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(54) Titre : INHIBITEURS DE PROTEINES KINASES D'ALKOXY INDOLINONE
(54) Title: ALKOXY INDOLINONE BASED PROTEIN KINASE INHIBITORS

(57) Abrégé/Abstract:
Alkoxy indolinone based acid and amide derivatives have enhanced and unexpected drug properties as inhibitors of protein kinases and are useful in treating disorders related to abnormal protein kinase activities such as cancer.

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(54) Title: ALKOXY INDOLINONE BASED PROTEIN KINASE INHIBITORS

(57) Abstract: Alkoxy indolinone based acid and amide derivatives have enhanced and unexpected drug properties as inhibitors of protein kinases and are useful in treating disorders related to abnormal protein kinase activities such as cancer.

ALKOXY INDOLINONE BASED PROTEIN KINASE INHIBITORS

Description

Field of Invention:

The invention relates to protein kinase inhibitors and to their use in treating disorders related to abnormal protein kinase activities such as cancer and inflammation. More particularly, the invention relates to alkoxy indolinone based derivatives and their pharmaceutically acceptable salts employable as protein kinase inhibitors.

Background:

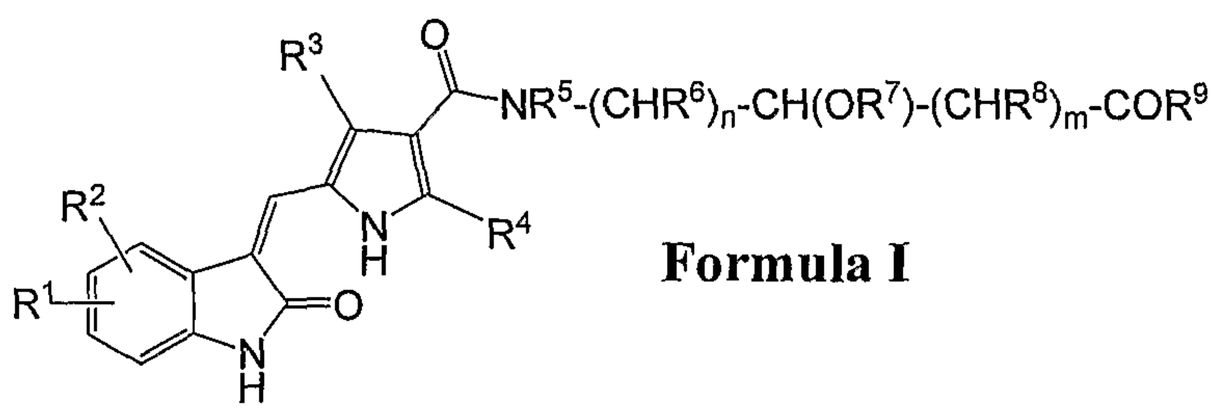
Protein kinases are enzymes that catalyze the phosphorylation of hydroxyl groups of tyrosine, serine, and threonine residues of proteins. Many aspects of cell life (for example, cell growth, differentiation, proliferation, cell cycle and survival) depend on protein kinase activities. Furthermore, abnormal protein kinase activity has been related to a host of disorders such as cancer and inflammation. Therefore, considerable effort has been directed to identifying ways to modulate protein kinase activities. In particular, many attempts have been made to identify small molecules that act as protein kinase inhibitors.

Several pyrrolyl-indolinone derivatives have demonstrated excellent activity as inhibitors of protein kinases (Larid et al. FASEB J. 16, 681, 2002; Smolich et al. Blood, 97, 1413, 2001; Mendel et al. Clinical Cancer Res. 9, 327, 2003; Sun et al. J. Med. Chem. 46, 1116, 2003). The clinical utility of these compounds has been promising, but has been partially compromised due to the relatively poor aqueous solubility and/or other drug properties. What is needed is a class of modified pyrrolyl-indolinone derivatives having both inhibitory activity and enhanced drug properties.

Summary:

The invention is directed to alkoxy indolinone based derivatives and to their use as inhibitors of protein kinases. It is disclosed herein that alkoxy indolinone based derivatives have enhanced and unexpected drug properties that advantageously distinguish this class of compounds over known pyrrolyl-indolinone derivatives having protein kinase inhibition activity. It is also disclosed herein that alkoxy indolinone based derivatives are useful in treating disorders related to abnormal protein kinase activities such as cancer.

One aspect of the invention is directed to a compound represented by Formula (**I**):

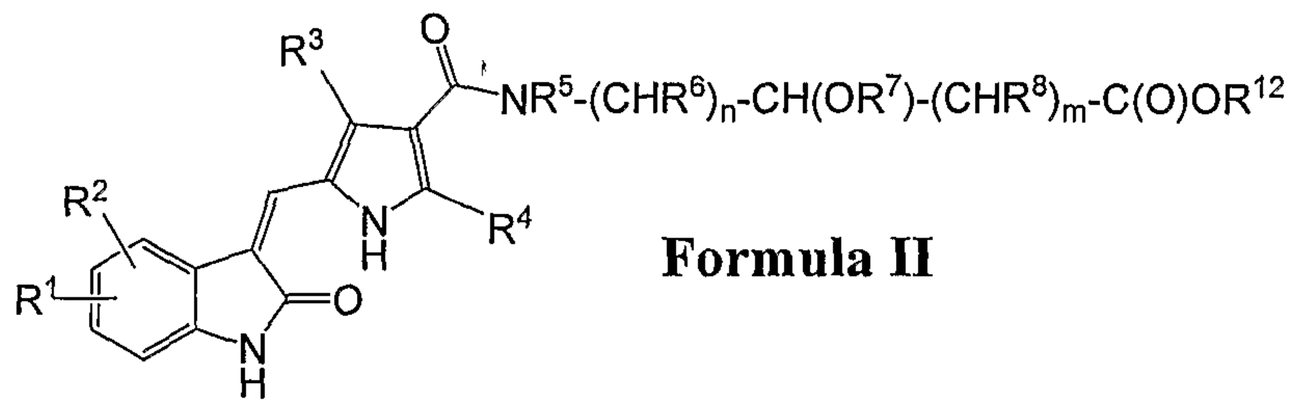


Formula I

In Formula (**I**), R^1 is selected from the group consisting of hydrogen, halo, (C1-C6) alkyl, (C3-C8) cycloalkyl, (C1-C6) haloalkyl, hydroxy, (C1-C6) alkoxy, amino, (C1-C6) alkylamino, amide, sulfonamide, cyano, substituted or unsubstituted (C6-C10) aryl; R^2 is selected from the group consisting of hydrogen, halo, (C1-C6) alkyl, (C3-C8) cycloalkyl, (C1-C6) haloalkyl, hydroxy, (C1-C6) alkoxy, (C2-C8) alkoxyalkyl, amino, (C1-C6) alkylamino, (C6-C10) arylamino; R^3 is selected from the group consisting of hydrogen, (C1-C6) alkyl, (C6-C10) aryl, (C5-C10) heteroaryl, and amide; R^4, R^5, R^6 and R^8 are independently selected from the group consisting of hydrogen and (C1-C6) alkyl; R^7 is (C1-C6) alkyl; R^9 is selected from the group consisting of hydroxy, (C1-C6) O-alkyl, (C3-C8) O-cycloalkyl, and $NR^{10}R^{11}$; where R^{10} and R^{11} are independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) hydroxyalkyl, (C2-C6) dihydroxyalkyl, (C1-C6) alkoxy , (C1-C6) alkyl carboxylic acid, (C1-C6) alkyl phosphonic acid, (C1-C6) alkyl sulfonic acid, (C1-C6) hydroxyalkyl carboxylic acid, (C1-C6) alkyl amide, (C3-C8) cycloalkyl, (C5-C8) heterocycloalkyl, (C6-C8) aryl, (C5-C8) heteroaryl, (C3-C8) cycloalkyl carboxylic acid, or R^{10} and R^{11} together with N forms a (C5-C8)

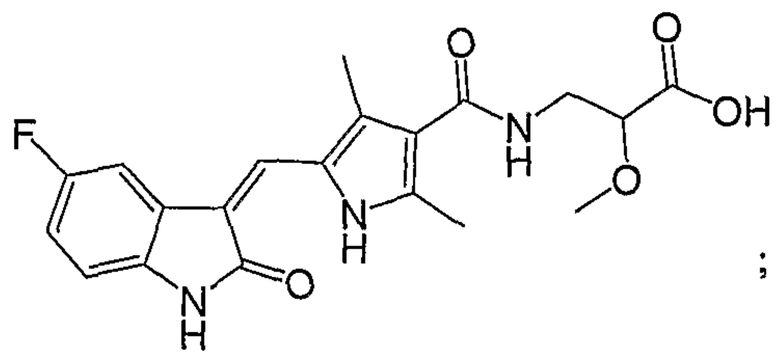
heterocyclic ring either unsubstituted or substituted with one or more hydroxyls, ketones, ethers, and carboxylic acids; **n** is 1, 2, or 3; and **m** is 0, 1, or 2. Alternatively, this aspect of the invention also is directed to a pharmaceutically acceptable salt, its tautomer, a pharmaceutically acceptable salt of its tautomer, or a prodrug of Formula (**I**).

A first preferred subgenus of this first aspect of the invention is directed to the compound, salt, tautomer, or prodrug represented by Formula (**II**):



Formula II

In Formula (**II**), R^{12} is selected from the group consisting of hydrogen, (C1-C6) alkyl, and (C3-C8) cycloalkyl. Other groups are as defined in Formula (**I**). In preferred embodiments, R^1 and R^2 are independently selected from the group consisting of hydrogen and fluoro; R^3 and R^4 are methyl; R^5, R^6, R^8, and R^{12} are hydrogen; R^7 is (C1-C6) alkyl; **n** is 1 or 2; and **m** is 0 or 1. Preferred species include the following compounds:



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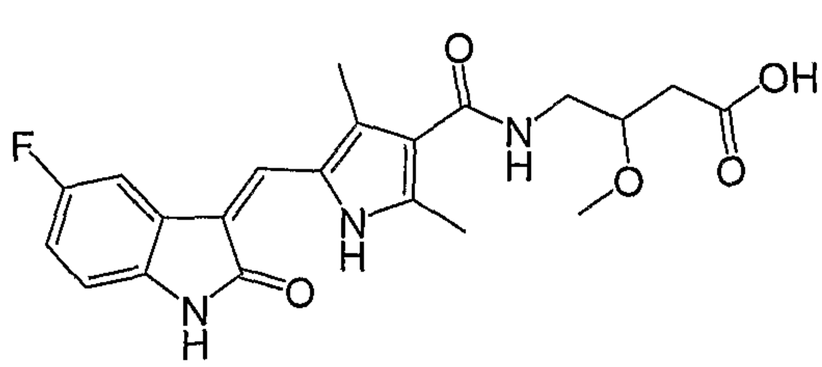

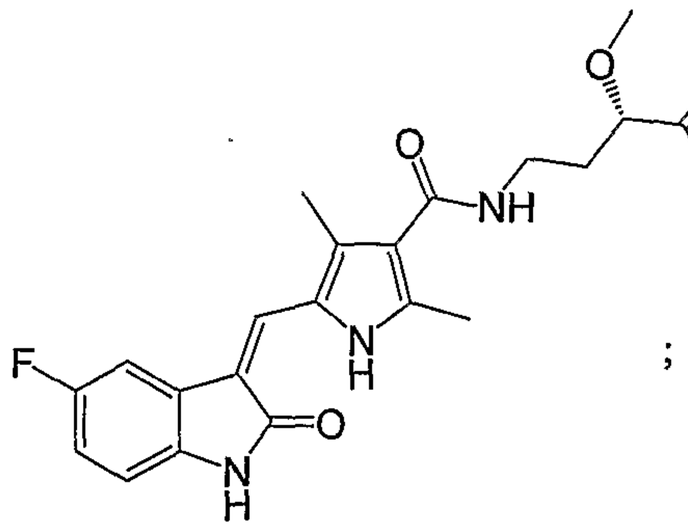

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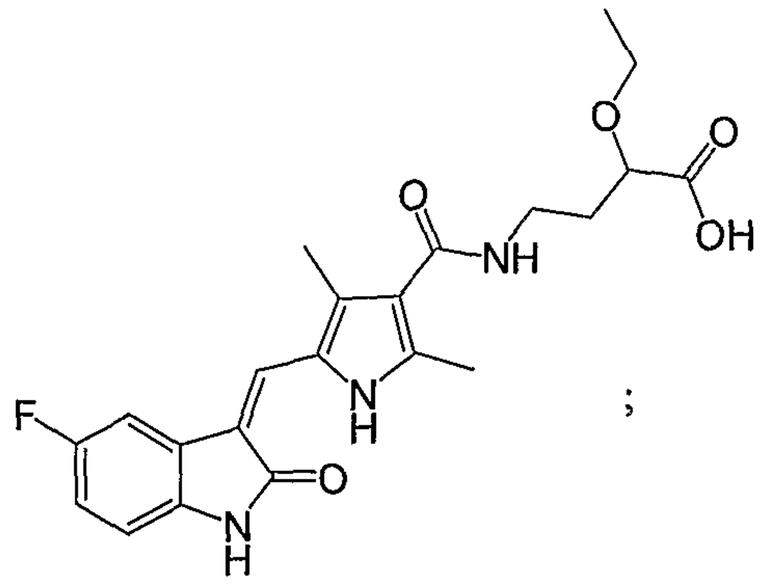

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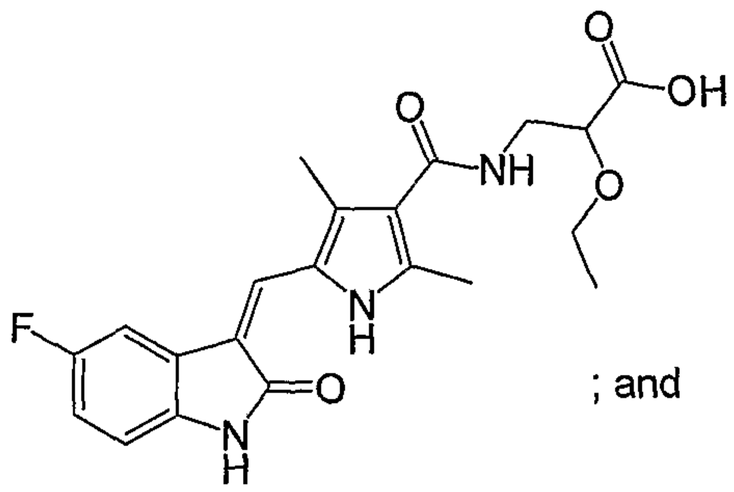
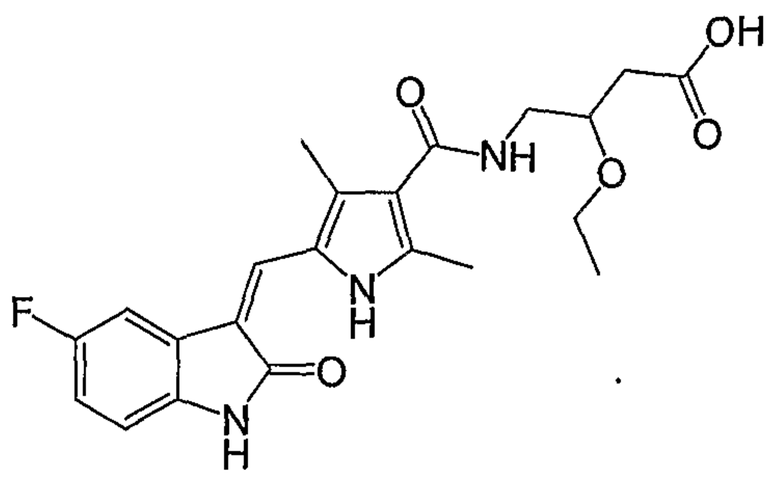


; and



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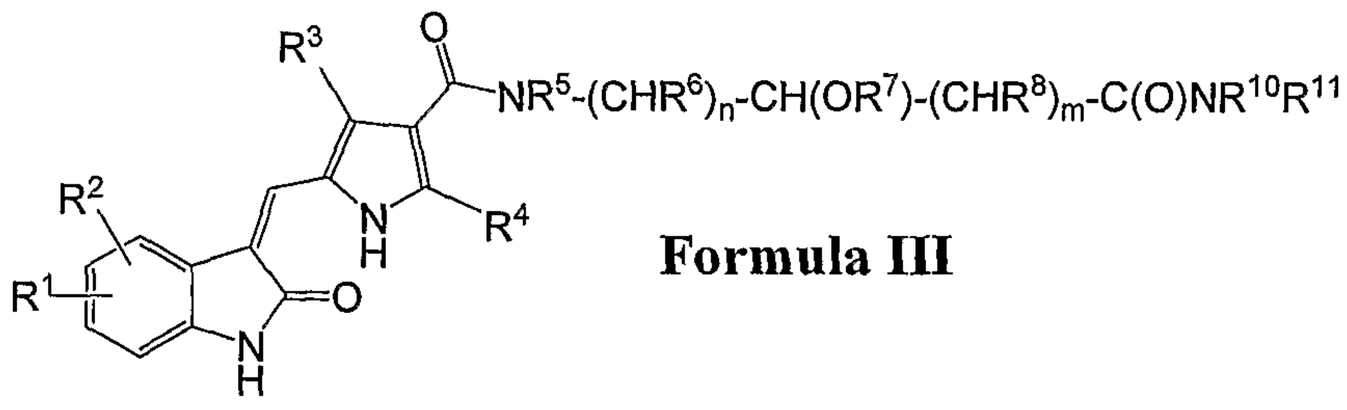
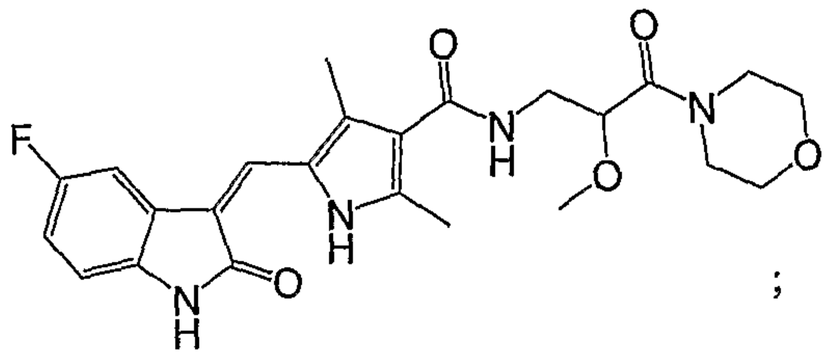
A second preferred subgenus of this first aspect of the invention is directed to a compound, salt, tautomer, or prodrug represented by Formula (**III**):



Formula III

In Formula (**III**), the various R groups are the same as Formula (**I**). In preferred embodiments, R^1 and R^2 are independently selected from the group consisting of hydrogen, halo, cyano; R^3 is selected from the group consisting of hydrogen, (C1-C6) alkyl, (C6-C10) aryl, (C5-C10) heteroaryl, and amide; R^4, R^5, R^6 and R^8 are independently selected from the group consisting of hydrogen and (C1-C6))alkyl; R^7 is (C1-C6) alkyl; **n** is 1 or 2; **m** is 0 or 1; and R^{10} and R^{11} are selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) hydroxyalkyl, (C2-C6) dihydroxyalkyl, (C1-C6) alkoxy , (C2-C6) alkyl carboxylic acid, (C1-C6) alkyl phosphonic acid, (C1-C6) alkyl sulfonic acid, (C2-C6) hydroxyalkyl carboxylic acid, (C1-C6) alkyl amide, (C3-C8) cycloalkyl, (C5-C8) heterocycloalkyl, (C6-C8) aryl, (C5-C8) heteroaryl, (C4-C8) cycloalkyl carboxylic acid, or R^{10} and R^{11} together with N forms a (C5-C8) heterocyclic ring either unsubstituted or substituted with one or more hydroxyls, ketones, ethers, and carboxylic acids.

In a first subgroup of this second subgenus, **m** is 0. Preferred species of this first subgroup are represented by the following structures: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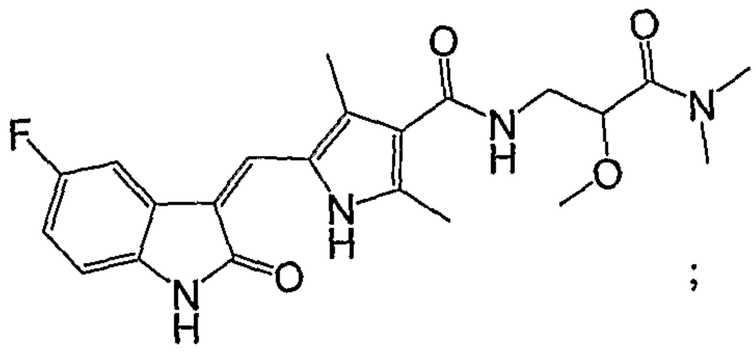
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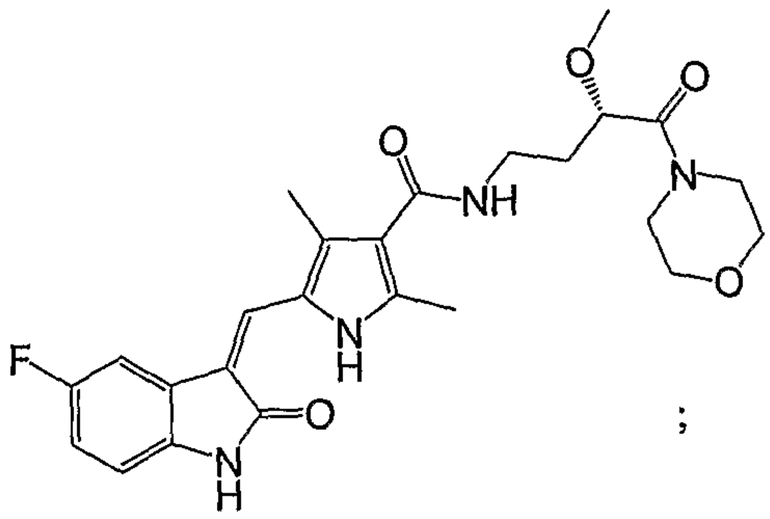
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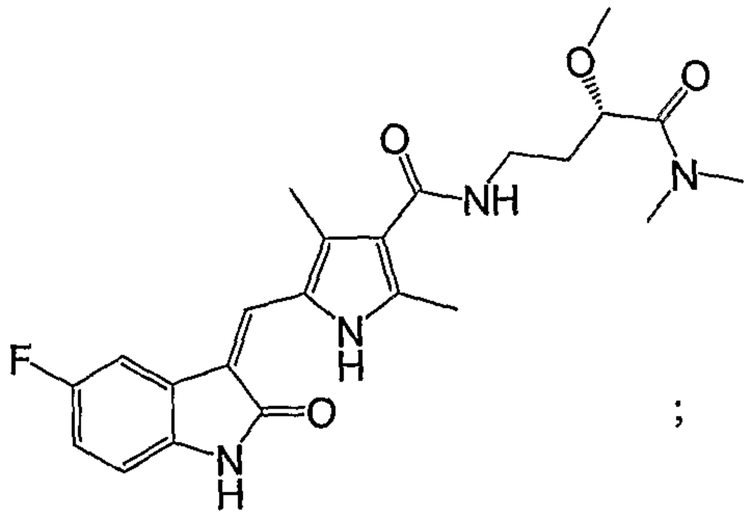
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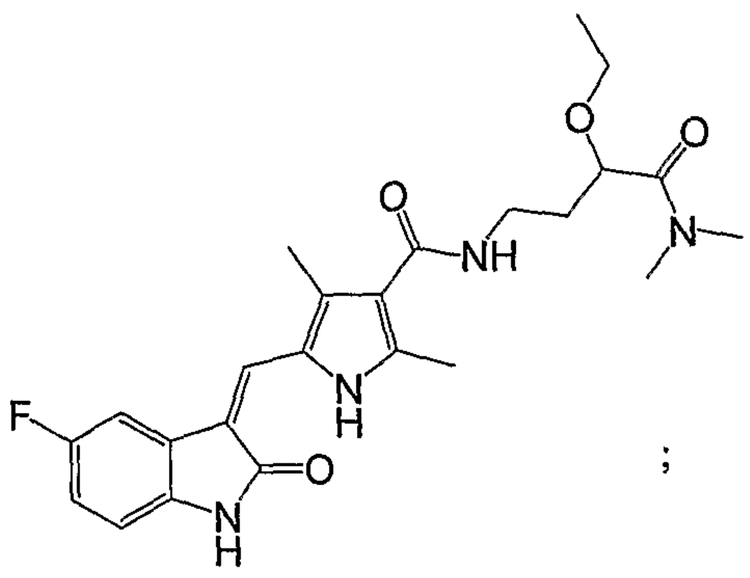
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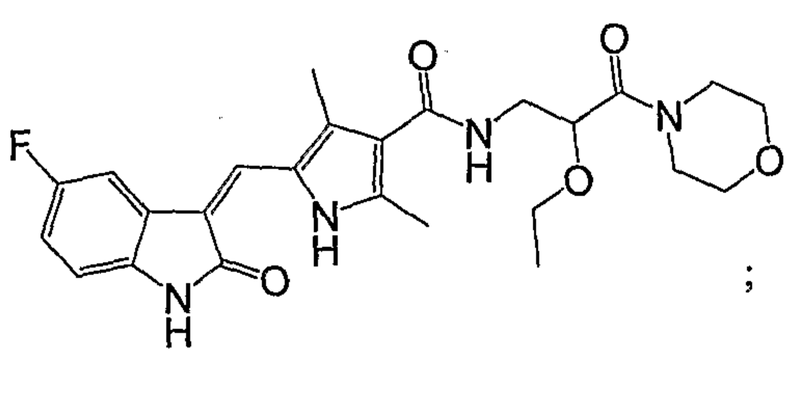
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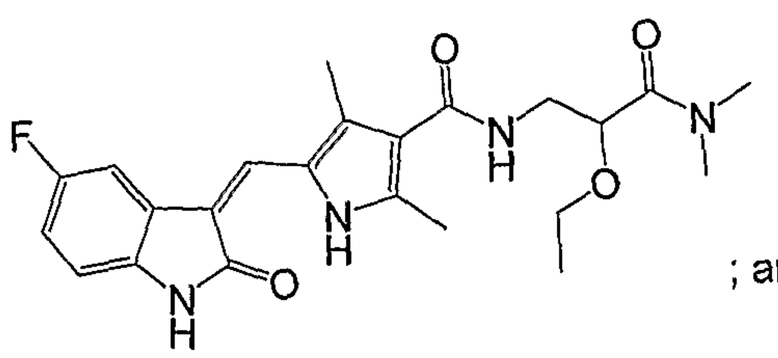
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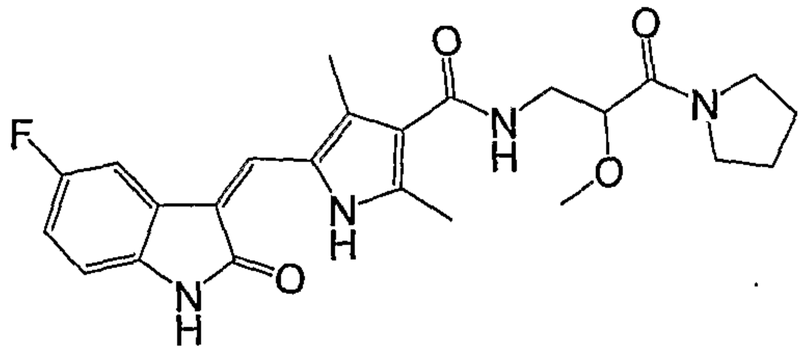
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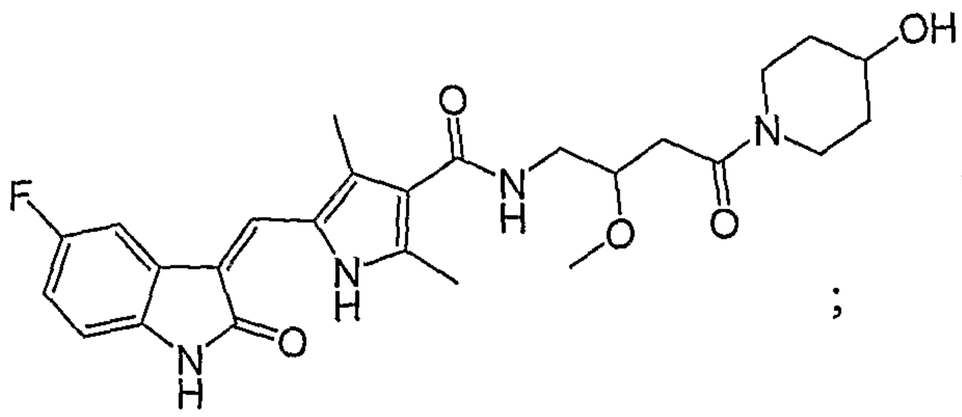
In a second subgroup of this second subgenus, **m** is 1. Preferred species of this second subgroup are represented by the following structures: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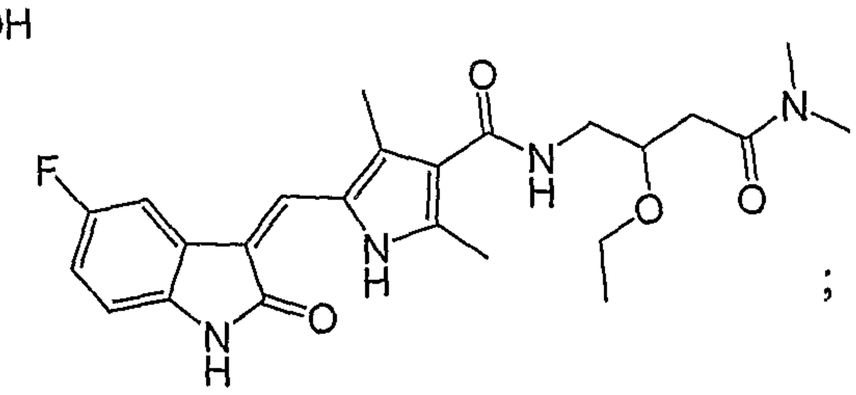
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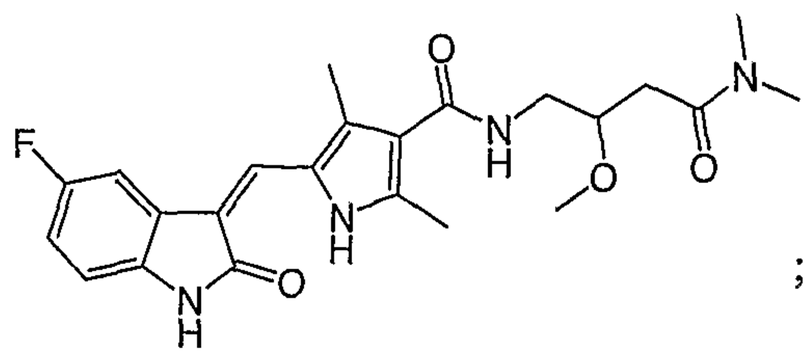
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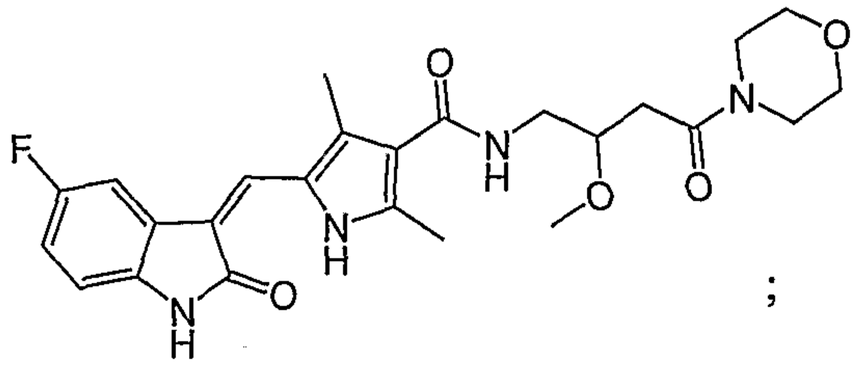
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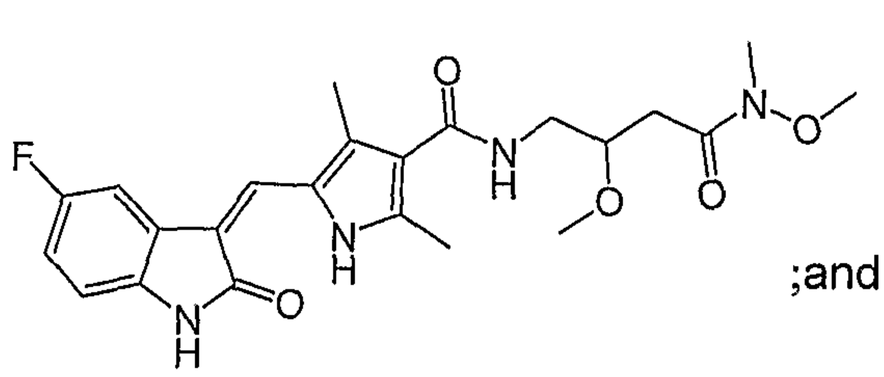
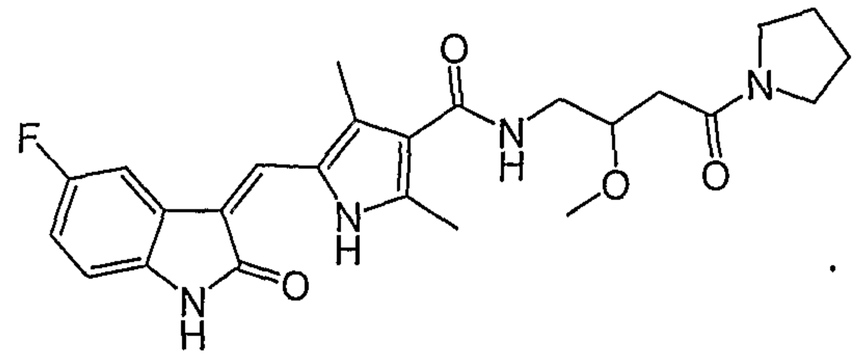

;and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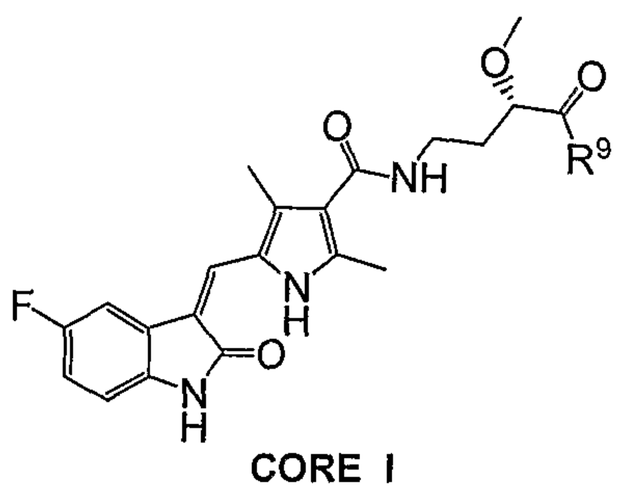
Further species of the second aspect of the invention are represented by the following structures: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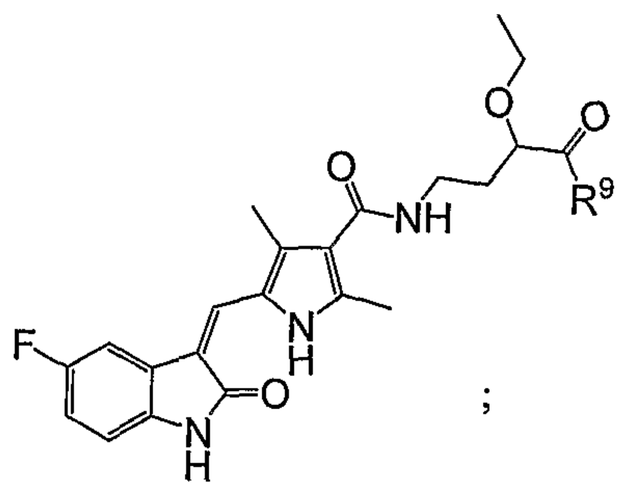
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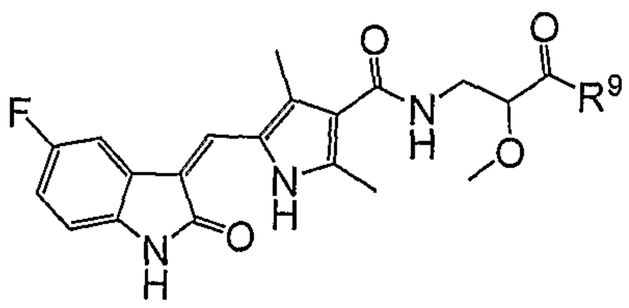
CORE I

CORE II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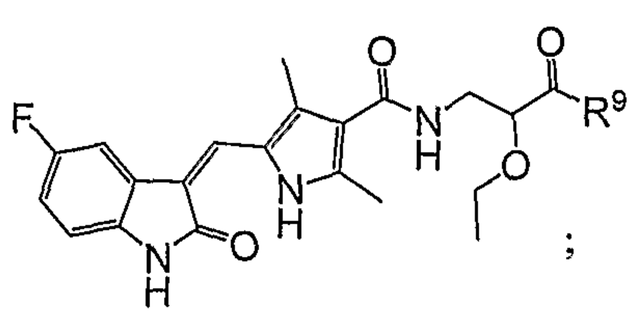
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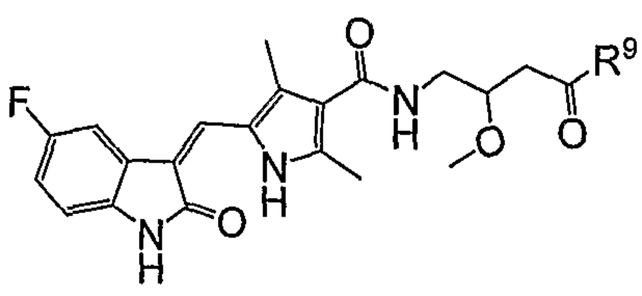
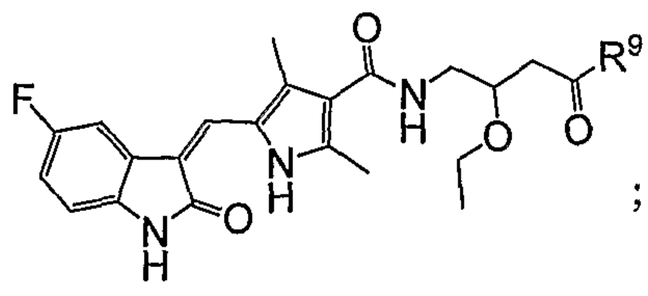
CORE III

CORE IV


; and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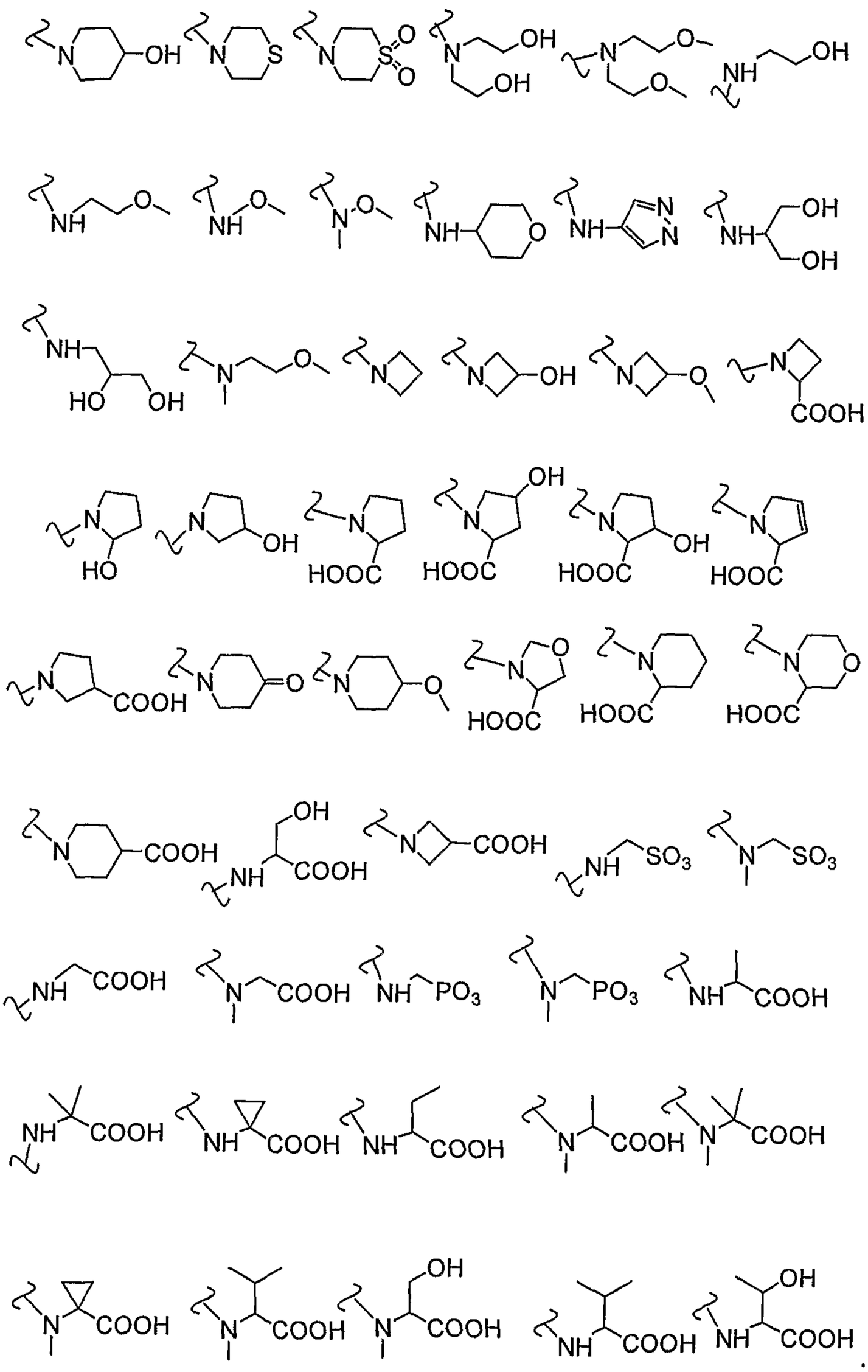
CORE V

CORE VI

wherein: R^9 is selected from the group consisting of radicals represented by the following structures:



Another aspect of the invention is directed to a method for the modulation of the catalytic activity of a protein kinase with a compound or salt of any one of the compounds of Formulas (**I-III**). In a preferred mode, the protein kinase is selected from the group consisting of VEGF receptors and PDGF receptors.

Brief Description of Figures:

Figure 1 illustrates a scheme that is used for the synthesis of the 3-alkoxy-4-acylaminoamide derivatives starting from methyl 3-hydroxy-4-aminobutanoate hydrochlorides and the activated acylating agent **1-3**.

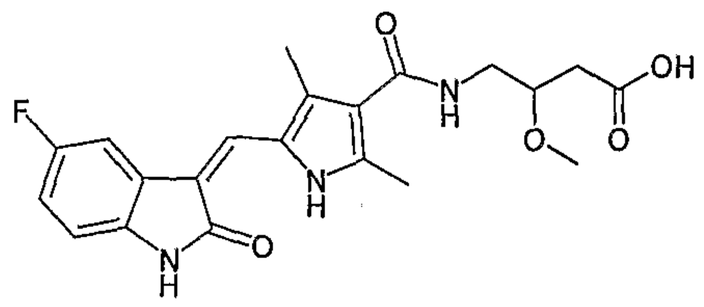
Figure 2 illustrates a scheme that is used for the synthesis of the 2-alkoxy-3-acylaminoamide derivatives starting from methyl 2-hydroxy-3-aminopropionate hydrochlorides and the activated acylating agent **1-3**.

Figure 3 illustrates a scheme that is used for the synthesis of the (2S)-2-alkoxy-4-acylamino-amide derivatives starting from methyl (2S)-2-hydroxy-4-aminobutanoate hydrochloride and the activated acylating agent **1-3**.

Detailed Description:

Examples 1-8: The synthesis of acids (**1-4**) and amides (**1-5**) is shown in **Figure 1**. Variations from this general synthetic procedure can be understood and carried out by those skilled in the art. Thus, the compounds of the present invention can be synthesized by those skilled in the art.

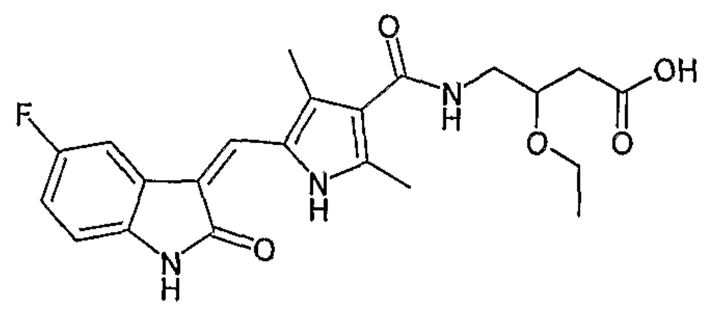
Example 1: 4-({5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-3-methoxy-butyric acid



To a suspension of methyl 4-amino-3-hydroxybutyrate (1.0 equiv, which was prepared by refluxing the free amino acid in dry methanol with 1.2 equiv HCl) and DIEA (5 equiv) in DCM, Mmt-Cl (1.1 equiv) was added portion-wise at 25 °C. After stirring overnight, the DCM was removed under reduced pressure. The residue was suspended in ethyl acetate, washed with brine (3x), dried over anhydrous Na_2SO_4. The ethyl acetate was then removed, and the residue was dried overnight under high vacuum, and subjected to flash chromatography to give compound **1-1**. To a solution of compound **1-1** in dry DMF, NaH (1.5 equiv) was added under argon. After stirring at 25 °C for 1h, MeI (5 equiv) was added to the solution, and the resulting suspension was gently shaken at 25 °C overnight. The DMF was removed under vacuum; the residue was suspended in ethyl acetate, washed with brine (3x), and dried over anhydrous Na_2SO_4. After the ethyl acetate was removed via evaporation the resulting residue was treated with 1% TFA in DCE/DCM for 30 min. The organic solvents were then removed under reduced pressure, and the resulting residue was triturated with hexane (3x) to obtain the free amino acid **1-2**. This amino acid was used directly in the next step without any purification and characterization. Thus, to a solution of **1-2** (2 equiv) and DIEA (5 equiv) in DMF, compound **1-3** (1 equiv) was added at 25 °C. After stirring for 30 min (LC-MS show the complete consumption of **1-3**), KOH (5 equiv)

in water was added, and the solution was stirred for another 2h (LC-MS demonstrated a complete hydrolysis). The solvents were removed under reduced pressure, and HCl (1N, excess) was added to give a precipitate. This precipitate was collected and washed (by water) by filtration, dried under high vacuum to give the title compound (95% based on compound **1-3**). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{21}H_{22}FN_3O_5$: 416, obtained: 416. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.67 (s, 1H), 12.18 (b, 1H), 10.90 (s, 1H), 7.75 (dd, *J* = 2.4 Hz, *J* = 9.6 Hz, 1H), 7.71 (s, 1H), 7.64 (t, *J* = 6.0 Hz, 1H), 6.92 (m, 1H), 6.83 (dd, *J* = 4.8 Hz, *J* = 8.4 Hz, 1H), 3.73 (m, 1H), 3.43-3.31 (m, 2H), 3.22 (s, 3H), 2.52-2.35 (m, 2H), 2.43 (s, 3H), 2.41 (s, 3H).

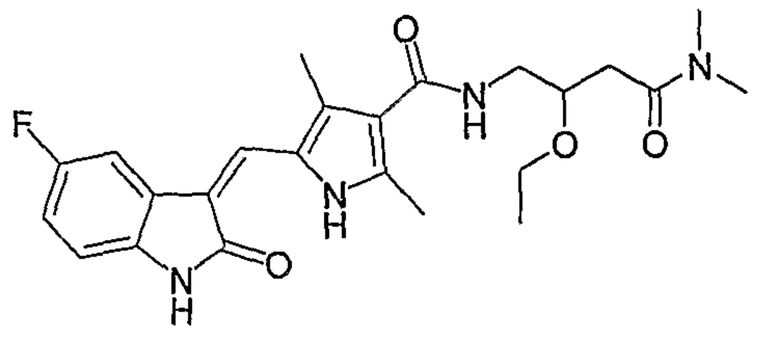
Example 2: 3-Ethoxy-4-({5-[5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-butyric acid



A similar route as that for the synthesis of **Example 1** was used to prepare the title compound. Iodoethane was used instead of iodomethane to obtain the 3-ethoxy compound (9.7% based on compound **1-3**). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{22}H_{24}FN_3O_5$: 430, obtained: 430.

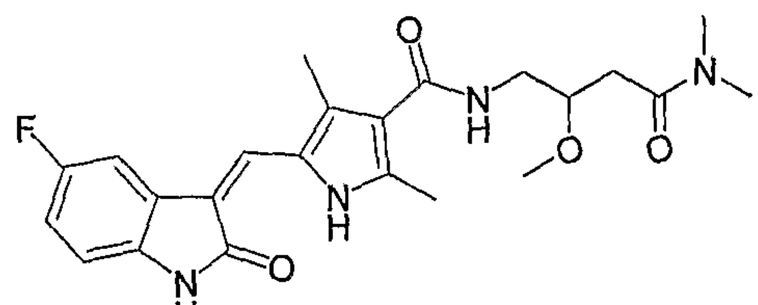
Examples 3-8: The general procedure for the synthesis of amides (**1-5**): An amine (2 equiv) was added to a solution of the acid (**1-4**), HATU (1.05 mmol), and DIEA (5 equiv) in DMF (5 mL). After the solution was stirred at 25 °C for 2h, aqueous HCl (2 mL, 1N) was added. This solution was subjected to preparative HPLC to obtain the pure amide product, which was subsequently characterized by LC-MS and NMR spectroscopy.

Example 3: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (3-dimethylcarbamoyl-2-ethoxy-propyl)-amide



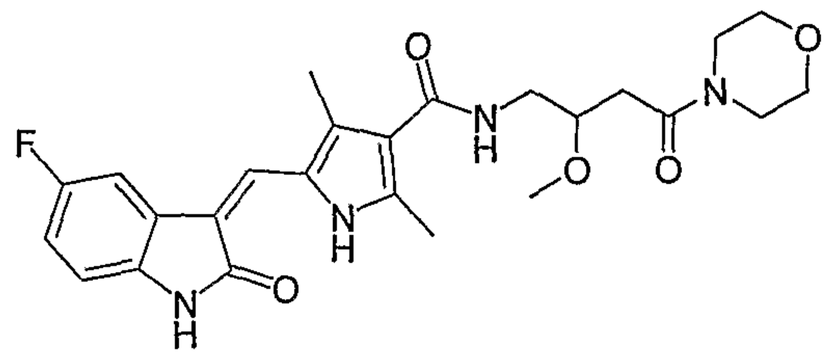
Preparative HPLC gave 13 mg of the title compound (41%) from 30 mg starting material (acid). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{24}H_{29}FN_4O_4$: 457, obtained: 457. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.68 (s, 1H), 10.89 (s, 1H), 7.76 (dd, *J* = 2.4 Hz, 9.2 Hz, 1H), 7.72 (s, 1H), 7.60 (t, *J* = 6.0 Hz, 1H), 6.92 (m, 1H), 6.83 (dd, *J* = 4.8 Hz, 8.4Hz, 1H), 3.89 (m, 1H), 3.58-3.45 (m, 2H), 3.40-3.27 (m, 2H, buried in water signals), 2.97 (s, 3H), 2.82 (s, 3H), 2.43 (s, 3H), 2.41 (s, 3H), 1.07 (t, *J* = 7.2 Hz, 3H).

Example 4: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (3-dimethylcarbamoyl-2-methoxy-propyl)-amide



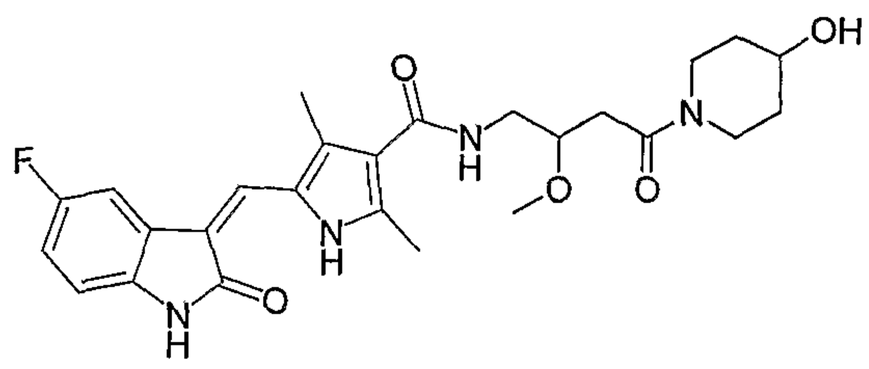
Preparative HPLC gave 46 mg of the title compound (36%) from 120 mg starting material (acid). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{23}H_{27}FN_4O_4$: 443, obtained: 443. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.68 (s, 1H), 10.89 (s, 1H), 7.76 (dd, *J* = 2.4 Hz, 9.2 Hz, 1H), 7.71 (s, 1H), 7.63 (t, *J* = 5.6 Hz, 1H), 6.92 (m, 1H), 6.83 (dd, *J* = 4.8 Hz, 8.8 Hz, 1H), 3.78 (m, 1H), 3.42-3.31 (m, 2H), 3.30 (s, 3H), 2.97 (s, 3H), 2.82 (s, 3H), 2.43 (s, 3H), 2.41 (s, 3H), 2.63-2.43 (m, 2H).

Example 5: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-methoxy-4-morpholin-4-yl-4-oxo-butyl)-amide



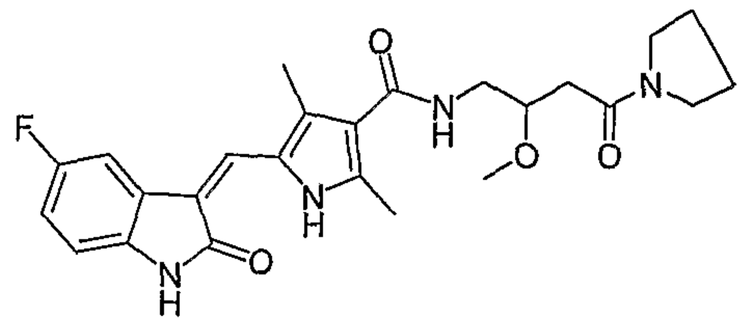
Preparative HPLC gave 48 mg of the title compound (37%) from 110 mg starting material (acid). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{25}H_{29}FN_4O_6$: 485, obtained: 485. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.68 (s, 1H), 10.89 (s, 1H), 7.76 (dd, *J* = 2.4 Hz, 9.2 Hz, 1H), 7.71 (s, 1H), 7.63 (t, *J* = 5.6 Hz, 1H), 6.92 (m, 1H), 6.83 (dd, *J* = 4.8 Hz, 8.4 Hz, 1H), 3.80 (m, 1H), 3.55 (m, 4H), 3.47 (m, 4H), 3.38 (m, 2H), 3.31 (s, 3H), 2.60 (m, 1H), 2.45 (m, 1H), 2.43 (s, 3H), 2.41 (s, 3H).

Example 6: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [4-(4-hydroxy-piperidin-1-yl)-2-methoxy-4-oxo-butyl]-amide



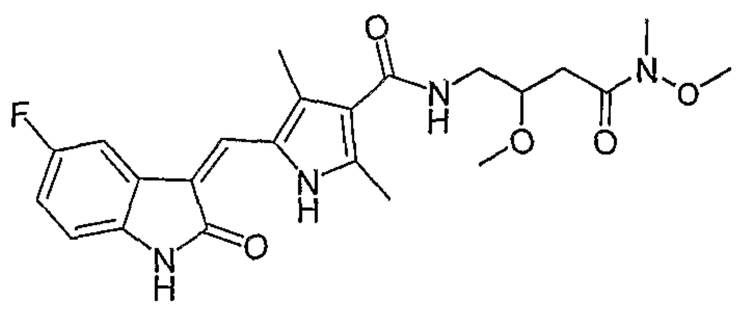
Preparative HPLC gave 20 mg of the title compound (33%) from 50 mg starting material (acid). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{26}H_{31}FN_4O_5$: 499, obtained: 499. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.68 (s, 1H), 10.89 (s, 1H), 7.76 (dd, *J* = 2.4 Hz, 9.6 Hz, 1H), 7.72 (s, 1H), 7.63 (t, *J* = 5.6 Hz, 1H), 6.93 (m, 1H), 6.83 (dd, *J* = 4.4 Hz, 8.4 Hz, 1H), 3.92 (m, 1H), 3.78 (m, 1H), 3.68 (b, 1H), 3.30 (s, 3H), 3.15 (m, 1H), 3.01 (m, 1H), 2.60 (m, 1H), 2.55 (m, 2H), 2.50 (m, 1H), 2.45 (m, 2H), 2.43 (s, 3H), 2.41 (s, 3H), 1.70 (m, 2H), 1.30 (m, 2H).

Example 7: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-methoxy-4-oxo-4-pyrrolidin-1-yl-butyl)-amide



Preparative HPLC gave 40 mg of the title compound (32%) from 110 mg starting material (acid). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{25}H_{29}FN_4O_4$: 469, obtained: 469. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.68 (s, 1H), 10.89 (s, 1H), 7.76 (dd, *J* = 2.4 Hz, 9.6 Hz, 1H), 7.71 (s, 1H), 7.63 (t, *J* = 5.6 Hz, 1H), 6.93 (m, 1H), 6.83 (dd, *J* = 4.8 Hz, 8.8 Hz, 1H), 3.82 (m, 1H), 3.50-3.25 (m, 6H), 3.30 (s, 3H), 2.55-2.45 (m, 2H), 2.43 (s, 3H), 2.41 (s, 3H), 1.86 (m, 2H), 1.76 (m, 2H).

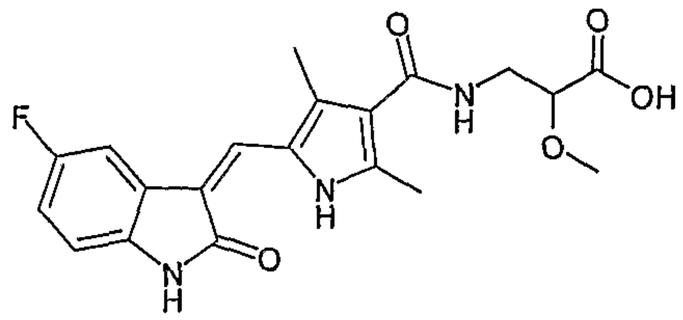
Example 8: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [2-methoxy-3-(methoxy-methyl-carbamoyl)-propyl]-amide



Preparative HPLC gave 15 mg of the title compound (15%) from 80 mg starting material (acid). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{23}H_{27}FN_4O_5$: 459, obtained: 459. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.68 (s, 1H), 10.90 (s, 1H), 7.76 (dd, *J* = 2.4 Hz, 9.2 Hz, 1H), 7.72 (s, 1H), 7.68 (t, *J* = 6.0 Hz, 1H), 6.93 (m, 1H), 6.84 (dd, *J* = 4.4 Hz, 8.4 Hz, 1H), 3.79 (m, 1H), 3.66 (s, 3H), 3.50-3.35 (m, 2H), 3.31 (s, 3H), 3.13 (s, 3H), 2.55-2.45 (m, 2H), 2.43 (s, 3H), 2.41 (s, 3H).

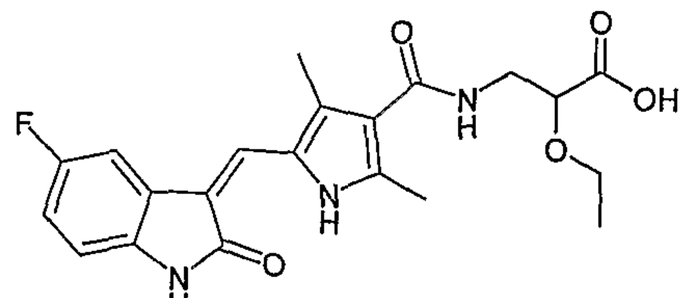
Examples 9-15: The synthesis of acids (**2-3**) and amides (**2-4**) is shown in **Figure 2**. Variations from this general synthetic procedure can be understood and carried out by those skilled in the art. Thus, the compounds of the present invention can be synthesized by those skilled in the art.

Example 9: 3-({5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-2-methoxy-propionic acid



To a suspension of methyl 3-amino-2-hydroxypropionate (1.0 equiv, which was prepared by refluxing the free amino acid isoserine in dry methanol with 1.2 equiv HCl) and DIEA (5 equiv) in DCM, Mmt-Cl (1.1 equiv) was added portion-wise at 25 °C. After stirring overnight, the DCM was removed under reduced pressure. The residue was suspended in ethyl acetate, washed with brine (3x), dried over anhydrous Na_2SO_4. The ethyl acetate was then removed, and the residue was dried overnight under high vacuum, and subjected to flash chromatography to give compound **2-1**. To a solution of compound **2-1** in dry DMF, NaH (1.5 equiv) was added under argon. After stirring at 25 °C for 1h, MeI (5 equiv) was added to the solution, and the resulting suspension was gently stirred at 25 °C overnight. The DMF was removed under vacuum; the residue was suspended in ethyl acetate, washed with brine (3x), and dried over anhydrous Na_2SO_4. After the ethyl acetate was removed via evaporation the resulting residue was treated with 1% TFA in DCE/DCM for 30 min. The organic solvents were then removed under reduced pressure, and the resulting residue was triturated with hexane (3x) to obtain the free amino acid **2-2**. This amino acid was used directly in the next step without any purification and characterizations. Thus, to a solution of **2-2** (2 equiv) and DIEA (5 equiv) in DMF, compound **1-3** (1 equiv) was added at 25 °C. After stirring for 30 min (LC-MS show the complete consumption of **1-3**), KOH (5 equiv) in water was added, and the solution was stirred for another 2h (LC-MS demonstrated a complete hydrolysis). The solvents were removed under reduced pressure, and HCl (1N, excess) was added to give a precipitate. This precipitate was collected by filtration, washed with water and dried under high vacuum to give the title compound (99% based on compound **1-3**). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{20}H_{20}FN_3O_5$: 402, obtained: 402. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.67 (s, 1H), 12.83 (b, 1H), 10.90 (s, 1H), 7.76 (dd, *J* = 2.4 Hz, *J* = 9.6 Hz, 1H), 7.71 (s, 1H), 7.69 (t, *J* = 6.0 Hz, 1H), 6.92 (m, 1H), 6.82 (dd, *J* = 4.8 Hz, *J* = 8.4 Hz, 1H), 3.90 (m, 1H), 3.55 (m, 1H), 3.41 (m, 1H), 3.32 (s, 3H), 2.42 (s, 3H), 2.40 (s, 3H).

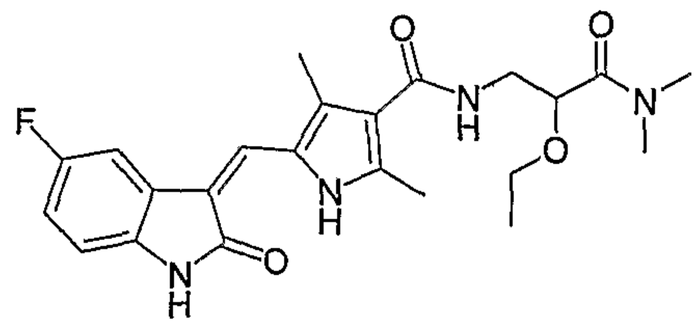
Example 10: 2-Ethoxy-3-({5-[5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-propionic acid



A similar route as that for the synthesis of **Example 9** was used to prepare the title compound. Iodoethane was used instead of iodomethane to obtain the 2-ethoxy compound (38% based on compound **1-3**). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{21}H_{22}FN_4O_5$: 416, obtained: 416. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.67 (s, 1H), 12.80 (b, 1H), 10.89 (s, 1H), 7.76 (dd, *J* = 2.4 Hz, *J* = 9.2 Hz, 1H), 7.71 (s, 1H), 7.68 (t, *J* = 6.0 Hz, 1H), 6.92 (m, 1H), 6.83 (dd, *J* = 4.8 Hz, *J* = 8.4 Hz, 1H), 4.00 (dd, *J* = 5.2 Hz, *J* = 7.6 Hz, 1H), 3.58 (m, 2H), 3.41 (m, 2H), 2.43 (s, 3H), 2.41 (s, 3H), 1.14 (t, *J* = 6.8 Hz, 3H).

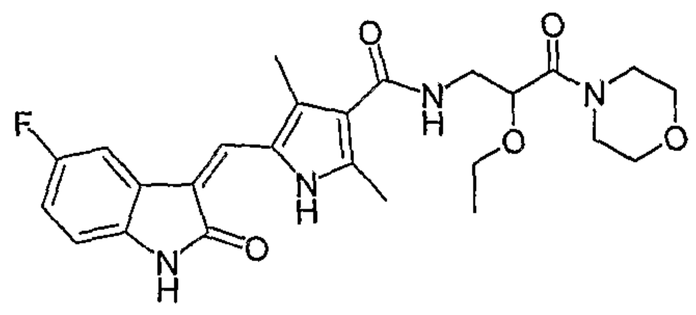
Examples 11-15: The general procedure for the synthesis of amides (**compounds 2-4**): A corresponding amine (2 equiv) was added to a solution of the acid (**compound 2-3**), HATU (1.05 mmol), and DIEA (5 equiv) in DMF (5 mL). After the solution was stirred at 25 °C for 2h, aqueous HCl (2 mL, 1N) was added. This solution was subjected to preparative HPLC to obtain the pure amide product, which was subsequently characterized by LC-MS and NMR spectroscopy.

Example 11: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-dimethylcarbamoyl-2-ethoxy-ethyl)-amide



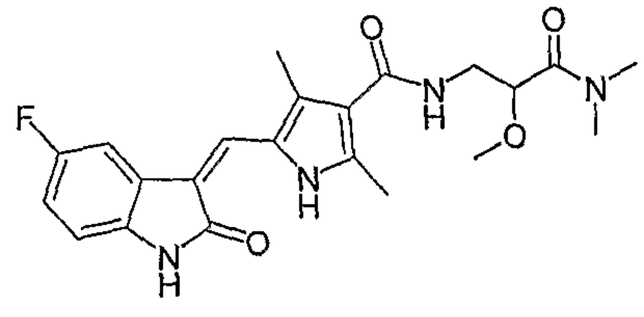
Preparative HPLC gave 46 mg of the title compound (62%) from 70 mg starting material (acid). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{23}H_{27}FN_4O_4$: 443, obtained: 443.

Example 12: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-ethoxy-3-morpholin-4-yl-3-oxo-propyl)-amide



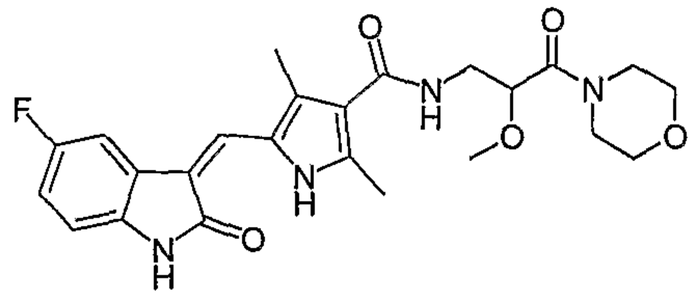
Preparative HPLC gave 40 mg of the title compound (49%) from 70 mg starting material (acid). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{25}H_{29}FN_4O_5$: 485, obtained: 485. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.67 (s, 1H), 10.89 (s, 1H), 7.76 (dd, J = 2.4 Hz, J = 9.6 Hz, 1H), 7.71 (s, 1H), 7.70 (m, 1H), 6.93 (m, 1H), 6.83 (dd, J = 4.8 Hz, J = 8.4 Hz, 1H), 4.40 (m, 1H), 3.73-3.35 (m, 12H), 2.43 (s, 3H), 2.41 (s, 3H), 1.12 (t, J = 7.2 Hz, 3H).

Example 13: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-dimethylcarbamoyl-2-methoxy-ethyl)-amide



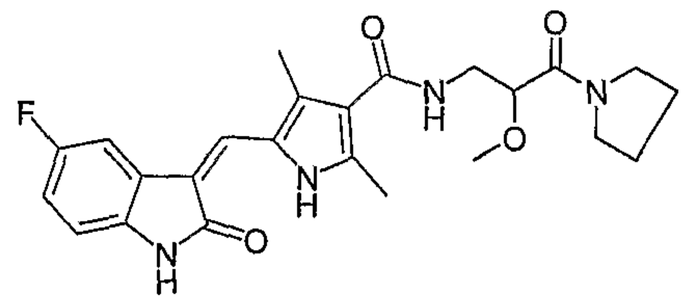
Preparative HPLC gave 93 mg of the title compound (76%) from 115 mg starting material (acid). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{22}H_{25}FN_4O_4$: 429, obtained: 429. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.68 (s, 1H), 10.90 (s, 1H), 7.75 (dd, J = 2.4 Hz, J = 9.6 Hz, 1H), 7.72 (m, 1H), 7.71 (s, 1H), 6.93 (m, 1H), 6.83 (dd, J = 4.8 Hz, J = 8.8 Hz, 1H), 4.40 (dd, J = 4.8 Hz, J = 7.2 Hz, 1H), 3.50 (m, 1H), 3.32 (m, 1H), 3.24 (s, 3H), 3.10 (s, 3H), 2.86 (s, 3H), 2.43 (s, 3H), 2.41 (s, 3H).

Example 14: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-methoxy-3-morpholin-4-yl-3-oxo-propyl)-amide



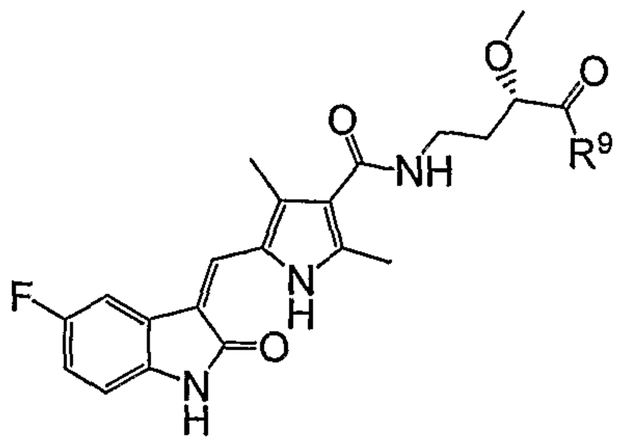
Preparative HPLC gave 98 mg of the title compound (73%) from 115 mg starting material (acid). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{24}H_{27}FN_4O_5$: 471, obtained: 471. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.67 (s, 1H), 10.89 (s, 1H), 7.75 (dd, *J* = 2.4 Hz, *J* = 9.6 Hz, 1H), 7.71 (s, 1H), 7.70 (m, 1H), 6.92 (m, 1H), 6.83 (dd, *J* = 4.8 Hz, *J* = 8.8 Hz, 1H), 4.34 (dd, *J* = 4.8 Hz, *J* = 7.2 Hz, 1H), 3.85-3.30 (m, 10H), 3.26 (s, 3H), 2.44 (s, 3H), 2.42 (s, 3H).

Example 15: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-methoxy-3-oxo-3-pyrrolidin-1-yl-propyl)-amide

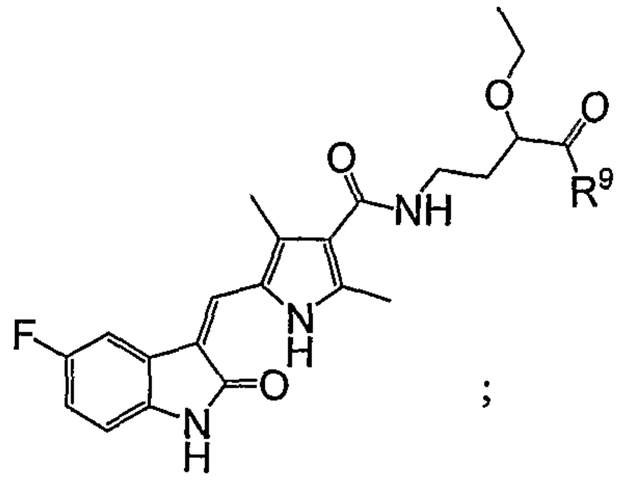


Preparative HPLC gave 86 mg of the title compound (66%) from 115 mg starting material (acid). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{24}H_{27}FN_4O_4$: 455, obtained: 455. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.67 (s, 1H), 10.89 (s, 1H), 7.76 (dd, *J* = 2.4 Hz, *J* = 9.6 Hz, 1H), 7.70 (m, 1H), 7.71 (s, 1H), 6.93 (m, 1H), 6.83 (dd, *J* = 4.4 Hz, *J* = 8.4 Hz, 1H), 4.20 (dd, *J* = 5.2 Hz, *J* = 7.2 Hz, 1H), 3.60-3.47 (m, 3H), 3.43-3.28 (m, 3H), 3.26 (s, 3H), 2.43 (s, 3H), 2.40 (s, 3H), 1.88 (m, 2H), 1.78 (m, 2H).

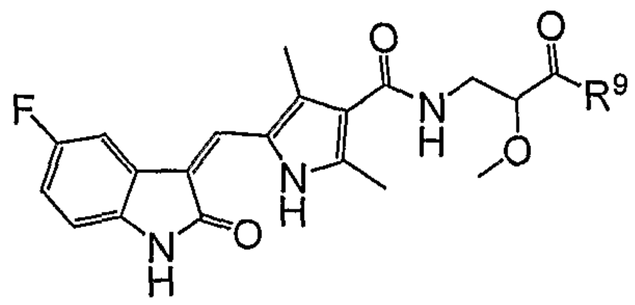
Examples 16 – 315: Still further amide examples are shown in the following table:



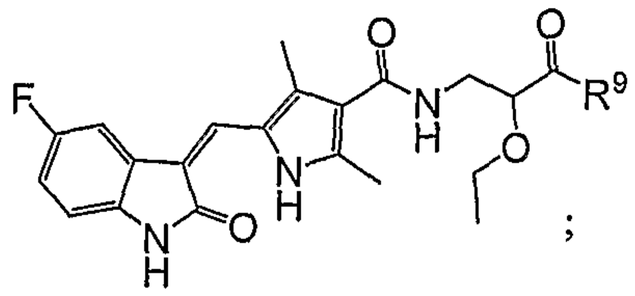
CORE I ;



CORE II ;



CORE III ;



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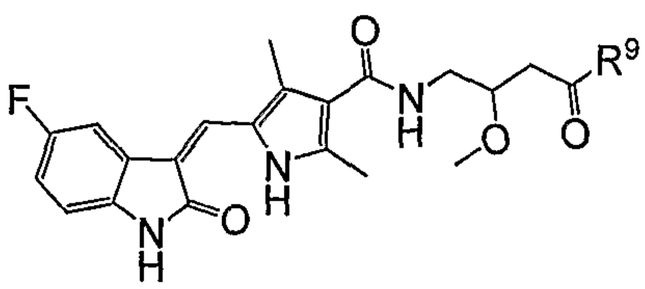
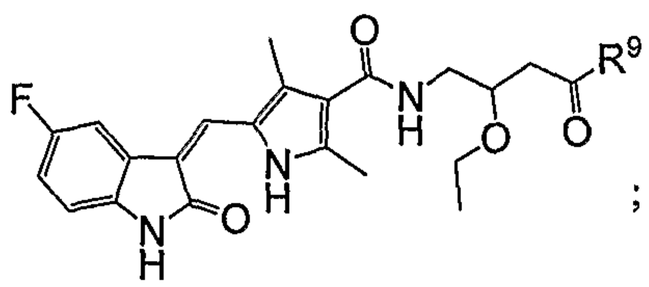


CORE V ; and



CORE VI ;

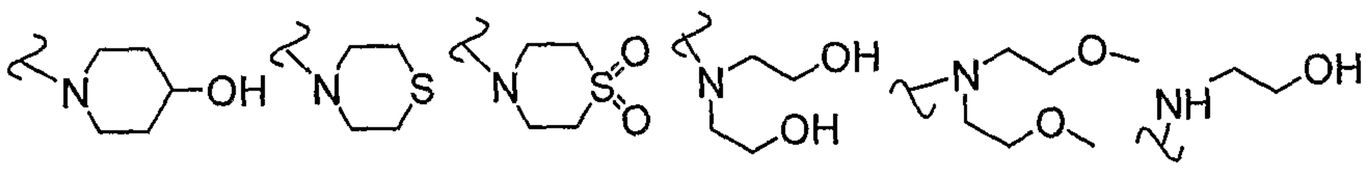
Ex#	Core	R	Ex#	Core	R	Ex#	Core	R
16	I	a	66	II	a	116	III	a
17	I	b	67	II	b	117	III	b
18	I	c	68	II	c	118	III	c
19	I	d	69	II	d	119	III	d
20	I	e	70	II	e	120	III	e
21	I	f	71	II	f	121	III	f
22	I	g	72	II	g	122	III	g
23	I	h	73	II	h	123	III	h
24	I	i	74	II	i	124	III	i
25	I	j	75	II	j	125	III	j
26	I	k	76	II	k	126	III	k
27	I	l	77	II	l	127	III	l
28	I	m	78	II	m	128	III	m
29	I	n	79	II	n	129	III	n
30	I	o	80	II	o	130	III	o

Ex#	Core	R	Ex#	Core	R	Ex#	Core	R
31	I	p	81	II	p	131	III	p
32	I	q	82	II	q	132	III	q
33	I	r	83	II	r	133	III	r
34	I	s	84	II	s	134	III	s
35	I	t	85	II	t	135	III	t
36	I	u	86	II	u	136	III	u
37	I	v	87	II	v	137	III	v
38	I	w	88	II	w	138	III	w
39	I	x	89	II	x	139	III	x
40	I	y	90	II	y	140	III	y
41	I	z	91	II	z	141	III	z
42	I	aa	92	II	aa	142	III	aa
43	I	ab	93	II	ab	143	III	ab
44	I	ac	94	II	ac	144	III	ac
45	I	ad	95	II	ad	145	III	ad
46	I	ae	96	II	ae	146	III	ae
47	I	af	97	II	af	147	III	af
48	I	ag	98	II	ag	148	III	ag
49	I	ah	99	II	ah	149	III	ah
50	I	ai	100	II	ai	150	III	ai
51	I	aj	101	II	aj	151	III	aj
52	I	ak	102	II	ak	152	III	ak
53	I	al	103	II	al	153	III	al
54	I	am	104	II	am	154	III	am
55	I	an	105	II	an	155	III	an
56	I	ao	106	II	ao	156	III	ao
57	I	ap	107	II	ap	157	III	ap
58	I	aq	108	II	aq	158	III	aq
59	I	ar	109	II	ar	159	III	ar
60	I	as	110	II	as	160	III	as
61	I	at	111	II	at	161	III	at
62	I	au	112	II	au	162	III	au
63	I	av	113	II	av	163	III	av
64	I	aw	114	II	aw	164	III	aw
65	I	ax	115	II	ax	165	III	ax

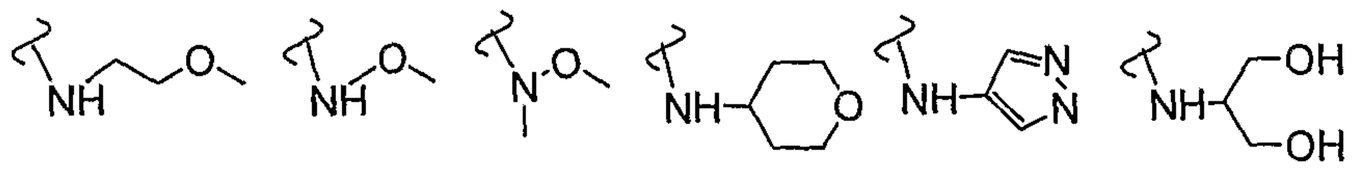
Ex#	Core	R	Ex#	Core	R	Ex#	Core	R
166	IV	a	216	V	a	266	VI	a
167	IV	b	217	V	b	267	VI	b
168	IV	c	218	V	c	268	VI	c
169	IV	d	219	V	d	269	VI	d
170	IV	e	220	V	e	270	VI	e
171	IV	f	221	V	f	271	VI	f
172	IV	g	222	V	g	272	VI	g
173	IV	h	223	V	h	273	VI	h
174	IV	i	224	V	i	274	VI	i
175	IV	j	225	V	j	275	VI	j
176	IV	k	226	V	k	276	VI	k
177	IV	l	227	V	l	277	VI	l
178	IV	m	228	V	m	278	VI	m
179	IV	n	229	V	n	279	VI	n
180	IV	o	230	V	o	280	VI	o
181	IV	p	231	V	p	281	VI	p
182	IV	q	232	V	q	282	VI	q
183	IV	r	233	V	r	283	VI	r
184	IV	s	234	V	s	284	VI	s
185	IV	t	235	V	t	285	VI	t
186	IV	u	236	V	u	286	VI	u
187	IV	v	237	V	v	287	VI	v
188	IV	w	238	V	w	288	VI	w
189	IV	x	239	V	x	289	VI	x
190	IV	y	240	V	y	290	VI	y
191	IV	z	241	V	z	291	VI	z
192	IV	aa	242	V	aa	292	VI	aa
193	IV	ab	243	V	ab	293	VI	ab
194	IV	ac	244	V	ac	294	VI	ac
195	IV	ad	245	V	ad	295	VI	ad
196	IV	ae	246	V	ae	296	VI	ae
197	IV	af	247	V	af	297	VI	af
198	IV	ag	248	V	ag	298	VI	ag
199	IV	ah	249	V	ah	299	VI	ah
200	IV	ai	250	V	ai	300	VI	ai
201	IV	aj	251	V	aj	301	VI	aj
202	IV	ak	252	V	ak	302	VI	ak
203	IV	al	253	V	al	303	VI	al
204	IV	am	254	V	am	304	VI	am
205	IV	an	255	V	an	305	VI	an
206	IV	ao	256	V	ao	306	VI	ao
207	IV	ap	257	V	ap	307	VI	ap
208	IV	aq	258	V	aq	308	VI	aq
209	IV	ar	259	V	ar	309	VI	ar
210	IV	as	260	V	as	310	VI	as
211	IV	at	261	V	at	311	VI	at

Ex#	Core	R	Ex#	Core	R	Ex#	Core	R
212	IV	au	262	V	au	312	VI	au
213	IV	av	263	V	av	313	VI	av
214	IV	aw	264	V	aw	314	VI	aw
215	IV	ax	265	V	ax	315	VI	ax

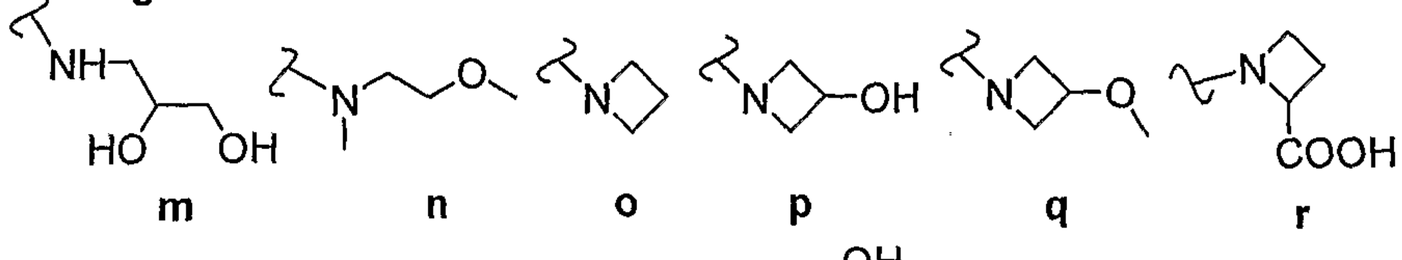
In the above table, R^9 is selected from the following radicals:



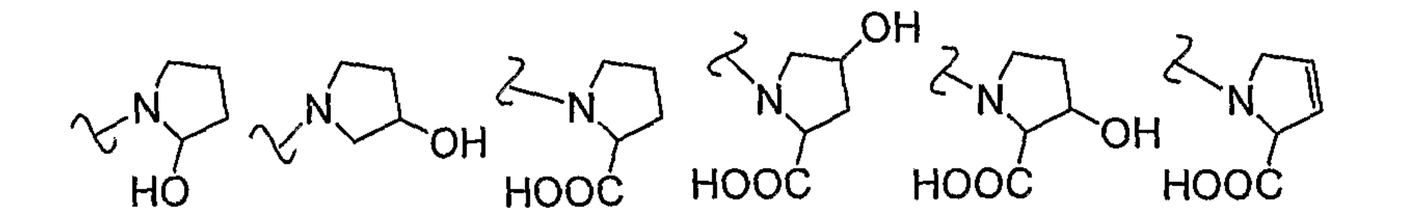
a b c d e f



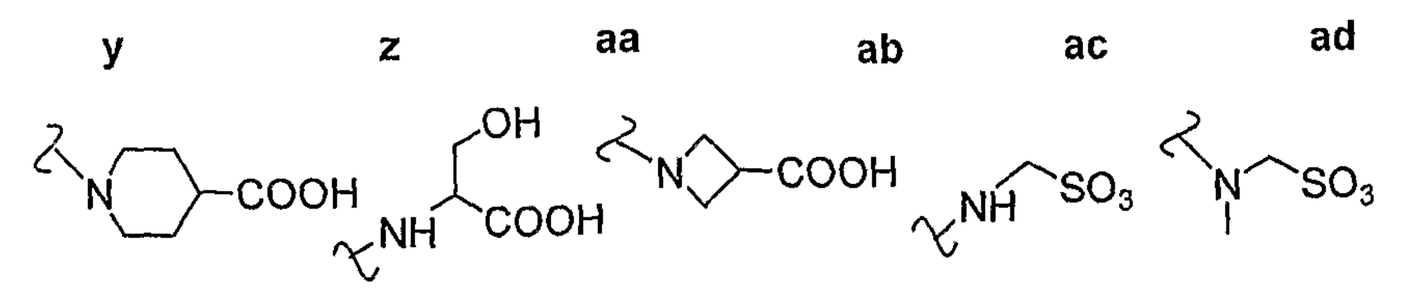
g h i j k l



m n o p q r

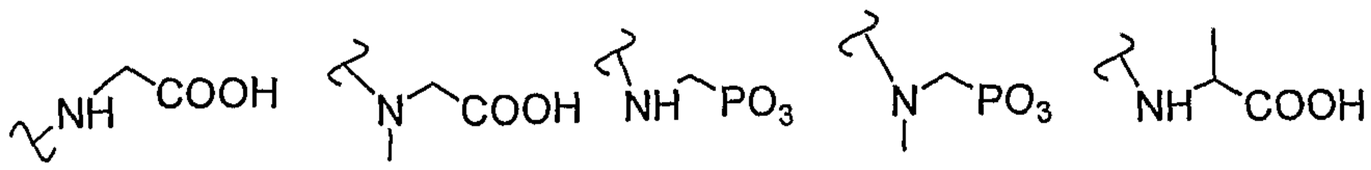


s t u v w x

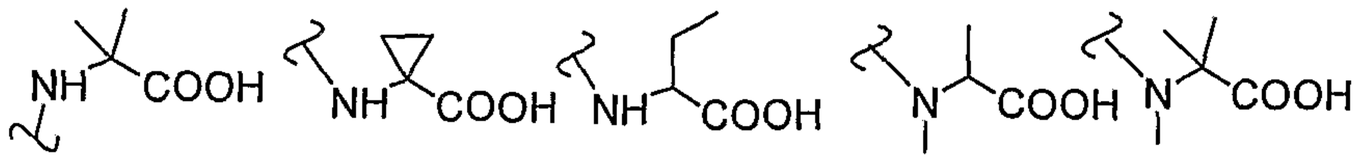


y z aa ab ac ad

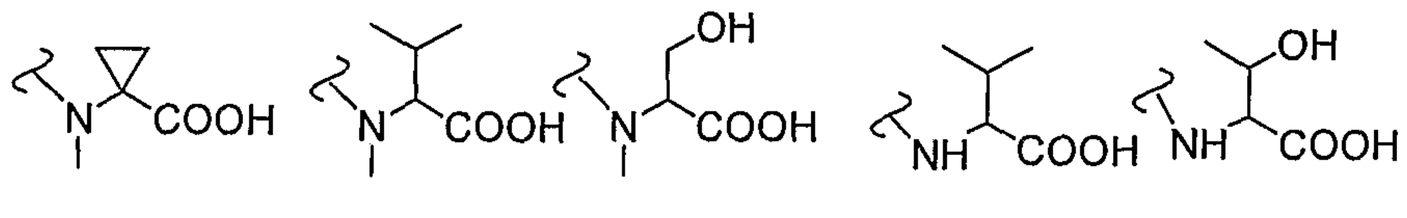
ae af ag ah ai



aj ak al am an



ao ap aq ar as

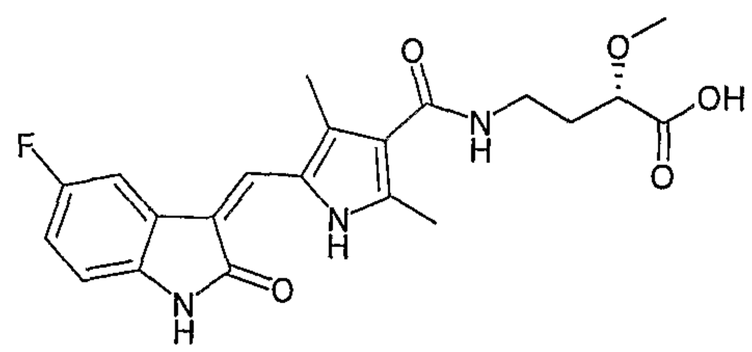


at au av aw ax

These amide examples **16 - 315** can be made by those skilled in the art following the above procedure and/or known procedures.

Examples 316-320: The synthesis of acids (**3-3**) and amides (**3-4**) is shown in **Figure 3**. Variations from this general synthetic procedure can be understood and carried out by those skilled in the art. Thus, the compounds of the present invention can be synthesized by those skilled in the art.

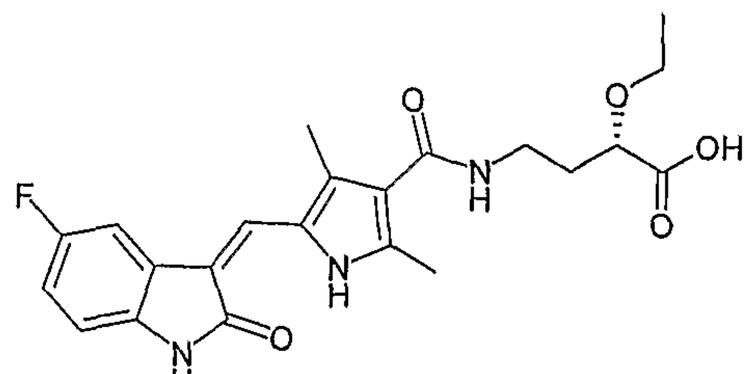
Example 316: (S)-4-({5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-2-methoxy-butyric acid



To a suspension of methyl 4-amino-2-hydroxybutyrate (1.0 equiv, which was prepared by refluxing the free amino acid in dry methanol with 1.2 equiv HCl) and DIEA (5 equiv) in DCM, Mmt-Cl (1.1 equiv) was added portion-wise at 25 °C. After stirring overnight, the DCM was removed under reduced pressure. The residue was suspended in ethyl acetate, washed with brine (3x), dried over anhydrous Na_2SO_4. The ethyl acetate was then removed, and the residue was dried overnight under high vacuum, and subjected to flash chromatography to give compound **3-1**. To a solution of compound **3-1** in dry DMF, NaH (1.5 equiv) was

added under argon. After stirring at 25 °C for 1h, MeI (5 equiv) was added to the solution, and the resulting suspension was gently stirred at 25 °C overnight. The DMF was removed under vacuum; the residue was suspended in ethyl acetate, washed with brine (3x), and dried over anhydrous Na_2SO_4. After the ethyl acetate was removed via evaporation the resulting residue was treated with 1% TFA in DCE/DCM for 30 min. The organic solvents were then removed under reduced pressure, and the resulting residue was triturated with hexane (3x) to obtain the free amino acid **3-2**. This amino acid was used directly in the next step without any purification and characterization. Thus, to a solution of **3-2** (2 equiv) and DIEA (5 equiv) in DMF, compound **1-3** (1 equiv) was added at 25 °C. After stirring for 30 min (LC-MS show the complete consumption of **1-3**), KOH (5 equiv) in water was added, and the solution was stirred for another 2h (LC-MS demonstrated a complete hydrolysis). The solvents were removed under reduced pressure, and HCl (1N, excess) was added to give a precipitate. This precipitate was collected and washed (by water) by filtration, dried under high vacuum to give the title compound (97% based on compound **1-3**). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{21}H_{22}FN_3O_5$: 416, obtained: 416. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.68 (s, 1H), 12.80 (b, 1H), 10.90 (s, 1H), 7.76 (dd, *J* = 2.4 Hz, *J* = 9.6 Hz, 1H), 7.71 (s, 1H), 7.65 (t, *J* = 5.6 Hz, 1H), 6.93 (m, 1H), 6.83 (dd, *J* = 4.8 Hz, *J* = 8.4 Hz, 1H), 3.77 (dd, *J* = 4.0 Hz, *J* = 8.8 Hz, 1H), 3.40-3.30 (m, 2H), 3.30 (s, 3H), 2.43 (s, 3H), 2.41 (s, 3H), 1.92 (m, 1H), 1.78 (m, 1H).

Example 317: (S)-2-Ethoxy-4-({5-[5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-butyric acid

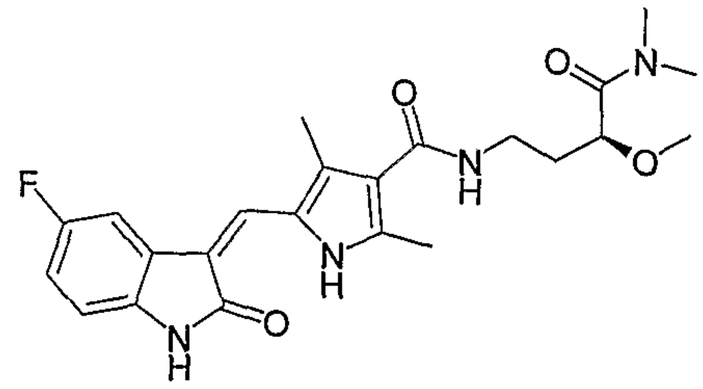


A similar route as that for the synthesis of **Example 316** was used to prepare the title compound. Iodoethane was used instead of iodomethane to obtain the 2-ethoxy compound (84% based on compound **1-3**). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{22}H_{24}FN_3O_5$: 430, obtained: 430. ^{1}H-NMR (DMSO-d_6, 400

MHz), δ 13.68 (s, 1H), 12.70 (b, 1H), 10.89 (s, 1H), 7.76 (dd, *J* = 2.4 Hz, *J* = 9.6 Hz, 1H), 7.71 (s, 1H), 7.66 (t, *J* = 5.6 Hz, 1H), 6.93 (m, 1H), 6.83 (dd, *J* = 4.8 Hz, *J* = 8.4 Hz, 1H), 3.85 (dd, *J* = 4.0 Hz, *J* = 8.4 Hz, 1H), 3.58 (m, 1H), 3.40-3.25 (m, 3H), 2.43 (s, 3H), 2.41 (s, 3H), 1.92 (m, 1H), 1.77 (m, 1H), 1.13 (t, *J* = 7.2 Hz, 3H).

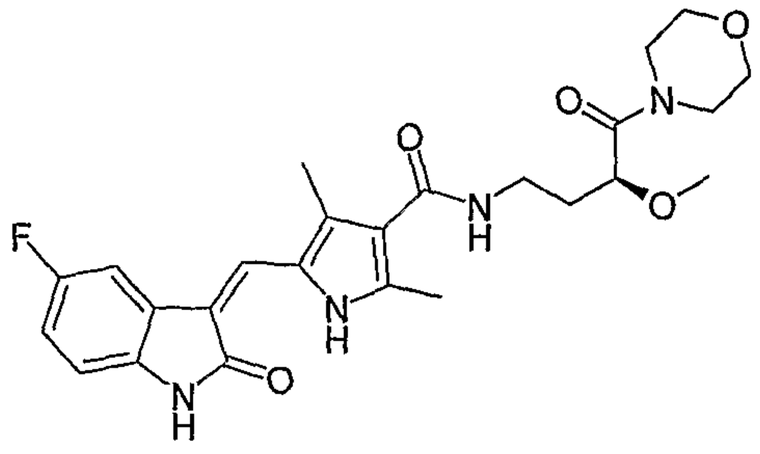
Example 318-320: The general procedure for the synthesis of amides (**compounds 3-4**): A corresponding amine (2 equiv) was added to a solution of the acid (**compound 3-3**), HATU (1.05 mmol), and DIEA (5 equiv) in DMF (5 mL). After the solution was stirred at 25 °C for 2h, aqueous HCl (2 mL, 1N) was added. This solution was subjected to preparative HPLC to obtain the pure amide product, which was subsequently characterized by LC-MS and NMR spectroscopy.

Example 318: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-3-dimethylcarbamoyl-3-methoxy-propyl)-amide



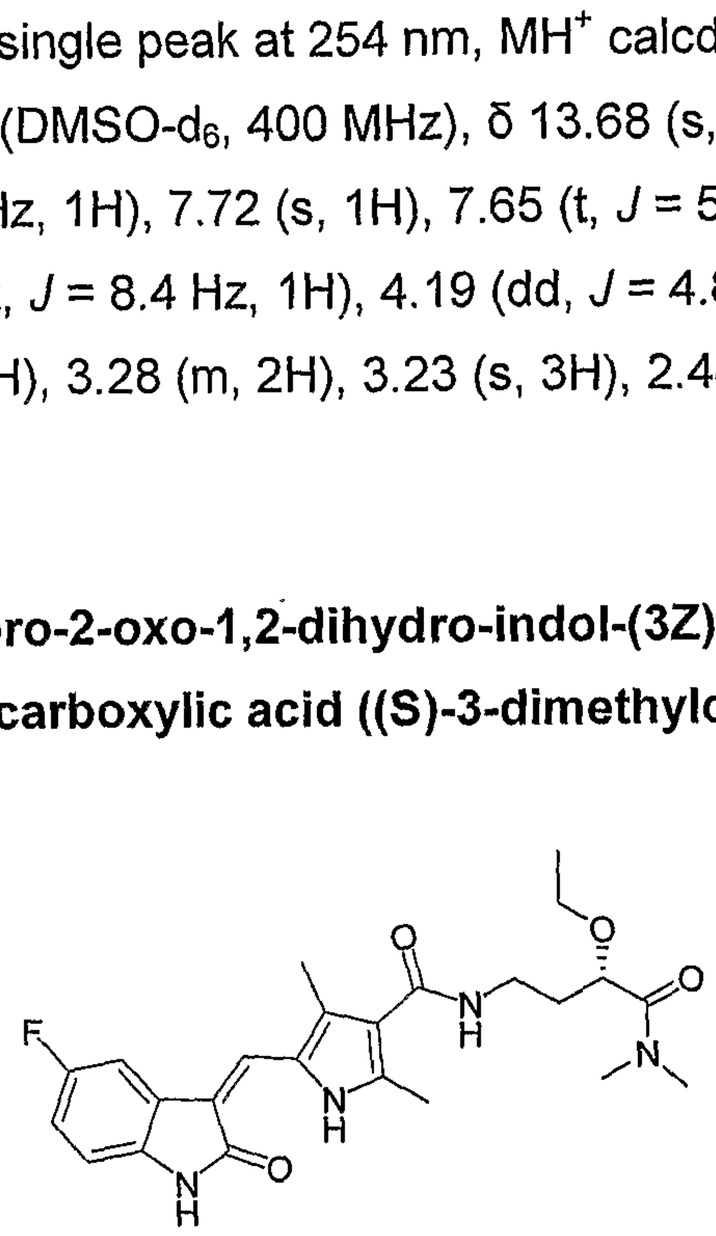
Preparative HPLC gave 37 mg of the title compound (58%) from 60 mg starting material (acid). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{23}H_{27}FN_4O_4$: 443, obtained: 443. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.68 (s, 1H), 10.89 (s, 1H), 7.76 (dd, *J* = 2.4 Hz, *J* = 9.6 Hz, 1H), 7.72 (s, 1H), 7.65 (t, *J* = 5.6 Hz, 1H), 6.93 (m, 1H), 6.83 (dd, *J* = 4.8 Hz, *J* = 8.4 Hz, 1H), 4.20 (dd, *J* = 4.0 Hz, *J* = 8.0 Hz, 1H), 3.30 (m, 2H), 3.27 (s, 3H), 3.04 (s, 3H), 2.88 (s, 3H), 2.43 (s, 3H), 2.41 (s, 3H), 1.80 (m, 2H).

Example 319: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-3-methoxy-4-morpholin-4-yl-4-oxo-butyl)-amide



Preparative HPLC gave 32 mg of the title compound (46%) from 60 mg starting material (acid). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{25}H_{29}FN_4O_5$: 485, obtained: 485. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.68 (s, 1H), 10.89 (s, 1H), 7.76 (dd, J = 2.4 Hz, J = 9.6 Hz, 1H), 7.72 (s, 1H), 7.65 (t, J = 5.6 Hz, 1H), 6.93 (m, 1H), 6.83 (dd, J = 4.8 Hz, J = 8.4 Hz, 1H), 4.19 (dd, J = 4.8 Hz, J = 8.0 Hz, 1H), 3.57 (m, 6H), 3.47 (m, 2H), 3.28 (m, 2H), 3.23 (s, 3H), 2.44 (s, 3H), 2.41 (s, 3H), 1.79 (m, 2H).

Example 320: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-3-dimethylcarbamoyl-3-ethoxy-propyl)-amide



Preparative HPLC gave 67 mg of the title compound (57%) from 120 mg starting material (acid). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{24}H_{29}FN_4O_4$: 457, obtained: 457. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.67 (s, 1H), 10.88 (s, 1H), 7.76 (dd, J = 2.4 Hz, J = 9.6 Hz, 1H), 7.71 (s, 1H), 7.56 (m, 1H), 6.91 (m, 1H), 6.83 (m, 1H), 4.25 (m, 1H), 3.45-3.25 (m, 4H), 3.03 (s, 3H), 2.83 (s, 3H), 2.43 (s, 3H), 2.41 (s, 3H), 1.80 (m, 2H).

The compounds described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. It will be readily apparent to one skilled in the art that varying

substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention.

VEGFR Biochemical Assay

The compounds were assayed for biochemical activity by Upstate Ltd at Dundee, United Kingdom, according to the following procedure. In a final reaction volume of 25 μl, KDR (h) (5-10 mU) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 0.33 mg/ml myelin basic protein, 10 mM MgAcetate and [γ-^{33}P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation for 40 minutes at room temperature, the reaction is stopped by the addition of 5 μl of a 3% phosphoric acid solution. 10 μl of the reaction is then spotted onto a P30 filtermat and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

Compounds of the present invention were tested in this assay and exhibited IC_{50} between 1 – 5,000 nM.

PDGFR phosphorylation assay

NIH3T3 cells are plated in a 96 well plate in DMEM + 10% FBS. Following cell attachment the cells are serum starved overnight before adding the chemical test compounds to a final concentration of 0.1% DMSO. Following a 1 hour incubation at 37 °C cells are removed from the incubator and allowed to cool to RT for 20 min before stimulation with PDGF-BB for 15 min at RT. Cells are placed on ice for 5 min, the media removed and the cells are lysed with 100 μL/well lysis buffer for 1 hour at 4 °C. Plates are spun at 2000 rpm for 30 min at 4 °C and solubilized phosphorylated PDGFR is quantitated by ELISA.

High binding microplates are incubated overnight at RT with anti-mouse PDGFR-b capture-antibody in PBS, washed with PBS+0.05% Tween20 and blocked for 4h at RT with PBS+1% BSA and washed again. 100 μL lysate/well is incubated

overnight at 4 °C. Plates are washed and wells are incubated with 100 μL/well of mouse anti-phosphotyrosine-HRP antibody for 2 h at 37 °C. Plates are washed again and colorimetric detection is performed using TMB as substrate.

Most of the compounds in this invention showed IC_{50} of less than 1 μM in this assay.

VEGFR phosphorylation assay

NIHT3T cells overexpressing mouse VEGFR-2 (FLK-1) are plated in a 96 well plate in DMEM+10% FBS. Following cell attachment for 4 hours the cells are serum starved overnight before adding the chemical test compounds to a final concentration of 0.1% DMSO. Following a 1 hour incubation at 37 °C cells are stimulated for 15 min at 37 °C with VEGF165. Cells are placed on ice for 5 min, the media removed, washed once with ice cold PBS and the cells are lysed with 50 μL/well lysis buffer for 1 hour at 4 °C. Plates are spun for 10 min at 2000 rpm at 4 °C and solubilized phosphorylated VEGFR is quantitated by ELISA.

High binding microplates are incubated overnight at room temperature with VEGFR antibody in 50 μL PBS, washed with PBS+0.05% Tween20 and blocked for 4 h at RT with PBS+1% BSA and washed again. 50 μL lysate/well is incubated overnight at 4 °C. Plates are washed and wells are incubated with 50 μL/well of mouse anti-phosphotyrosine-HRP antibody for 2 h at 37 °C. Plates are washed again and colorimetric detection is performed using TMB as substrate.

Most of the compounds in this invention showed IC_{50} of less than 1 μM in this assay.

<u>Cellular Assay</u>: HUVEC: VEGF induced proliferation

The compounds were assayed for cellular activity in the VEGF induced proliferation of HUVEC cells. HUVEC cells (Cambrex, CC-2517) were maintained in EGM (Cambrex, CC-3124) at 37°C and 5% CO_2. HUVEC cells were plated at a density 5000 cells/well (96 well plate) in EGM. Following cell attachment (1 hour)

the EGM-medium was replaced by EBM (Cambrex, CC-3129) + 0.1% FBS (ATTC, 30-2020) and the cells were incubated for 20 hours at 37°C. The medium was replaced by EBM +1% FBS, the compounds were serial diluted in DMSO and added to the cells to a final concentration of 0 – 5,000 nM and 1% DMSO. Following a 1 hour pre-incubation at 37°C cells were stimulated with 10ng/ml VEGF (Sigma, V7259) and incubated for 45 hours at 37°C. Cell proliferation was measured by BrdU DNA incorporation for 4 hours and BrdU label was quantitated by ELISA (Roche kit, 16472229) using 1M H_2SO_4 to stop the reaction. Absorbance was measured at 450nm using a reference wavelength at 690nm.

Detailed Description of Figures:

Figure 1 shows a scheme that is used for the synthesis of the 3-alkoxy-4-acylaminoamide derivatives starting from methyl 3-hydroxy-4-aminobutanoate hydrochlorides and the activated acylating agent **1-3**. The amino ester hydrochloride starting material was prepared by refluxing the free amino acid in anhydrous methanol in the presence of 1.2 eq of HCl. The amino group was protected as its monomethoxytrityl derivative in the presence of the secondary hydroxyl group to give the neutral hydroxy ester **1-1**. The hydroxyl group was alkylated using methyl- or ethyl iodide to form the protected amino alkoxy ester. The Mmt group was removed in 1% trifluoroacetic acid leaving the amino hydrochloride or trifluoracetate compound **1-2**. This compound was quickly acylated with the preformed acylating agent **1-3** and the methyl ester was hydrolyzed by potassium hydroxide in water/DMF to give **1-4**. The free acid was then exposed to HATU, amine and diisopropylethyl amine in DMF to give the alkoxy amide **1-5**.

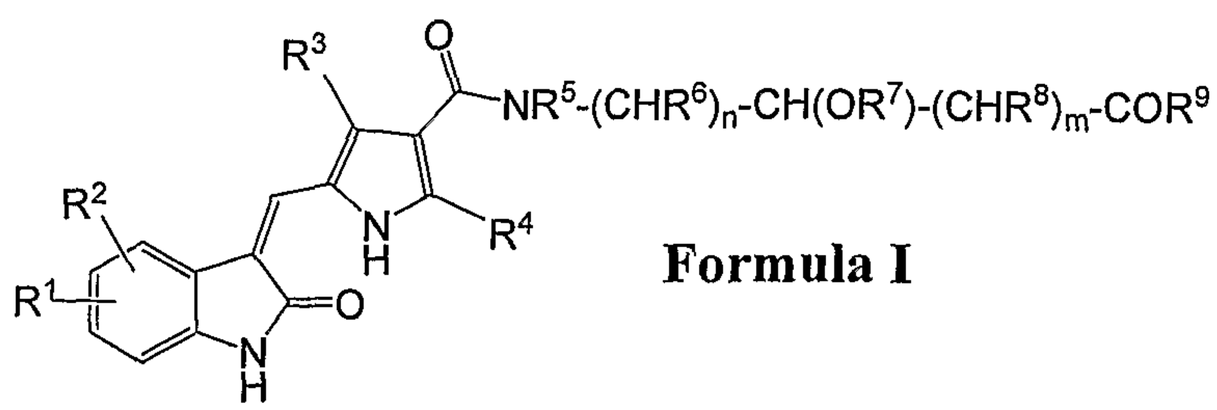
Figure 2 shows a scheme that is used for the synthesis of the 2-alkoxy-3-acylaminoamide derivatives starting from methyl 2-hydroxy-3-aminopropionate hydrochlorides and the activated acylating agent **1-3**. The amino ester hydrochloride starting material was prepared by refluxing the free amino acid in anhydrous methanol in the presence of 1.2 eq of HCl. The amino group was protected as its monomethoxytrityl derivative in the presence of the secondary hydroxyl group to give **2-1**. The hydroxyl group was alkylated using methyl- or

ethyl iodide to form the protected amino alkoxy ester. The Mmt group was removed in 1% trifluoroacetic acid leaving the amino hydrochloride or trifluoracetate compound **2-2**. This compound was quickly acylated with the preformed acylating agent **1-3** and the methyl ester was hydrolyzed by potassium hydroxide in water/DMF to give **2-4**. The free acid was then exposed to HATU, amine and diisopropylethyl amine in DMF to give the alkoxy amide **2-5**.

Figure 3 shows a scheme that is used for the synthesis of the (2S)-2-alkoxy-4-acylamino-amide derivatives starting from methyl (2S)-2-hydroxy-4-aminobutanoate hydrochloride and the activated acylating agent **1-3**. The amino ester hydrochloride starting material was prepared by refluxing the free amino acid in anhydrous methanol in the presence of 1.2 eq of HCl. The amino group was protected as its monomethoxytrityl derivative in the presence of the secondary hydroxyl group to give the neutral hydroxy ester **3-1**. The hydroxyl group was alkylated using methyl- or ethyl iodide to form the protected amino alkoxy ester. The Mmt group was removed in 1% trifluoroacetic acid leaving the amino hydrochloride or trifluoracetate compound **3-2**. This compound was quickly acylated with the preformed acylating agent **1-3** and the methyl ester was hydrolyzed by potassium hydroxide in water/DMF to give **3-4**. The free acid was then exposed to HATU, amine and diisopropylethyl amine in DMF to give the alkoxy amide **3-5**.

What is claimed is:

1. A compound represented by Formula (I):



Formula I

wherein:

R^1 is selected from the group consisting of hydrogen, halo, (C1-C6) alkyl, (C3-C8) cycloalkyl, (C1-C6) haloalkyl, hydroxy, (C1-C6) alkoxy, amino, (C1-C6) alkylamino, amide, sulfonamide, cyano, substituted or unsubstituted (C6-C10) aryl;

R^2 is selected from the group consisting of hydrogen, halo, (C1-C6) alkyl, (C3-C8) cycloalkyl, (C1-C6) haloalkyl, hydroxy, (C1-C6) alkoxy, (C2-C8) alkoxyalkyl, amino, (C1-C6) alkylamino, (C6-C10) arylamino;

R^3 is selected from the group consisting of hydrogen, (C1-C6) alkyl, (C6-C10) aryl, (C5-C10) heteroaryl, and amide;

R^4, R^5, R^6 and R^8 are independently selected from the group consisting of hydrogen and (C1-C6) alkyl;

R^7 is (C1-C6) alkyl;

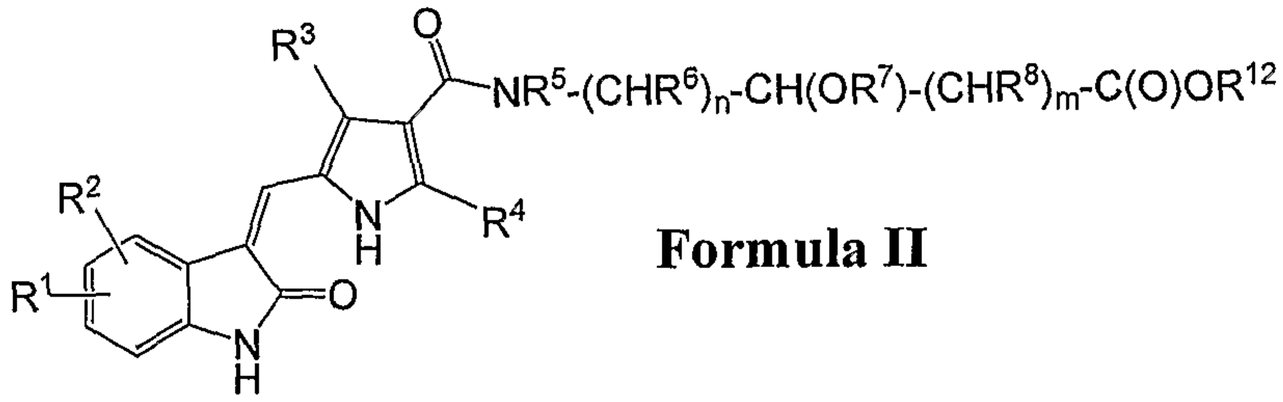
R^9 is selected from the group consisting of hydroxy, (C1-C6) O-alkyl, (C3-C8) O-cycloalkyl, and $NR^{10}R^{11}$; where R^{10} and R^{11} are independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) hydroxyalkyl, (C2-C6) dihydroxyalkyl, (C1-C6) alkoxy , (C2-C6) alkyl carboxylic acid, (C1-C6) alkyl phosphonic acid, (C1-C6) alkyl sulfonic acid, (C2-C6) hydroxyalkyl carboxylic acid, (C1-C6) alkyl amide, (C3-C8) cycloalkyl, (C5-C8) heterocycloalkyl, (C6-C8) aryl, (C5-C8) heteroaryl, (C3-C8) cycloalkyl carboxylic acid, or R^{10} and R^{11} together with N forms a (C5-C8) heterocyclic ring either unsubstituted or substituted with one or more hydroxyls, ketones, ethers, and carboxylic acids;

n is 1, 2, or 3; and

m is 0, 1, or 2;

or, a pharmaceutically acceptable salt, its tautomer, a pharmaceutically acceptable salt of its tautomer, or a prodrug thereof.

2. The compound, salt, tautomer, or prodrug according to claim 1 represented by Formula (**II**):



Formula II

wherein R^{12} is selected from the group consisting of hydrogen, (C1-C6) alkyl, and (C3-C8) cycloalkyl.

3. The compound, salt, tautomer, or prodrug according to claim 2, wherein:

R^1 and R^2 are independently selected from the group consisting of hydrogen and fluoro;

R^3 and R^4 are methyl;

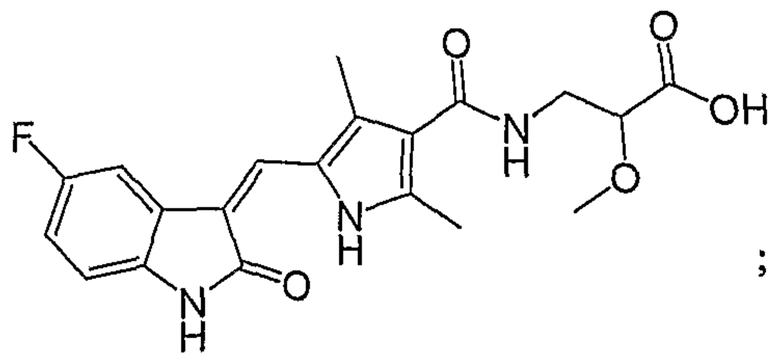
R^5, R^6, R^8, and R^{12} are hydrogen;

R^7 is (C1-C6) alkyl;

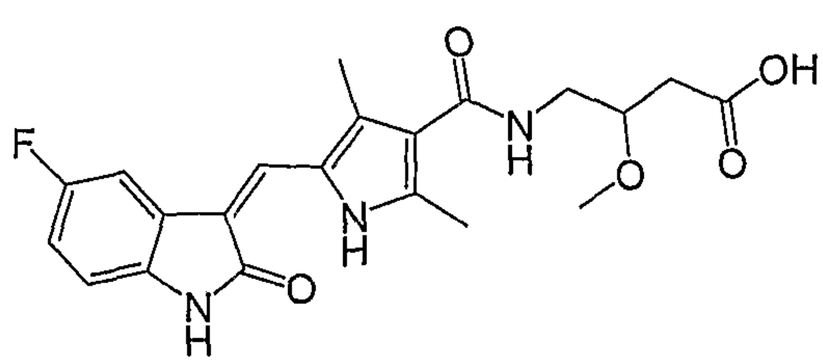
n is 1 or 2; and

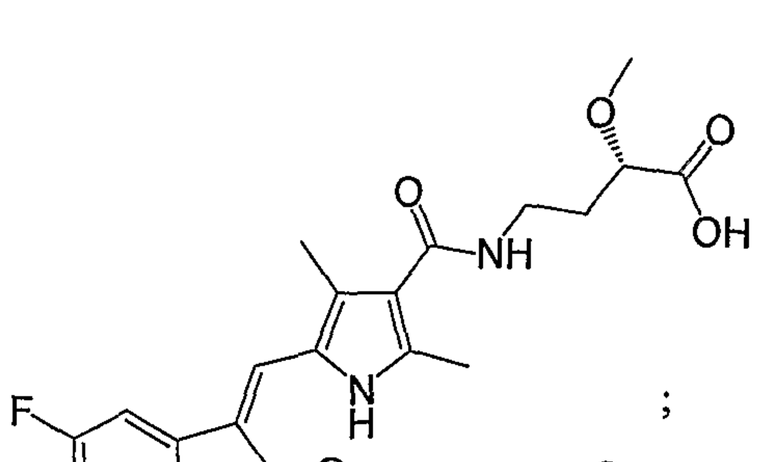
m is 0 or 1.

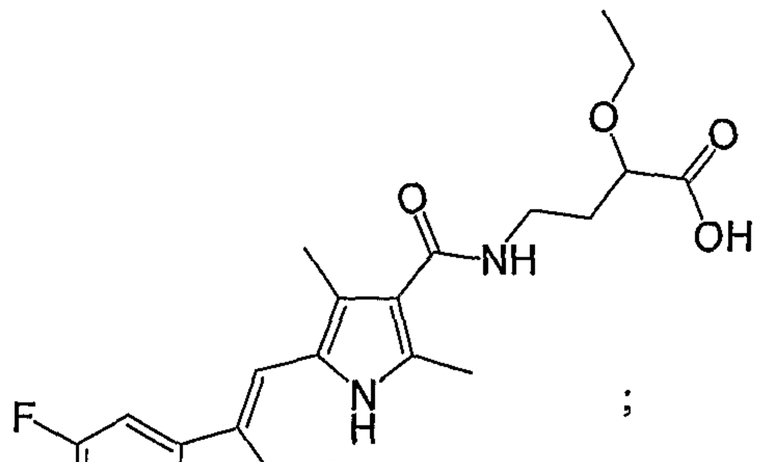
4. The compound, salt, tautomer, or prodrug according to claim 3 selected from the group consisting of:



;




;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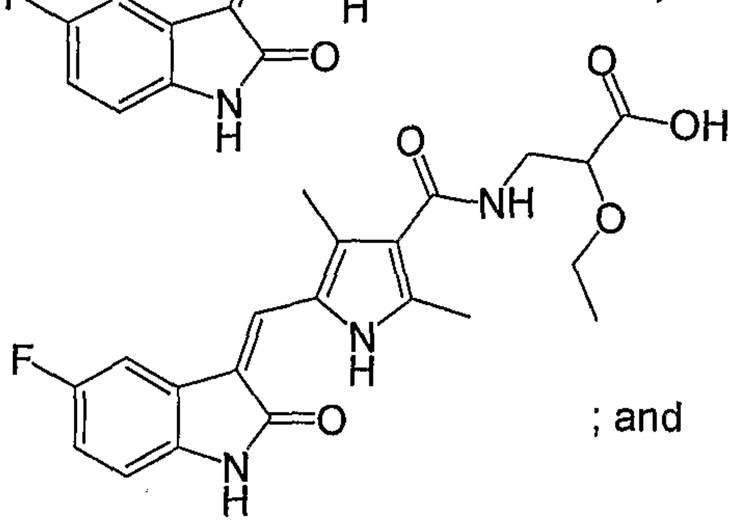
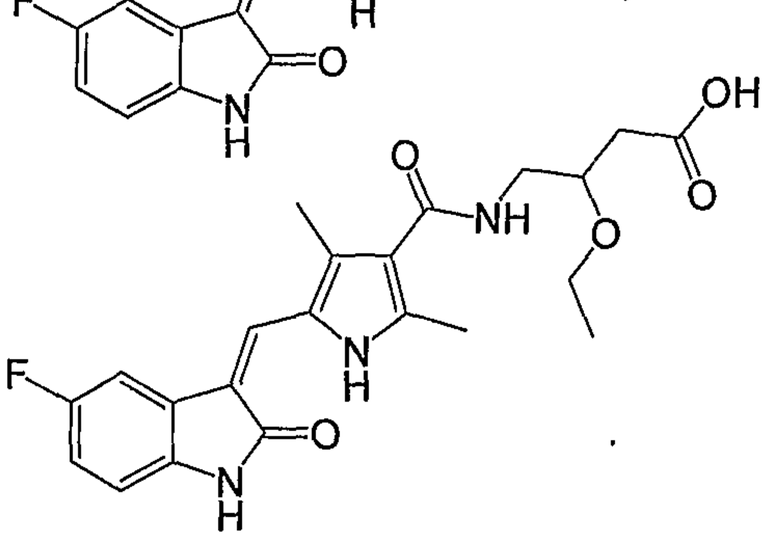
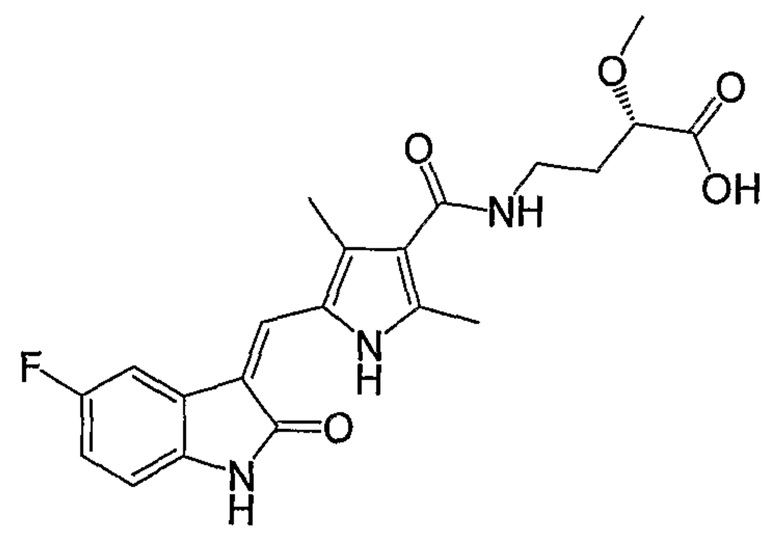
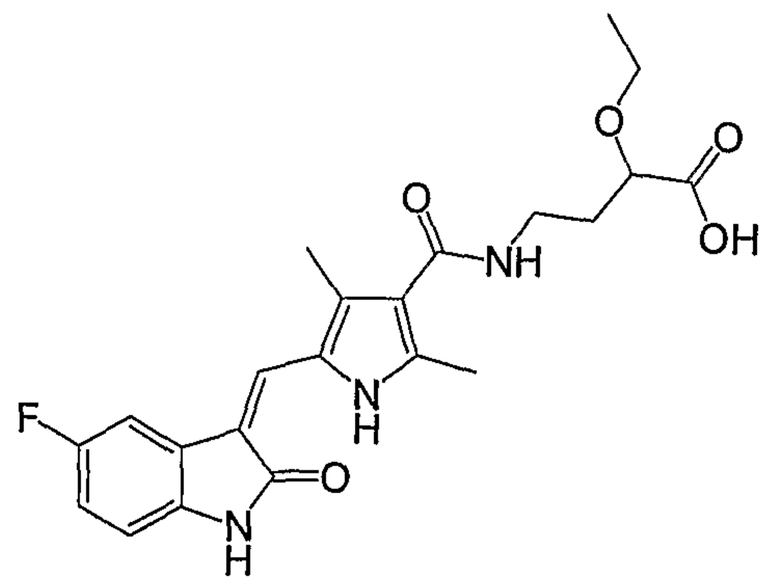

; and


.

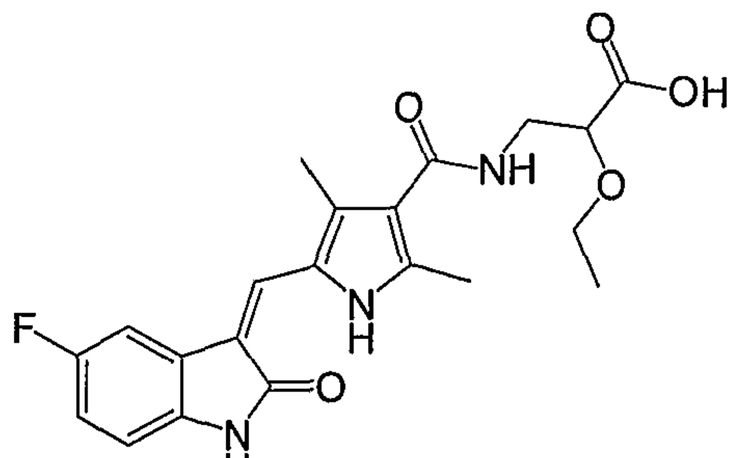
5. The compound, salt, tautomer, or prodrug according to claim 3 represented by the following structure:



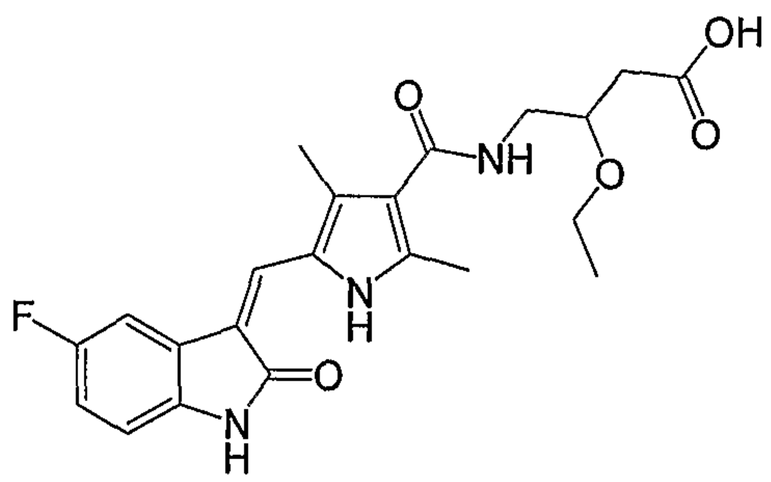
6. The compound, salt, tautomer, or prodrug according to claim 3 represented by the following structure:


.

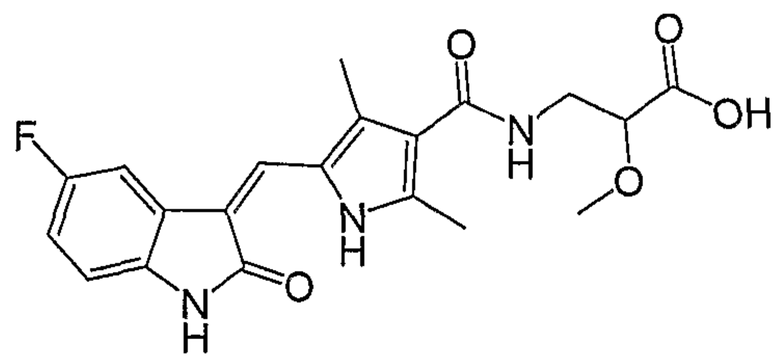
7. The compound, salt, tautomer, or prodrug according to claim 3 represented by the following structure:



8. The compound, salt, tautomer, or prodrug according to claim 3 represented by the following structure:

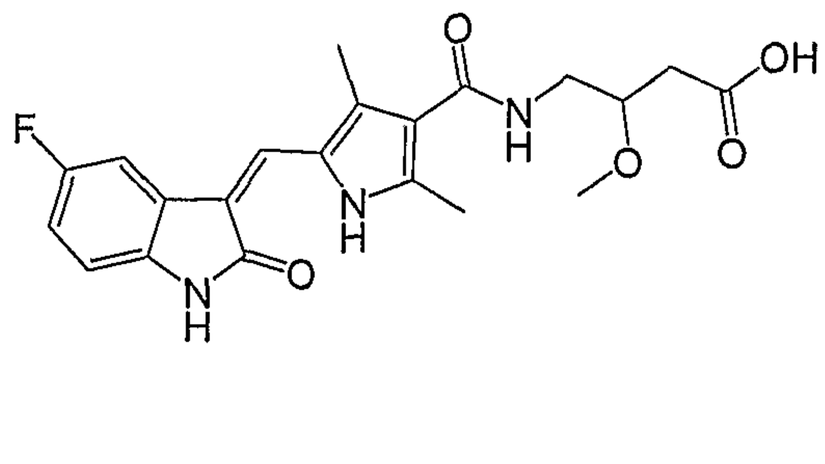


9. The compound, salt, tautomer, or prodrug according to claim 3 represented by the following structure:



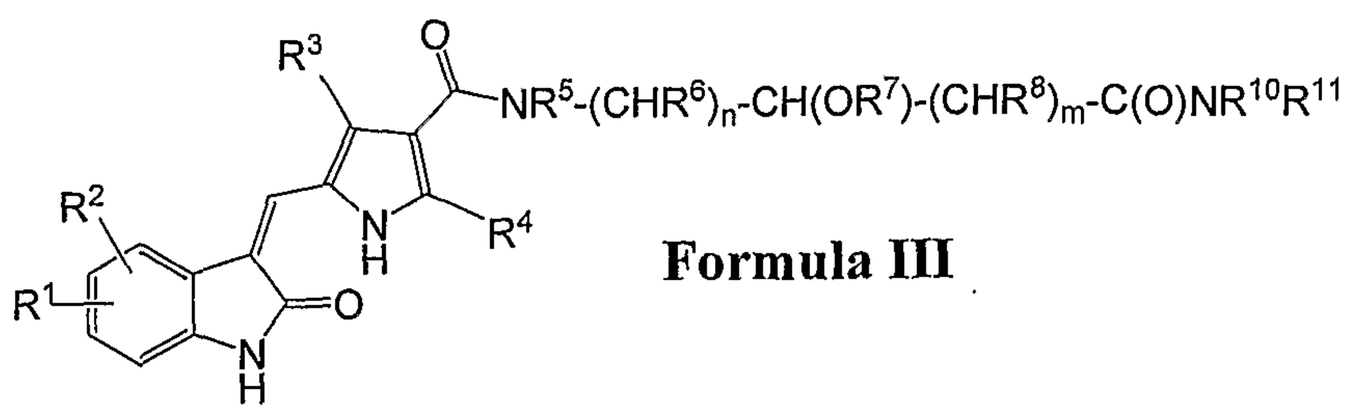
10

10. The compound, salt, tautomer, or prodrug according to claim 3 represented by the following structure:



15

11. A compound, salt, tautomer, or prodrug according to claim 1 represented by Formula (**III**):



Formula III

12. The compound, salt, tautomer, or prodrug of claim 9, wherein:

R^1 and R^2 are independently selected from the group consisting of hydrogen, halo, cyano;

R^3 is selected from the group consisting of hydrogen, (C1-C6) alkyl, (C6-C10) aryl, (C5-C10) heteroaryl, and amide;

R^4, R^5, R^6 and R^8 are independently selected from the group consisting of hydrogen and (C1-C6))alkyl;

R^7 is (C1-C6) alkyl;

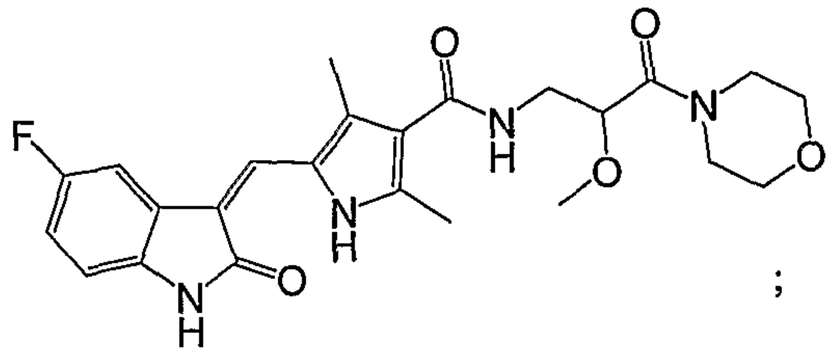
n is 1 or 2;

m is 0 or 1; and

R^{10} and R^{11} are selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) hydroxyalkyl, (C2-C6) dihydroxyalkyl, (C1-C6) alkoxy , (C2-C6) alkyl carboxylic acid, (C1-C6) alkyl phosphonic acid, (C1-C6) alkyl sulfonic acid, (C2-C6) hydroxyalkyl carboxylic acid, (C1-C6) alkyl amide, (C3-C8) cycloalkyl, (C5-C8) heterocycloalkyl, (C6-C8) aryl, (C5-C8) heteroaryl, (C4-C8) cycloalkyl carboxylic acid, or R^{10} and R^{11} together with N forms a (C5-C8) heterocyclic ring either unsubstituted or substituted with one or more hydroxyls, ketones, ethers, and carboxylic acids.

13. The compound, salt, tautomer, or prodrug according to claim 12 wherein **m** is 0.

14. The compound, salt, tautomer, or prodrug according to claim 13 selected from the group represented by the following structures: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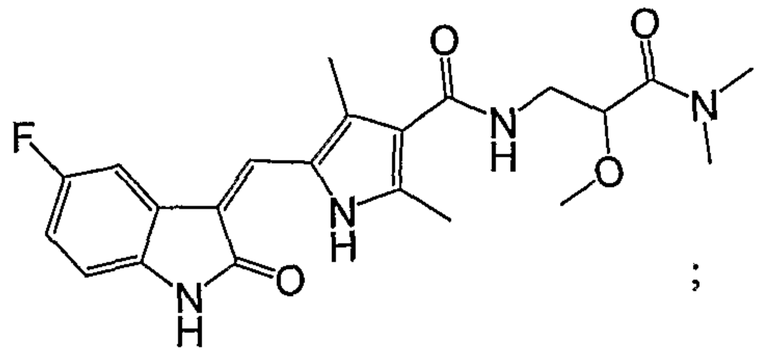
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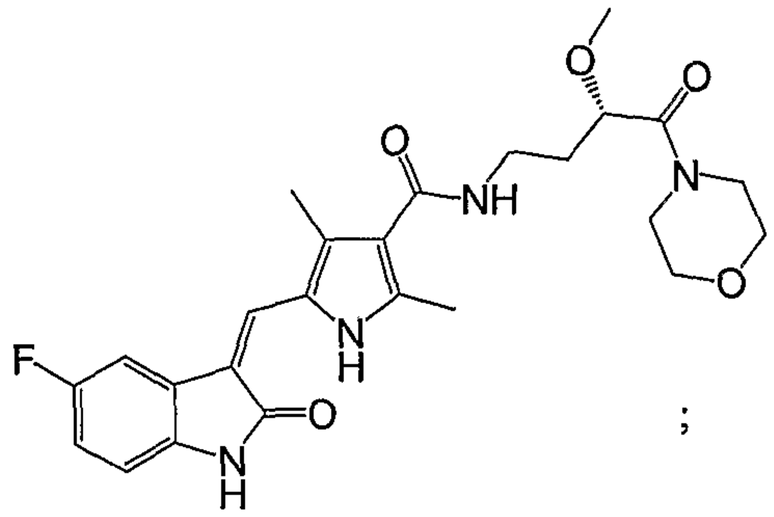
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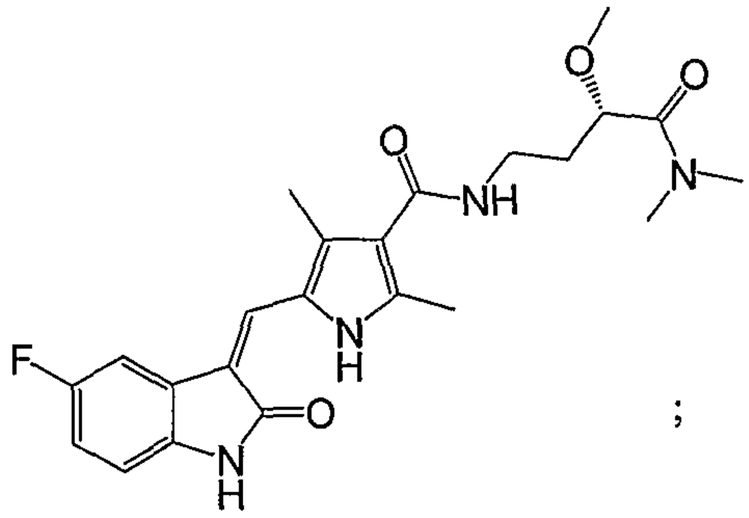
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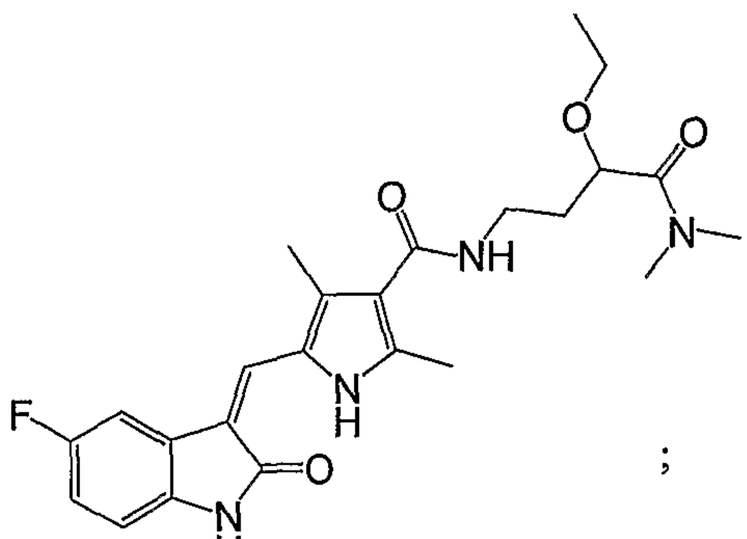
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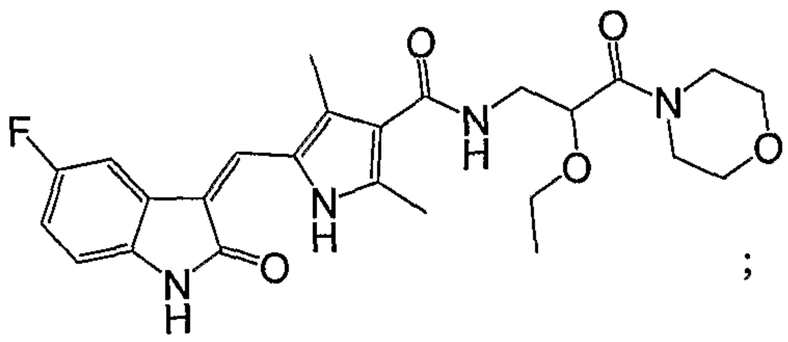
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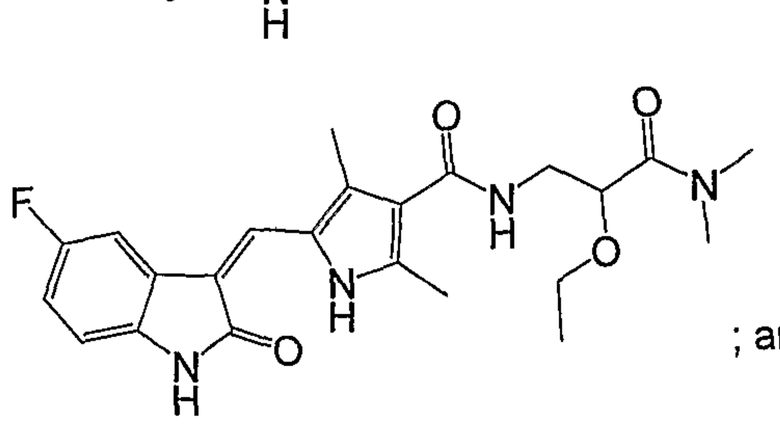
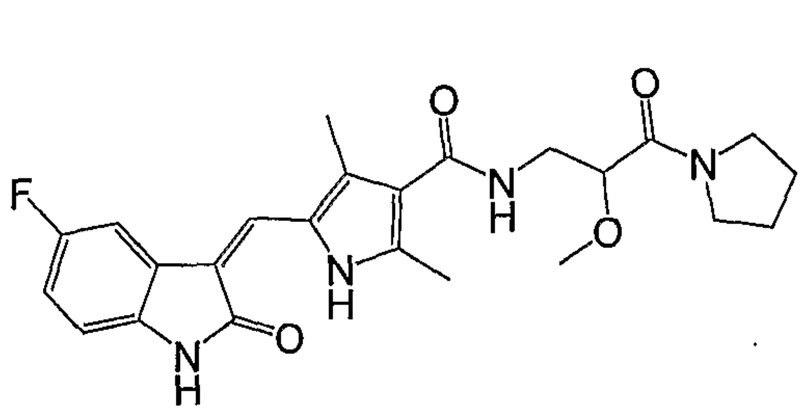
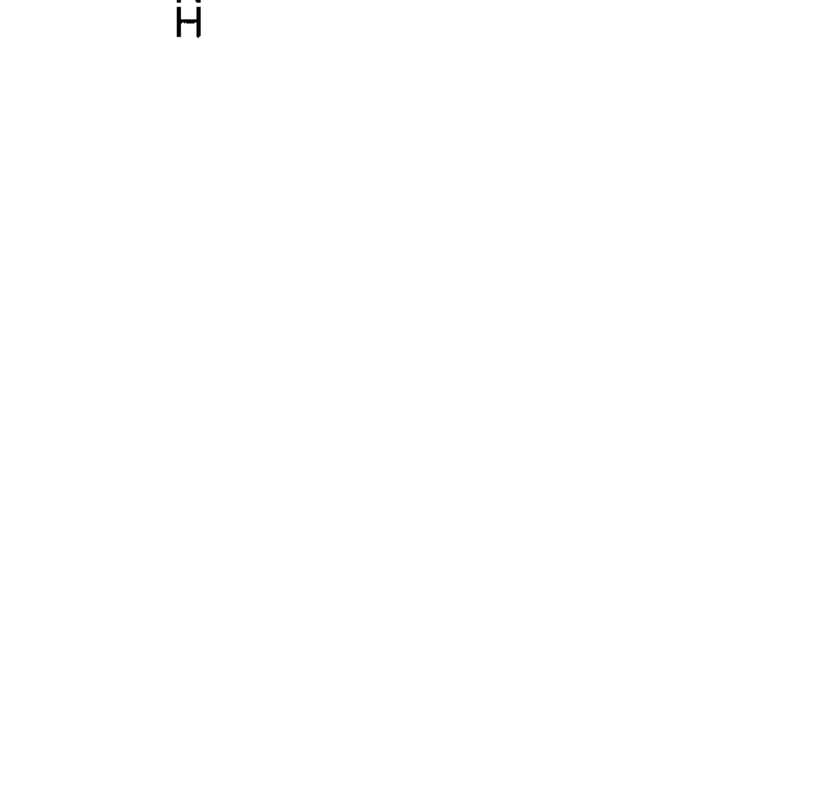

; and



15. The compound, salt, tautomer, or prodrug according to claim 14 represented by the following structure: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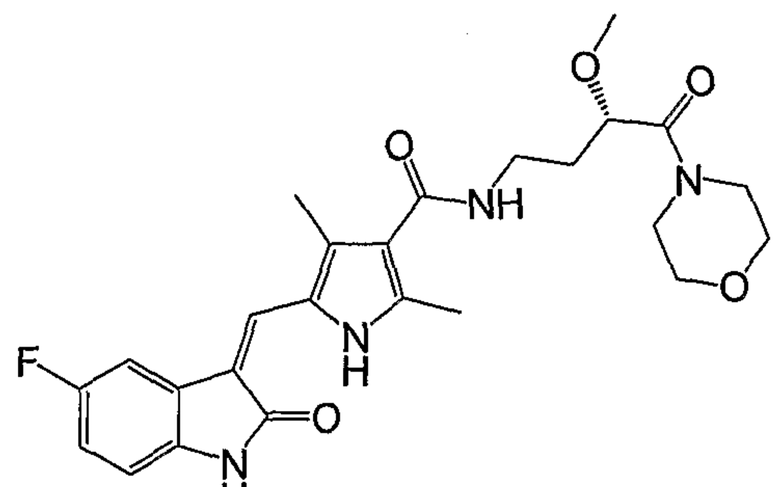
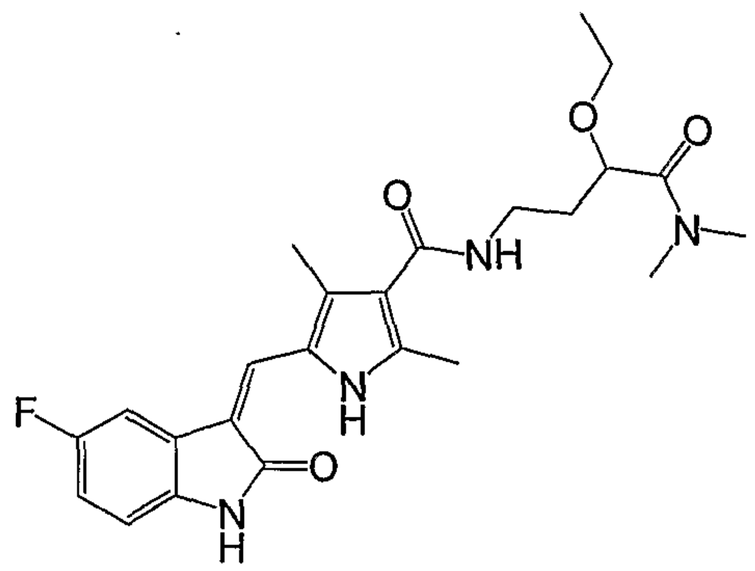
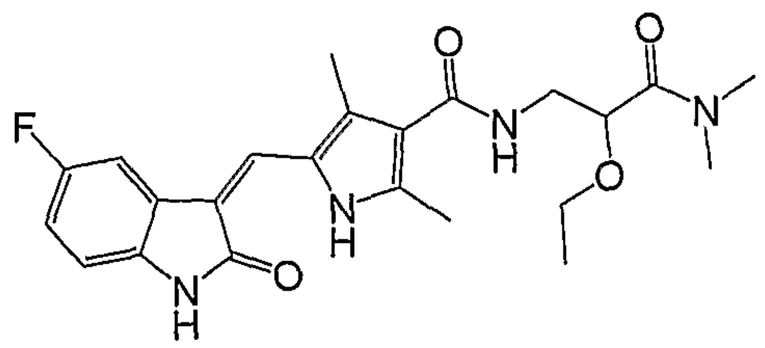
16. The compound, salt, tautomer, or prodrug according to claim 14 represented by the following structure:



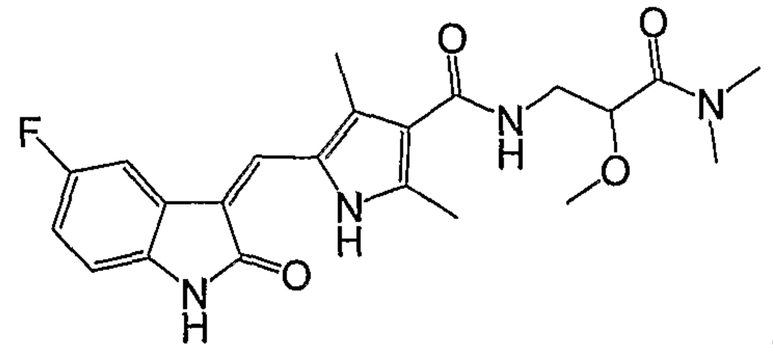
17. The compound, salt, tautomer, or prodrug according to claim 14 represented by the following structure:



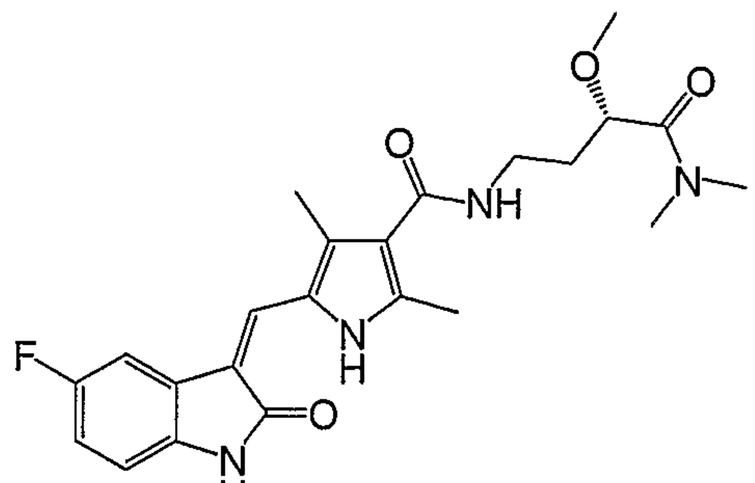
18. The compound, salt, tautomer, or prodrug according to claim 14 represented by the following structure:



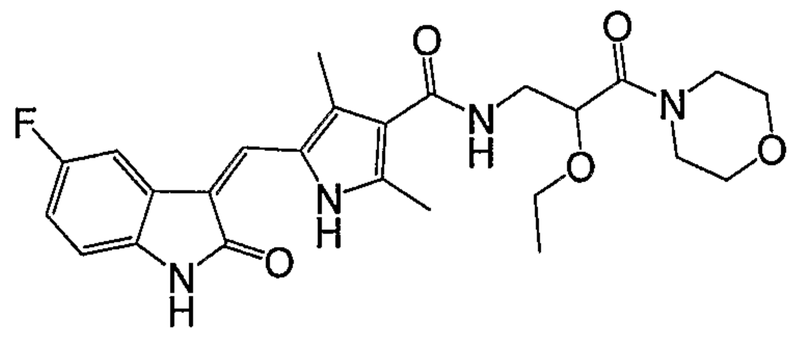
19. The compound, salt, tautomer, or prodrug according to claim 14 represented by the following structure:



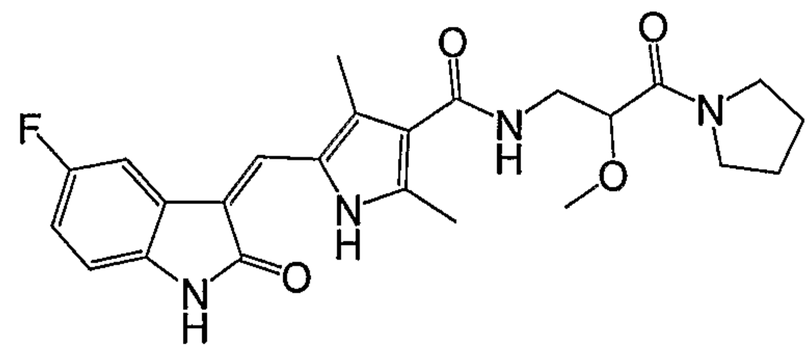
20. The compound, salt, tautomer, or prodrug according to claim 14 represented by the following structure:



21. The compound, salt, tautomer, or prodrug according to claim 14 represented by the following structure:

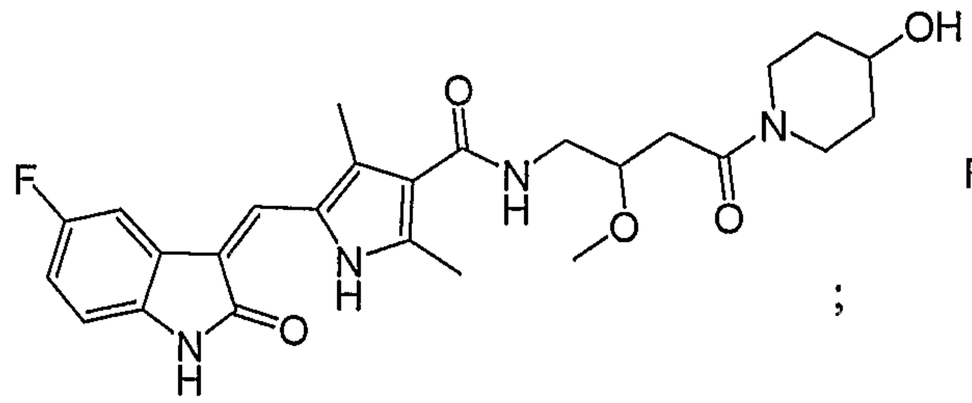


22. The compound, salt, tautomer, or prodrug according to claim 14 represented by the following structure:



23. The compound, salt, tautomer, or prodrug according to claim 12 wherein **m** is 1.

24. The compound, salt, tautomer, or prodrug according to claim 23 represented by the following structures:



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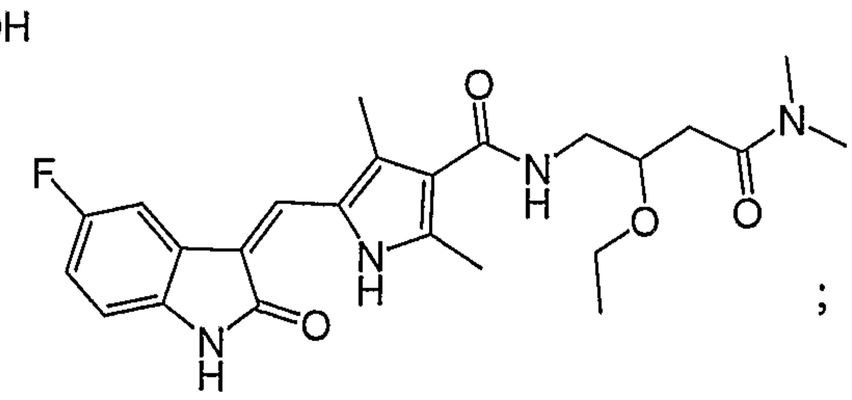

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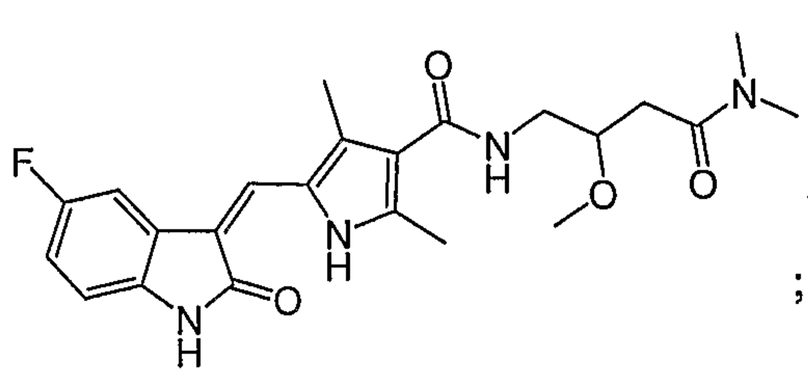
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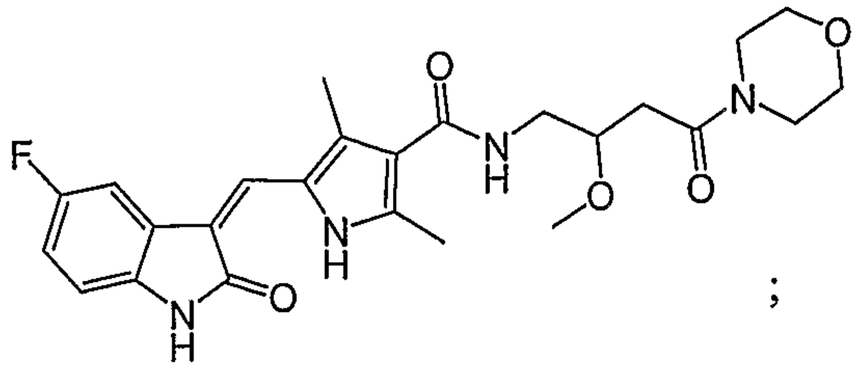
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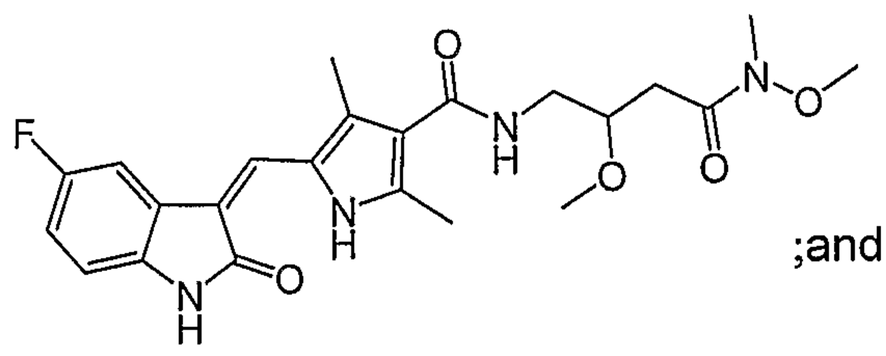
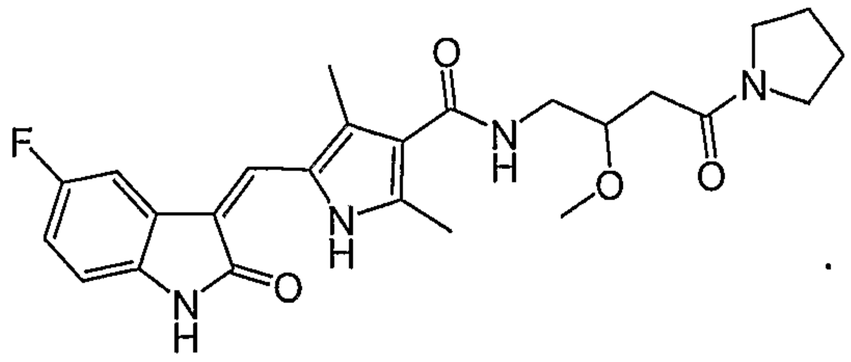
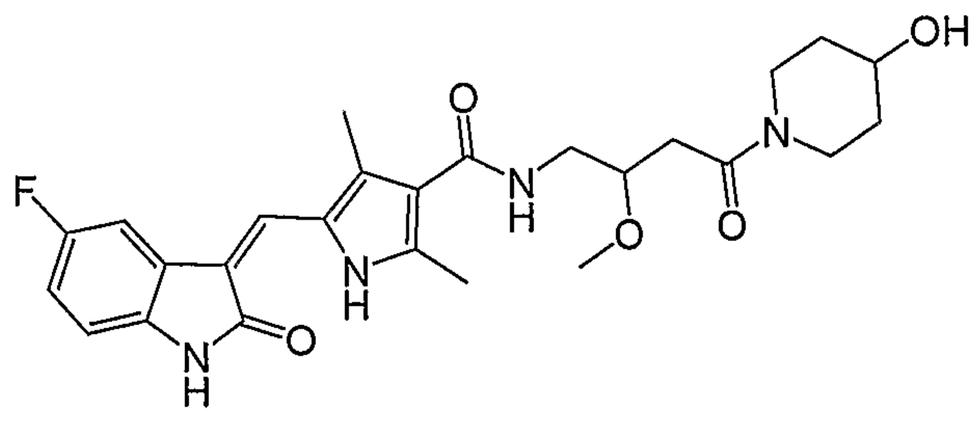
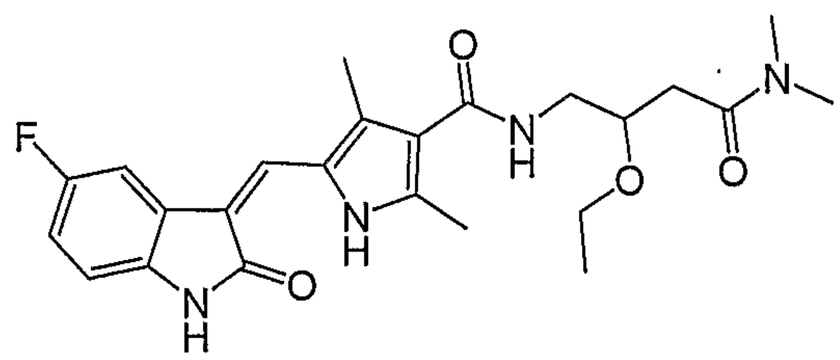

;and


.

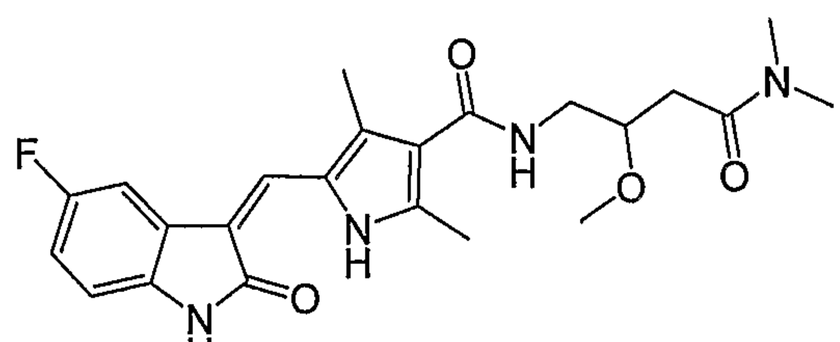
25. The compound, salt, tautomer, or prodrug according to claim 24 represented by the following structure:


.

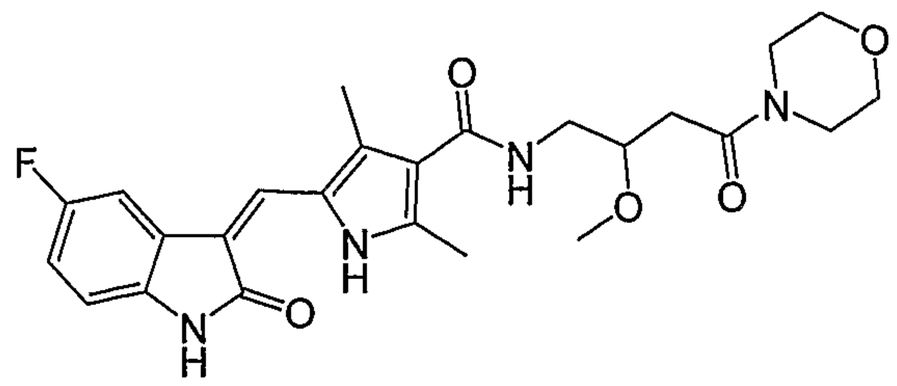
26. The compound, salt, tautomer, or prodrug according to claim 24 represented by the following structure:


.

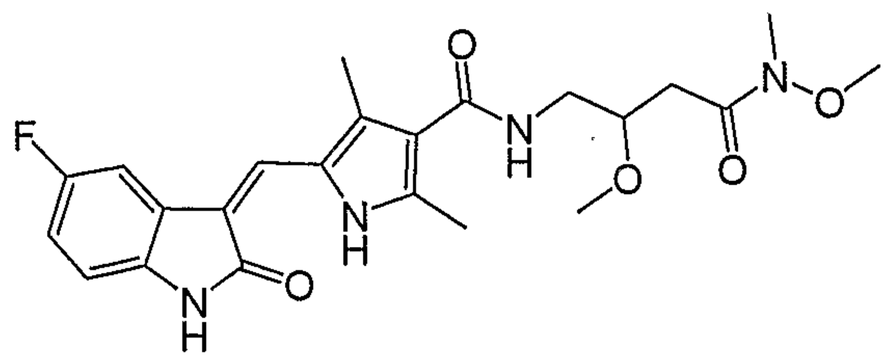
27. The compound, salt, tautomer, or prodrug according to claim 24 represented by the following structure:


.

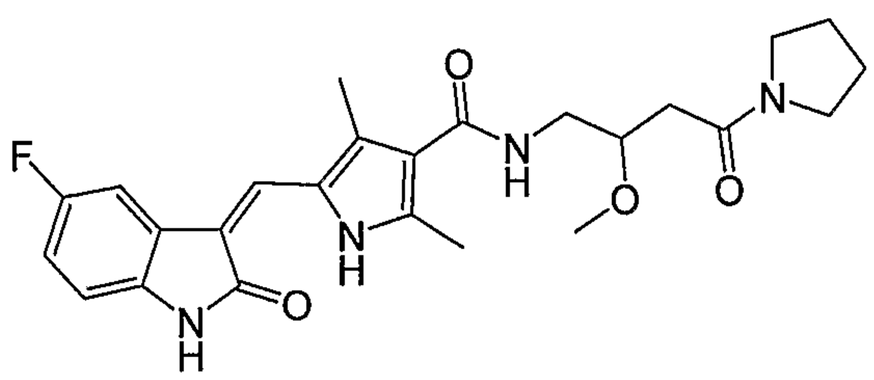
28. The compound, salt, tautomer, or prodrug according to claim 24 represented by the following structure:



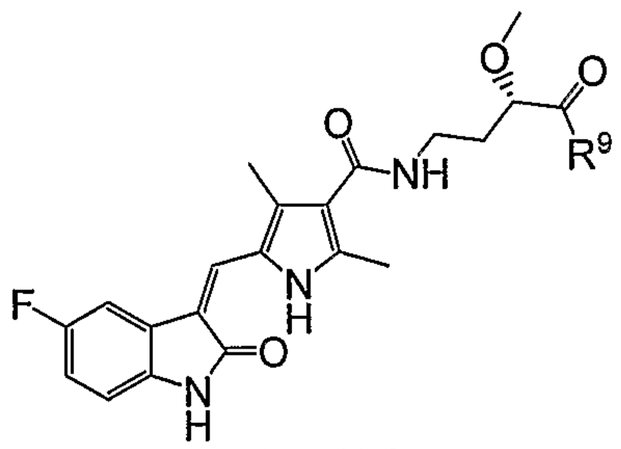
29. The compound, salt, tautomer, or prodrug according to claim 24 represented by the following structure:



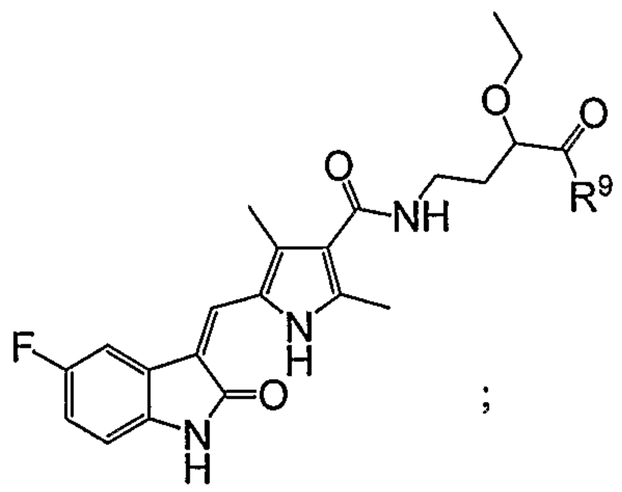
30. The compound, salt, tautomer, or prodrug according to claim 24 represented by the following structure:



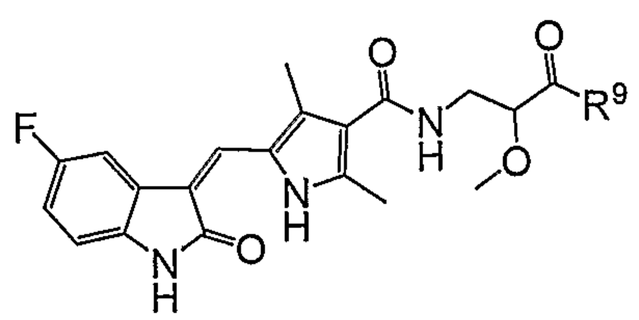
31. The compound, salt, tautomer, or prodrug according to claim 1 selected from the group represented by the following structures:



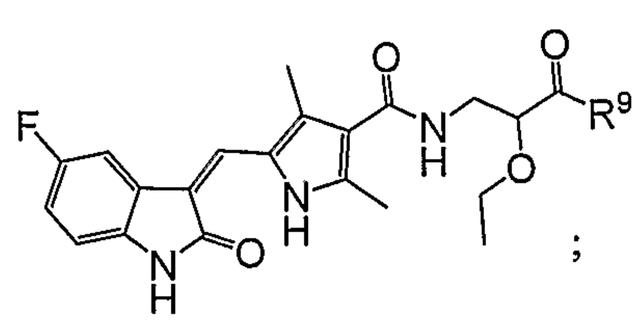
CORE I ;



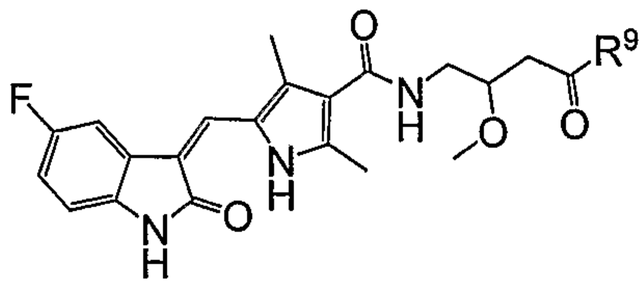
CORE II ;



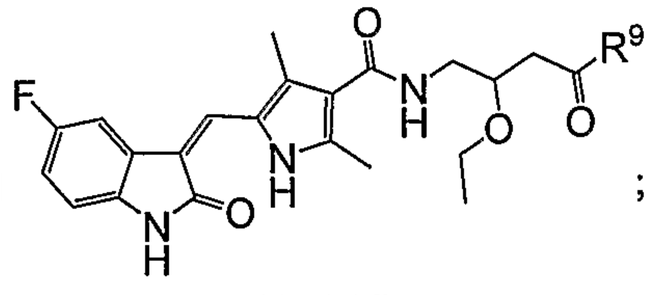
CORE III ;



CORE IV ;

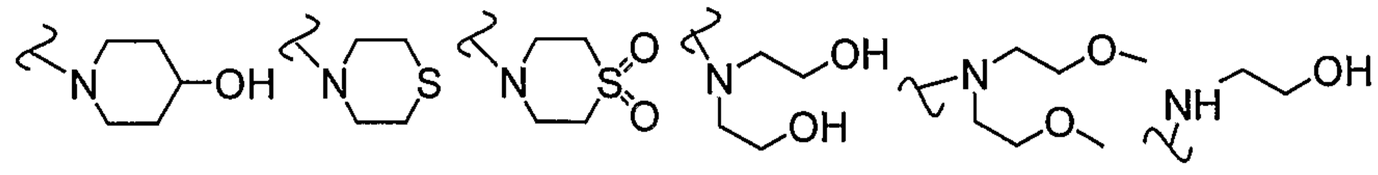


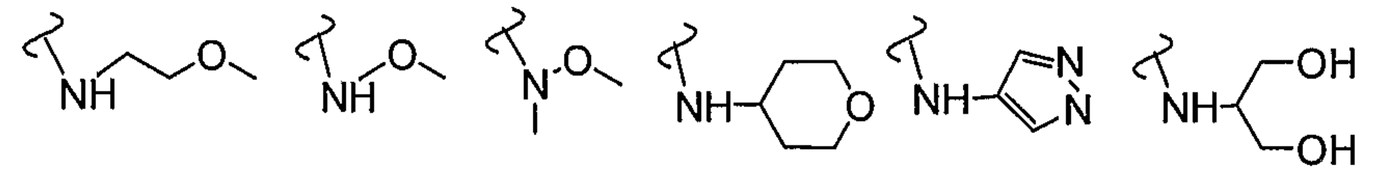
CORE V ; and

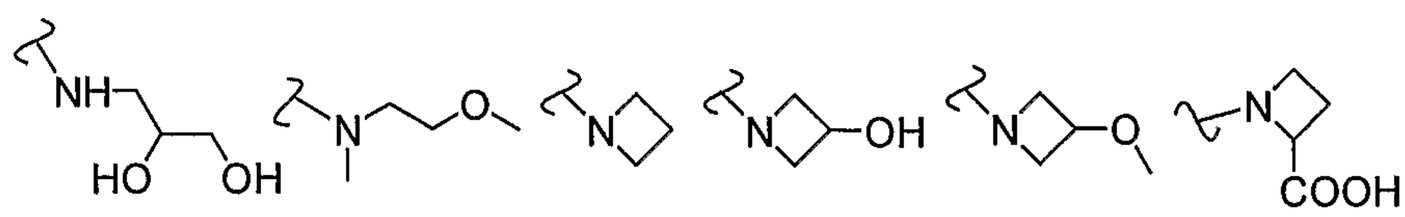


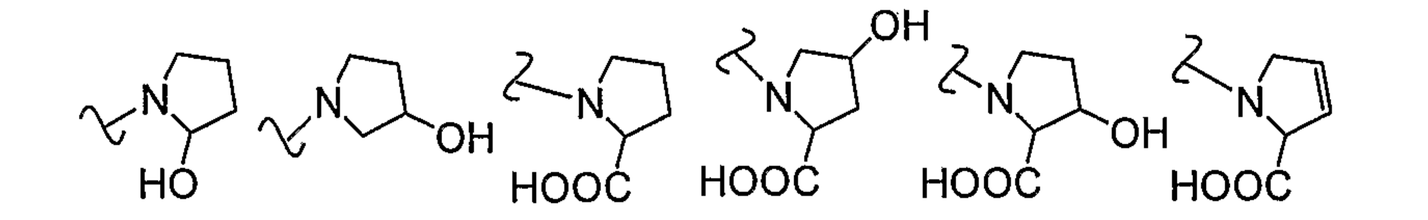
CORE VI ;

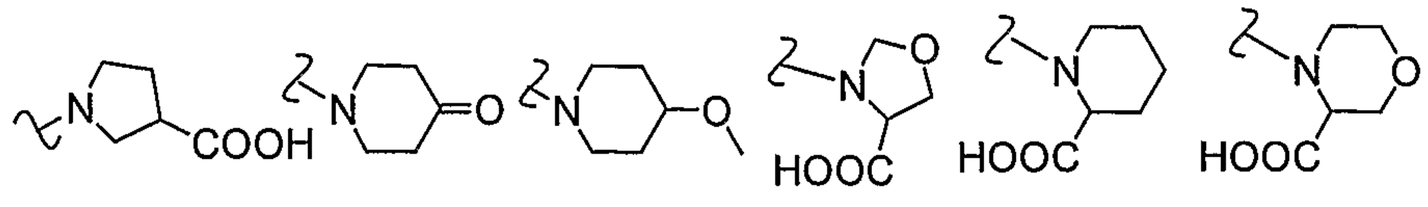
wherein: R is selected from the group consisting of radical represented by the following structures:

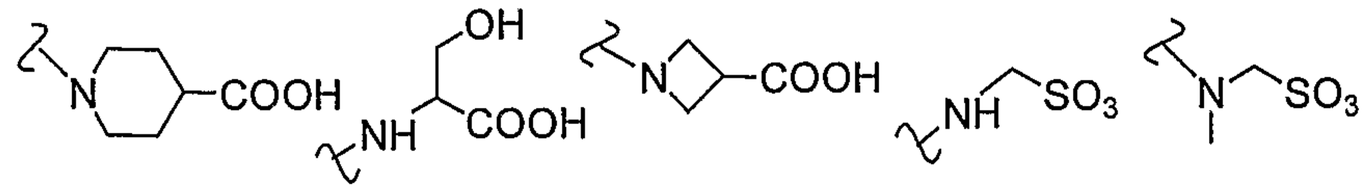


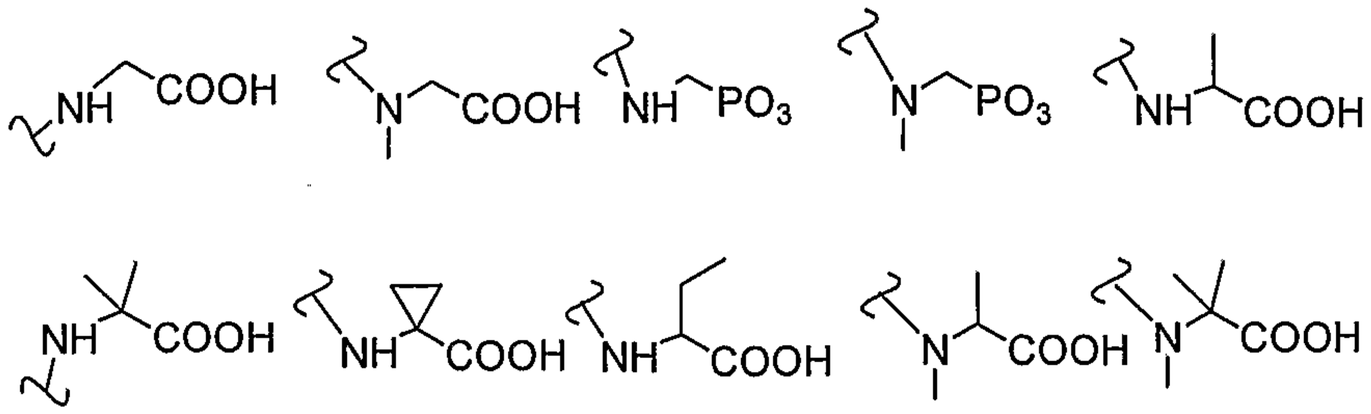


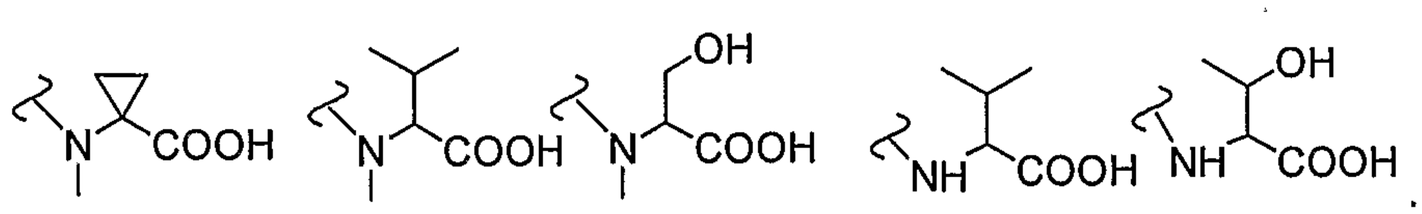












32. A method for the modulation of the catalytic activity of a protein kinase with a compound or salt of any one of claims 1-31.

33. The method of claim 32, wherein said protein kinase is selected from the group consisting of VEGF receptors and PDGF receptors.

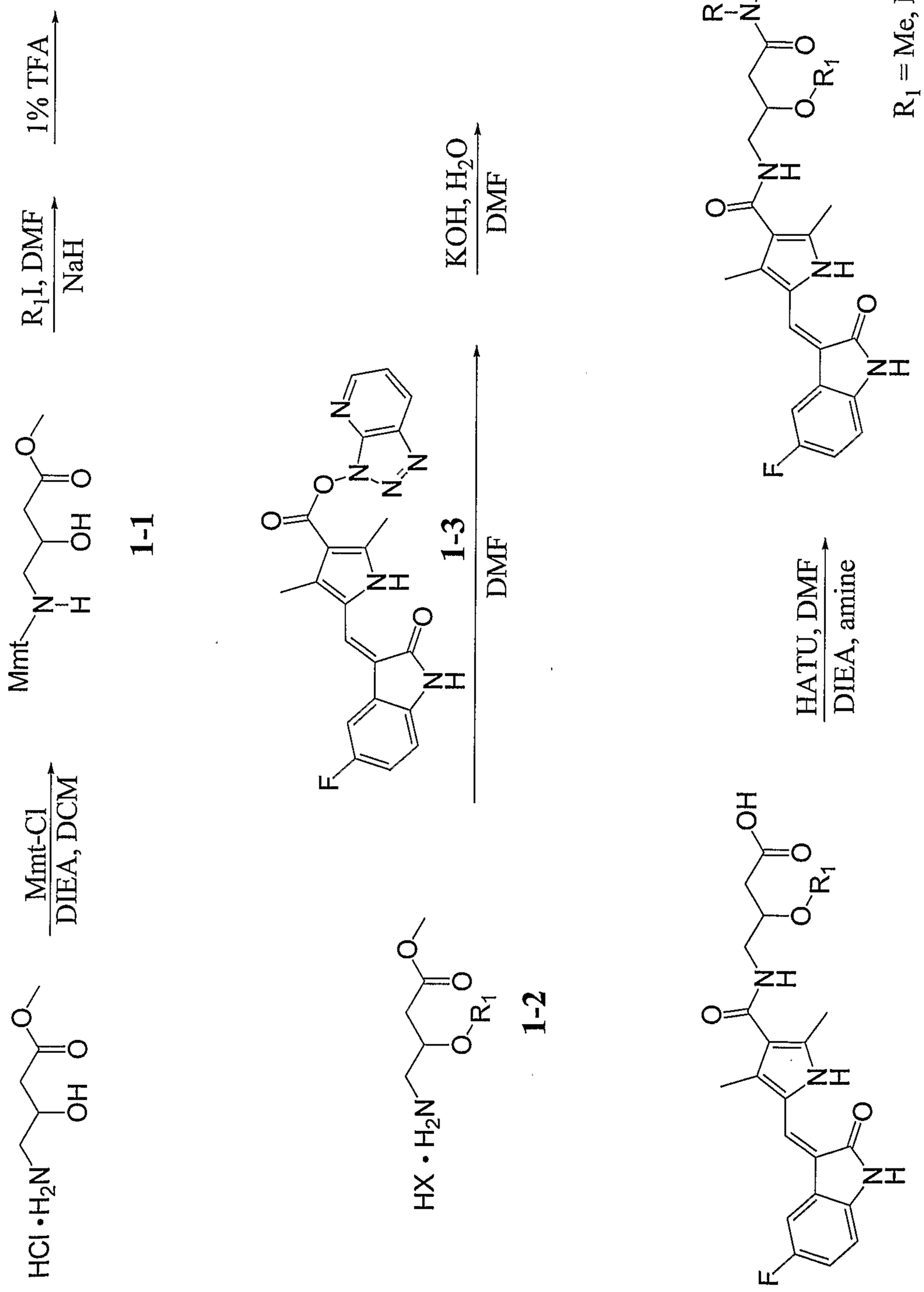

1% TFA
R1I, DMF
NaH
KOH, H2O
DMF
DMF
HATU, DMF
DIEA, amine
Mmt-Cl
DIEA, DCM
HCl • H2N
HX •
R1 = Me, Ethyl
1-1
1-2
1-3
1-4
1-5

Figure 1

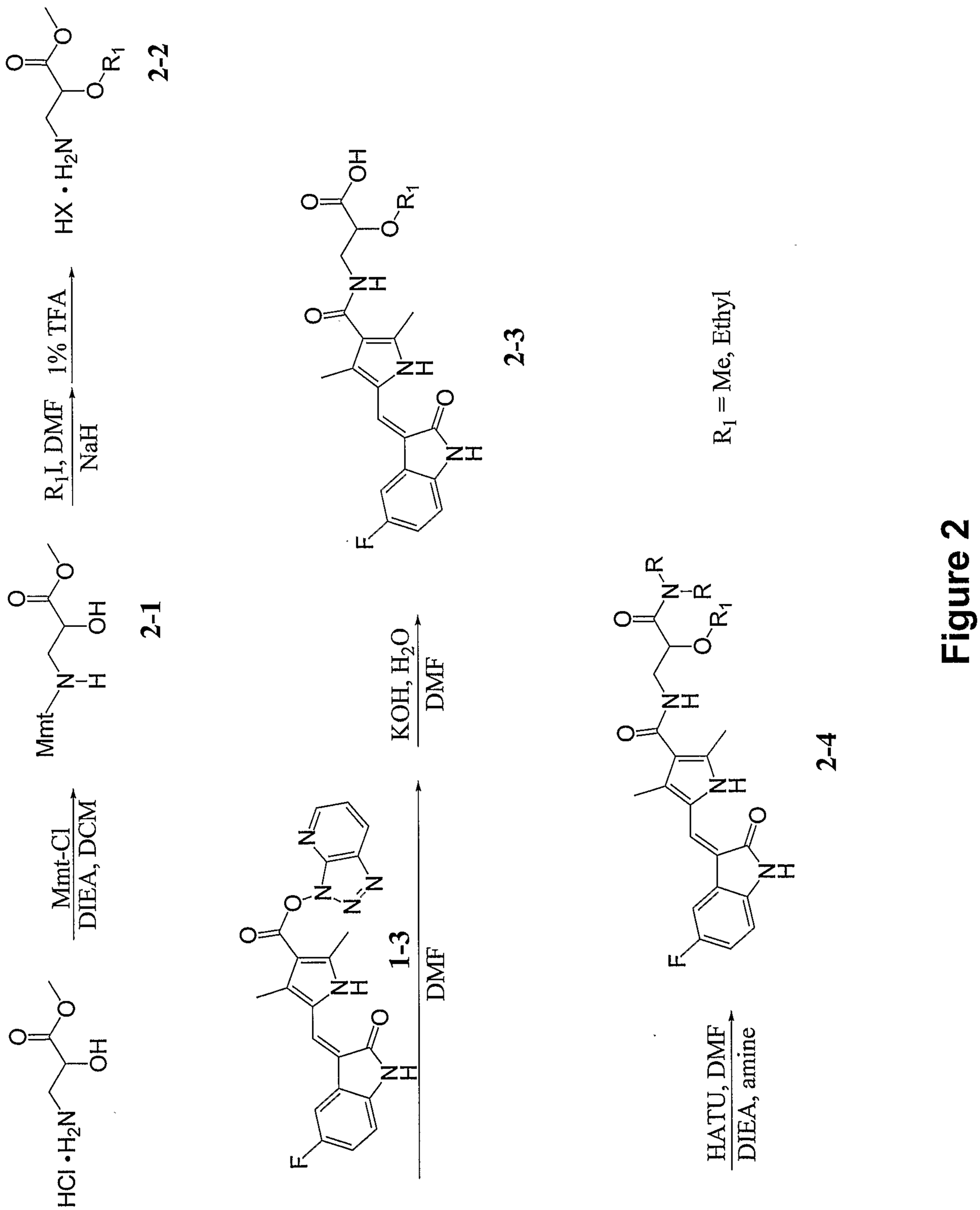

HCl • H2N
O
OH
2-1
Mmt-Cl
DIEA, DCM
Mmt
N
H
R1I, DMF
NaH
1% TFA
HX • H
2-2
1-3
DMF
KOH, H2O
DMF
2-3
R1 = Me, Ethyl
HATU, DMF
DIEA, amine
2-4
F
NH

Figure 2

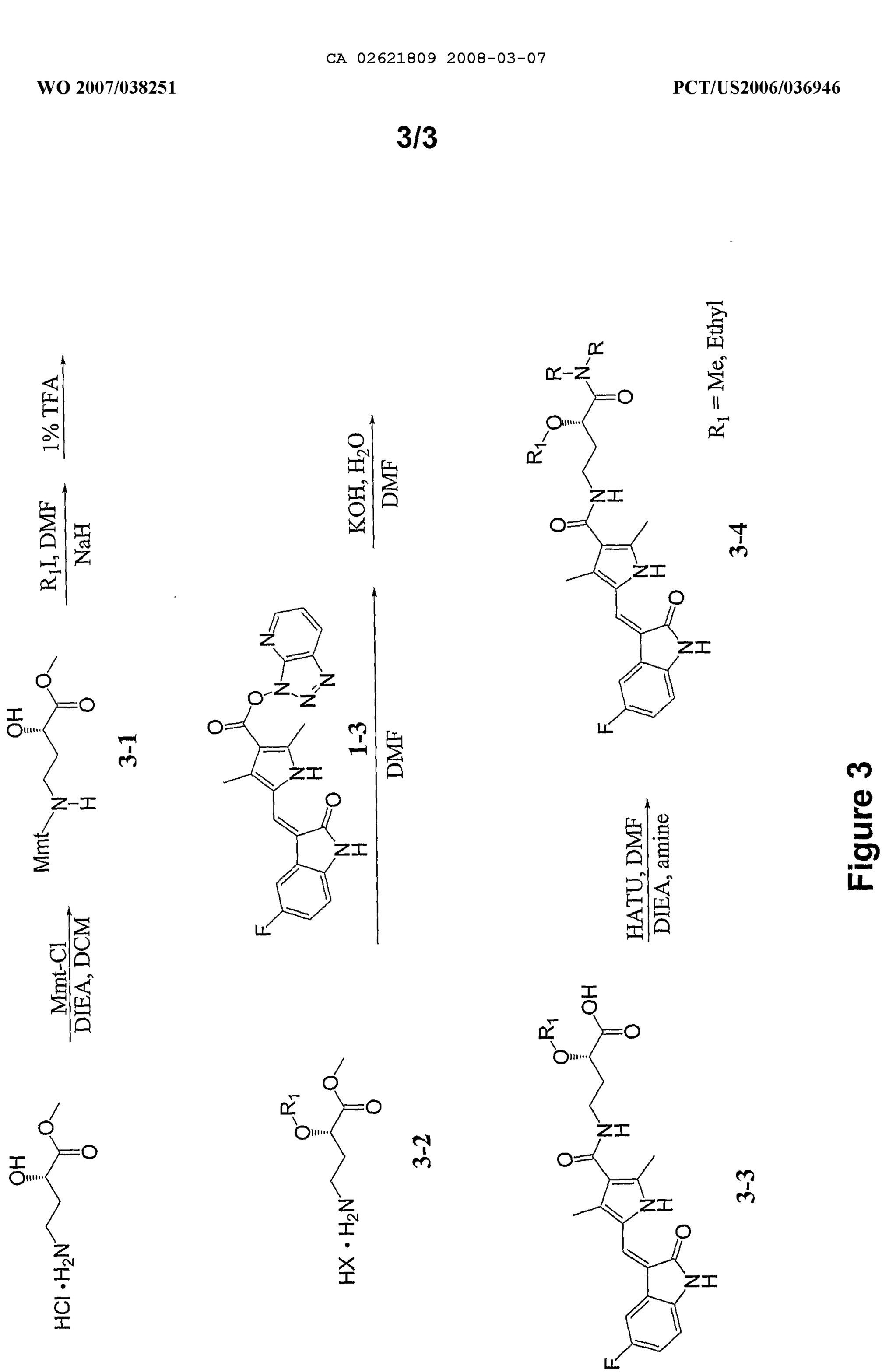

HCl • H2N
3-1
Mmt-Cl
DIEA, DCM
Mmt
R1I, DMF
NaH
1% TFA
HX • H2N
3-2
1-3
KOH, H2O
DMF
DMF
HATU, DMF
DIEA, amine
3-3
3-4
R1 = Me, Ethyl

Figure 3