 x 30 ml/mmol) and the combined organic layers are dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. All volatiles were removed under reduced pressure and the crude product was purified by flash column chromatography to give compound **228**. MS (m/z): 357 [M<sup>+</sup>H].

**3-(3-Benzyloxy-2,4-dimethoxyphenyl)-2-butenic acid (229)****229**

**[00216]** A mixture of ethyl ester (**228**) (6.94 g, 19.5 mmol) and alcoholic potassium hydroxide (4.0 g, 71 mmol KOH/100 mL EtOH) was stirred at room temperature for 12 h. Solvent was removed and the residue was purified by flash column chromatography to give the acid (**229**). MS (m/z): 329 [M+H].

**3-(3-Benzyloxy-2,4-dimethoxyphenyl)-1-nitro-2-butene (230)****230**

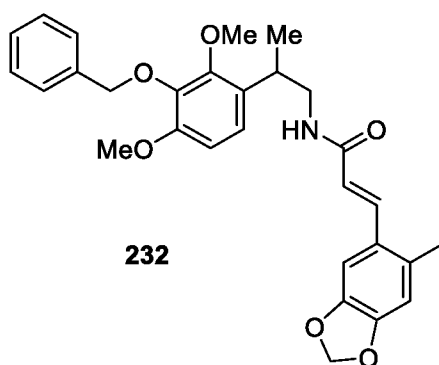
**[00217]** A mixture of 3-(3-benzyloxy-2,4-dimethoxyphenyl)-2-butenic acid (**229**) (6.16 g, 18.8 mmol), CuBr (270 mg, 1.9 mmol), tertiary butyl nitrite (8.9 mL, 37.6 mmol) and acetonitrile (50 mL) was stirred at 80°C for 12-18 h until judged complete by TLC. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue was purified by flash chromatography to provide compound **230**. MS (m/z): 330 [M<sup>+</sup>H].

**2-Methyl-2-(3-benzyloxy-4-methoxyphenyl)-1-aminoethane (231)****231**

**[00218]** To a solution of 3-(3-benzyloxy-2,4-dimethoxyphenyl)-1-nitro-2-butene (**230**) (4.34 g, 13.2 mmol) in 40 mL of anhydrous THF was added a 2.0 M solution of LiAlH<sub>4</sub> in THF (40 mL, 80 mmol) under argon and the reaction mixture was heated at reflux for 2 h. The solution then was cooled, the excess reagent was destroyed by dropwise addition of H<sub>2</sub>O and 15% aqueous NaOH. After partial evaporation of the filtered portion, the aqueous solution was

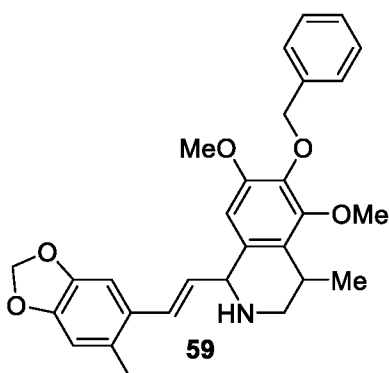
extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x30 mL) and the organic layers were treated with 5% aqueous HCl. The resulting aqueous acid layer was made basic (5% aqueous NH<sub>4</sub>OH, pH 9) and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic solution was washed with brine (2x30 mL) and H<sub>2</sub>O (2x30 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, and evaporated to give 2-methyl-2-(3-benzyloxy-2,4-dimethoxyphenyl)-1-aminoethane (**231**). MS (m/z): 302 [M<sup>+</sup>H].

**(E)-N-[2-(3-benzyloxy-2,4-dimethoxy-phenyl)propyl]-3-(6-methyl-1,3-benzodioxol-5-yl)prop-2-enamide (**232**)**



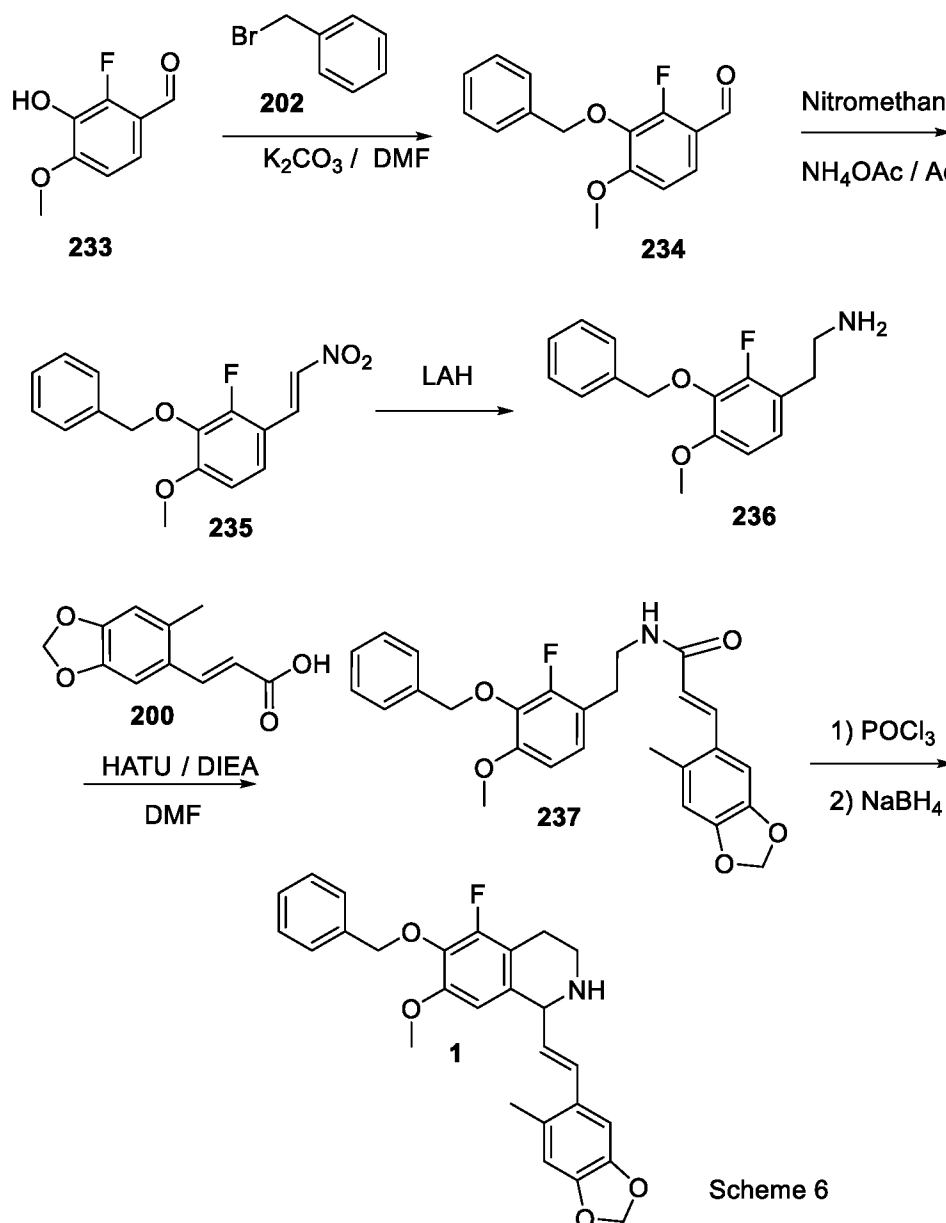
**[00219]** To a stirred solution of (E)-3-(6-methyl-1,3-benzodioxol-5-yl)prop-2-enoic acid (140mg, 0.68 mmol) (**200**) and 2-(3-benzyloxy-2,4-dimethoxy-phenyl)propylamine (**231**) (205 mg, 0.68 mmol) in DMF (5 mL) was added HATU (310 g, 0.82 mmol) and diisopropylethylamine (351mg, 0.473 mL, 15.0 mmol). The reaction mixture was stirred at room temperature for 1 h, diluted with EtOAc (50 mL), washed with 10% citric acid, saturated aqueous solution of NaHCO<sub>3</sub>, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated to give a residue, which was purified by flash chromatography (ethyl acetate/hexanes) to give compound **232**. MS (m/z): 490 [M<sup>+</sup>H].

**Example 5: 6-Benzyloxy-5,7-dimethoxy-4-methyl-1-[(E)-2-(6-methyl-1,3-benzodioxol-5-yl)vinyl]-1,2,3,4-tetrahydroisoquinoline (**59**)**

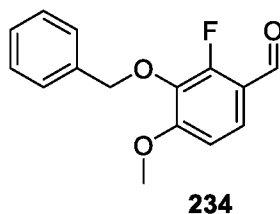


**[00220]** A suspension of (E)-N-[2-(3-benzyloxy-2,4-dimethoxy-phenyl)propyl]-3-(6-methyl-1,3-benzodioxol-5-yl)prop-2-enamide (**232**) (118 mg, 0.24 mmol) in dry acetonitrile (10 mL) was stirred and heated at reflux. Then phosphorus oxychloride (400 mg, 0.24 mL, 2.6 mmol) was added drop wise and heating at reflux was continued for an additional 1h. The reaction mixture was then evaporated under vacuum to give a residue which was dissolved in chloroform (20 mL), washed with 2M KOH (10mL) and water (2x10mL). The organic layer was dried and evaporated to give an oil which was dissolved in ethanol (8mL) to which sodium borohydride (9.8mg, 0.26 mmol) was slowly added. The reaction mixture was stirred at room temperature for 30 min, excess reagent was destroyed by dropwise addition of 2M HCl. The reaction mixture was then basified with 2M NaOH and extracted with chloroform (3x20 mL). The combined organic extracts were dried and evaporated to provided 6-benzyloxy-5,7-dimethoxy-4-methyl-1-[(E)-2-(6-methyl-1,3-benzodioxol-5-yl)vinyl]-1,2,3,4-tetrahydroisoquinoline (**59**). MS(m/z): 474 [ $M^+H$ ].

**[00221]** Scheme 6 illustrate the synthesis of compound **1**.



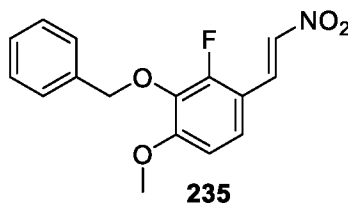
### 3-Benzyloxy-2-fluoro-4-methoxy-benzaldehyde (234)



**[00222]** A mixture of 2-fluoro-3-hydroxy-4-methoxybenzaldehyde (**233**) (1 g, 5.4 mmol, 1.0 eq), benzyl bromide (**202**) (1.36 g, 7.93 mmol, 1.5 eq) and anhydrous  $K_2CO_3$  (0.9 g, 5.29 mmol) in DMF (15 mL) was stirred at 60<sup>0</sup> C for 12 h. The reaction mixture was diluted with

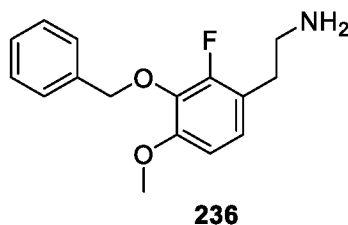
ethylacetate (50 mL) and then washed with water (2x25 mL) and brine (1x25 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated to give a residue, which was purified by column chromatography to 3-benzyloxy-2-fluoro-4-methoxy-benzaldehyde (**234**). MS(m/z): 261 [M<sup>+</sup>H].

**2-benzyloxy-3-fluoro-1-methoxy-4-[(E)-2-nitrovinyl]benzene (235)**



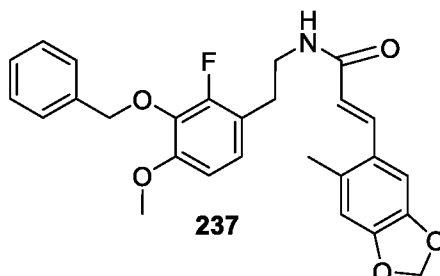
**[00223]** A mixture of 3-benzyloxy-2-Fluoro-4-methoxy-benzaldehyde (**234**) (1.4 g, 5.4 mmol), nitromethane (3 g, 2.7 mL, 50 mmol) and NH<sub>4</sub>OAc (1 g, 13 mmol) in AcOH (11 mL) was refluxed for 4 h. After cooling, the mixture was diluted with H<sub>2</sub>O (100 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x30 mL). The combined organic extracts were washed with brine (2x50 mL) and H<sub>2</sub>O (2x30 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness to afford the corresponding 2-benzyloxy-3-fluoro-1-methoxy-4-[(E)-2-nitrovinyl]benzene (**235**). MS (m/z): 304 [M<sup>+</sup>H].

**2-(3-benzyloxy-2-Fluoro-4-methoxy-phenyl)ethanamine (236)**



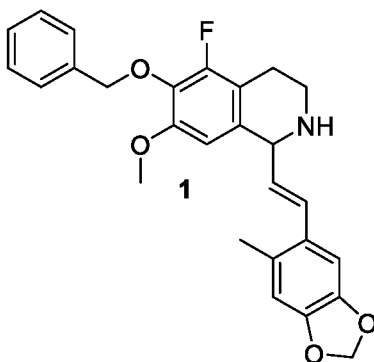
**[00224]** To a solution of 2-benzyloxy-3-fluoro-1-methoxy-4-[(E)-2-nitrovinyl]benzene (**235**) (1.6 g, 5.29 mmol) in THF (20 mL) in an ice bath was added dropwise LiAlH<sub>4</sub> in THF (15.85 mL, 31.7 mmol). After addition was complete, the reaction mixture was heated at reflux for 12 h, cooled to 0 °C and water (1.2 mL) and 15% NaOH (1.2 mL) were added followed by water (3x1.2 mL) and the reaction mixture was stirred at room temperature for 30 min. Ethyl acetate (100 mL) was added, the reaction mixture stirred for an additional 30 min, filtered through a pad of celite, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give 2-(3-benzyloxy-2-fluoro-4-methoxy-phenyl)ethanamine (**236**) as a viscous solid, which was used in the next step without further purification. MS(m/z): 276 [M<sup>+</sup>H].

**(E)-N-[2-(3-Benzyloxy-2-fluoro-4-methoxy-phenyl)ethyl]-3-(6-methyl-1,3-benzodioxol-5-yl)prop-2-enamide (237)**



**[00225]** To a stirred solution of the (E)-3-(6-methyl-1,3-benzodioxol-5-yl)prop-2-enoic acid (**200**) (140mg, 0.68 mmol) and 2-(3-benzyloxy-2-fluoro-4-methoxy-phenyl)ethanamine (**236**) (187 mg, 0.68 mmol) in DMF (10 mL) was added HATU (312 g, 0.82 mmol) followed by diisopropylethylamine (439 mg, 3.4 mmol). The reaction mixture was stirred at room temperature for 1 h, diluted with EtOAc (50 mL), washed with 10% citric acid, saturated aqueous NaHCO<sub>3</sub>, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and purified by flash chromatography (ethyl acetate/hexanes) to give compound **237**. MS (m/z): 464 [M<sup>+</sup>H].

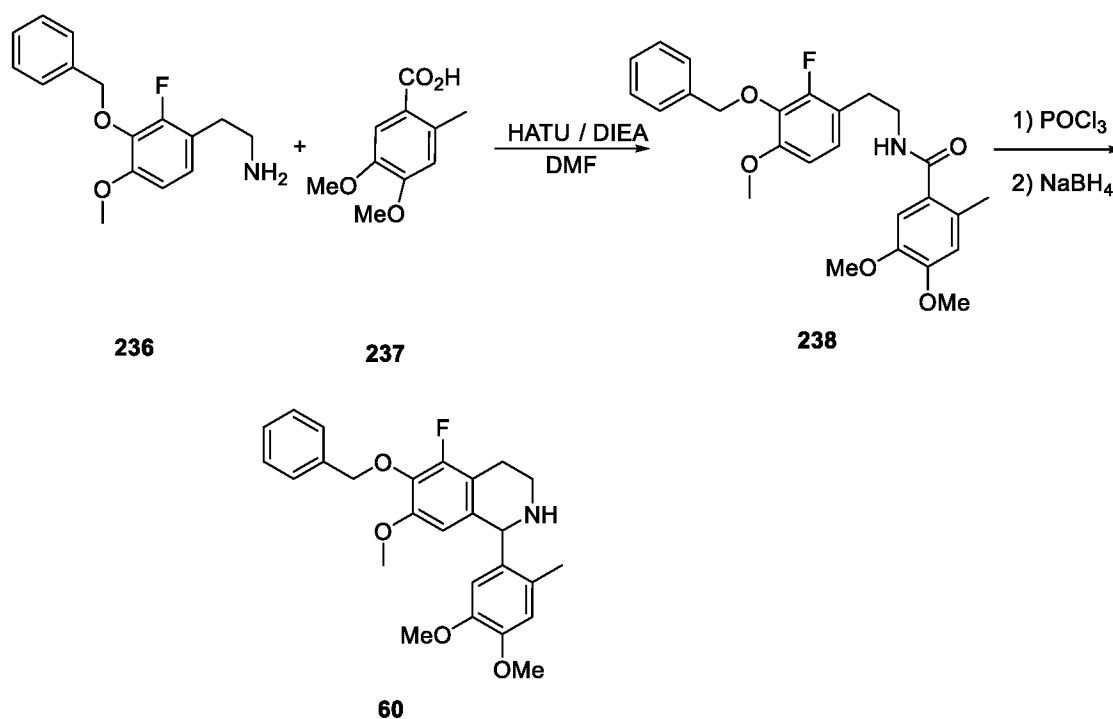
**Example 6: 6-Benzyloxy-5-fluoro-7-methoxy-1-[(E)-2-(6-methyl-1,3-benzodioxol-5-yl)vinyl]-1,2,3,4-tetrahydroisoquinoline (1)**



**[00226]** A suspension of (E)-N-[2-(3-benzyloxy-2-fluoro-4-methoxy-phenyl)ethyl]-3-(6-methyl-1,3-benzodioxol-5-yl)prop-2-enamide (**237**) (111 mg, 0.24 mmol) in dry acetonitrile (10 mL) was stirred and heated to reflux. Then phosphorus oxychloride (400 mg, 0.24 mL, 2.6 mmol) was added dropwise and heated at reflux for another 1h. The solution was evaporated to dryness under high vacuum to remove excess POCl<sub>3</sub>. The residue was dissolved in chloroform (10 mL), shaken with 2M KOH (10mL) and ether (20mL). The separated upper layer was washed with water (2x10mL). and evaporated in vacuo to give an oil which was dissolved in

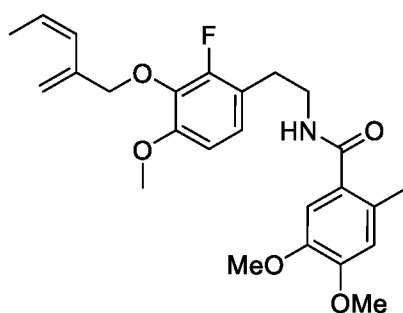
methanol (8mL). Then sodium borohydride (9.8mg, 0.26 mmol) was added. The mixture was stirred at room temperature for 2h. Solvent was evaporated and the residue was taken in ethyl acetate and then saturate  $\text{NaHCO}_3$  solution was added and the reaction mixture was stirred at room temperature for 30 min. The organic layer was dried ( $\text{MgSO}_4$ ) and evaporated to give a residue, which was purified by column chromatography (dichloromethane/methanol) to give the desired 6-benzyloxy-5-fluoro-7-methoxy-1-[(E)-2-(6-methyl-1,3-benzodioxol-5-yl)vinyl]-1,2,3,4-tetrahydroisoquinoline (**1**). MS (m/z): 448 [ $\text{M}^+\text{H}$ ].

[00227] Scheme 7 illustrates the preparation of compound **60**.



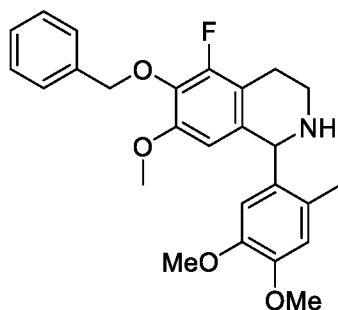
Scheme 7

(E)-N-[2-(3-Benzyloxy-2-fluoro-4-methoxy-phenyl)ethyl]-3-(6-methyl-1,3-benzodioxol-5-yl)prop-2-enamide (**238**)

**238**

**[00228]** To a stirred solution of 4,5-dimethoxy-2-methyl-benzoic acid (**237**) (133mg, 0.68 mmol) and 2-(3-benzyloxy-2-fluoro-4-methoxy-phenyl)ethanamine (**236**) (187 mg, 0.68 mmol) in DMF (5 mL) were added HATU (312 g, 0.82 mmol) and diisopropylethylamine (439 mg, 3.4 mmol). The reaction mixture was stirred at room temperature for 1 h. The solution was diluted with EtOAc (50 mL), washed with 10% aq. HCl acid, saturated aqueous NaHCO<sub>3</sub>, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and was purified by flash chromatography (ethyl acetate/hexanes) to give compound **238**. MS (m/z): 454 [M<sup>+</sup>H].

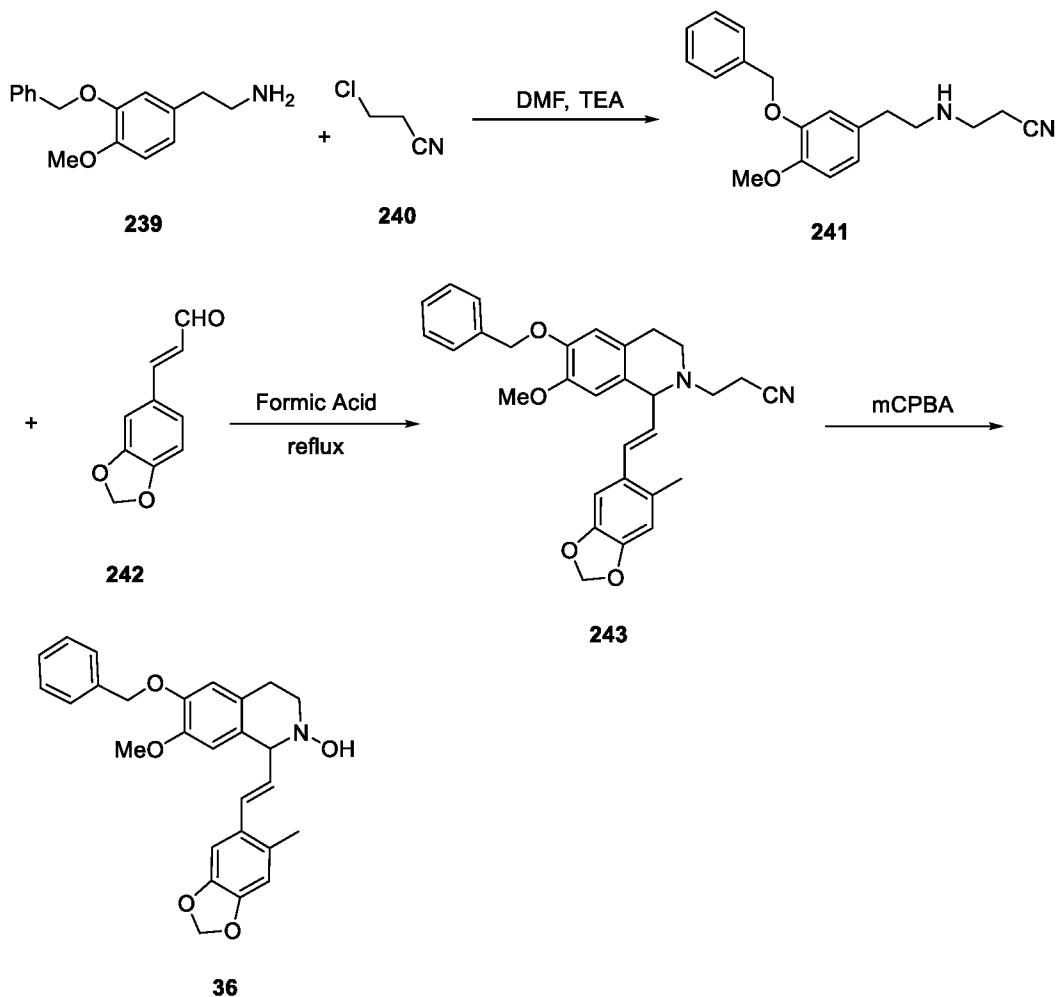
#### Example 7: Preparation of Compound 60

**60**

**[00229]** A suspension of the amide (109 mg, 0.24 mmol) in dry acetonitrile (10 mL) was stirred and heated to reflux. Then phosphorus oxychloride (400 mg, 0.24 mL, 2.6 mmol) was added drop wise and heating at reflux was continued for another 1h. The solution was evaporated to dryness under high vacuum to remove excess POCl<sub>3</sub>. The residue was dissolved in chloroform (10 mL), shaken with 2M KOH (10mL) and ether (20mL). The separated upper layer was washed with water (2x10mL), evaporated in vacuo to give an oil and dissolved in methanol (8mL). Then sodium borohydride (9.8mg, 0.26 mmol) was added and the mixture stirred at room temperature for 2h. The solvent was evaporated and the residue was taken in ethyl acetate and then saturated NaHCO<sub>3</sub> solution was added and the reaction mixture was stirred

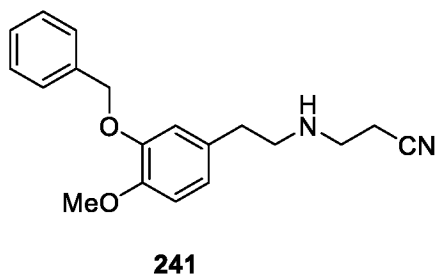
at room temperature for 30 min. The organic layer was dried ( $\text{MgSO}_4$ ) and evaporated to give a residue, which was purified by column chromatography (dichloromethane/methanol) to give the 1,2,3,4-tetrahydroisoquinoline (**60**). MS ( $m/z$ ): 438 [ $\text{M}^+\text{H}$ ].

[00230] Scheme 8 illustrates the preparation of compound **36**.



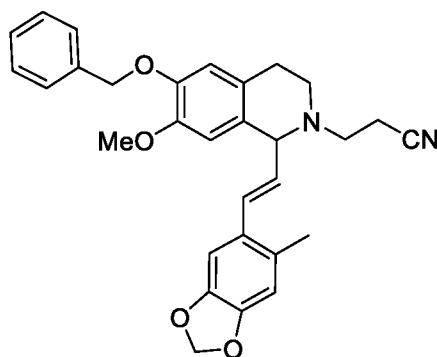
Scheme 8

#### Preparation of Amine 241



**[00231]** To a solution of amine (1.29 g, 5.0 mmol, 1.0 eq) in Dry DMF (5 mL) were added triethylamine (606 mg, 6.0 mmol, 1.2 eq) and 3-chloropropionitrile (68 mg, 5.5 mmol, 1.1 eq) and the reaction mixture was stirred at rt. The reaction mixture was quenched by addition of water (20 mL) and extracted with DCM (3 x 30 mL), combined organic layers were washed with saturated NaCl solution (1 x 30 mL), dried (MgSO<sub>4</sub>) and evaporated under vacuum to give a residue which was purified by column chromatography (DCM, MeOH) to give amine **241**. MS(m/z): 311 [M<sup>+</sup>H].

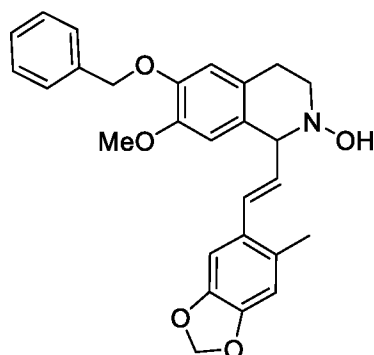
**3-[6-benzyloxy-7-methoxy-1-[(E)-2-(6-methyl-1,3-benzodioxol-5-yl)vinyl]-3,4-dihydro-1H-isoquinolin-2-yl]propanenitrile (243)**



**243**

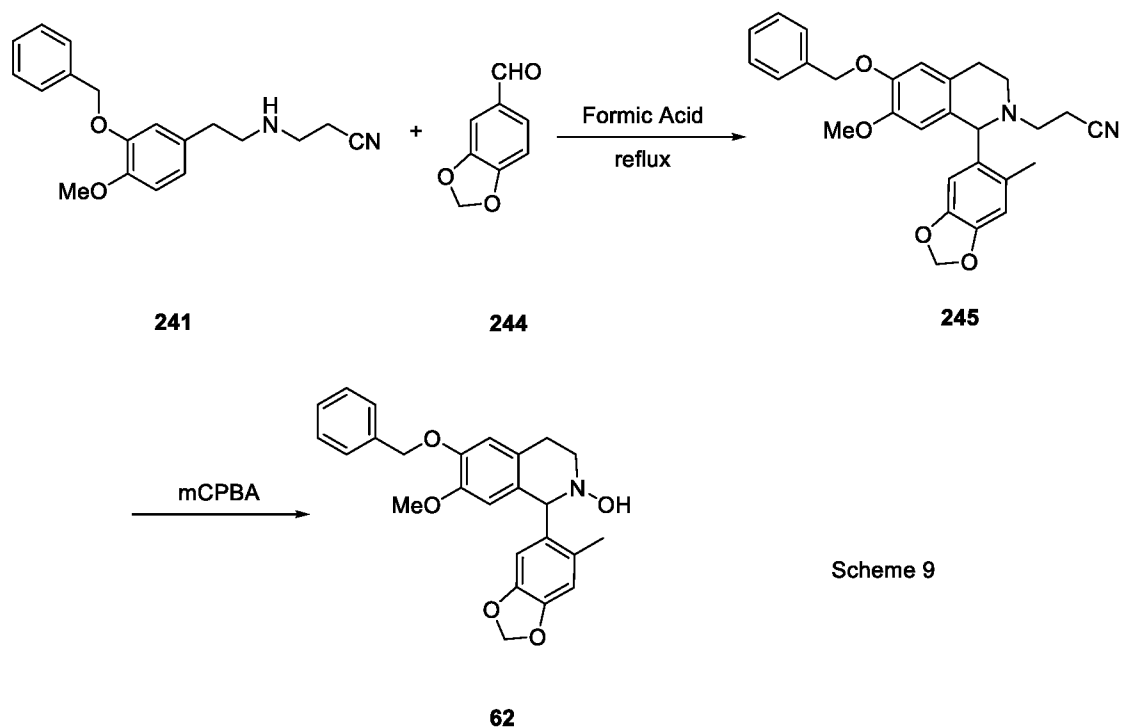
**[00232]** A solution of amine (**241**) (100 mg, 0.323 mmol, 1.0 eq) and aldehyde (**242**) (68 mg, 0.387 mmol, 1.2 eq) in formic acid (mL) was heated at 80 °C for 24 h. Excess formic acid was removed under vacuum to give a residue. The residue was taken in ethylacetate and then saturated NaHCO<sub>3</sub> was carefully added and the mixture was stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were dried (MgSO<sub>4</sub>) and evaporated under vacuum to give a residue which was purified by column chromatography (DCM, MeOH) to give 3-[6-benzyloxy-7-methoxy-1-[(E)-2-(6-methyl-1,3-benzodioxol-5-yl)vinyl]-3,4-dihydro-1H-isoquinolin-2-yl]propanenitrile (**243**). MS(m/z):483 [M+H].

**Example 8: 6-benzyloxy-2-hydroxy-7-methoxy-1-[(E)-2-(6-methyl-1,3-benzodioxol-5-yl)vinyl]-3,4-dihydro-1H-isoquinoline (36)**

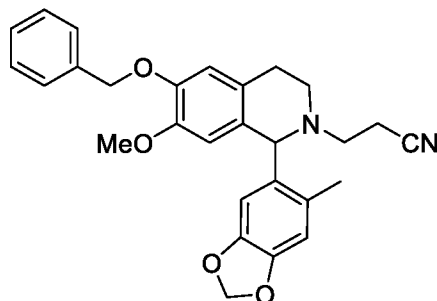
**36**

**[00233]** To a solution of 3-[6-benzyloxy-7-methoxy-1-[(E)-2-(6-methyl-1,3-benzodioxol-5-yl)vinyl]-3,4-dihydro-1H-isoquinolin-2-yl]propanenitrile (**243**) (48 mg, 0.1 mmol) at  $-78^{\circ}\text{C}$ , under argon was added with stirring m-chloroperoxybenzoic acid (19mg, 0.11mmol) in dichloromethane (0.2ml). After 1h at  $-78^{\circ}\text{C}$  for 1h the reaction was allowed to warm to room temperature and stirred there overnight. The mixture was evaporated to dryness and the residue purified via RP chromatography (acetonitrile 0.1% TFA/water 0.1% TFA) to give 6-benzyloxy-2-hydroxy-7-methoxy-1-[(E)-2-(6-methyl-1,3-benzodioxol-5-yl)vinyl]-3,4-dihydro-1H-isoquinoline. MS (m/z): 446  $[\text{M}^+\text{H}]$ .

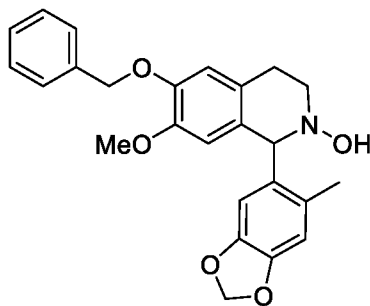
**[00234]** Scheme 9 illustrates the preparation of compound **62**.



Scheme 9

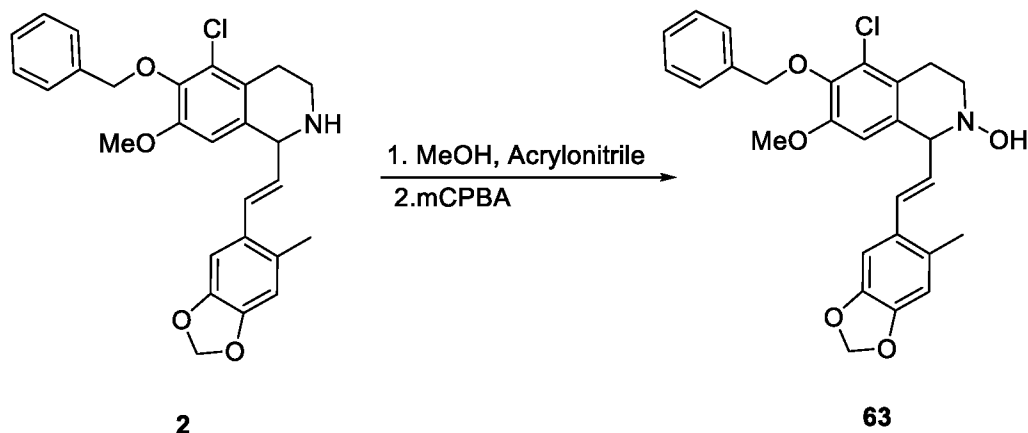
**Preparation of Compound 245****245**

**[00235]** A solution of amine (**241**) (100 mg, 0.323 mmol, 1.0 eq) and aldehyde (**244**) (58 mg, 0.387 mmol, 1.2 eq) in formic acid (mL) was heated at 80 °C for 24 h. Excess formic acid was removed under vacuum to give a residue. The residue was taken in ethyl acetate and then saturated NaHCO<sub>3</sub> was carefully added and the mixture was stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were dried (MgSO<sub>4</sub>) and evaporated under vacuum to give a residue which was purified by column chromatography (DCM, MeOH) to give compound **245**. MS (m/z): 457 [M<sup>+</sup>H].

**Example 9: Preparation of Compound 62****62**

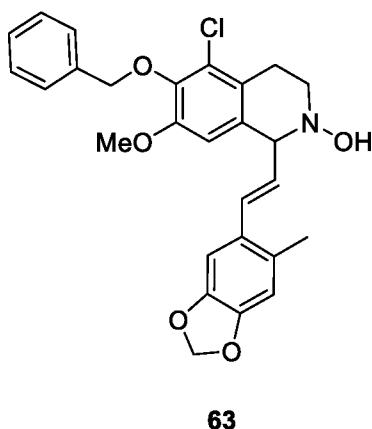
**[00236]** To a solution of nitrile (**245**) (46 mg, 0.1 mmol) at -78<sup>0</sup> C under argon was added m-chloroperoxybenzoic acid (19 mg, 0.11mmol) with stirring in dichloromethane (0.2ml). After stirring at -78<sup>0</sup> C for 1h, the reaction was allowed to warm to room temperature and stirred overnight. The mixture was evaporated to dryness and the residue purified via RP chromatography (acetonitrile 0.1% TFA/Water 0.1% TFA) to give compound **62**. MS (m/z): 420 [M<sup>+</sup>H].

[00237] Scheme 10 illustrates the preparation of compound **63**.



Scheme 10

**Example 10: 6-benzyloxy-5-Chloro-2-hydroxy-7-methoxy-1-[(E)-2-(6-methyl-1,3-benzodioxol-5-yl)vinyl]-3,4-dihydro-1H-isoquinoline (**63**)**



[00238] Using the procedure of Grassl et al, Organic Letters (2019), 21(2), 494-497, a solution of 6-benzyloxy-5-Chloro-7-methoxy-1-[(E)-2-(6-methyl-1,3-benzodioxol-5-yl)vinyl]-1,2,3,4-tetrahydroisoquinoline (**2**) (46 mg, 0.1 mmol) in MeOH (0.2ml) was treated at room temperature with acrylonitrile (33ul, 0.5mmol) and stirred overnight at 55<sup>0</sup> C. The mixture was evaporated to dryness affording 3-[4-chloro-6-benzyloxy-7-methoxy-1-[(E)-2-(6-methyl-1,3-benzodioxol-5-yl)vinyl]-3,4-dihydro-1H-isoquinolin-2-yl]propanenitrile which was then taken up into dichloromethane (0.2ml). The solution was cooled to -78<sup>0</sup> C, under argon and with rapid stirring m-chloroperoxybenzoic acid (19mg, 0.11mmol) in dichloromethane (0.2ml) was slowly added. After stirring at -78<sup>0</sup> C for 1h the reaction was allowed to warm to room temperature and stirred overnight. The mixture was evaporated to dryness and the residue purified via RP chromatography (acetonitrile 0.1% TFA/water 0.1% TFA) to give 6-benzyloxy-5-chloro-2-

hydroxy-7-methoxy-1-[(E)-2-(6-methyl-1,3-benzodioxol-5-yl)vinyl]-3,4-dihydro-1H-isoquinoline (**63**). MS(m/z): 480 [M+H].

### Nematode Assay

**[00239]** Nematodes were grown on standard NGM (Nematode Growth Media) plates until day 1 of adulthood, at which point they were collected and placed in 96-well plates and treated with the appropriate dose of compound or controls. Recordings of nematode movement were immediately started using WMicroTracker ONE instruments, providing an output of “Well Activity” over time. All drug treatments were performed in biological triplicates (Patten et al., JCI Insight. 2017 Nov 16;2(22):e97152. doi: 10.1172/jci.insight.97152. PMID: 29202456; PMCID: PMC5752378.)

### Inhibition of HIV-1 replication. MT-2 spreading infection assay.

**[00240]** Inhibition of HIV-1 viral replication was assayed in a spreading infection using MT-2 cells and NL4-3 RLuc reporter virus. For dose-response curves, compounds were initially diluted with DMSO to 100-fold the starting concentration in a 96-well plate and subjected to a series of 3-fold dilutions in DMSO for a total of eight or nine dilutions. If a single compound concentration was tested, the compound was diluted to 100-fold the desired concentration in DMSO. Compounds were then diluted 50-fold with infection media prepared by diluting NL4-3 RLuc virus stock to 400 IU/100 ul with complete RPMI. Then, 100 ul of 50-fold-diluted compound was transferred to 20,000 MT-2 cells that were preseeded in 96-well plates in 100ul of complete RPMI for a final volume of 200 ul, followed by incubation at 37°C for 96 h. The final MOI in infected plates was 0.02, and the final DMSO concentration in all wells was 1%. All assays were run with three replicates. For each replicate, one well received DMSO only, and one well received medium only for normalization and background correction. To assay the inhibition of HIV-1 replication, 100ul of medium was removed and discarded, and 10 u l of 15 uM EnduRen luciferase substrate was added to each well, followed by incubation for 1.5 h at 37°C. Plates were read on a luminescence plate reader (Synergy H1; BioTek Instruments, Inc.).

**[00241]** Table 2, below, reports the biological activity of select compounds as measured by the nematode assay and the MT-2 spreading infection assay.

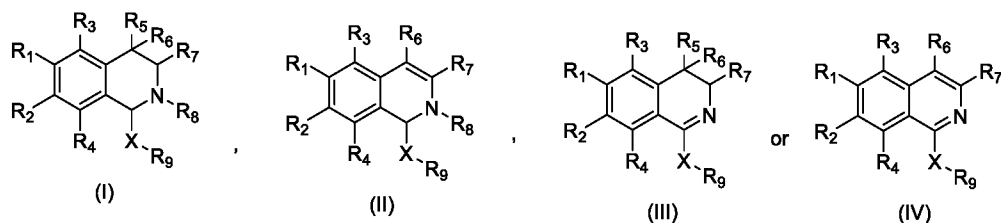
Table 2

| <b>Compound #</b> | Nematode assay<br>(Movements observed<br>over time normalized to<br>vehicle control with<br>maximum activity then<br>divided by that of the<br>positive control<br>compound Pimozide that<br>has been shown to protect<br>against neurodegeneration<br>at 40uM.) | HIV activity (μM) |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| <b>12</b>         | 2.2                                                                                                                                                                                                                                                              | 1.4               |
| <b>10</b>         | 0.44                                                                                                                                                                                                                                                             | 2.5               |
| <b>6</b>          | 1.14                                                                                                                                                                                                                                                             | 0.37              |
| <b>61</b>         | 0.51                                                                                                                                                                                                                                                             | 2.5               |
| <b>24</b>         | 0.59                                                                                                                                                                                                                                                             | 0.5               |
| <b>36</b>         | 0.63                                                                                                                                                                                                                                                             | 0.053             |

## CLAIMS

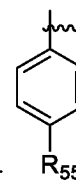
What is claimed is:

1. A compound of structural Formula (I), (II), (III) or (IV):



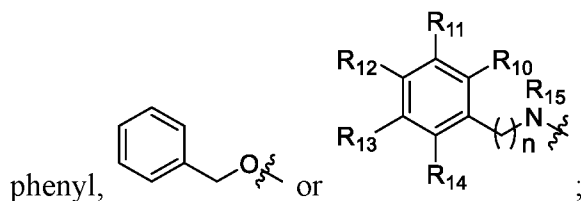
or a solvate, hydrate or salt thereof wherein:

X is absent,  $-\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}_2\text{NR}_{56}\text{R}_{57}$ ,  $-\text{C}=\text{C}-$ , cycloheteroalkyl,

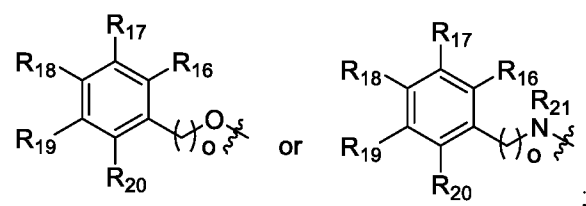


cycloheteroalkenyl, substituted cycloheteroalkyl, substituted cycloheteroalkyl or

$\text{R}_1$  is hydrogen,  $-\text{OR}_{22}$ , alkyl, alkenyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl,  $-\text{NR}_{43}\text{R}_{44}$ ,  $-\text{OPh}$ , where Ph is optionally substituted



$\text{R}_2$  is hydrogen,  $-\text{OR}_{23}$ ,  $-\text{CF}_3$ , alkyl, alkenyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, heteroaryl, substituted heteroaryl,  $-\text{NR}_{45}\text{R}_{46}$ ,



or  $\text{R}_1$  and  $\text{R}_2$  along with the carbon atoms to which they are attached form an aryl, substituted aryl, heteroaryl or substituted heteroaryl ring;

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

is 0, 1, 2 or 3;

$\text{R}_3$  and  $\text{R}_4$  are independently hydrogen, halo, alkyl, alkenyl,  $-\text{OR}_{24}$  or  $-\text{NR}_{25}\text{R}_{26}$ ;

R<sub>5</sub> is hydrogen, fluoro, alkyl or alkenyl;

R<sub>6</sub> is hydrogen, fluoro, alkyl, alkenyl, -OR<sub>27</sub> or -NR<sub>28</sub>R<sub>29</sub>;

R<sub>7</sub> is hydrogen, alkyl, alkenyl, -CO<sub>2</sub>R<sub>30</sub>, -CONR<sub>31</sub>R<sub>32</sub>, -CH<sub>2</sub>NR<sub>33</sub>R<sub>34</sub>, -CH<sub>2</sub>R<sub>42</sub> or -CH<sub>2</sub>OR<sub>35</sub>;

R<sub>8</sub> is hydrogen, -SO<sub>2</sub>R<sub>47</sub>, -OR<sub>48</sub>, -SO<sub>2</sub>NR<sub>69</sub>R<sub>70</sub>, -CONR<sub>71</sub>R<sub>72</sub>, -COR<sub>73</sub>, -CO<sub>2</sub>R<sub>74</sub>, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R<sub>9</sub> is aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloheteroalkyl, cycloheteroalkenyl, substituted cycloheteroalkyl or substituted cycloheteroalkenyl;

R<sub>10</sub>-R<sub>14</sub> and R<sub>16</sub>-R<sub>20</sub> are independently hydrogen, alkyl, alkenyl, halo, -CH<sub>2</sub>OR<sub>36</sub>, -CO<sub>2</sub>R<sub>37</sub>, -CONR<sub>38</sub>R<sub>39</sub>, -NR<sub>40</sub>R<sub>41</sub>, cycloheteroalkyl, cycloheteroalkenyl, substituted cycloheteroalkyl or substituted cycloheteroalkenyl;

R<sub>15</sub> and R<sub>21</sub> are independently hydrogen, alkyl or alkenyl;

R<sub>22</sub> and R<sub>23</sub> are independently alkyl, alkenyl, halo substituted alkyl, substituted alkenyl, heteroaryl or substituted heteroaryl;

R<sub>24</sub>, R<sub>27</sub>, R<sub>35</sub> and R<sub>36</sub> are independently alkyl, alkenyl, halo substituted alkyl or halo substituted alkenyl;

R<sub>28</sub>, R<sub>29</sub>, R<sub>30</sub>-R<sub>33</sub>, R<sub>38</sub>-R<sub>41</sub>, R<sub>63</sub>-R<sub>74</sub>, R<sub>75</sub>, R<sub>77</sub> and R<sub>79</sub>-R<sub>83</sub> are independently hydrogen, alkyl or alkenyl;

R<sub>25</sub> and R<sub>26</sub> are independently hydrogen, alkyl, alkenyl or together with the nitrogen atom to which they are attached form an aryl or substituted aryl group;

R<sub>34</sub> is hydrogen, -SO<sub>2</sub>R<sub>63</sub>, -SO<sub>2</sub>NR<sub>64</sub>R<sub>65</sub>, -CONR<sub>66</sub>R<sub>67</sub> or -COR<sub>68</sub>;

R<sub>76</sub> and R<sub>78</sub> are independently hydrogen, -SO<sub>2</sub>R<sub>79</sub>, -SO<sub>2</sub>NR<sub>80</sub>R<sub>81</sub>, -CONR<sub>82</sub>R<sub>83</sub> or -COR<sub>84</sub>;

R<sub>42</sub> is cycloheteroalkenyl, substituted cycloheteroalkyl or substituted cycloheteroalkenyl;

R<sub>43</sub>-R<sub>46</sub> are independently hydrogen, alkyl, alkenyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R<sub>47</sub> is alkyl, alkenyl, aryl or heteroaryl;

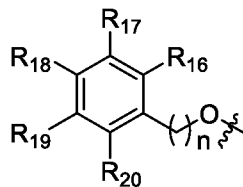
R<sub>48</sub> is hydrogen, alkyl, alkenyl, substituted alkyl, substituted alkenyl, or aryl;

R<sub>55</sub> is heteroarylalkyl, substituted heteroarylalkyl, heteroarylalkenyl, substituted heteroarylalkenyl, -NR<sub>75</sub>R<sub>76</sub> or -CH<sub>2</sub>R<sub>77</sub>R<sub>78</sub>;

R<sub>56</sub> is hydrogen, alkyl or alkenyl,

R<sub>57</sub> is substituted aryl, heteroaryl or substituted heteroaryl

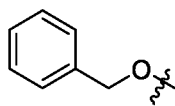
provided that when R<sub>1</sub> is hydrogen or -OR<sub>22</sub>, R<sub>22</sub> is alkyl and X is -C≡C-, that R<sub>2</sub> is not



hydrogen, -OR<sub>23</sub>, -CF<sub>3</sub> or

where R<sub>23</sub> is alkyl, n is 1 and R<sub>16</sub>-R<sub>20</sub> are hydrogen

in the compound of Formula (I);



provided that when R<sub>1</sub> is

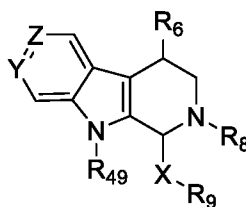
that at least one of R<sub>3</sub>-R<sub>7</sub> are not hydrogen in the

compound of Formula (I) when X is -C≡C-, or if each of R<sub>3</sub>-R<sub>7</sub> are hydrogen that R<sub>8</sub> is not

hydrogen, -CONR<sub>71</sub>R<sub>72</sub>, -COR<sub>73</sub> or -CO<sub>2</sub>R<sub>74</sub> in the compound of Formula (I) when X is -C≡C-;

and provided that both R<sub>1</sub> and R<sub>2</sub> are not both alkyl.

2. The compound of claim 1 of structural Formula (V):



(V)

wherein R<sub>49</sub> is hydrogen or alkyl;

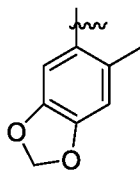
Y is -CR<sub>50</sub>- or -N-;

Z is -CR<sub>51</sub>- or -N-;

R<sub>50</sub> and R<sub>51</sub> are independently, hydrogen, halo, alkyl, -OR<sub>52</sub> or -NR<sub>53</sub>R<sub>54</sub>;

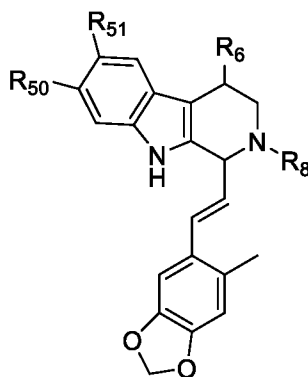
R<sub>52</sub> is alkyl; and

R<sub>53</sub> and R<sub>54</sub> are independently hydrogen or alkyl.



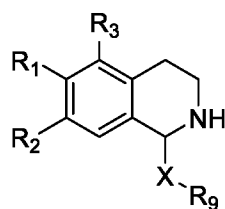
3. The compound of claim 2, wherein R<sub>9</sub> is

4. The compound of claim 2 of structural formula (VI):



(VI)

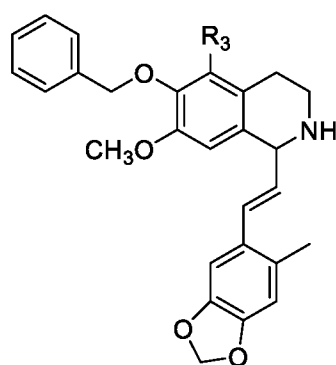
5. The compound of claim 1 of structural formula (IX):



(IX)

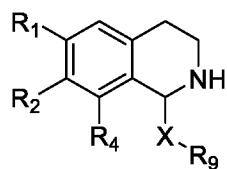
wherein R<sub>3</sub> is F, Cl, Br, -CH<sub>3</sub>, alkyl, alkenyl, -CF<sub>3</sub>, -OCR<sub>24</sub> or -NR<sub>25</sub>R<sub>26</sub>.

6. The compound of claim 5 of structural formula (X):



(X)

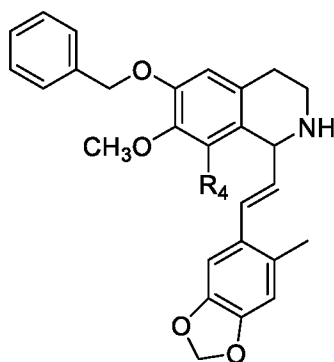
7. The compound of claim 1 of structural formula (XI):



(XI)

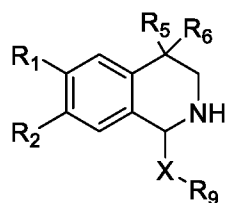
wherein  $R_4$  is F, Cl, Br,  $-CH_3$ , alkyl, alkenyl,  $-CF_3$ ,  $-OCR_{24}$  or  $-NR_{25}R_{26}$ .

8. The compound of claim 7 of structural formula (XII):



(XII)

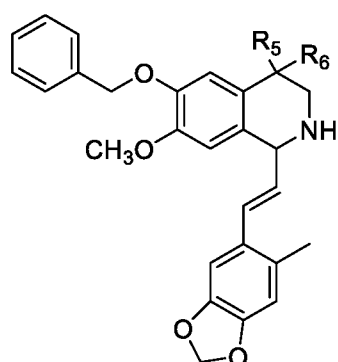
9. The compound of claim 1 of structural formula (XIII):



(XIII)

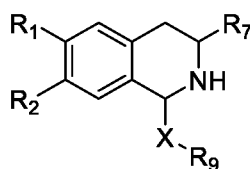
wherein  $R_5$  is hydrogen or fluorine and  $R_6$  is alkyl, methyl, alkenyl, fluorine,  $-OR_{27}$  or  $-NR_{28}R_{29}$ .

10. The compound of claim 9 of structural formula (XIV):



(XIV)

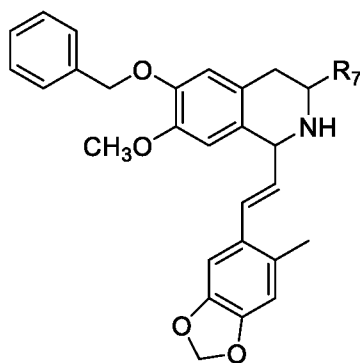
11. The compound of claim 1 of structural formula (XV):



(XV)

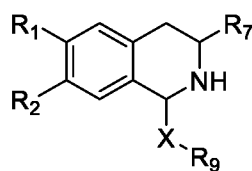
wherein R<sub>7</sub> is alkyl, alkenyl, -CO<sub>2</sub>R<sub>30</sub>, -CONR<sub>31</sub>R<sub>32</sub>, -CH<sub>2</sub>NR<sub>33</sub>R<sub>34</sub>, -CH<sub>2</sub>R<sub>42</sub> or -CH<sub>2</sub>OR<sub>35</sub>

12. The compound of claim 11 of structural formula (XVI):



(XVI)

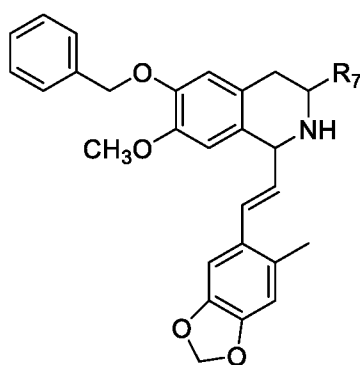
13. The compound of claim 1 of structural formula (XVII):



(XVII)

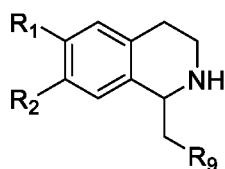
wherein  $R_7$  is alkyl, alkenyl,  $-CO_2R_{30}$ ,  $-CONR_{31}R_{32}$ ,  $-CH_2NR_{33}R_{34}$ ,  $-CH_2R_{42}$  or  $-CH_2OR_{35}$

14. The compound of claim 13 of structural formula (XVIII):



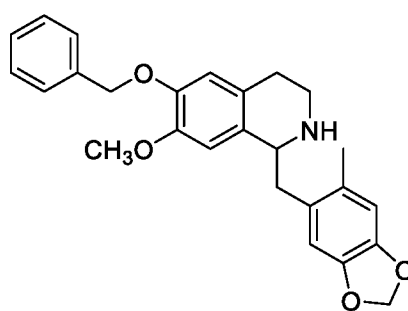
(XVIII)

15. The compound of claim 1 of structural formula (XIX):



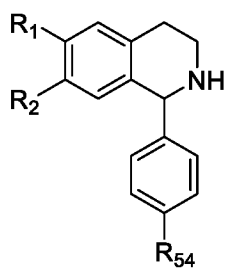
(XIX)

16. The compound of claim 15 of structural formula (XX):



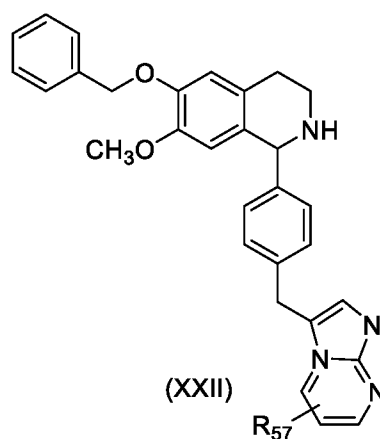
(XX)

17. The compound of claim 1 of structural formula (XXI):



(XXI)

18. The compound of claim 17 of structural formula (XXII):



(XXII)

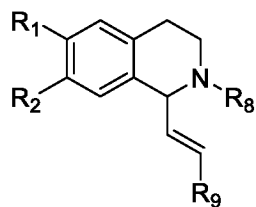
wherein R<sub>58</sub> is hydrogen, alkyl, alkenyl, -CO<sub>2</sub>R<sub>59</sub>, -CONR<sub>60</sub>R<sub>61</sub>, or -CH<sub>2</sub>OR<sub>62</sub>;

R<sub>59</sub> is hydrogen, alkyl or alkenyl;

R<sub>60</sub> and R<sub>61</sub> are independently hydrogen, alkyl or alkenyl; and

R<sub>62</sub> is alkyl or alkenyl.

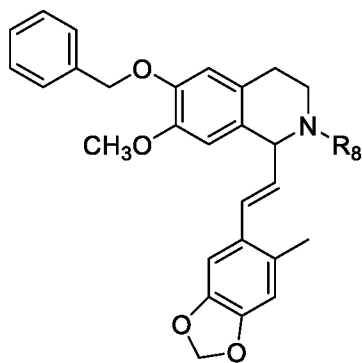
19. The compound of claim 1 of structural formula (XXVII):



(XXVII)

wherein  $R_8$  is hydrogen,  $-SO_2R_{47}$ ,  $-OR_{48}$ ,  $-SO_2NR_{69}R_{70}$ ,  $-CONR_{71}R_{72}$  or  $-COR_{73}$ , alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl.

20. The compound of claim 19 of structural formula (XXVIII):



(XXVIII)

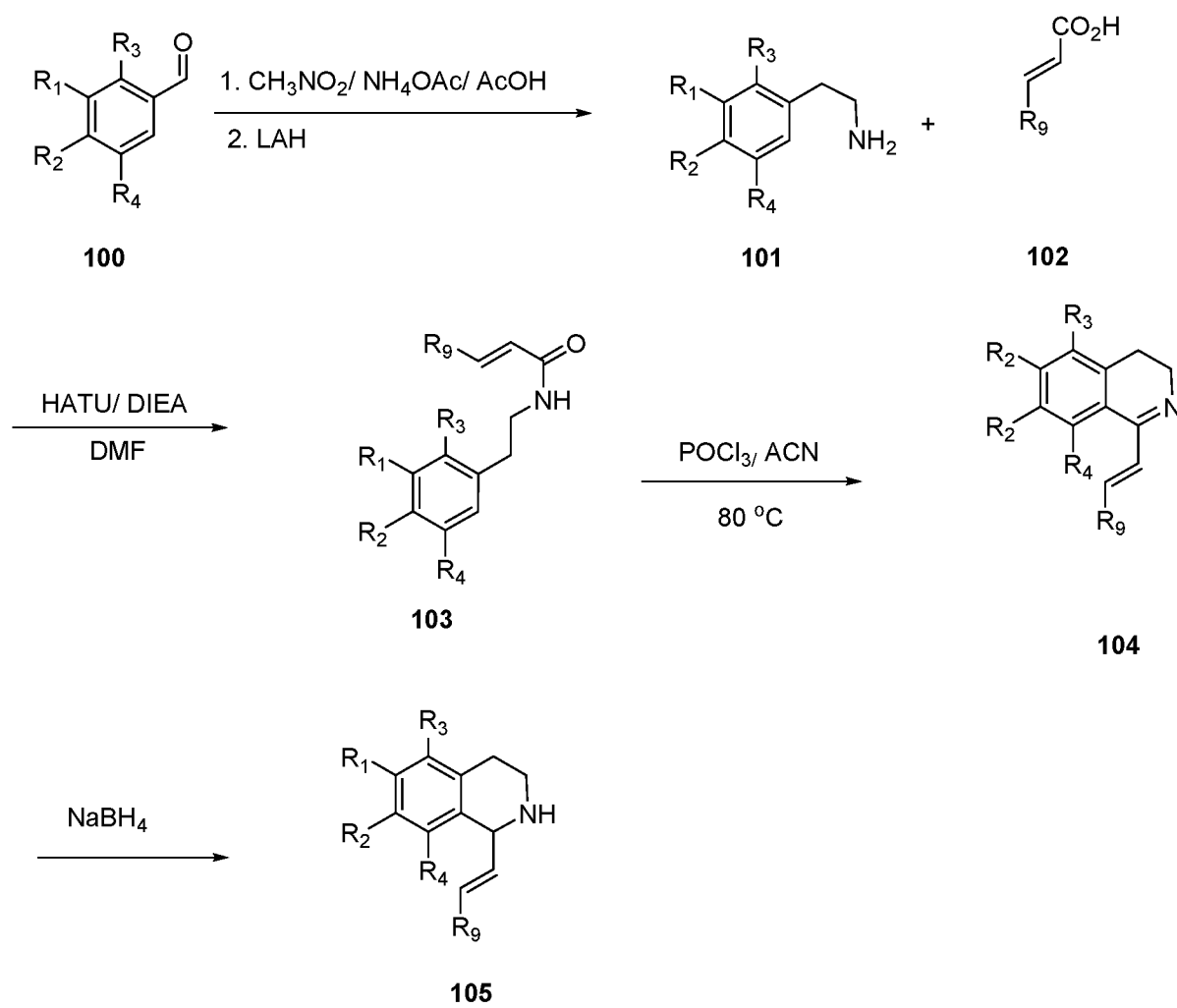


Fig. 1

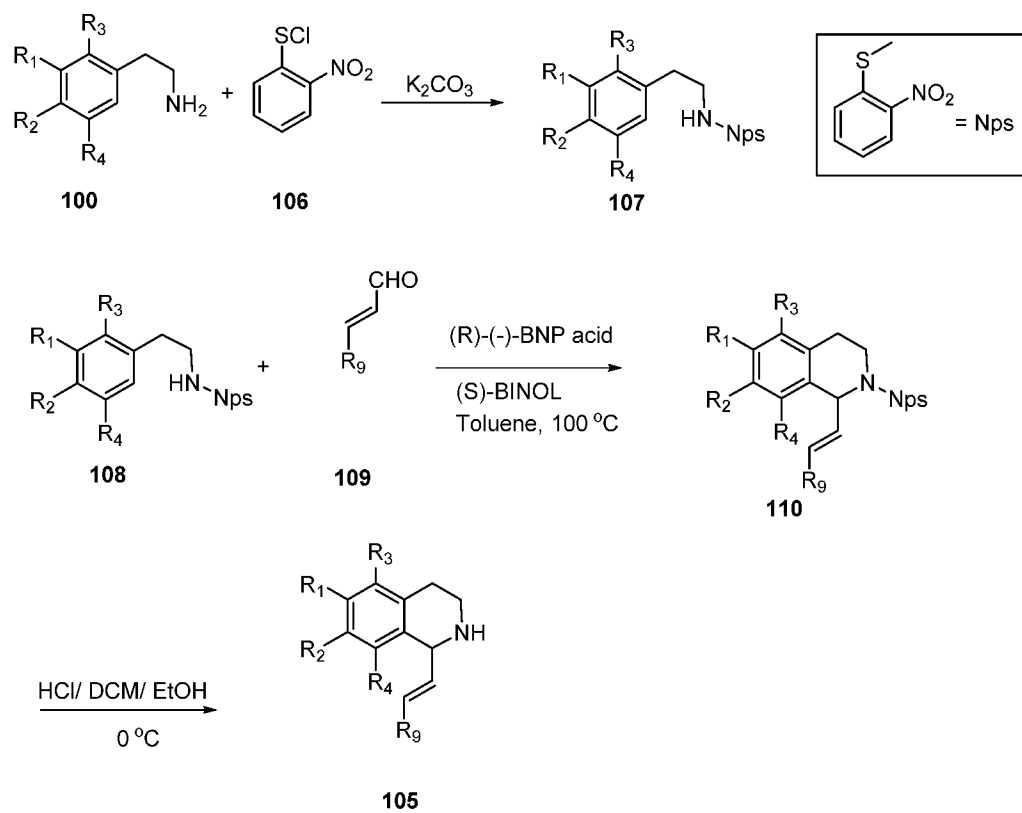


Fig. 2

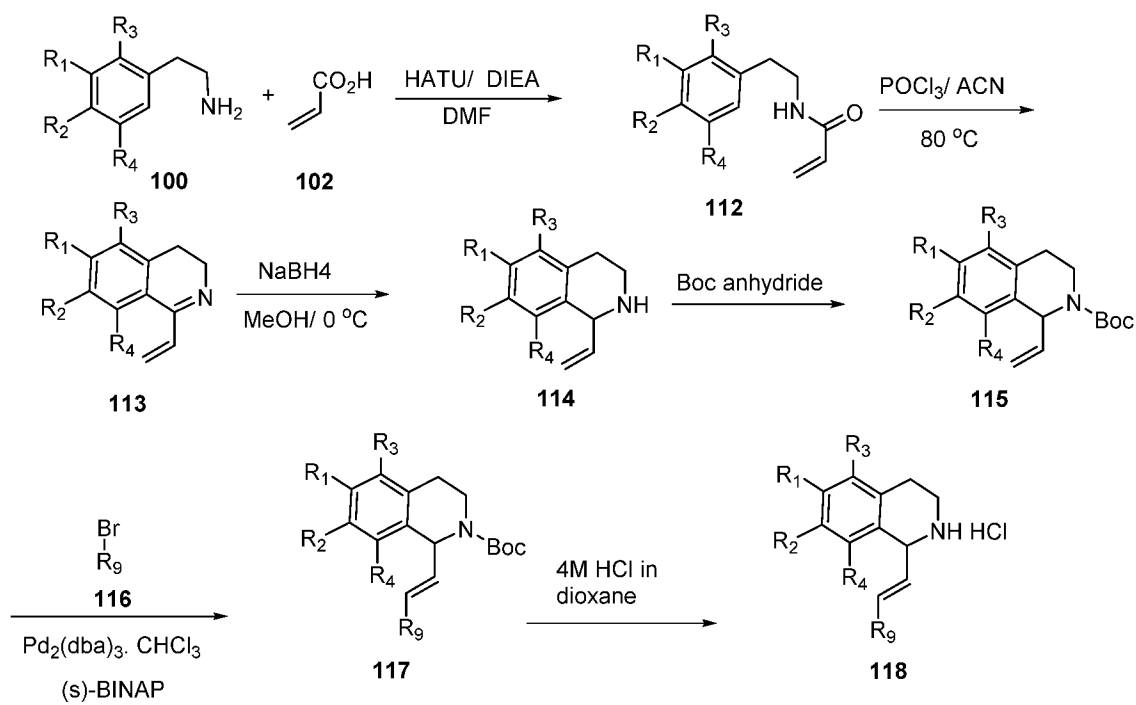


Fig. 3

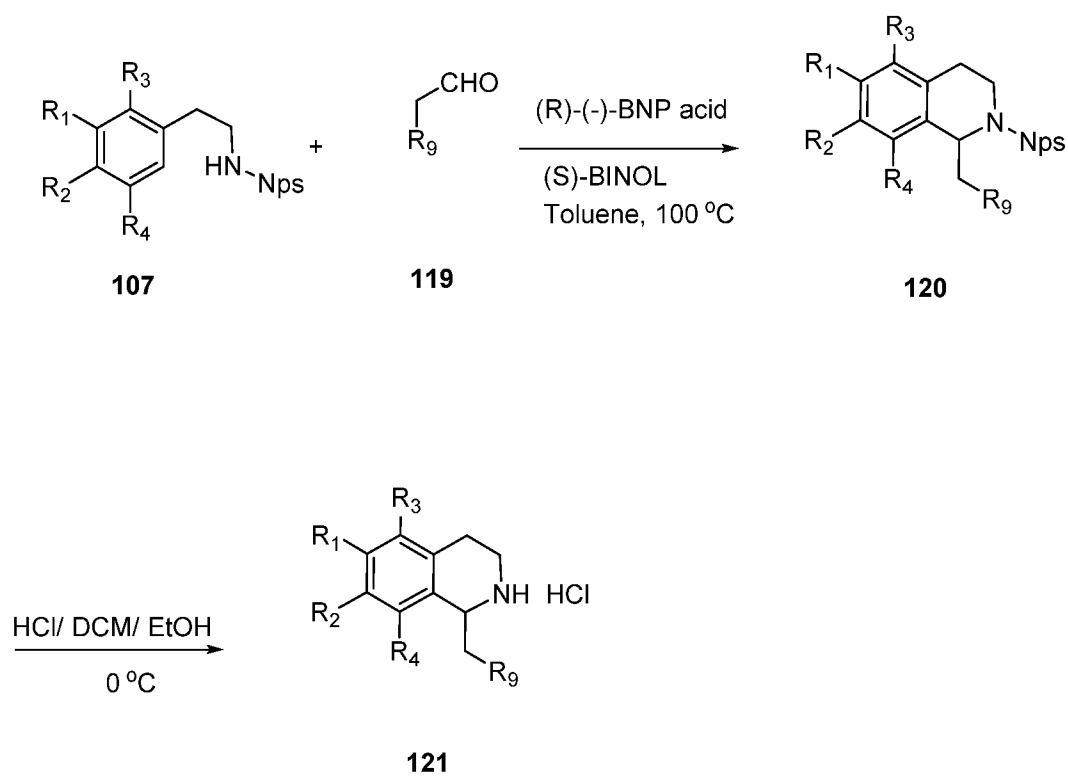


Fig. 4

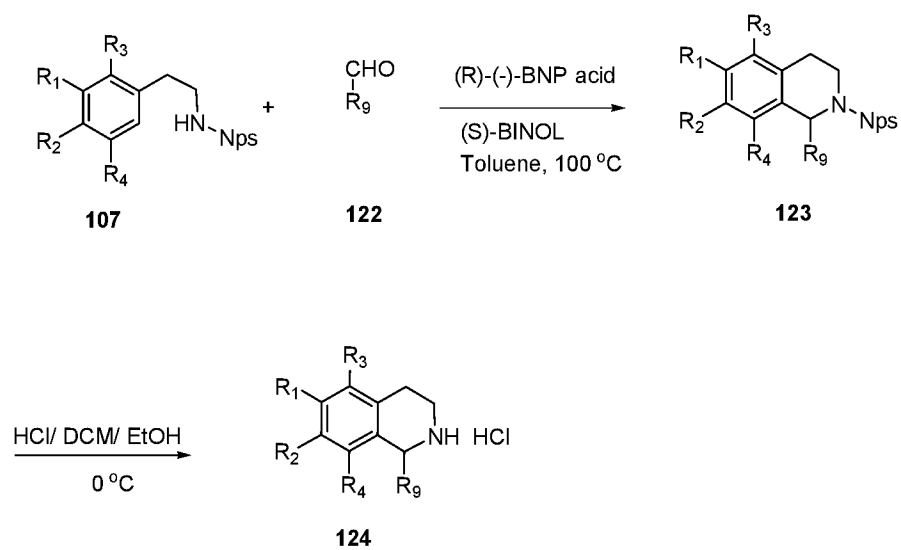


Fig. 5

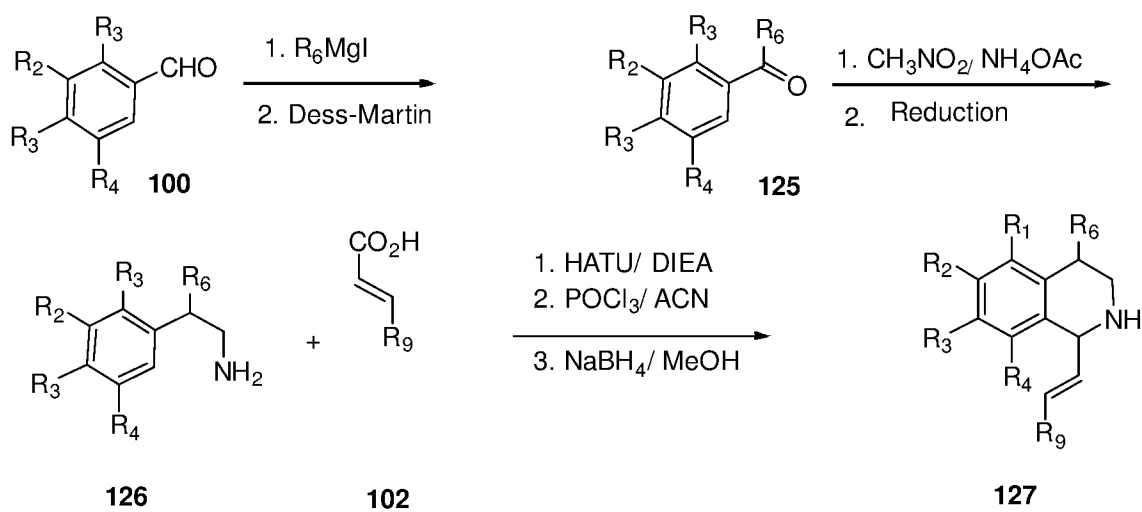


Fig. 6

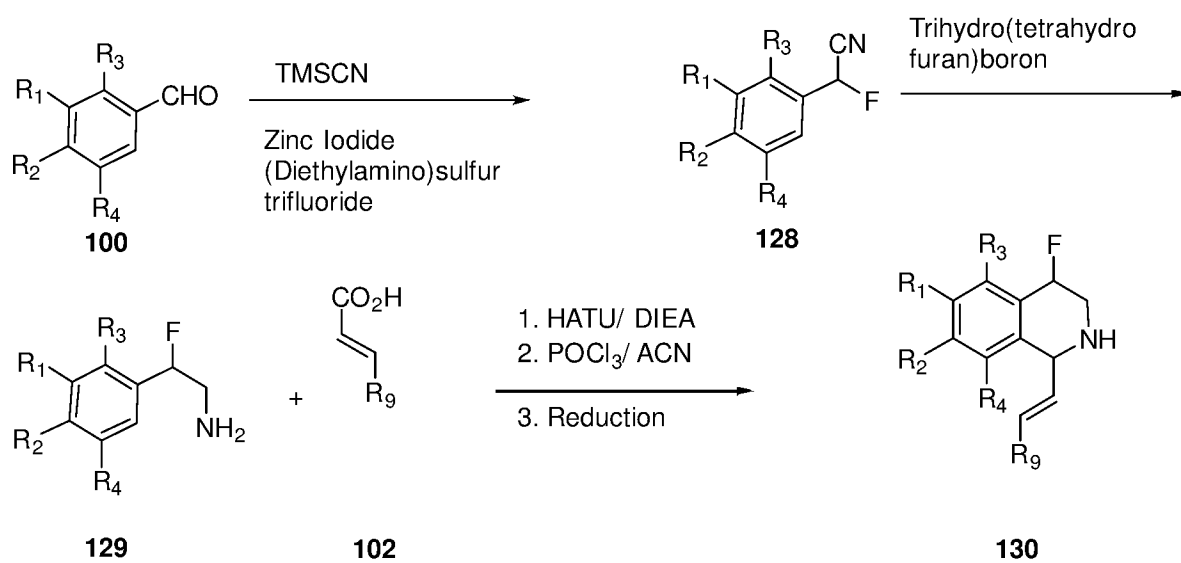


Fig. 7

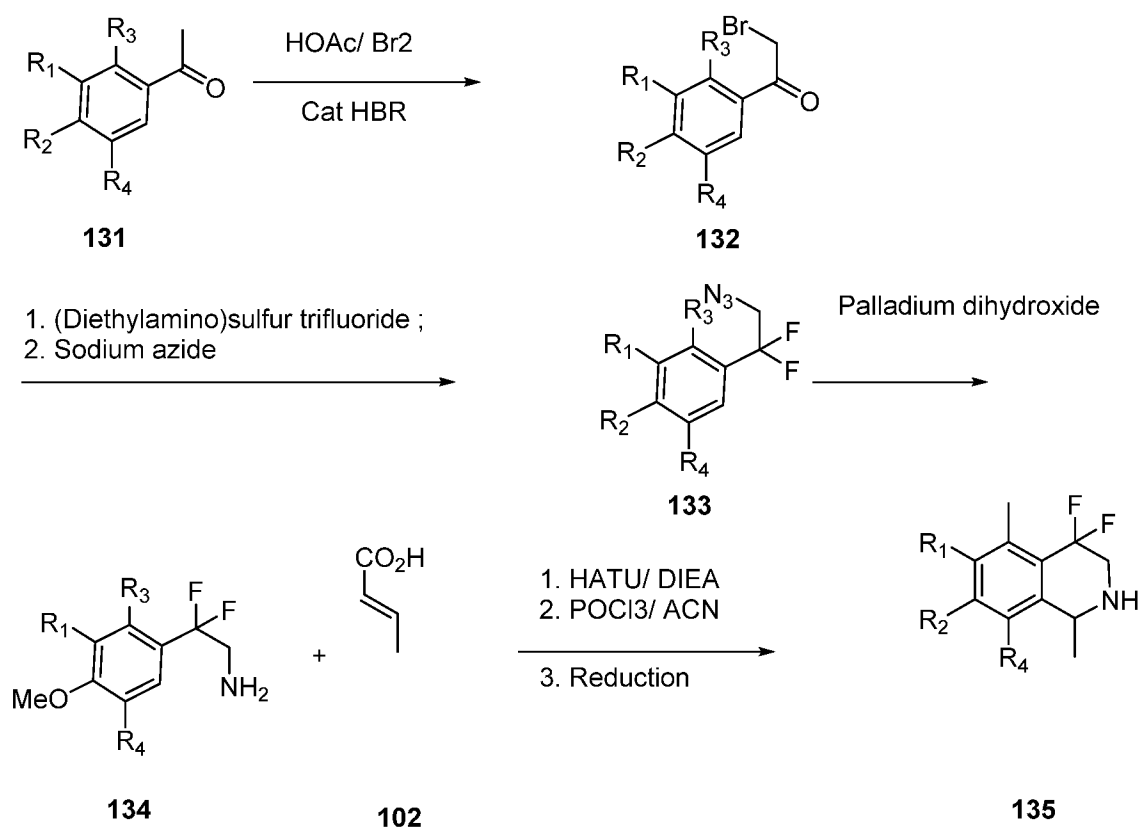


Fig. 8

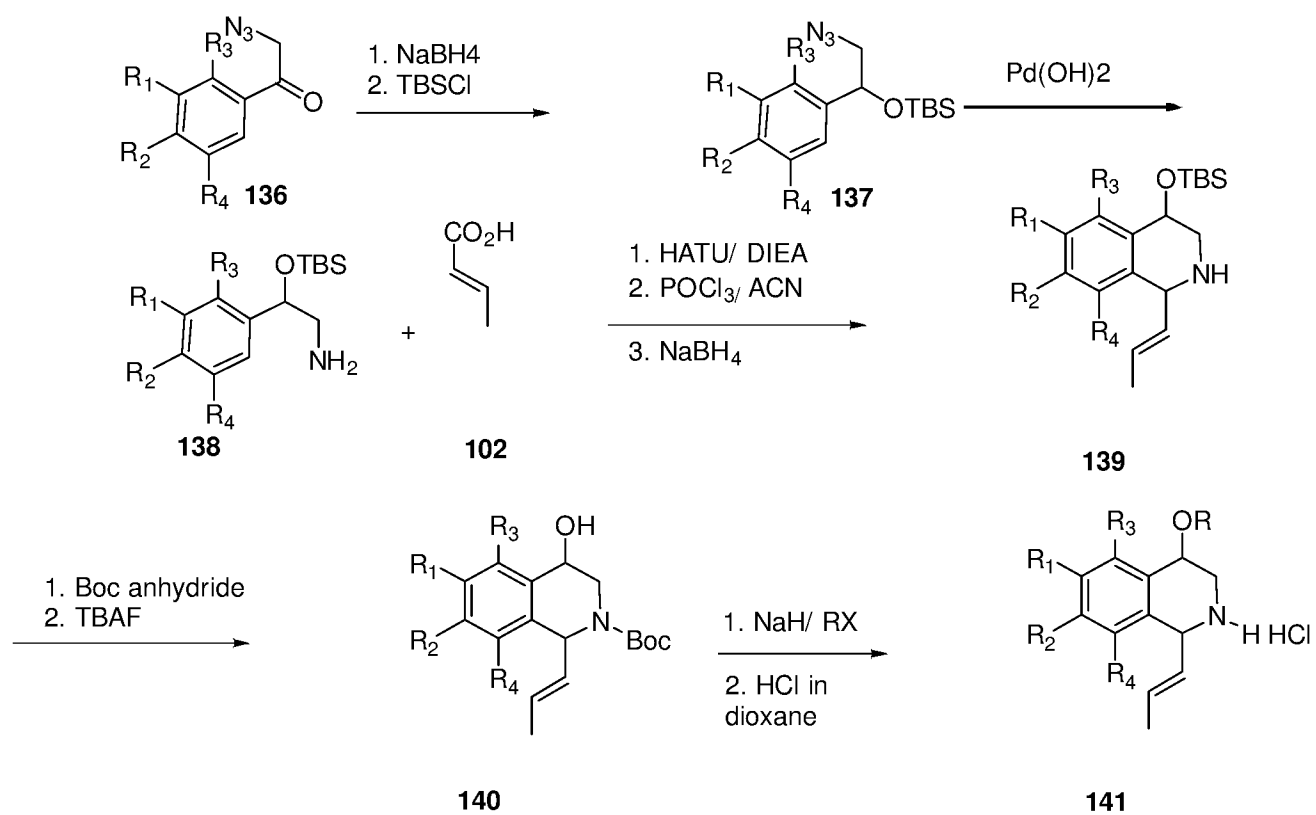


Fig. 9

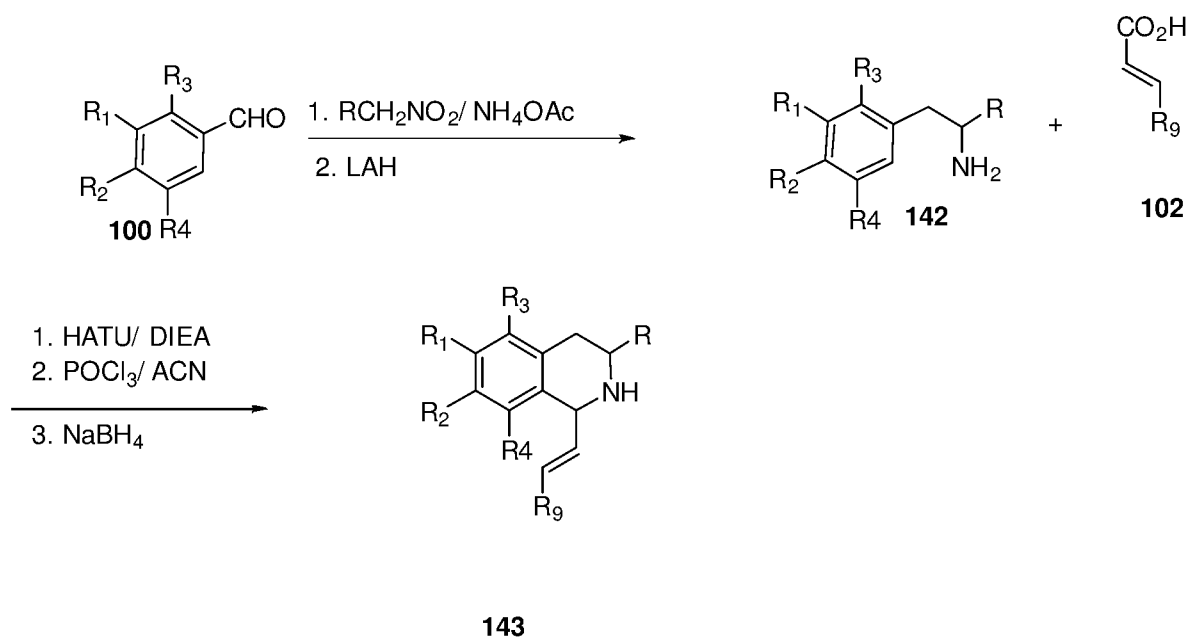


Fig. 10

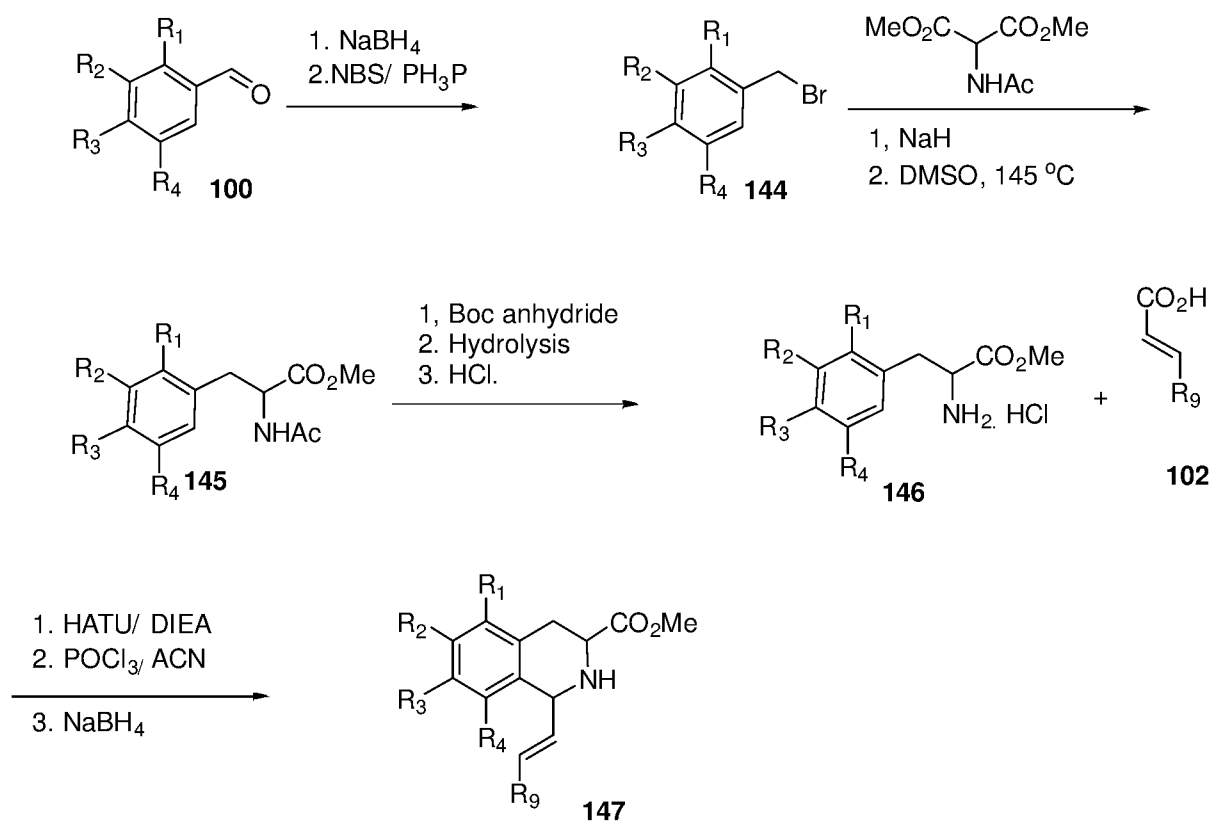


Fig. 11

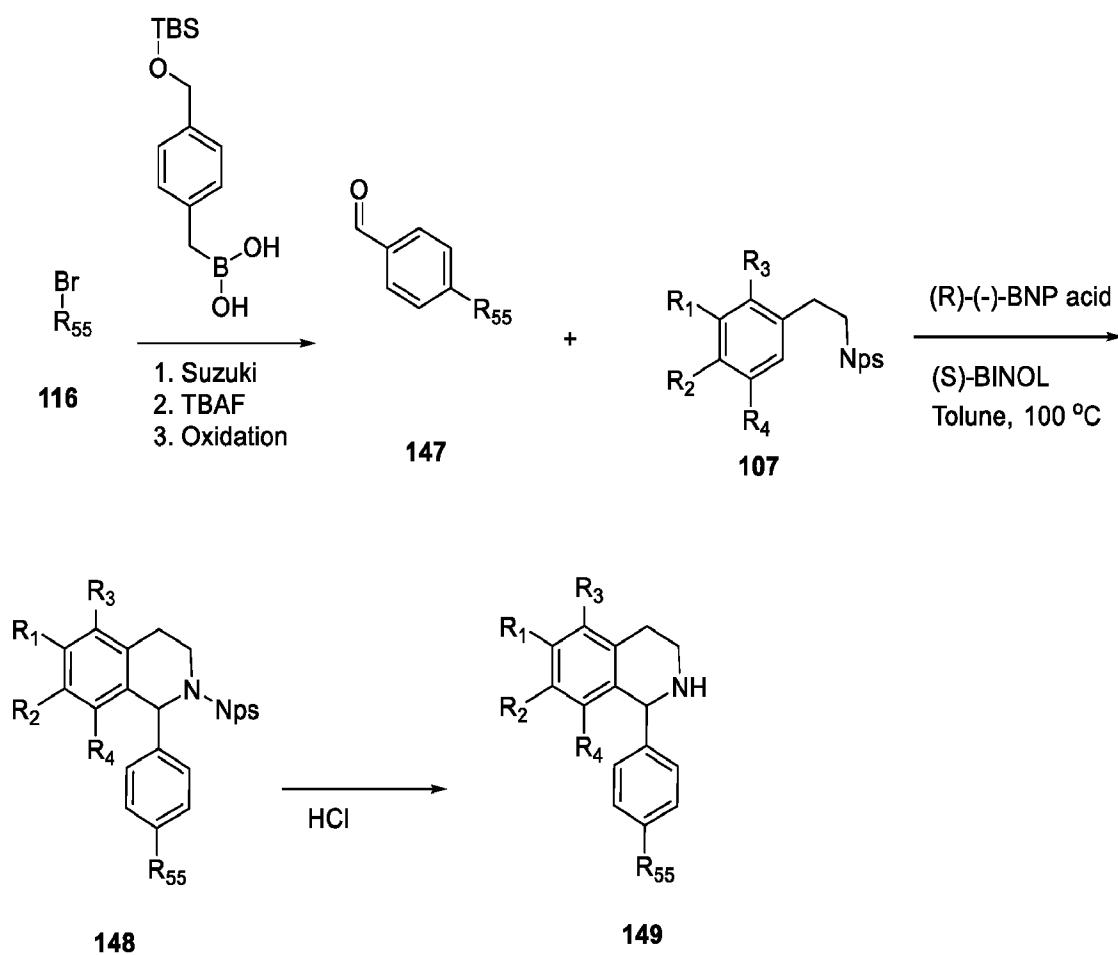


Fig. 12

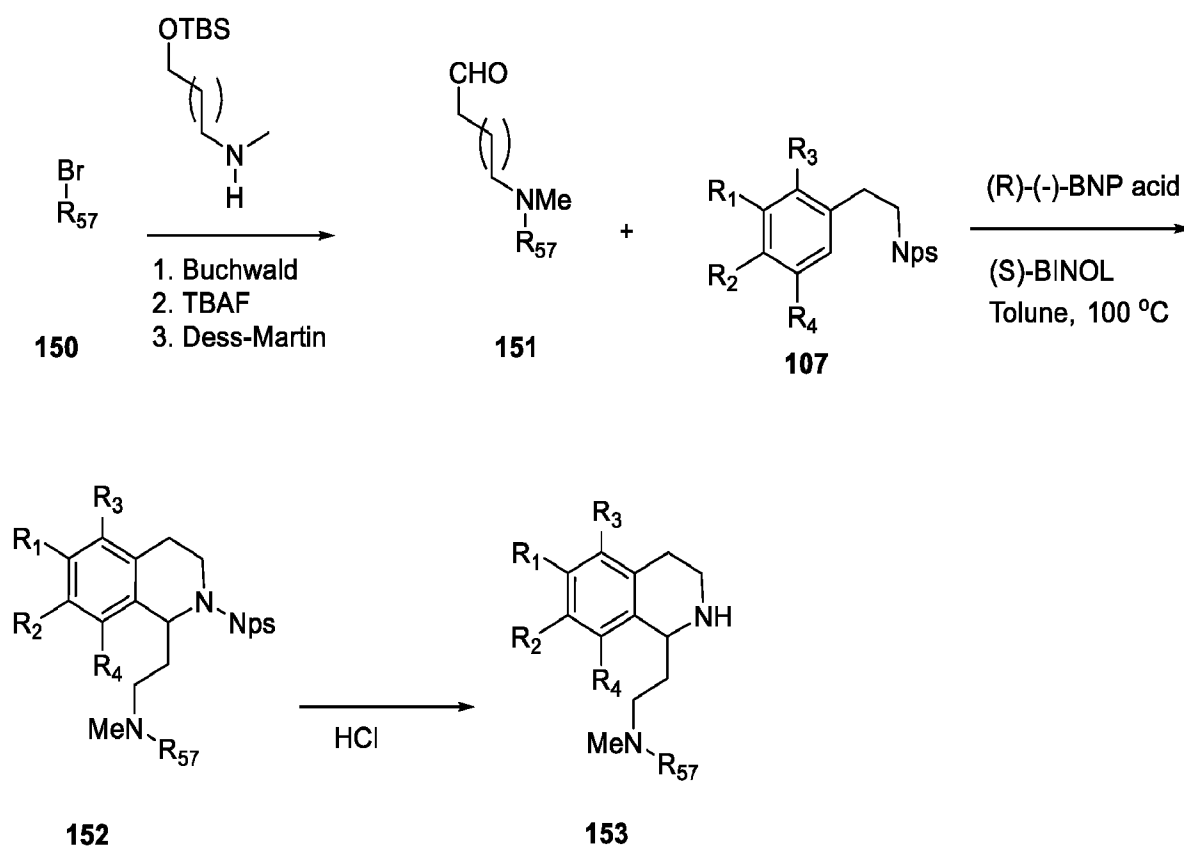


Fig. 13

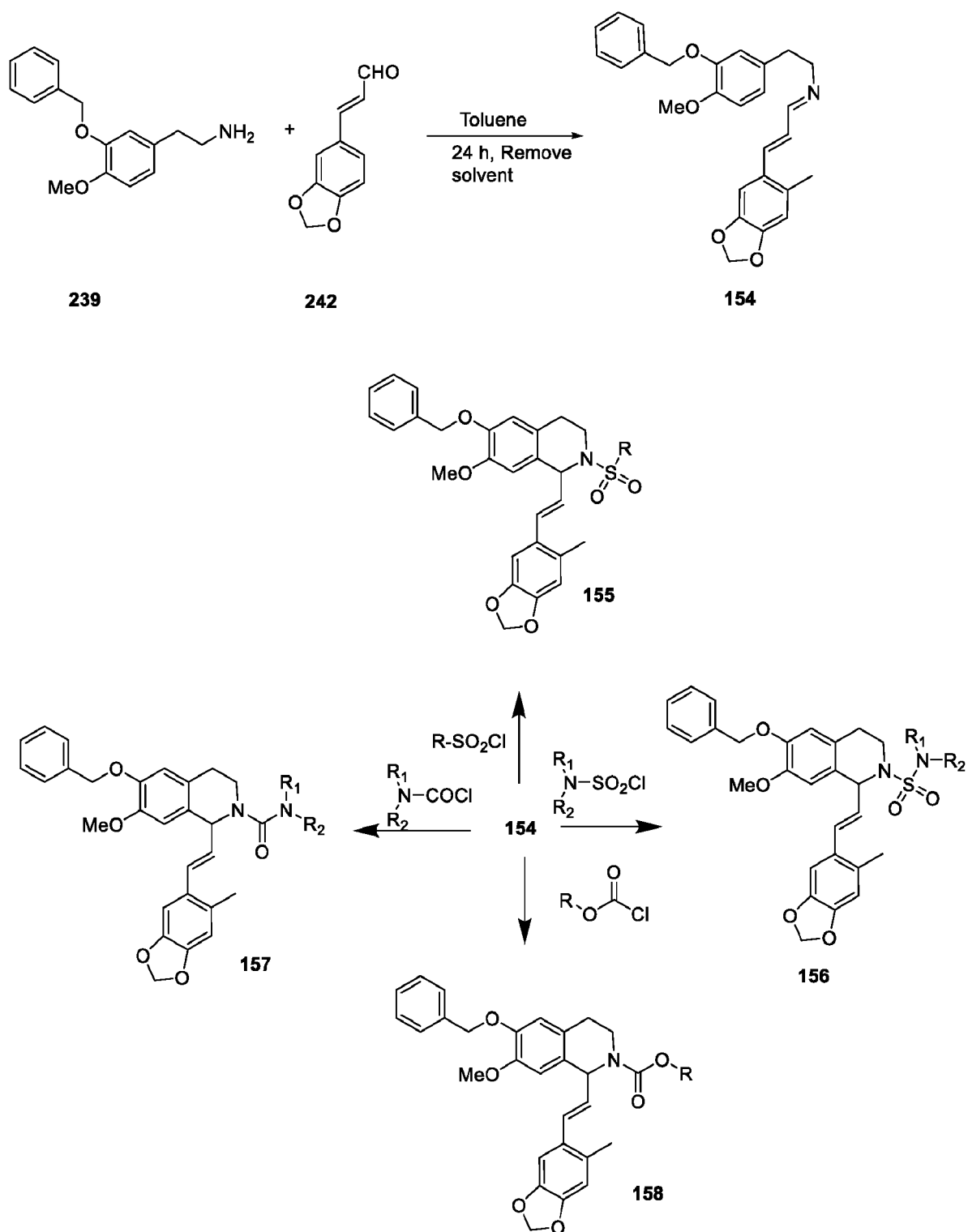


Fig. 14

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 21/39821

## A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/472; A61K 31/473; A61P 25/00 (2021.01)

CPC - A61P 25/00; A61P 27/00; A61P 3/00; A61P 35/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                            | Relevant to claim No. |
|-----------|---------------------------------------------------------------------------------------------------------------|-----------------------|
| X         | PubChem-SID-329792124, Modify Date: 14 March 2018 (14.03.2018), pg 2, figure, this is a purchasable chemical. | 1,17                  |
| A         | PubChem-SID-329766657, Modify Date: 14 March 2018 (14.03.2018), pg 2, figure, this is a purchasable chemical  | 1,17                  |
| A         | US 2017/0210736 A1 (TAISHO PHARMACEUTICAL CO LTD) 27 July 2017 (27.07.2017), entire document.                 | 1,17                  |

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

3 November 2021 (03.11.2021)

Date of mailing of the international search report

DEC 15 2021

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents  
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Kari Rodriguez

Telephone No. PCT Helpdesk: 571-272-4300

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 21/39821

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:  
(see extra sheet)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1,17

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

**--BOX III - LACK OF UNITY--**

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I+: Claims 1-20 directed to a compound of structural Formula (I), (II), (III) or (IV); or a solvate, hydrate or salt thereof. The compound of Formula (I) will be searched to the extent that it encompasses the first species of claim 1, wherein X is absent; R1 is hydrogen; R2 is hydrogen; R3 and R4 are hydrogen; R5 is hydrogen; R6 is hydrogen; R7 is hydrogen; R8 is hydrogen; R9 is aryl (unsubstituted). It is believed that claims 1 and 17 encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass the first species of claim 1. Applicant is invited to elect additional compounds of Formula (I), wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of claim 1, wherein X is CH<sub>2</sub>; R1 is hydrogen; R2 is hydrogen; R3 and R4 are hydrogen; R5 is hydrogen; R6 is hydrogen; R7 is hydrogen; R8 is hydrogen; R9 is aryl (unsubstituted) (i.e. claims 1 and 15).

The groups of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

**Special Technical Features:**

Group I+ includes the technical feature of a unique compound of Formula (I), which is not required by any other invention of Group I+.

**Common technical features:**

The inventions of Groups I+ share the technical feature of a compound having the structure of Formula (I), (II), (III) or (IV).

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by the document entitled PubChem-SID-329766657 (hereinafter 'PubChem-657').

PubChem-657 teaches a compound of Formula (IV) wherein X is absent; R1 is hydrogen; R2 is hydrogen; R3 and R4 are hydrogen; R6 is hydrogen; R7 is hydrogen; R9 is aryl (pg 2, figure, this is a purchasable chemical).

As said compound was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the inventions of Group I+.

The inventions of Group I+ thus lack unity under PCT Rule 13.

Note: Claim 17 lacks clarity regarding substituent R54 which is not defined in claim 17 or in the claim it depends from, claim 1. A definition for R54 is found in claim 2 (R54 is hydrogen or alkyl). For the purpose of completing this ISR, this definition for R54 was used for claim 17.