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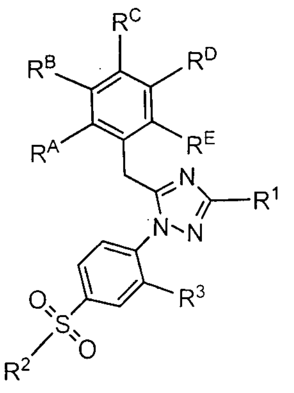
(54) Title: 1- [4- (SULFONYL) -PHENYL] -5- (BENZYL) -IH-I, 2, 4-TRIAZOL DERIVATIVES AS INHIBITORS OF CARBONIC ANHYDRASE FOR TREATING GLAUCOMA OR OCULAR HYPERTENSION



(I)

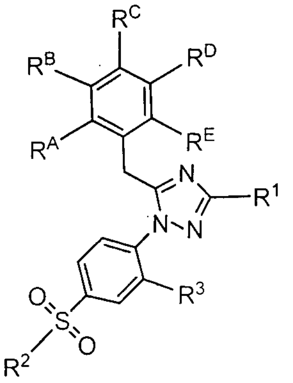
(57) Abstract: The invention relates to compounds of formula (I) and to pharmaceutically acceptable salts and solvates thereof, wherein R^1, R^2, R^3, R^4 and R^A through R^E are as defined herein. The invention also relates to methods of treating glaucoma, ocular hypertension, age-related macular degeneration, diabetic macular edema, diabetic retinopathy, hypertensive retinopathy, retinal vasculopathies and intraocular pressure in mammals by administering the compounds of formula I, and to pharmaceutical compositions which contain the compounds of formula I for such treatments. The invention also relates to methods of preparing the compounds of formula (I).

WO 2008/075152 A1

1-[4-(SULFONYL)-PHENYL]-5-(BENZYL)-1H-1,2,4-TRIAZOL DERIVATIVES AS INHIBITORS OF CARBONIC ANHYDRASE FOR TREATING GLAUCOMA OR OCULAR HYPERTENSION

Field of the Invention

The present invention relates to compounds of formula I:



(I)

and to pharmaceutically acceptable salts and solvates thereof, wherein R^1, R^2, R^3, R^4 and R^A through R^E are as defined herein. Methods for their preparation, pharmaceutical compositions containing these compounds, and methods of using these compounds and compositions for inhibiting carbonic anhydrase, and thereby lowering intraocular pressure and treating glaucoma are also provided.

Background of the Invention

Glaucoma is optic nerve damage, often associated with increased intraocular pressure (IOP), that leads to progressive, irreversible loss of vision. Almost 3 million people in the United States and 14 million people worldwide have glaucoma; this is the third leading cause of blindness worldwide. Glaucoma occurs when an imbalance in production and drainage of fluid in the eye (aqueous humor) increases eye pressure to unhealthy levels.

It is known that elevated IOP can be at least partially controlled by administering drugs which either reduce the production of aqueous humor within the eye or increase the fluid drainage, such as beta-adrenergic antagonists, α-adrenergic agonists, cholinergic agents, prostaglandin analogs or carbonic anhydrase inhibitors.

Several side effects are associated with the drugs conventionally used to treat glaucoma. Topical beta-adrenergic antagonists show serious pulmonary side effects, depression, fatigue, confusion, impotence, hair loss, heart failure and bradycardia. Topical α-adrenergic agonists have a fairly high incidence of allergic or toxic reactions;

topical cholinergic agents (miotics) can cause visual side effects. The topical prostaglandin analogs (bimatoprost, latanoprost, travoprost and unoprostone) used in the treatment of glaucoma can produce ocular side effects, such as increased pigmentation of the iris, ocular irritation, conjunctival hyperaemia, iritis, uveitis and macular edema (Martindale, Thirty-third edition, p. 1445).

Finally, the side effects associated with oral carbonic anhydrase inhibitors include fatigue, anorexia, depression, paresthesias and serum electrolyte abnormalities (The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, M. H. Beers and R. Berkow Editors, Sec. 8, Ch. 100).

WO2006/052899 discloses novel nitrosated and/or nitrosylated compounds or pharmaceutically acceptable salts thereof, and novel compositions, for treating ophthalmic disorders comprising at least one nitrosated and/or nitrosylated compound, and, optionally, at least one nitric oxide donor and/or at least one therapeutic agent selected from the group consisting of an α-adrenergic receptor agonist, an ACE inhibitor, an antimicrobial, a β-adrenergic antagonist, a carbonic anhydrase inhibitor, a non-steroidal anti-inflammatory drug, a prostaglandin, a COX-2 inhibitor and a steroid.

Summary of the Invention

The present invention relates to new carbonic anhydrase inhibitor derivatives. More particularly, the present invention relates to unique triazole-benzenesulfonamides, pharmaceutical compositions containing them, and their use as drugs for treating glaucoma, ocular hypertension, age-related macular degeneration, diabetic macular edema, diabetic retinopathy, hypertensive retinopathy and retinal vasculopathies.

An object of the present invention to provide new derivatives of carbonic anhydrase inhibitors able not only to eliminate or at least reduce the side effects associated with the parent compounds, but also to improve pharmacological activity. It has been surprisingly found that nitrooxyderivatives of carbonic anhydrase inhibitors have a significantly improved overall profile as compared to native carbonic anhydrase inhibitors both in terms of wider pharmacological activity, enhanced tolerability and long-acting ocular hypotensive activity. In particular, it has been recognized that the carbonic anhydrase inhibitor nitroderivatives of the present invention can be employed for treating ocular hypertension and preventing glaucoma. Moreover, they have been found to be effective for the treatment of age-related macular degeneration, diabetic macular edema, diabetic retinopathy, hypertensive retinopathy and retinal vasculopathies.

The compounds of the present invention are indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or with chronic angle-closure glaucoma who underwent peripheral iridotomy or laser iridoplasty.

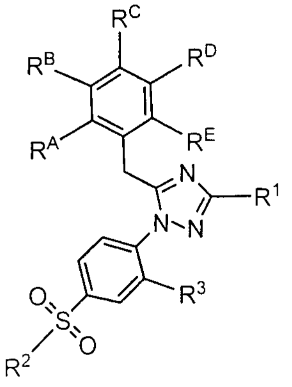
An object of the present invention is a method for treating eye disorders, in particular glaucoma, ocular hypertension, age-related macular degeneration, diabetic macular edema, diabetic retinopathy, hypertensive retinopathy and retinal vasculopathies in a patient in need thereof comprising administering a therapeutically effective amount of a carbonic anhydrase inhibitor able to release nitric oxide.

A carbonic anhydrase inhibitor is a compound having an inhibition constant (K_i) against the isoenzyme CAII in the range of 0,01-200 nM. The carbonic anhydrase activity is measured according to the test on carbonic anhydrase inhibition as reported below.

A carbonic anhydrase inhibitor able to release nitric oxide is a compound having an EC_{50} value in the range of 1-50μM, in vasorelaxation.

The compounds of the present invention are triazoles which inhibit carbonic anhydrase activity, and are thereby useful for lowering intraocular pressure and treating glaucoma, without producing significant systemic side effects when delivered topically to the eye.

In one aspect according to the invention, there is provided a compound of formula (I):



(I)

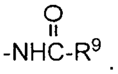
wherein R^1 is H, $(C_1\text{-}C_{10})$alkyl, $-OR^5$, $-C(O)R^5$, $-C(O)OR^5$, or $-C(O)\overset{O}{\overset{\|}{C}}-R^9$; R^2 is $(C_1\text{-}C_6)$alkyl or NR^6R^7; R^3 is H or halo; each R^A, R^B, R^C, R^D, and R^E is independently H, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $-OR^5$, or $-C(O)R^5$; each R^5 is independently H, -OH, $-NO_2$, $-ONO_2$, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_6\text{-}C_{10})$aryl, or $(C_6\text{-}C_{10})$heteroaryl, wherein each of said $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_6\text{-}C_{10})$aryl, and $(C_6\text{-}C_{10})$heteroaryl moieties of said R^5 groups is optionally substituted by one or more R^9 moieties; each R^6 and R^7, which may be the same or different, is independently H, -OH, $-C(O)R^8$, or $-\overset{O}{\overset{\|}{C}}-R^9$; each R^8 is independently $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, or $(C_6\text{-}C_{10})$heteroaryl, wherein each of said $(C_3\text{-}C_{10})$cycloalkyl, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, and $(C_6\text{-}C_{10})$heteroaryl moieties of said R^8 groups are optionally substituted by $-NO_2$ or $-ONO_2$; each R^9 is independently $-NO_2$, $-ONO_2$, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_{10})$cycloalkyl, $[(C_1\text{-}C_6)alkyl(O)]_m$, $-C[O(C_1\text{-}C_6)alkyl]_m$, $-[O(C_1\text{-}C_6)alkyl]_m$, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_1\text{-}C_6)alkyl(NH)_nC(=O)$, $-(NH)_n(C_1\text{-}C_6)$alkoxy, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, or $(C_6\text{-}C_{10})$heteroaryl, wherein each of said $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $[(C_1\text{-}C_6)alkyl(O)]_m$, $-C[O(C_1\text{-}C_6)alkyl]_m$, $-[O(C_1\text{-}C_6)alkyl]_m$, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_1\text{-}C_6)alkyl(NH)_nC(=O)$, $-(NH)_n(C_1\text{-}C_6)$alkoxy, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, and $(C_6\text{-}C_{10})$heteroaryl moieties of said R^9 groups are optionally substituted by $-NO_2$, $-ONO_2$, $[(C_1\text{-}C_{10})alkoxy]NO_2$, $[(C_1\text{-}C_{10})alkoxy]ONO_2$, $[(C_1\text{-}C_6)alkyl]ONO_2$, or $[(C_1\text{-}C_6)alkyl]NO_2$; and m and n are each independently an integer from 1 to 4; or a pharmaceutically acceptable salt or solvate thereof.

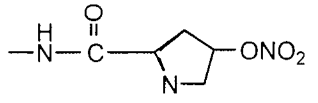
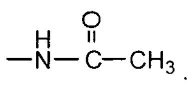
In another aspect of the invention, there is provided a compound according to formula (I) wherein R^1 is $-C(O)R^5$ or $-C(O)\overset{O}{\overset{\|}{C}}-R^9$.

In a further aspect of the invention, there is provided a compound according to formula (I) wherein R^1 is $-COH$, $-C(O)NO_2$, $-C(O)\overset{O}{\overset{\|}{C}}-C[O(C_1\text{-}C_6)alkyl]_m-ONO_2$,

$-C(O)\overset{O}{\overset{\|}{C}}-[(C_1\text{-}C_6)alkyl]_m-ONO_2$, $-C(O)\overset{O}{\overset{\|}{C}}-[(C_6\text{-}C_{10})aryl][(C_1\text{-}C_6)alkyl]-ONO_2$,

$-C(O)\overset{O}{\overset{\|}{C}}-[(C_1\text{-}C_6)alkyl](NH)_nC(=O)(C_1\text{-}C_6)alkyl-ONO_2$, or $-C(O)\overset{O}{\overset{\|}{C}}-[O(C_1\text{-}C_6)alkyl]_m-ONO_2$.

In yet another aspect of the invention, there is provided a compound according to formula (I) wherein R^2 is NH_2 or  $\text{-NH}\overset{O}{\overset{\|}{C}}\text{-R}^9$.

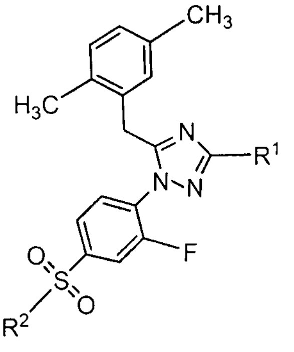
In another aspect of the invention, there is provided a compound according to formula (I) wherein R^2 is NH_2 ,  , or  $-\overset{H}{N}-\overset{O}{\overset{\|}{C}}-CH_3$.

In a further aspect of the invention, there is provided a compound according to formula (I) wherein R^3 is selected from Br, Cl, F, and I.

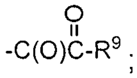
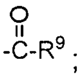
In yet another aspect of the invention, there is provided a compound according to formula (I) wherein each R^A, R^B, R^C, R^D, and R^E is independently H or $(C_1\text{-}C_6)$alkyl.

In another aspect of the invention, there is provided a compound according to formula (I) wherein R^A and R^D are $(C_1\text{-}C_6)$alkyl, or R^B and R^E are $(C_1\text{-}C_6)$alkyl.

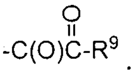
In a further aspect of the invention, there is provided a compound according to formula (IIa):

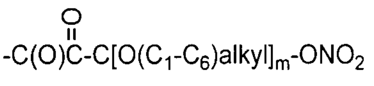


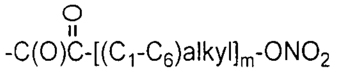
(IIa)

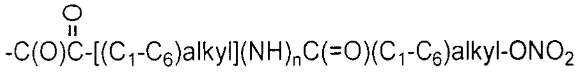
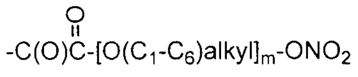
wherein R^1 is H, $(C_1\text{-}C_{10})$alkyl, $-OR^5$, $-C(O)R^5$, $-C(O)OR^5$, or  $\text{-C(O)}\overset{O}{\overset{\|}{C}}\text{-R}^9$; R^2 is $(C_1\text{-}C_6)$alkyl or NR^6R^7; each R^5 is independently H, -OH, $-NO_2$, $-ONO_2$, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_6\text{-}C_{10})$aryl, or $(C_6\text{-}C_{10})$heteroaryl, wherein each of said $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_6\text{-}C_{10})$aryl, and $(C_6\text{-}C_{10})$heteroaryl moieties of said R^5 groups is optionally substituted by one or more R^9 moieties; each R^6 and R^7, which may be the same or different, is independently H, -OH, $-C(O)R^8$, or  $\text{-}\overset{O}{\overset{\|}{C}}\text{-R}^9$; each R^8 is independently $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, or $(C_6\text{-}C_{10})$heteroaryl, wherein each of said $(C_3\text{-}C_{10})$cycloalkyl, $(C_4\text{-}C_{10})$heterocycloalkyl,

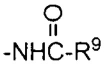
$(C_6\text{-}C_{10})$aryl, and $(C_6\text{-}C_{10})$heteroaryl moieties of said R^8 groups are optionally substituted by $\text{-}NO_2$ or $\text{-}ONO_2$; each R^9 is independently $\text{-}NO_2$, $\text{-}ONO_2$, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_{10})$cycloalkyl, $[(C_1\text{-}C_6)\text{alkyl}(O)]_m$, $\text{-}C[O(C_1\text{-}C_6)\text{alkyl}]_m$, $\text{-}[O(C_1\text{-}C_6)\text{alkyl}]_m$, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_1\text{-}C_6)\text{alkyl}(NH)_nC(=O)$, $\text{-}(NH)_n(C_1\text{-}C_6)$alkoxy, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, or $(C_6\text{-}C_{10})$heteroaryl, wherein each of said $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $[(C_1\text{-}C_6)\text{alkyl}(O)]_m$, $\text{-}C[O(C_1\text{-}C_6)\text{alkyl}]_m$, $\text{-}[O(C_1\text{-}C_6)\text{alkyl}]_m$, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_1\text{-}C_6)\text{alkyl}(NH)_nC(=O)$, $\text{-}(NH)_n(C_1\text{-}C_6)$alkoxy, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, and $(C_6\text{-}C_{10})$heteroaryl moieties of said R^9 groups are optionally substituted by $\text{-}NO_2$, $\text{-}ONO_2$, $[(C_1\text{-}C_{10})\text{alkoxy}]NO_2$, $[(C_1\text{-}C_{10})\text{alkoxy}]ONO_2$, $[(C_1\text{-}C_6)\text{alkyl}]ONO_2$, or $[(C_1\text{-}C_6)\text{alkyl}]NO_2$; and m and n are each independently an integer from 1 to 4; or a pharmaceutically acceptable salt or solvate thereof.

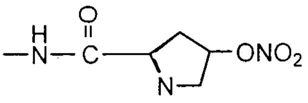
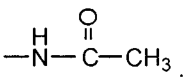
In still another aspect according to the invention, there is provided a compound according to formula (IIa) wherein R^1 is $\text{–}C(O)R^5$ or  $\text{-}C(O)\overset{O}{\overset{\|}{C}}\text{-}R^9$.

In another aspect according to the invention, there is provided a compound according to formula (IIa) wherein R^1 is –COH, $\text{-}C(O)NO_2$,  $\text{-}C(O)\overset{O}{\overset{\|}{C}}\text{-}C[O(C_1\text{-}C_6)\text{alkyl}]_m\text{-}ONO_2$,

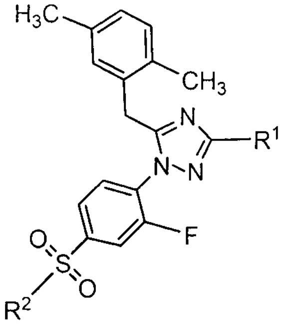
 $\text{-}C(O)\overset{O}{\overset{\|}{C}}\text{-}[(C_1\text{-}C_6)\text{alkyl}]_m\text{-}ONO_2$,  $\text{-}C(O)\overset{O}{\overset{\|}{C}}\text{-}[(C_6\text{-}C_{10})\text{aryl}][(C_1\text{-}C_6)\text{alkyl}]\text{-}ONO_2$,

 $\text{-}C(O)\overset{O}{\overset{\|}{C}}\text{-}[(C_1\text{-}C_6)\text{alkyl}](NH)_nC(=O)(C_1\text{-}C_6)\text{alkyl-}ONO_2$, or  $\text{-}C(O)\overset{O}{\overset{\|}{C}}\text{-}[O(C_1\text{-}C_6)\text{alkyl}]_m\text{-}ONO_2$.

In yet a further aspect according to the invention, there is provided a compound according to formula (IIa) wherein R^2 is NH_2 or  $\text{-}NH\overset{O}{\overset{\|}{C}}\text{-}R^9$.

In still another aspect according to the invention, there is provided a compound according to formula (IIa) wherein R^2 is NH_2 ,  , or  $\text{—}\overset{H}{N}\text{—}\overset{O}{\overset{\|}{C}}\text{—}CH_3$.

In another aspect according to the invention, there is provided a compound according to formula (IIb):



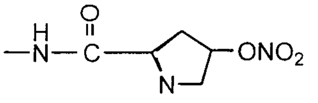
(IIb)

wherein: R^1 is H, $(C_1\text{-}C_{10})$alkyl, $-OR^5$, $-C(O)R^5$, $-C(O)OR^5$, or $-C(O)\overset{O}{\overset{\|}{C}}-R^9$; R^2 is $(C_1\text{-}C_6)$alkyl or NR^6R^7; each R^5 is independently H, -OH, $-NO_2$, $-ONO_2$, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_6\text{-}C_{10})$aryl, or $(C_6\text{-}C_{10})$heteroaryl, wherein each of said $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_6\text{-}C_{10})$aryl, and $(C_6\text{-}C_{10})$heteroaryl moieties of said R^5 groups is optionally substituted by one or more R^9 moieties; each R^6 and R^7, which may be the same or different, is independently H, -OH, $-C(O)R^8$, or $-\overset{O}{\overset{\|}{C}}-R^9$; each R^8 is independently $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, or $(C_6\text{-}C_{10})$heteroaryl, wherein each of said $(C_3\text{-}C_{10})$cycloalkyl, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, and $(C_6\text{-}C_{10})$heteroaryl moieties of said R^8 groups are optionally substituted by $-NO_2$ or $-ONO_2$; each R^9 is independently $-NO_2$, $-ONO_2$, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_{10})$cycloalkyl, $[(C_1\text{-}C_6)alkyl(O)]_m$, $-C[O(C_1\text{-}C_6)alkyl]_m$, $-[O(C_1\text{-}C_6)alkyl]_m$, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_1\text{-}C_6)alkyl(NH)_nC(=O)$, $-(NH)_n(C_1\text{-}C_6)$alkoxy, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, or $(C_6\text{-}C_{10})$heteroaryl, wherein each of said $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $[(C_1\text{-}C_6)alkyl(O)]_m$, $-C[O(C_1\text{-}C_6)alkyl]_m$, $-[O(C_1\text{-}C_6)alkyl]_m$, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_1\text{-}C_6)alkyl(NH)_nC(=O)$, $-(NH)_n(C_1\text{-}C_6)$alkoxy, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, and $(C_6\text{-}C_{10})$heteroaryl moieties of said R^9 groups are optionally substituted by $-NO_2$, $-ONO_2$, $[(C_1\text{-}C_{10})alkoxy]NO_2$, $[(C_1\text{-}C_{10})alkoxy]ONO_2$, $[(C_1\text{-}C_6)alkyl]ONO_2$, or $[(C_1\text{-}C_6)alkyl]NO_2$; and m and n are each independently an integer from 1 to 4; or a pharmaceutically acceptable salt or solvate thereof.

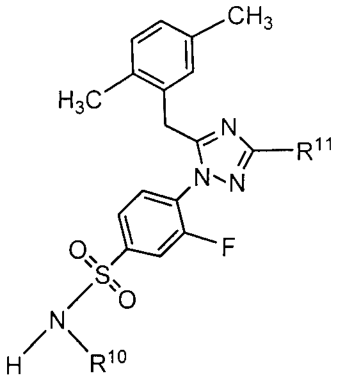
In yet another aspect according to the invention, there is provided a compound according to formula (IIb) wherein R^1 is $-C(O)R^5$ or $-C(O)\overset{O}{\overset{\|}{C}}-R^9$.

In still another aspect according to the invention, there is provided a compound according to formula (IIb) wherein R^1 is –COH, -C(O)NO_2, $-C(O)\overset{\overset{O}{\|}}{C}-C[O(C_1\text{-}C_6)\text{alkyl}]_m\text{-}ONO_2$, $-C(O)\overset{\overset{O}{\|}}{C}-[(C_1\text{-}C_6)\text{alkyl}]_m\text{-}ONO_2$, $-C(O)\overset{\overset{O}{\|}}{C}-[(C_6\text{-}C_{10})\text{aryl}][(C_1\text{-}C_6)\text{alkyl}]\text{-}ONO_2$, $-C(O)\overset{\overset{O}{\|}}{C}-[(C_1\text{-}C_6)\text{alkyl}](NH)_nC(=O)(C_1\text{-}C_6)\text{alkyl-}ONO_2$, or $-C(O)\overset{\overset{O}{\|}}{C}-[O(C_1\text{-}C_6)\text{alkyl}]_m\text{-}ONO_2$.

In a further aspect according to the invention, there is provided a compound according to formula (IIb) wherein R^2 is NH_2 or $-NH\overset{\overset{O}{\|}}{C}-R^9$.

In yet another aspect according to the invention, there is provided a compound according to formula (IIb) wherein R^2 is NH_2 ,  , or $-\overset{H}{N}-\overset{\overset{O}{\|}}{C}-CH_3$.

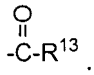
In another aspect according to the invention, there is provided a compound according to formula (IIIa):

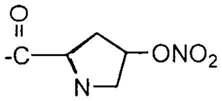
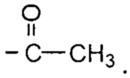


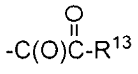
(IIIa)

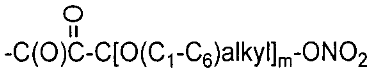
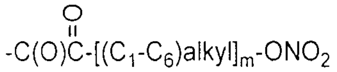
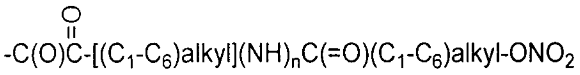
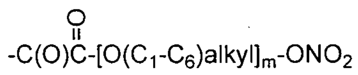
wherein: R^{10} is H or $\overset{\overset{O}{\|}}{C}-R^{13}$; R^{11} is H, $(C_1\text{-}C_{10})$alkyl, $-OR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, or $-C(O)\overset{\overset{O}{\|}}{C}-R^{13}$; each R^{12} is independently H, -OH, $-NO_2$, $-ONO_2$, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_6\text{-}C_{10})$aryl, or $(C_6\text{-}C_{10})$heteroaryl, wherein each of said $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_6\text{-}C_{10})$aryl, and $(C_6\text{-}C_{10})$heteroaryl moieties of said R^{12} groups is optionally substituted by one or more R^{13} moieties; R^{13} is independently $-NO_2$, $-ONO_2$, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_{10})$cycloalkyl, $[(C_1\text{-}C_6)\text{alkyl}(O)]_m$, $-C[O(C_1\text{-}C_6)\text{alkyl}]_m$, -

$[O(C_1\text{-}C_6)alkyl]_m$, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_1\text{-}C_6)$alkyl$(NH)_nC(=O)$, $\text{-}(NH)_n(C_1\text{-}C_6)$alkoxy, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, or $(C_6\text{-}C_{10})$heteroaryl, wherein each of said $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $[(C_1\text{-}C_6)alkyl(O)]_m$, $\text{-}C[O(C_1\text{-}C_6)alkyl]_m$, $\text{-}[O(C_1\text{-}C_6)alkyl]_m$, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_1\text{-}C_6)$alkyl$(NH)_nC(=O)$, $\text{-}(NH)_n(C_1\text{-}C_6)$alkoxy, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, and $(C_6\text{-}C_{10})$heteroaryl moieties of said R^9 groups are optionally substituted by $\text{-}NO_2$, $\text{-}ONO_2$, $[(C_1\text{-}C_{10})alkoxy]NO_2$, $[(C_1\text{-}C_{10})alkoxy]ONO_2$, $[(C_1\text{-}C_6)alkyl]ONO_2$, or $[(C_1\text{-}C_6)alkyl]NO_2$; and m and n are each independently an integer from 1 to 4; or a pharmaceutically acceptable salt or solvate thereof.

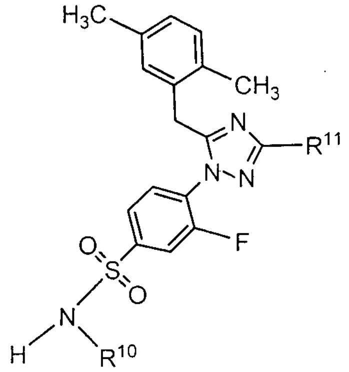
In still another aspect according to the invention, there is provided a compound according to formula (IIIa) wherein R^{10} is H or  $\text{-}\overset{O}{\overset{\parallel}{C}}\text{-}R^{13}$.

In a further aspect according to the invention, there is provided a compound according to formula (IIIa) wherein R^{10} is H,  , or  $\text{-}\overset{O}{\overset{\parallel}{C}}\text{-}CH_3$.

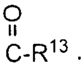
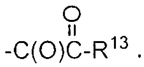
In yet another aspect according to the invention, there is provided a compound according to formula (IIIa) wherein R^{11} is $\text{-}C(O)R^{12}$ or  $\text{-}C(O)\overset{O}{\overset{\parallel}{C}}\text{-}R^{13}$.

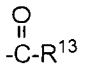
In another aspect according to the invention, there is provided a compound according to formula (IIIa) wherein R^{11} is $\text{-}COH$, $\text{-}C(O)NO_2$,  $\text{-}C(O)\overset{O}{\overset{\parallel}{C}}\text{-}C[O(C_1\text{-}C_6)alkyl]_m\text{-}ONO_2$,  $\text{-}C(O)\overset{O}{\overset{\parallel}{C}}\text{-}[(C_1\text{-}C_6)alkyl]_m\text{-}ONO_2$,  $\text{-}C(O)\overset{O}{\overset{\parallel}{C}}\text{-}[(C_6\text{-}C_{10})aryl][(C_1\text{-}C_6)alkyl]\text{-}ONO_2$,  $\text{-}C(O)\overset{O}{\overset{\parallel}{C}}\text{-}[(C_1\text{-}C_6)alkyl](NH)_nC(=O)(C_1\text{-}C_6)alkyl\text{-}ONO_2$, or  $\text{-}C(O)\overset{O}{\overset{\parallel}{C}}\text{-}[O(C_1\text{-}C_6)alkyl]_m\text{-}ONO_2$.

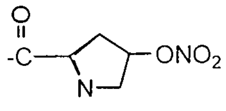
In still a further aspect according to the invention, there is provided a compound according to a compound of formula (IIIb):

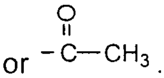


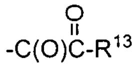
(IIIb)

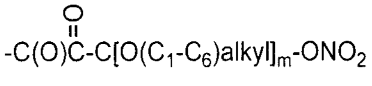
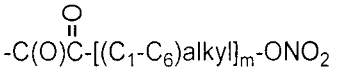
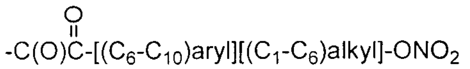
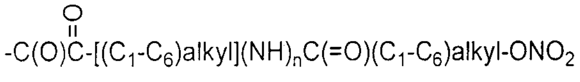
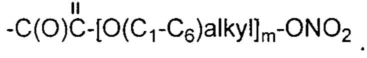
wherein: R^{10} is H or  $\overset{\overset{O}{\|}}{C}\text{-}R^{13}$; R^{11} is H, $(C_1\text{-}C_{10})$alkyl, $-OR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, or  $\text{-}C(O)\overset{\overset{O}{\|}}{C}\text{-}R^{13}$; each R^{12} is independently H, -OH, $-NO_2$, $-ONO_2$, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_6\text{-}C_{10})$aryl, or $(C_6\text{-}C_{10})$heteroaryl, wherein each of said $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_6\text{-}C_{10})$aryl, and $(C_6\text{-}C_{10})$heteroaryl moieties of said R^{12} groups is optionally substituted by one or more R^{13} moieties; R^{13} is independently $-NO_2$, $-ONO_2$, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_{10})$cycloalkyl, $[(C_1\text{-}C_6)alkyl(O)]_m$, $-C[O(C_1\text{-}C_6)alkyl]_m$, $-[O(C_1\text{-}C_6)alkyl]_m$, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_1\text{-}C_6)alkyl(NH)_nC(=O)$, $-(NH)_n(C_1\text{-}C_6)$alkoxy, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, or $(C_6\text{-}C_{10})$heteroaryl, wherein each of said $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $[(C_1\text{-}C_6)alkyl(O)]_m$, $-C[O(C_1\text{-}C_6)alkyl]_m$, $-[O(C_1\text{-}C_6)alkyl]_m$, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_1\text{-}C_6)alkyl(NH)_nC(=O)$, $-(NH)_n(C_1\text{-}C_6)$alkoxy, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, and $(C_6\text{-}C_{10})$heteroaryl moieties of said R^9 groups are optionally substituted by $-NO_2$, $-ONO_2$, $[(C_1\text{-}C_{10})alkoxy]NO_2$, $[(C_1\text{-}C_{10})alkoxy]ONO_2$, $[(C_1\text{-}C_6)alkyl]ONO_2$, or $[(C_1\text{-}C_6)alkyl]NO_2$; and m and n are each independently an integer from 1 to 4; or a pharmaceutically acceptable salt or solvate thereof.

In another aspect according to the invention, there is provided a compound according to formula (IIIb) wherein R^{10} is H or  $\text{-}\overset{\overset{O}{\|}}{C}\text{-}R^{13}$.

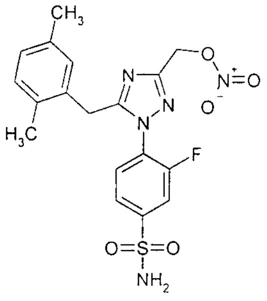
In still another aspect according to the invention, there is provided a compound according to formula (IIIb) wherein R^{10} is H, 

, or  $-\overset{\overset{O}{\|}}{C}\text{—}CH_3$.

In yet another aspect according to the invention, there is provided a compound according to formula (IIIb) wherein R^{11} is $-C(O)R^{12}$ or  $-C(O)\overset{O}{\overset{\|}{C}}-R^{13}$.

In a further aspect according to the invention, there is provided a compound according to formula (IIIb) wherein R^{11} is $-COH$, $-C(O)NO_2$,  $-C(O)\overset{O}{\overset{\|}{C}}-C[O(C_1\text{-}C_6)alkyl]_m\text{-}ONO_2$,  $-C(O)\overset{O}{\overset{\|}{C}}-[(C_1\text{-}C_6)alkyl]_m\text{-}ONO_2$,  $-C(O)\overset{O}{\overset{\|}{C}}-[(C_6\text{-}C_{10})aryl][(C_1\text{-}C_6)alkyl]\text{-}ONO_2$,  $-C(O)\overset{O}{\overset{\|}{C}}-[(C_1\text{-}C_6)alkyl](NH)_nC(=O)(C_1\text{-}C_6)alkyl\text{-}ONO_2$, or  $-C(O)\overset{O}{\overset{\|}{C}}-[O(C_1\text{-}C_6)alkyl]_m\text{-}ONO_2$.

In another aspect according to the invention, there is provided a compound selected from the group consisting of:



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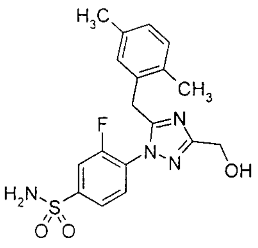

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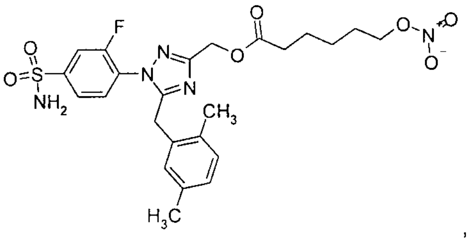

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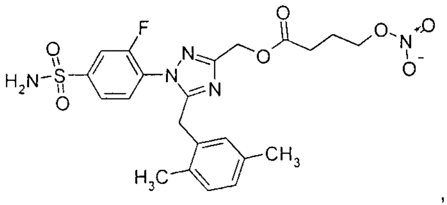

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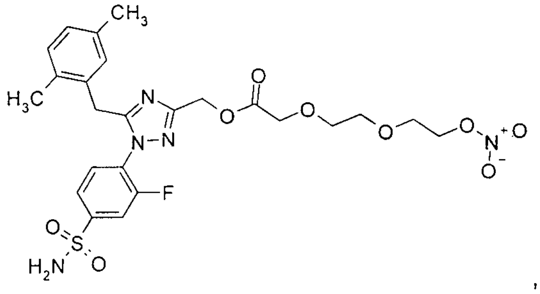

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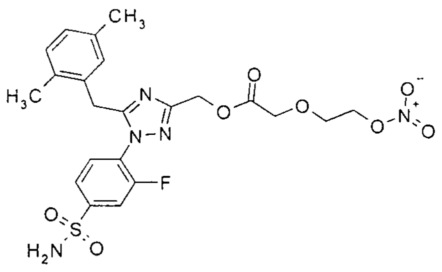

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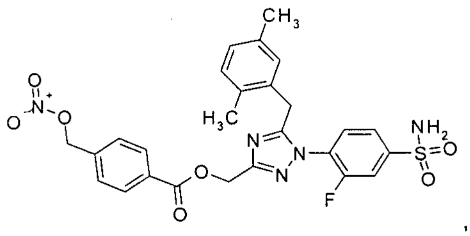

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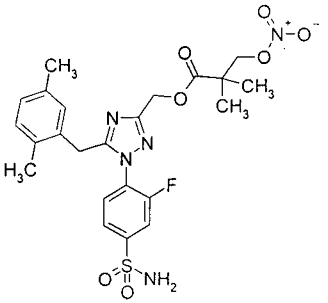
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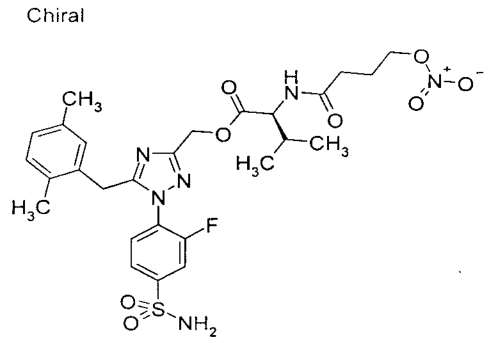

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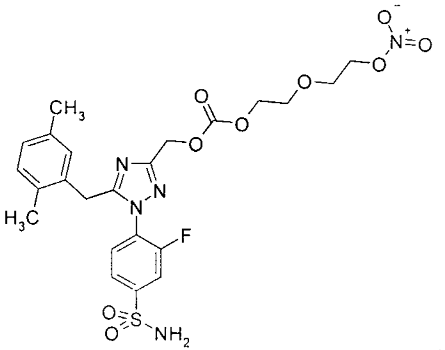
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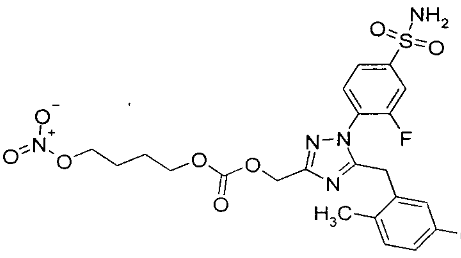
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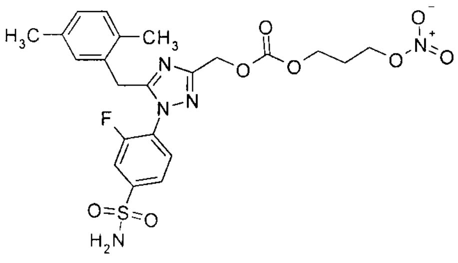
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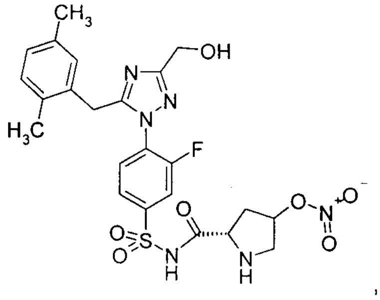
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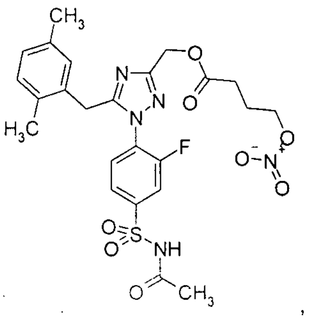
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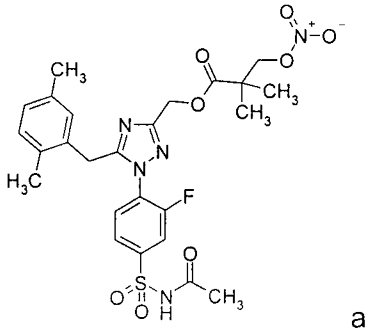

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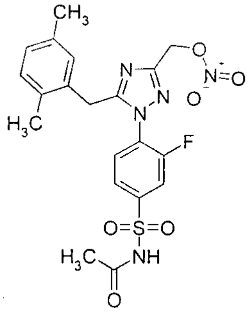

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or a pharmaceutically acceptable salt or solvate thereof.

In still a further aspect according to the invention, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of one or more compounds according to the above disclosure.

In another aspect according to the invention, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound according to the above disclosure in a suitable form for topical administration.

In yet another aspect according to the invention, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound according to the above disclosure for the treatment of glaucoma and ocular hypertension.

In still another aspect according to the invention, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound according to the above disclosure, wherein the compound of formula I is administered as a solution, suspension or emulsion in an ophthalmically acceptable vehicle.

In a further aspect according to the invention, there is provided a method for treating glaucoma or ocular hypertension, wherein the method comprises contacting an effective intraocular pressure reducing amount of a pharmaceutical composition according to the above disclosure with the eye in order to reduce eye pressure and to maintain the pressure at a reduced level.

In another aspect according to the invention, there is provided a method for treating eye disorders in a patient in need thereof comprising administering a therapeutically effective amount of a carbonic anhydrase inhibitor according to the above disclosure able to release nitric oxide and/or where the eye disorder is selected from glaucoma, ocular hypertension, age-related macular degeneration, diabetic macular edema, diabetic retinopathy, hypertensive retinopathy and retinal vasculopathies.

In yet another aspect according to the invention, there is provided a method for treating eye disorders in a patient in need thereof comprising administering a therapeutically effective amount of a carbonic anhydrase inhibitor according to the above disclosure able to release nitric oxide wherein the carbonic anhydrase inhibitor is a compound having an inhibition constant (K_i) against the isoenzyme CAII in the range of 0.01 to 200 nM.

In still yet another aspect according to the invention, there is provided a method for treating eye disorders in a patient in need thereof comprising administering a therapeutically effective amount of a carbonic anhydrase inhibitor according to the above disclosure able to release nitric oxide wherein the carbonic anhydrase inhibitor able to release nitric oxide is a compound having an EC_{50} value in the range of 1 to 50 μM.

In a further aspect according to the invention, there is provided a method for the treatment of glaucoma, ocular hypertension, age-related macular degeneration, diabetic macular edema, diabetic retinopathy, hypertensive retinopathy and retinal vasculopathies comprising administering one or more compounds or pharmaceutical compositions according to the above disclosure.

In yet another aspect of the invention, there is provided one or more compounds as disclosed above for use as a medicament, or for the preparation of a medicament for treating glaucoma or ocular hypertension.

In a further aspect of the invention, there is provided a pharmaceutical composition comprising a mixture of a compound as disclosed above and (i) a beta-adrenergic antagonist or (ii) a prostaglandin analog or (iii) an α-adrenergic agonist or a nitrooxy derivative thereof.

In another aspect of the invention, there is provided a pharmaceutical composition comprising a mixture of a compound as disclosed above and timolol or a nitrooxy derivative thereof.

In still another aspect of the invention, there is provided a pharmaceutical composition comprising a mixture of a compound as disclosed above and latanoprost or a nitrooxy derivative thereof.

In yet another aspect of the invention, there is provided a pharmaceutical kit for simultaneous, successive or previous administration of a pharmaceutical composition as disclosed above and (i) a beta-adrenergic antagonists or (ii) a prostaglandin analog or (iii) an α-adrenergic agonist or a nitrooxy derivative thereof.

In a further aspect of the invention, there is provided a method for the treatment of glaucoma, ocular hypertension, age-related macular degeneration, diabetic macular edema, diabetic retinopathy, hypertensive retinopathy and retinal vasculopathies comprising administering a pharmaceutical composition as disclosed above.

Definitions

As used herein, the terms “comprising” and “including” are used in their open, non-limiting sense.

As used herein, the term “substituted,” means that the specified group or moiety bears one or more substituents. The term “unsubstituted,” means that the specified group bears no substituents.

As used herein, the term “optionally substituted” means that the specified group is unsubstituted or is substituted by one or more substituents.

As used herein, the terms “treat,” "treating" or "treatment" includes preventative (e.g., prophylactic) and palliative treatment.

As used herein, the term "pharmaceutically acceptable" means the carrier, diluent, excipients and/or salt must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

As used herein, the term “alkyl” means a straight or branched chain saturated hydrocarbon. Exemplary alkyl groups include but are not limited to methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, hexyl, isohexyl, heptyl, octyl and the like.

As used herein, the term “alkenyl” means a straight or branched chain hydrocarbon having at least one double bond, i.e., a C=C. Exemplary alkenyl groups include but are not limited to vinyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl and the like.

As used herein, the term "alkynyl" means a straight or branched chain hydrocarbon having at least one triple bond, i.e., a C≡C. Exemplary alkynyl groups include but are not limited to acetylenyl, propargyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl and the like.

As used herein, the term "cycloalkyl" means a cyclic saturated hydrocarbon. Exemplary cycloalkyl groups include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

As used herein, the term "cycloalkenyl" means a cyclic hydrocarbon having at least one double bond, i.e., a C=C. Exemplary cycloalkenyl groups include but are not limited to cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl and the like.

As used herein, the term "cycloalkynyl" means a cyclic hydrocarbon having at least one triple bond, i.e., a C≡C. Exemplary cycloalkynyl groups include but are not limited to cyclohexynyl, cycloheptynyl, cyclooctynyl and the like.

As used herein, the term "alkoxy" means a straight or branched chain saturated alkyl group bonded through oxygen. Exemplary alkoxy groups include but are not limited to methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, isopentoxy, neopentoxy, tert-pentoxy, hexoxy, isohexoxy, heptoxy, octoxy and the like.

As used herein, the term "alkylene" means a straight chain or branched chain saturated hydrocarbon wherein a hydrogen atom is removed from each of the terminal carbons. Exemplary alkylene groups include but are not limited to methylene, ethylene, propylene, butylene, pentylene, hexylene, heptylene and the like.

As used herein, the term "cycloalkylaryl" and "$(CH_2)_t(C_3\text{-}C_{12})$cycloalkyl$(C_6\text{-}C_{10})$aryl" includes linear and/or fused ring systems such as 2,3-didydro-1H-indene, 2-methyl-2,3-didydro-1H-indene, 1,2,3,4-tetrahydronaphthalene, 2-methyl-1,2,3,4-tetrahydronaphthalene, 1-cyclopentylbenzene, 1-(2-methylcyclopentyl)benzene, 1-(3-methylcyclopentyl)benzene, 1-cyclohexylbenzene, 1-(2-methylcyclohexyl)benzene, 1-(3-methylcyclohexyl)benzene, 1-(4-methylcyclohexyl)benzene, and the like,

As used herein, the term "halo" or "halogen" means fluoro, chloro, bromo or iodo.

As used herein, the term "aryl" means an organic radical derived from an aromatic hydrocarbon by removal of hydrogen. Exemplary aryl groups include but are not limited to phenyl, biphenyl, naphthyl, and the like.

As used herein, the terms "heterocyclic" and "heterocyclyl" means an aromatic or non-aromatic cyclic group containing one to four heteroatoms each independently selected from O, S and N, wherein each group has from 3 to 10 atoms in its ring system. Non-aromatic heterocyclic groups include groups having only 3 atoms in their ring system, whereas aromatic heterocyclic groups have at least 5 atoms in their ring system. Heterocyclic groups include fused ring systems such as benzo-fused rings and the like. An exemplary 3 membered heterocyclic group is aziridine; 4 membered heterocyclic group is azetidinyl (derived from azetidine); 5 membered heterocyclic group is thiazolyl; 7 membered ring heterocyclic group is azepinyl; and a 10 membered heterocyclic group is quinolinyl.

Examples of non-aromatic heterocyclic groups include but are not limited to pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl.

Examples of aromatic heterocyclic (heteroaryl) groups include but are not limited to pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl.

The foregoing groups may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be imidazol-1-yl (N-attached) or imidazol-3-yl (C-attached). Heterocyclic groups may be optionally substituted on any ring carbon, sulfur or nitrogen atom(s) by one to two oxygens (oxo), per ring. An example of a heterocyclic group wherein 2 ring carbon atoms are substituted with oxo moieties is 1,1-dioxo-thiomorpholinyl.

Exemplary five to six membered heterocyclic aromatic rings having one or two heteroatoms selected independently from oxygen, nitrogen and sulfur include but are not limited to isothiazolyl, pyridinyl, pyridiazinyl, pyrimidinyl, pyrazinyl and the like.

Exemplary partially saturated, fully saturated or fully unsaturated five to eight membered heterocyclic rings having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen include but are not limited to 3H-1,2-oxathiolyl, 1,2,3-oxadizaolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl and the like. Further exemplary five membered rings are furyl, thienyl, 2H-pyrrolyl, 3H-pyrroyl, pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 1,3-dioxolanyl, oxazolyl, thiazolyl, thiazolyl, imidazolyl, 2H-imidazolyl, 2-imidazolinyl, imidazolidinyl, pyrazolyl, 2-pyrazolinyl, pyrazolinyl, isoxazolyl, isothiazolyl, 1,2-dithiolyl, 1,3-dithiolyl, 3H-1,2-oxathiolyl, 1,2,3-oxadizaolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-trizaolyl, 1,3,4-thiadiazolyl, 1,2,3,4-oxatriazolyl, 1,2,3,5-oxatrizaolyl, 3H-1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-dioxazolyl, 5H-1,2,5-oxathiazolyl and 1,3-oxathiolyl. Further exemplary six member rings are 2H-pyranyl, 4H-pyranyl, pyridinyl, piperidinyl, 1,2-dioxinyl, 1,3-dioxinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-trizainyl, 1,3,5-trithianyl, 4H-1,2-oxazinyl, 2H-1,3-oxazinyl, 6H-1,3-oxazinyl, 6H-1,2-oxazinyl, 1,4-oxazinyl, 2H-1,2-oxazinyl, 4H-1,4-oxazinyl, 1,2,5-oxathiazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,2,6-oxathiazinyl, 1,4,2-oxadiazinyl and 1,3,5,2-oxadiazinyl. Further exemplary seven membered rings are azepinyl, oxepinyl, thiepinyl and 1,2,4-diazepinyl. Further exemplary eight membered rings are cyclooctyl, cyclooctenyl and cyclooctadienyl.

Exemplary bicyclic rings are composed of two fused partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen are indolizinyl, indolyl, isoindolyl, 3H-indolyl, 1H-isoindolyl, indolinyl, cyclopenta(b)pyridinyl, pyrano(3,4-b)pyrrolyl, benzofuryl, isobenzofuryl, benzo(b)thienyl, benzo(c)thienyl, 1H-indazolyl, indoxazinyl, benzoxazolyl, anthranilyl, benzimidazolyi, benzthiazolyl, purinyl, 4Hquinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, indenyl, isoindenyl, naphthyl, tetralinyl, decalinyl, 2H-1-benzopyranyl, pyrido(3,4-b)-pyridinyl, pyrido(3,2-b)-pyridinyl, pyrido(4,3-b)-pyridinyl, 2H-1,3-benzoxazinyl, 2H-1,4-benzoxazinyl, 1H-2,3-benzoxazinyl, 4H-3, 1-benzoxazinyl, 2H-1,2-benzoxazinyl and 4H-1,4-benzoxazinyl.

Exemplary 3-10 membered heterocyclyl groups include but are not limited to oxetane, azetidine, tetrahydrofuran, pyrrolidine, 2,5-dihydro-1H-pyrrole, 1,3-dioxalane, isoxazolidine, oxazolidine, pyrazolidine, imidazolidine, pyrrolidin-2-one, tetrahydrothiophene-1,1-dioxide, pyrrolidine-2,5-dione, tetrahydro-2H-pyran, piperidine, 1,2,3,6-tetrahydropyridine, 1,4-dioxane, morpholine, piperazine, thiomorpholine, piperidin-2-one, piperidin-4-one, thiomorpholine-1,1-dioxide, 1,3-oxazinan-2-one, morpholin-3-one, piperazine-2-one, azepane, 1,4-oxazepane, 1,4-diazepane, azepan-2-one, 1,4-diazepan-5-one, quinuclidine, 2-aza-bicyclo[2.2.1]heptane, 8-aza-bicyclo[3.2.1]octane, 5-oxa-2-aza-bicyclo[2.2.1]heptane, 2-oxa-5-aza-bicyclo[2.2.1]heptan-3-one, 2-oxa-5-aza-bicyclo[2.2.2]octan-3-one, 1-methyl-5,6-pyrrolyl-7-oxa-bicyclo[2.2.1]heptane, 6-aza-bicyclo[3.2.1]octane, 3,8-diaza-bicyclo[3.2.1]octan-2-one, 2,2-dimethyl-tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrole, 3,3-cyclohexylpyrrolidine, 1,5-diaxo-9-azaspiro[5.5]undecane, octahydro-1H-isoindole, decahydroquinoline, decahydroisoquinoline, octahydropyrrolo[1,2a]pyrazine, octahydro'1H-pyrido[1,2a]pyrazine, octahydropyrrolo[3,4-c]pyridine-3-one, decahydropyrazino[1,2-a]azepine, furan, 1H-pyrrole, isoxazole, oxazole, 1H-pyrazole, 1H-imidazole, thiazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 4H-1,2,4-triazole, 1H-tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, pyridine-2(1H)-one, 1,4,5,6-tetrahydrocyclopenta[c]pyrazole, 6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole, 2,3-dihydroimidazo[2,1-b]thiazole, imidazo[2,1-b][1,3,4-c]pyridine, 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine, 5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine, 4,5,6,7-tetrahydrothiazole[5,4-c]pyridine, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, quinoline, isoquinoline, 2,3-dihydrobenzofuran, 5,6,7,8-tetrahydroquinoline, 3,4-dihydro-1H-isochromene, 1,2,3,4-tetrahydroisoquinoline, 4H-benzo[d][1,3]dioxane, 5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine, benzofuran, 1H-indole, benzo[d]oxazole, 1H-benzo[d]imidazole, H-imidazo[1,2-a]pyridine, imidazo[1,2-a]pyrimidine, 5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine-3(2H)-one, 2,3,4,5-tetrahydro-1H-benzo[d]azepine, 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine, 5,6,7,8-tetrahydro-4H-isoxazolo[4,3-d]azepine and6,7,8,9-tetrahydro-2H-[1,2,4]triazolo[4,3-g][1,4]diazepin-3(5H)-one.

It is to be understood that if a carbocyclic or heterocyclic moiety may be bonded or otherwise attached to a designated substrate, through differing ring atoms without denoting a specific point of attachment, then all possible points are intended, whether through a carbon atom or, for example, a trivalent nitrogen atom. For example, the term "pyridyl" means 2-, 3-, or 4-pyridyl, the term "thienyl" means 2-, or 3-thienyl, and so forth.

Pharmaceutically acceptable salts of the compounds of the invention include the acid addition and base salts (including disalts) thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts. For a review on suitable salts, see “Handbook of Pharmaceutical Salts: Properties, Selection, and Use” by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

A pharmaceutically acceptable salt of a compound of the invention may be readily prepared by mixing together solutions of a compound of the invention and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionization in the salt may vary from completely ionized to almost non-ionized.

The compounds of the invention may exist in both unsolvated and solvated forms. The term ‘solvate’ is used herein to describe a molecular complex comprising a compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol, water and the like. The term ‘hydrate’ is included within the meaning of the term “solvate” and is frequently used when the solvent is water. Pharmaceutically acceptable solvates in accordance with the invention include solvates (hydrates) wherein the solvent of crystallization may be isotopically substituted, e.g. D_2O, d_6-acetone, d_6-DMSO.

The compounds of the invention which are complexes, such as clathrates and drug-host inclusion complexes are within the scope of the invention. In contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionized, partially ionized, or non-ionized. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Haleblian (August 1975).

The compounds of the invention include all compounds of the invention, polymorphs and isomers thereof, including optical, geometric and tautomeric isomers as hereinafter defined and isotopically-labeled compounds.

The compounds of the invention containing one or more asymmetric carbon atoms may exist as two or more stereoisomers. Where a compound contains an alkenyl or alkenylene group, geometric cis/trans (or Z/E) isomers are possible. Where the compound contains, for example, a keto or oxime group or an aromatic moiety, tautomeric isomerism ('tautomerism') can occur. It follows that a single compound may exhibit more than one type of isomerism.

All stereoisomers, geometric isomers and tautomeric forms of the compounds of the invention are included within the scope of the invention, including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counterion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine.

Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallization.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of the invention contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% isopropanol, typically from 2 to 20%, and from 0 to 5% of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

Mixtures of stereoisomers may be separated by conventional techniques known to those skilled in the art [see, for example, "Stereochemistry of Organic Compounds" by E.L. Eliel (Wiley, New York, 1994)].

The invention includes all pharmaceutically acceptable isotopically-labeled compounds of the invention, wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

Certain isotopically-labelled compounds of the invention, for example those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, i.e., ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations, using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

As used herein, the expressions "reaction-inert solvent" and "inert solvent" refers to a solvent which does not interact with starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

The parenthetical negative or positive sign used herein in the nomenclature denotes the direction plane polarized light is rotated by the particular stereoisomer.

One of ordinary skill will recognize that certain compounds of the invention may contain one or more atoms which may be in a particular stereochemical or geometric configuration, giving rise to stereoisomers and configurational isomers. All such isomers and mixtures thereof are included in the invention. Solvates (hydrates) of the compounds of the invention are also included.

Other features and advantages will be apparent from the specification and claims which describe the invention.

Detailed Description of the Invention

In general, the compounds of the invention may be prepared by processes known in the chemical arts, particularly in light of the description contained herein. Certain processes for the manufacture of the compounds of the invention are provided as further features of the invention and are illustrated in the reaction schemes provided below and in the experimental section. The use of various protecting groups in these reactions are also well known and are exemplified in Protective Groups In Organic Synthesis, Second Edition, T.W. Greene and P.G.M. Wuts, John Wiley and Sons, Inc. 1991, pages 227-229, which is hereby incorporated by reference in its entirety for all purposes.

The utility of the compounds of the invention as medical agents for the reduction of intraocular pressure and accordingly to treat glaucoma is demonstrated by the activity of the compounds in conventional assays, including the in vivo assay and a receptor binding assay. Such assays also provide a means whereby the activities of the compounds can be compared to each other and with the activities of other known compounds. The results of these comparisons are useful for determining dosage levels in mammals, including humans, for the treatment of such diseases.

The compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

The compounds of the invention intended for pharmaceutical use may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in 'Remington's Pharmaceutical Sciences', 19th Edition (Mack Publishing Company, 1995).]

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid formulations, such as tablets, capsules containing particulates, liquids, or powders; lozenges (including liquid-filled), chews; multi- and nano-particulates; gels, solid solution, liposome, films (including muco-adhesive), ovules, sprays and liquid formulations.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986 by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from 1 wt% to 80 wt% of the dosage form, more typically from 5 wt% to 60 wt% of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 wt% to 25 wt%, preferably from 5 wt% to 20 wt% of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 wt% to 5 wt% of the tablet, and glidants may comprise from 0.2 wt% to 1 wt% of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 wt% to 10 wt%, preferably from 0.5 wt% to 3 wt% of the tablet.

Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 wt% to about 90 wt% binder, from about 0 wt% to about 85 wt% diluent, from about 2 wt% to about 10 wt% disintegrant, and from about 0.25 wt% to about 10 wt% lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tabletting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated. The formulation of tablets is discussed in "Pharmaceutical Dosage Forms: Tablets, Vol. 1", by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., N.Y., 1980 (ISBN 0-8247-6918-X).

The foregoing formulations for the various types of administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Verma et al, Pharmaceutical Technology On-line, 25(2), 1-14 (2001). The use of chewing gum to achieve controlled release is described in WO00/35298.

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of the invention used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Thus, compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and PGLA [define] microspheres.

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated [see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999).]

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (e.g. Powderject™, Bioject™, etc.) injection.

The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurized container, pump, spray, atomizer (preferably an atomizer using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurized container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenization, or spray drying.

Capsules (made, for example, from gelatin or HPMC), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as l-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomizer using electrohydrodynamics to produce a fine mist may contain from 1 µg to 20 mg of the compound of the invention per actuation and the actuation volume may vary from 1 µl to 100 µl. A typical formulation may comprise a compound of the invention, propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavors, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, poly(DL-lactic-coglycolic acid (PGLA). Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

The compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (e.g. absorbable gel sponges, collagen) and non-biodegradable (e.g. silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid; a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose; or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

The compounds of the invention can be incorporated into various types of ophthalmic formulations for delivery to the eye. These compounds may be combined with ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride and water to form an aqueous, sterile ophthalmic suspensions or solutions. In order to prepare sterile ophthalmic ointment formulations, the active ingredient is combined with a preservative in an appropriate vehicle, such as, mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations may be prepared by suspending the active ingredient in a hydrophilic base prepared from the combination of, for example, carbopol-940 or the like according to the published formulations for analogous ophthalmic preparations; preservatives and tonicity agents can be incorporated. Ophthalmic solution formulations may be prepared by dissolving the active ingredient in a physiologically acceptable isotonic aqueous buffer. Further, the ophthalmic solution may include an ophthalmologically acceptable surfactant to assist in dissolving the active ingredient. Furthermore, the ophthalmic solution may contain a thickener such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methyl-cellulose, polyvinylpyrrolidone, or the like to improve the retention of the medicament in the conjunctival sac.

The compounds of the invention are preferably formulated as topical ophthalmic suspensions or solutions, with a pH of about 4.5 to 7.8. The compounds will normally be contained in these formulations in an amount of 01% to 10% by weight, but preferably in an amount of 0.25% to 5.0% by weight. Thus, for topical presentation 1 to 3 drops of these formulations would be delivered to the surface of the eye 1 to 4 times a day according to the routine discretion of a skilled clinician.

The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, i.e. as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

Dosage ranges are based on an average human subject having a weight of about 65 kg to 70 kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly. Depending on the disease and condition of the patient, the term "treatment" as used herein may include one or more of curative, palliative and prophylactic treatment.

The ability of the compounds of the invention to reduce intraocular pressure may be measured using the assay described below.

The following non-limiting preparations and Examples illustrate the preparation of the compounds of the invention.

Examples

In the examples described below, unless otherwise indicated, all temperatures are set forth in degrees Celsius and all parts and percentages are by weight. Reagents may be purchased from commercial suppliers, such as Sigma-Aldrich Chemical Company, Acros Organics, or Lancaster Synthesis Ltd. and may be used without further purification unless otherwise indicated. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2 or DCM), N, N-dimethylacetamide (DMA), acetonitrile (MeCN), and *N,N*-dimethylformamide (DMF) may be purchased from Aldrich in Sure-Seal bottles and used as received. All solvents may be purified using standard methods known to those skilled in the art, unless otherwise indicated. Diethyl ether is abbreviated as Et_2O. Ethyl acetate is abbreviated as EtOAc. Trifluoroacetic acid is abbreviated as TFA. Acetic acid is abbreviated as HOAc or AcOH. Similarly, acetyl chloride is abbreviated as AcCl. Coupling reagent *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetra-methyluronium hexafluorophosphate is abbreviated as HATU. Trifluoromethanesulfonate, or triflate, is abbreviated as "OTf." t-Butyldimethylsilyl is abbreviated as TBS. *tert*-Butoxycarbonyl is abbreviated as BOC. N,N-Di-isopropyl-N-ethylamine is abbreviated as *i*-Pr_2NEt. 4-(N,N-Dimethylamino)pyridine is abbreviated as DMAP.

The reactions set forth below were done generally under a positive pressure of argon or nitrogen or with a drying tube, at ambient temperature (unless otherwise stated), in anhydrous solvents, and the reaction flasks were fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried. Analytical thin layer chromatography (TLC) was performed using glass-backed silica gel 60 F 254 pre-coated plates (Merck Art 5719) and eluted with appropriate solvent ratios (v/v). Reactions were assayed by TLC or LCMS and terminated as judged by the consumption of starting material. Visualization of the TLC plates was done with UV light (254 nm wavelength) or with an appropriate TLC visualizing solvent and activated with heat. Analytical HPLC performed with Waters or Agilent instruments. Flash column chromatography (Still et al., *J. Org. Chem.*, **1978**, *43*, 2923) was performed using silica gel 60 (Merck Art 9385) or various MPLC systems, such as Biotage or ISCO purification system. Preparative HPLC routinely performed on Prep LC 4000 system from Water with Ultra 120 10 mm C8 column from Peeke Scientific for single compounds; combinational, solution-based samples described in detail herein. Microwave chemistry was carried out using an EmrysTM Optimizer EXP from Personal Chemistry, Inc. (now Biotage).

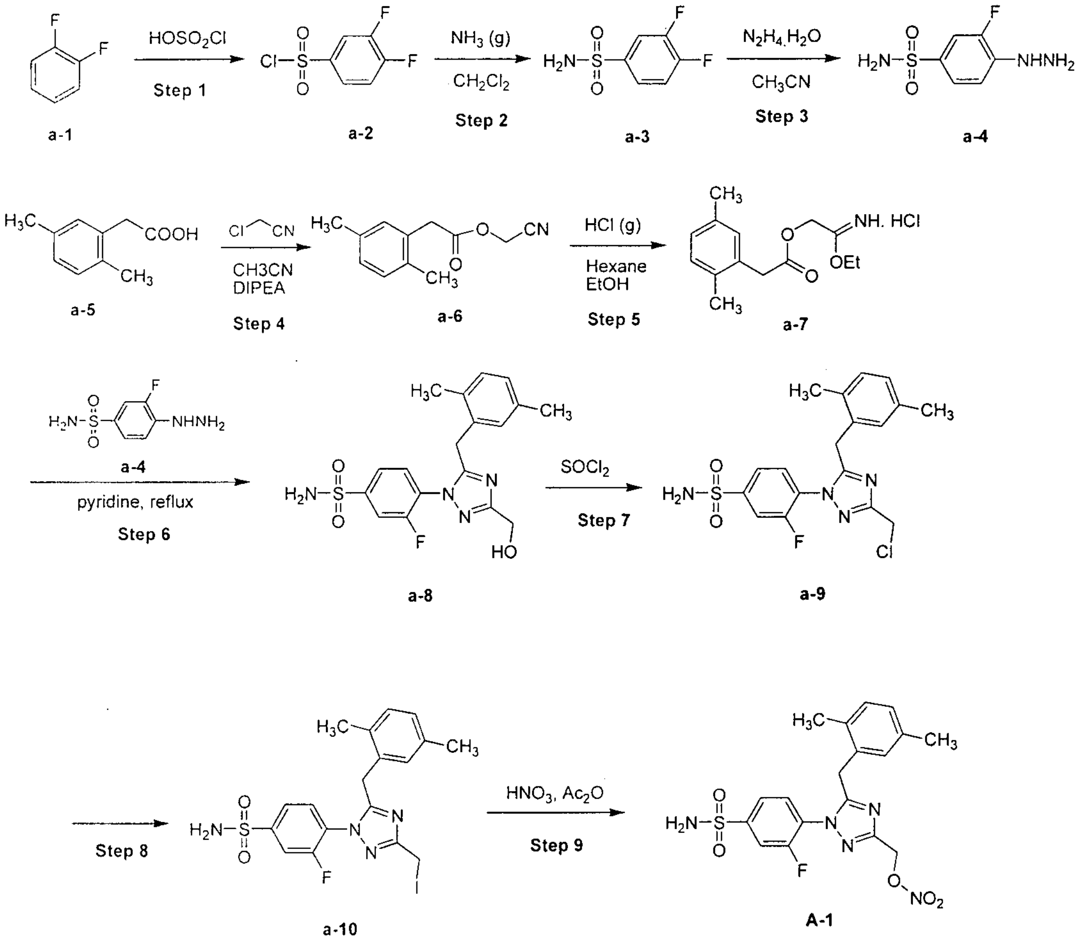
The compound structures in the examples below were confirmed by one or more of the following methods: proton magnetic resonance spectroscopy, mass spectroscopy, and elemental microanalysis. Proton magnetic resonance (^{1}H NMR) spectra were determined using a Bruker spectrometer operating at field strength of 300 or 400 megahertz (MHz). Chemical shifts are reported in parts per million (ppm, δ) downfield from an internal tetramethylsilane standard. Alternatively, ^{1}H NMR spectra were referenced relative to signals from residual protons in deuterated solvents as follows: $CDCl_3$ = 7.25 ppm; DMSO-d_6 = 2.49 ppm; CD_3CN = 1.94 ppm, CD_3OD or methanol-d_4 = 3.30 ppm; C_6D_6 = 7.16 ppm. Peak multiplicities are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; dt, doublet of triplets; q, quartet; br, broadened; m, multiplet. Coupling constants are given in Hertz (Hz). Mass spectra (MS) data were obtained using Agilent LC mass spectrometer with APCI or ESI ionization. High resolution MS (HRMS) were performed on an Agilent G3250AA LCMSD/TOF mass spectrometer. Elemental microanalyses were performed by Atlantic

Microlab Inc. and gave results for the elements stated within ±0.4% of the theoretical values.

Preferred compounds in accordance with the invention may be prepared in manners analogous to those specifically described below.

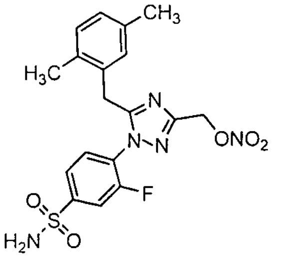
The examples and preparations provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations. The skilled artisan will recognize that different acids, amines, alkyl halides, aryl halides, coupling reagents, and heterocycles may be substituted in the following descriptions to suit the preparations of a desired embodiment. The following methods may be scaled upwards or downwards to suit the amount of desired material.

Scheme A

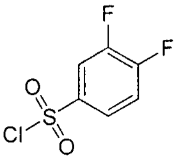


Example A-1

[1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl Nitrate (A-1)

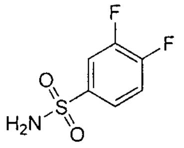


Step 1: 3, 4-Difluorobenzenesulfonyl Chloride (a-2)



Chlorosulfonic acid (600 mL, 8.5 mol) was added slowly to 1,2-difluorobenzene (200 g, 1.76 mol) while maintaining the temperature below 0°C. After the addition, the reaction mixture was stirred until gas evolution ceased. Then the reaction mixture was stirred at 110°C for about 30 hours. TLC (Petroleum ether: EtOAc = 5:1) showed that the reaction was complete. Then the reaction mixture was poured into ice with rapid stirring. The resulting mixture was extracted with CH_2Cl_2 (500 mL×3). The organic phase was washed with sat. aq. $NaHCO_3$ and sat. aq. NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuum to give compound (200 g, 52%) as a brown liquid, which was used in the next step without further purification.

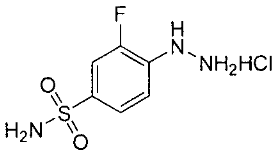
Step 2: 3, 4-Difluorobenzenesulfonamide (a-3)



Through a solution of crude sulfonyl chloride a-2 (200 g, 0.92 mol) in anhydrous CH_2Cl_2 (1.5 L) at –30°C was bubbled NH_3 (g). 10 min later, white syrup was formed. 30 min later, TLC (EtOAc: Petroleum ether = 1:2) showed that the reaction was complete. The mixture was evaporated in vacuum to give crude compound, which was purified via column chromatography (EtOAc: Petroleum ether = 1:5~1:2~1:0) to give pure compound **a-3** (170 g, ~92.8%) as a white solid, which was used in next step without further purification.

^1H NMR (400 MHz, DMSO): δ 7.82 (t, 1H), 7.67 (m, 2H), 7.52 (s, 1H).

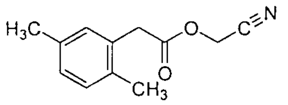
Step 3: 3-Fluoro-4-hydrazinylbenzenesulfonamide Hydrochloride (a-4)



To a solution of compound **a-3** (200 g, 1.04 mol) in CH_3CN (3 L) was added dropwise hydrazine hydrate (85%, 200 mL, 5.3 mol). After the addition, the reaction mixture was heated at reflux (70°C) overnight. TLC (CH_2Cl_2: MeOH = 10:1) showed that the reaction was complete. CH_3CN was evaporated on vacuum. H_2O (1.5 L) was added with rapidly stirring and a suspension was formed. The precipitate was filtered to give crude product. The crude product was recrystallized from MeOH. Then the product was poured into a solution of EtOH (500 mL) and saturated with HCl (g) at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was evaporated in vacuum and the crude product was recrystallized from MeOH to give pure hydrazine hydrochloride **a-4** (110 g, 48.7%) as a light yellow solid that matched that described in literature (Pal, M. et al *J. Med. Chem.* **2003**, *46*, 3975-3984).

^{1}H NMR (400 MHz, DMSO): δ 10.58 (s, 3H), 8.87 (s, 1H), 7.57 (s, 1H), 7.55 (d, 1H), 7.34 (s, 2H), 7.24 (t, 1H).

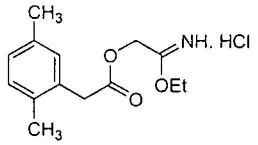
Step 4: Cyanomethyl 2-(2,5-Dimethylphenyl)acetate (a-6)



Chloroacetonitrile (0.58 mL, 9.3 mmol) was added to a solution of 2-(2,5-dimethylphenyl)acetic acid (1.5 g, 9.3 mmol) and di-isopropyl-ethyl-amine (DIPEA; 1.8 mL, 10 mmol) in acetonitrile (9.3 mL). The reaction was heated to 80°C for 1 hour then concentrated by rotary evaporation. The residue was suspended in ethyl acetate and washed sequentially with water, aqueous sodium bicarbonate and brine. The ethyl acetate layer was dried with magnesium sulfate, filtered and concentrated by rotary evaporation to yield cyanomethyl 2-(2,5-dimethylphenyl)acetate (a-6; 1.83 g, 97%).

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.25 (s, 3 H), 2.30 (s, 3 H), 3.68 (s, 2 H), 4.71 (s, 2 H), 6.99 (s, 1 H), 7.00 - 7.03 (m, 1 H), 7.04 -7.10 (m, 1 H)
LCMS $(M+H)^+$: 220.1.

Step 5: 2-Ethoxy-2-iminoethyl 2-(2,5-dimethylphenyl)acetate Hydrochloride (a-7)

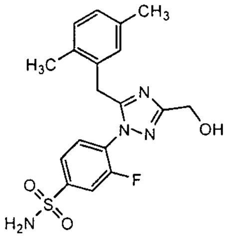


HCl gas was bubbled into a 0°C mixture of cyanomethyl 2-(2,5-dimethylphenyl)acetate (a-6; 1.83 g, 9.0 mmol), ethanol (0.58 mL, 9.9 mmol) and diethylether (1.8 mL) for 3 minutes. After 15 minutes more diethylether (6 mL) was added. After an additional 20 minutes the cooling bath was removed and the reaction was allowed to warm to room temperature. The reaction was filtered to afford 2-ethoxy-2-iminoethyl 2-(2,5-dimethylphenyl)acetate hydrochloride (a-7; 2.29 g), which was used without further purification.

^{1}H NMR (400 MHz, DMSO-*d*6) δppm 1.30 (t, *J*=6.95 Hz, 3 H), 2.19 (s, 3 H), 2.25 (s, 3 H), 3.82 (s, 2 H), 4.43 (q, *J*=6.91 Hz, 2 H), 4.98 (s, 2 H), 7.00 (d, *J*=7.83 Hz, 1 H), 7.03 (s, 1 H), 7.04 - 7.09 (m, 1 H)

LCMS $(M+H)^+$: 220.1.

Step 6: 4-[5-2, 4-Dimethylbenzyl-3-(hydroxymethyl)-1*H*-1,2,4-triazol-1-yl]-3-fluorobenzenesulfonamide (a-8)

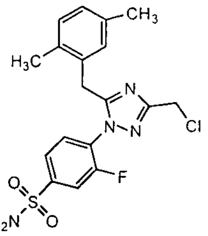


To a 1 L round bottom was added crude 2-ethoxy-2-iminoethyl 2-(2,5-dimethylphenyl)acetate hydrochloride (a-7; 28.0 g, ~73.5 mmol), 3-fluoro-4-hydrazinylbenzenesulfonamide hydrochloride (a-4; 17.8 g, 73.5 mmol), pyridine (400 mL) and 4Å, 8-12 mesh molecular sieves (13.2 g). A nitrogen inlet was added and the mixture was evacuated and filled with nitrogen three times. The mixture was heated to 70°C for one hour than heated to 80°C overnight. The reaction was concentrated by rotary evaporation and the residue was partitioned between ethyl acetate and water. The aqueous layer was adjusted to pH 1 with 1M HCl. The layers were separated and the ethyl acetate layer was washed with brine then dried with magnesium sulfate, filtered and concentrated by rotary evaporation. The crude material was suspended in 30 mL of boiling ethanol and left standing overnight. The suspension was diluted with 30 mL of ether:ethanol (9:1), filtered and washed with ether:ethanol (9:1) to give 4-(5-(2,5-dimethylbenzyl)-3-(hydroxymethyl)-1H-1,2,4-triazol-1-yl)-3-fluorobenzenesulfonamide (a-8; 18.2 g).

^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 2.03 (s, 3 H), 2.12 (s, 3 H), 4.01 (s, 2 H), 4.44 (d, *J*=6.32 Hz, 2 H), 5.39 (t, *J*=6.06 Hz, 1 H), 6.63 (s, 1 H), 6.86 - 6.91 (m, 1 H), 6.93 - 7.00 (m, 1 H), 7.70 (s, 2 H), 7.76 - 7.82 (m, 2 H), 7.82 - 7.87 (m, 1 H)

LCMS $(M+H)^+$: 391.1.

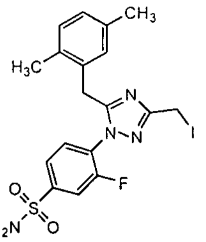
Step 7: 4-[3-(Chloromethyl)-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-1-yl]-3-fluorobenzenesulfonamide (a-9)



A mixture of 4-[5-(2,5-dimethylbenzyl)-3-(hydroxymethyl)-1*H*-1,2,4-triazol-1-yl]-3-fluoro-benzene-sulfonamide (1.0 g, 2.6 mmol) in thionyl chloride (30 mL, 240 mmol) was stirred at room temperature for 2 hours then concentrated to dryness. The residue was treated with toluene (25 mL) and concentrated to dryness. The residue was placed under high vacuum for 2 hours to remove any residual thionyl chloride to give the title compound (1.1 g, 99 %) as a light brown oil, which was used in the next step without further purification.

LCMS $(M+H)^+$: 409.2.

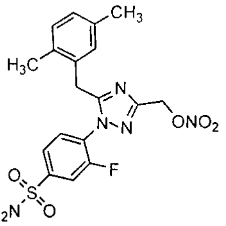
Step 8: 4-[5-(2,5-dimethylbenzyl)-3-(iodomethyl)-1*H*-1,2,4-triazol-1-yl]-3-fluorobenzenesulfonamide (a-10)



To a mixture of 4-[3-(chloromethyl)-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-1-yl]-3-fluoro-benzene-sulfonamide (a-9; 1.1 g, 2.6 mmol) in tetrahydrofuran (30 mL) was added sodium iodide (1.9 g, 13 mmol). The mixture was stirred at room temperature for 1 hour. Solids were filtered off and the filtrate concentrated to dryness. The residue was dissolved in EtOAc (75 mL), washed with 10 % aqueous $Na_2S_2O_3$, water, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give the title compound (1.29 g, 99 %) as a light brown oil, which was used in the next step without further purification.

LCMS $(M+H)^+$: 501.0.

Step 9: [1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl Nitrate (A-1)

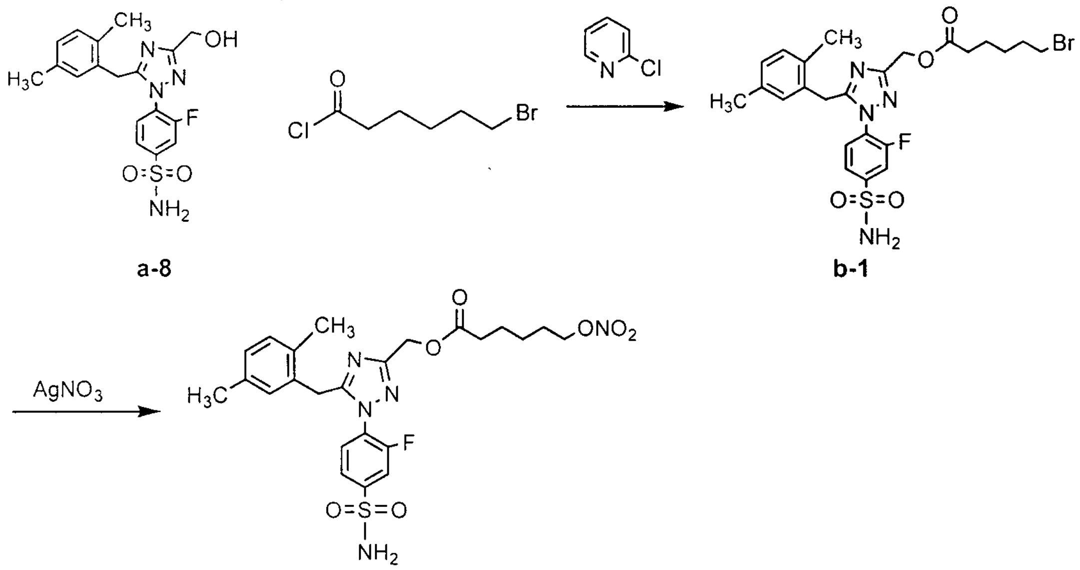


To a mixture of 4-[5-(2,5-dimethyl-benzyl)-3-(iodomethyl)-1*H*-1,2,4-triazol-1-yl]-3-fluoro-benzene-sulfonamide (a-10; 0.81 g, 1.6 mmol) in acetonitrile (19 mL) and *N*,*N*-dimethylformamide (19 mL) was added silver nitrate (1.2 g, 7.3 mmol). The mixture was stirred at 80°C for 4 hours. After cooling to ambient temperature, brine was added (20 mL), the mixture sonicated, solids filtered and washed with acetonitrile, and filtrate concentrated to dryness. The residue was purified by chromatography with silica gel and elution with a gradient of ethyl acetate/hexanes (12-100 %) to give the title compound (0.59 g, 83 %) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ 2.03 (s, 3 H), 2.13 (s, 3 H), 4.07–4.14 (m, 2 H), 5.69–5.74 (m, 2 H), 6.64 (m, 1 H), 6.88–7.02 (m, 2 H), 7.70–7.91 (m, 5 H).

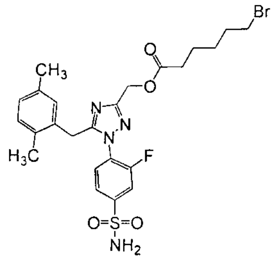
LCMS $(M+H)^+$: 436.2.

Scheme B



B-1

[1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1H-1,2,4-triazol-3-yl]methyl 6-Bromo-hexanoate (b-1)

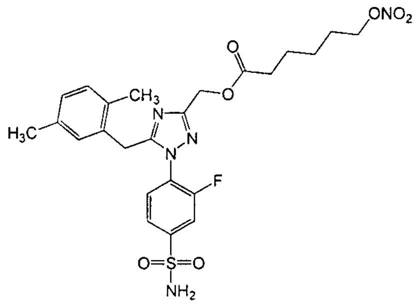


To alcohol **a-8** (250 mg, 0.640 mmol) in dichloromethane (5 mL) was added sequentially DMA (1 mL) and 2-chloropyridine (70 uL, 0.75 mmol), then cooled to 0°C. 6-Bromohexanoyl chloride (86 uL; 0.56 mmol) was added portionwise and the cooling bath was removed. TLC with 20% EtOAc/CH_2Cl_2 showed little reaction after 4 hours, and more 6-bromohexanoyl chloride (20 uL) added. After stirring overnight, the LC/MS shows ~ 20% product. Cooled to 0 C and added more chloropyridine (89 uL) and more 6-bromohexanoyl chloride (80 uL). Let stir for 30 minutes at 0°C and allowed to warm to ambient temperature. After 30 minutes, LC/MS monitored, cooled to 0°C and added chloropyridine (189 uL) and acid chloride (180 uL). After 3.5 hours LC/MS indicated completion. Diluted with more dichloromethane and washed with water. Concentrated and chromatography with 10-50% EtOAc/dichloromethane eluent gave 210 mg of clear oil (~58%), which was used without further purification.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ 1.50 (m, 2 H), 1.60 b(s, 3 H), 1.65 - 1.77 (m, 2 H), 1.83 - 1.92 (m, 2 H), 2.06 (s, 3 H), 2.16 (s, 3 H), 2.44 (t, *J*=7.5 Hz, 2 H), 3.39 (t, *J*=6.8 Hz, 2 H), 4.08 (s, 2 H), 5.03 (s, 2 H), 5.23 (s, 2 H), 6.60 (s, 1 H), 6.88-6.96 (m, 2 H), 7.40 m, 1 H), 7.71-7.77 (m, 2 H).

LC/MS APCI m/z 567

[1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl 6-(Nitro-oxy)-hexanoate (B-1)



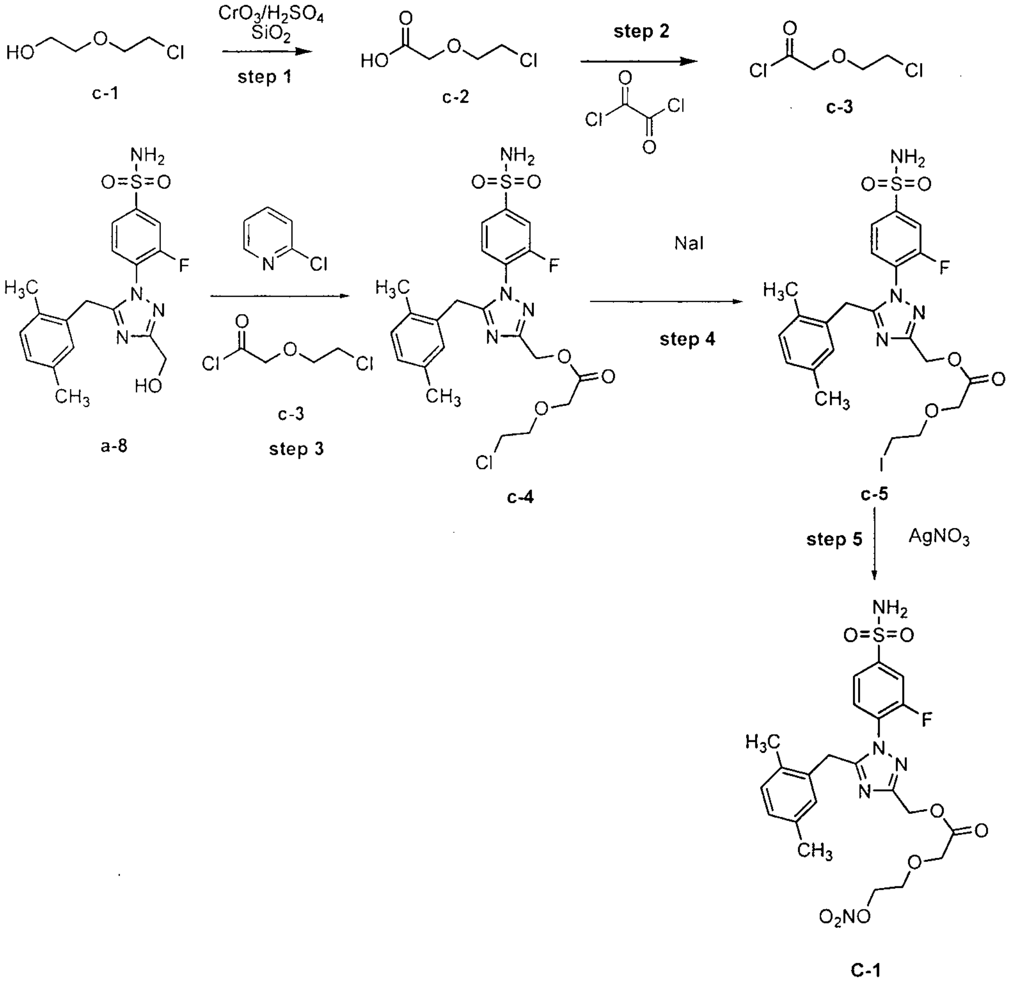
To 4-(5-(2,5-dimethylbenzyl)-3-(hexanoylbromideoxymethyl)-1H-1,2,4-triazol-1-yl)-3-fluoro-benzene-sulfonamide (b-1; 210 mg; 0.370 mmol) in acetonitrile (2 mL) in a reaction vessel covered in foil was added silver nitrate (250 mg, 1.47 mmol). After 5 hours at ambient temperature, the mixture was diluted with CH_2Cl_2 and washed with water and brine. Concentration followed by trituration with diethyl ether gave 210 mg of a white solid in quantitative yield.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ 1.42-1.53 (m, 2 H), 1.67-1.78 (m, 4 H), 2.05 (s, 3 H), 2.16 (s, 3 H), 2.44 (t, *J*=7.3 Hz, 2 H), 4.07 (s, 2 H), 4.42 (t, *J*=6.6 Hz, 2 H), 5.10 (s, 2 H), 5.23 (s, 2 H), 6.60 (s, 1 H), 6.88-6.96 (m, 2 H), 7.35-7.41 (m, 1 H), 7.70-7.77 (m, 2 H).

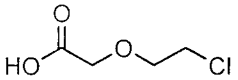
LC/MS APCI m/z 550

Other examples **B-2, B-3** were prepared in similar fashion to **B-1** and their respective analytical data is furnished in Table 1.

Scheme C



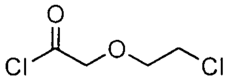
Step 1: 2-(2-Chloroethoxy)acetic Acid (c-2)



To concentrated H_2SO_4 (6 mL) was added CrO_3 (4 g, 40.1 mmol). To this mixture ice water (15 mL), was added dropwise. Once all the material was dissolved, the solution was added dropwise to 5 g of silica gel while stirring. To the adsorbed Jones's reagent, 50 mL of DCM were added and the mixture was cooled to 0 °C. A solution of the alcohol (1.00 g, 8.03 mmol), was added dropwise and stirred for 30 min. The reaction was filtered and the silica cake was washed with DCM (100 mL). The solvent was removed and the residue was fractioned between ether (3 x 20 mL), and 10 % aqueous K_2CO_3 (3 x 50 mL). The organic layer was discarded and the aqueous layer was taken to pH=1 with aqueous 3 N HCl. The aqueous layer was saturated with Na_2SO_4 and extracted with MeCN. The organic layer was concentrated and the residue dissolved in 50 mL of DCM. The solution was dried over Na_2SO_4 and concentrated to give 0.8 g of a colorless oil, which was used without further purification.

^{1}H NMR (400 MHz, DMSO-d_6): δ 3.73 (s, 4 H), 4.07 (s, 2 H), 12.72 (br s., 1 H).

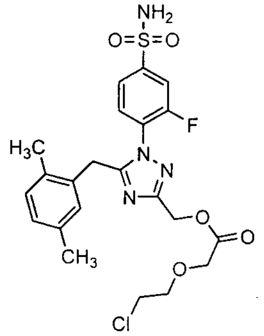
Step 2: 2-(2-Chloroethoxy)acetyl Chloride (c-3)



To the acid, oxalyl chloride (50 mL), was added. The reaction was stirred at room temperature for 8 h. The solids were filtered and washed with DCM. The volatiles were removed and to give the product (560 mg), as a light yellow oil, which was used without further purification.

^{1}H NMR (400 MHz, CHLOROFORM-d), δ ppm 3.67 (t, J=5.5 Hz, 2 H), 3.88 (t, J=5.7 Hz, 2 H), 4.52 (s, 2 H).

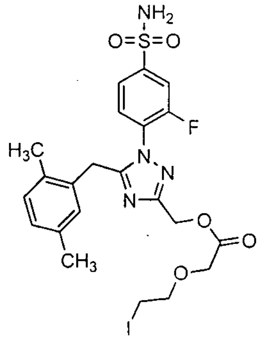
Step 3: [1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1H-1,2,4-triazol-3-yl]methyl (2-Chloroethoxy)acetate (c-4)



Similar to step 1 of Scheme B; the esterification to **b-1**. To a solution of the alcohol **a-8** (350 mg, 0.896 mmol), in CH_2Cl_2 (20 mL)/DMA (2 mL), and 2-chloropyridine, (0.505 mL, 5.38 mmol); a solution of the acid chloride **c-3** (560 mg, 3.56 mmol), in DCM (20 mL), was added at 0°C. The solution was stirred at room temperature for 4 h. The volatiles were removed and the product was purified by column chromatography to give the product as a light yellow oil. (350 mg, 85 %), which was used without further purification. LC-MS (M+1), = 511 AMU.

^{1}H NMR (400 MHz, MeOD), δ ppm 2.02 (s, 3 H), 2.12 (s, 3 H), 3.28-3.33 (m, 2 H), 3.68 (t, J=8.0 Hz, 2 H), 3.81 (t, J=8 Hz, 2 H), 4.13 (s, 2 H), 5.26 (s, 2 H), 6.57 (s, 1 H), 6.90 (s, 2 H), 7.59 (s, 1 H), 7.76 (s, 2 H).

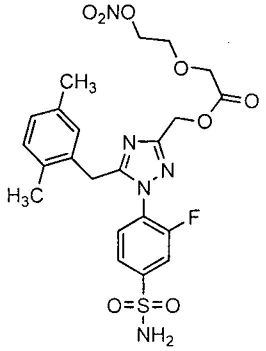
Step 4: [1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1H-1,2,4-triazol-3-yl]methyl (2-Iodoethoxy)acetate (c-5)



To a solution of the chloride (350 mg, 0.631 mmol), in acetone (50 mL), NaI was added (1g, 6.67 mmol). The mixture was sonicated until all the salts dissolved and heated to 65 °C for 8 h. The volatiles were removed and the residue was fractioned between water and DCM (3 x 50 mL). The organics were dried over Na_2SO_4 and evaporated to dryness to give the product as a light yellow solid, which was used without further purification. LC-MS (M+1), = 603 AMU

^{1}H NMR (400 MHz, MeOD), δ ppm 2.03 (s, 3 H), 2.12 (s, 3 H), 3.79 (t, *J*=6.67 Hz, 2 H), 3.84-3.88 (m, 2 H), 4.08 (s, 2 H), 4.11 (s, 2 H), 4.44 (s, 2 H), 6.57 (s, 1 H), 6.84-6.91 (m, 1 H), 6.90-6.98 (m, 1 H), 7.63 (m, 1 H), 7.77 (s, 2 H).

Step 5: [1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl [2-(Nitrooxy)ethoxy]acetate (C-1)

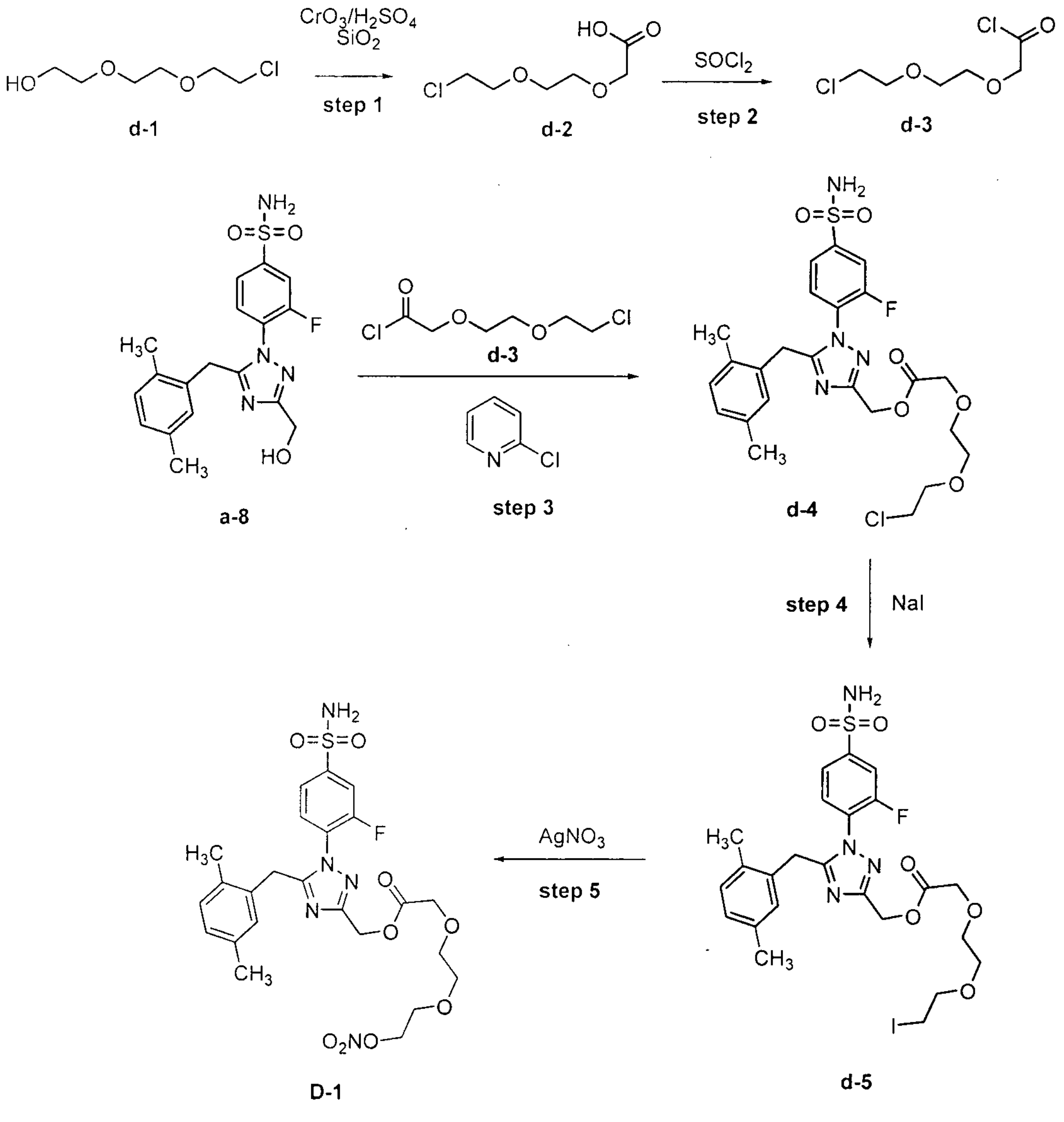


To a solution of the iodide (380 mg, 0.631 mmol), in MeCN (50 mL), was added $AgNO_3$ (430 mg, 2.52 mmol). The solution was stirred at room temperature for 8 h. The volatiles were removed and the residue was fractioned between water and EtOAc (3 x 50 mL). The organic layer was dried over Na_2SO_4 and evaporated. The residue was dissolved in MeCN/water 1:1 (10 mL), and freeze-dried to give the product as a white solid (325 mg, 95 %).

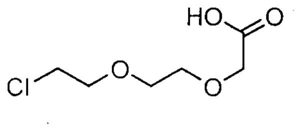
Exact mass: Calculated for $C_{22}H_{24}FN_5O_8S$:538.14 (M+1); Measured= 538.13998.

^{1}H NMR (400 MHz, DMSO-*d*$_6$), δ ppm 2.03 (s, 3 H), 2.11 (s, 3 H), 3.76-3.85 (m, 2 H), 4.05 (s, 2 H), 4.25 (s, 2 H), 4.54-4.75 (m, 2 H), 5.18 (s, 2 H), 6.61 (s, 1 H), 6.83-6.93 (m, 1 H), 6.92-7.02 (m, 1 H), 7.70 (s, 2 H), 7.82 (m, 3 H).

Scheme D



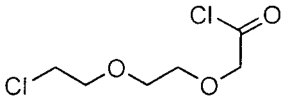
Step 1: 2-(2-(2-Chloroethoxy)ethoxy)acetic Acid (d-2)



CrO_3 (5.3 g, 40.1 mmol) was dissolved in 8 mL of H_2SO_4, and added to 25 mL of ice water dropwise. Once all the material was dissolved, the solution was added dropwise to 5 g of silica gel while stirring. To the adsorbed Jones's reagent, 50 mL of DCM was added and the mixture was cooled to 0°C. A solution of alcohol **a-8** (3g, 17.79 mmol) was added dropwise (the orange mixture turned dark-green), and stirred for 30 min. The reaction was filtered and the silica cake was washed with DCM (100 mL). The solvent was removed and the residue was fractioned between ether (3 x 20 mL), and 10 % aqueous K_2CO_3 (3 x 50 mL). The organic layer was discarded and the aqueous layer was taken to pH=1 with aqueous 3 N HCl. The aqueous layer was saturated with Na_2SO_4 and extracted with MeCN. The organic layer was concentrated and the residue dissolved in 50 mL of DCM. The solution was dried over Na_2SO_4 and concentrated to give 0.8 g of a colorless oil, which was used without further purification.

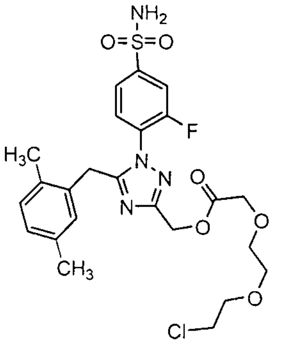
^{1}H NMR (400 MHz, DMSO-d_6), δ ppm 3.43-3.50 (m, 4 H), 3.72 (t, J=5.54 Hz, 2 H), 4.06-4.11 (m, 2 H), 4.18 (t, J=4 Hz, 2 H).

Step 2: 2-(2-(2-Chloroethoxy)ethoxy)acetyl Chloride (d-3)



Thionyl chloride (5 mL), was added to the acid and the reaction was stirred at room temperature for 2 h. The solids were filtered and washed with DCM. The volatiles were removed to give the product as light yellow oil (560 mg), which was used for the next step as obtained.

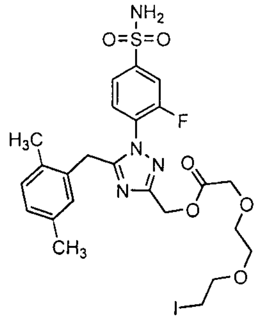
Step 3: [1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl [2-(2-Chloroethoxy)ethoxy]acetate (d-4)



Similar to step 1 of Scheme B esterification to **b-1**. To a solution of the alcohol (350 mg, 0.896 mmol), in CH_2Cl_2 (20 mL)/DMA (2 mL), and 2-chloropyridine, (0.505 mL, 5.38 mmol); a solution of the acid chloride, (560 mg, 2.79 mmol), in DCM (20 mL), was added at 0°C. The solution was stirred at room temperature for 4 h. The volatiles were removed and the product was purified by column chromatography to give the product as a light yellow oil (350 mg, 85 %), that was used without further purification.

LC-MS (M+1), = 556 AMU.

Step 4: [1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl [2-(2-Iodoethoxy)ethoxy]acetate (d-5)

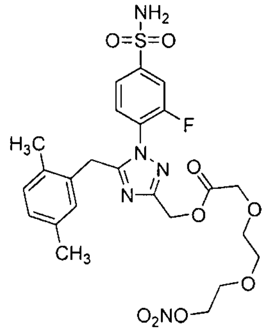


To a solution of the chloride (350 mg, 0.631 mmol), in acetone (50 mL) was added NaI (1.00 g, 6.67 mmol). The mixture was sonicated until all the salts dissolved and heated to 65 °C for 8 h. The volatiles were removed and the residue was fractioned between water and DCM (3 x 50 mL). The organics were dried over Na_2SO_4 and evaporated to dryness to give 230 mg of a light yellow oil, which was used without further purification.

LC-MS (M+1), = 647 AMU.

^1H NMR (400 MHz, MeOD), δ ppm 2.02 (s, 3 H), 2.12 (s, 3 H), 3.18-3.29 (m, 2 H), 3.66 (s, 2 H), 3.69-3.78 (m, 4 H), 4.13 (s, 2 H), 4.28 (s, 2 H), 5.27 (s, 2 H), 6.56 (s, 1 H), 6.82-6.89 (m, 1 H), 6.89-6.96 (m, 1 H), 7.51-7.60 (m, 1 H), 7.71-7.84 (m, 2 H).

Step 5: [1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl {2-[2-(Nitrooxy)ethoxy]ethoxy}acetate (D-1)



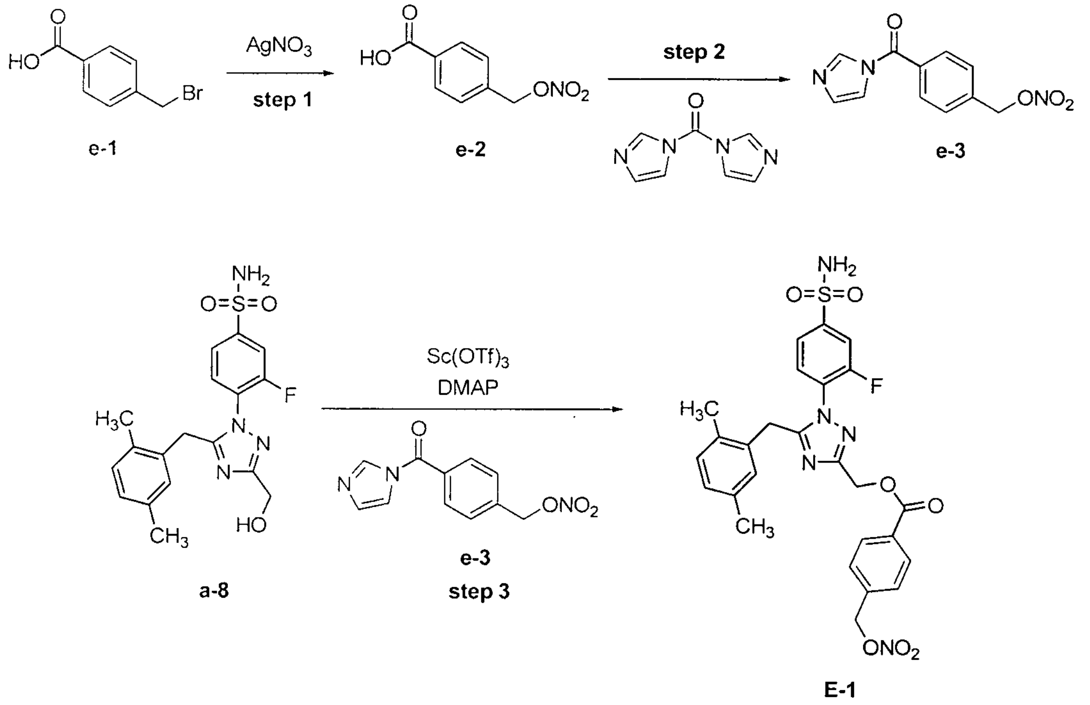
To a solution of the iodide (230 mg, 0.356 mmol), in MeCN (20 mL), $AgNO_3$ (242 mg, 1.42 mmol), was added and the solution was heated to 60°C for 1 h. Another 4 equivalents of $AgNO_3$ were added and heated for another hour. The volatiles were removed and the residue was fractioned between water and ethyl acetate (3 x 20 mL). The organic layer was dried over Na_2SO_4 and evaporated to dryness to give 130 mg of the product as colorless oil.

LC-MS (M+1)= 582.1 (100 %).

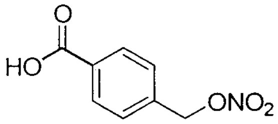
HRMS calculated for $C_{24}H_{28}FN_5O_9S$: 581.15918, Found (M+1), = 582.16694.

^1H NMR (400 MHz, DMSO-d_6), δ ppm 2.02 (s, 3 H), 2.11 (s, 3 H), 3.58 (m, 4 H), 3.71 (m, 2 H), 4.06 (s, 2 H), 4.17 (s, 2 H), 4.57-4.69 (m, 2 H), 5.18 (s, 2 H), 6.61 (s, 1 H), 6.89 (m, 1 H), 6.93-7.00 (m, 1 H), 7.71 (s, 2 H), 7.82 (m, 3 H).

Scheme E



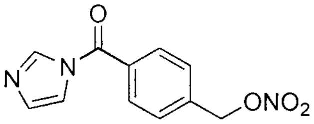
Step 1: 4-[(Nitrooxy)methyl]benzoic Acid (e-2)



To a slurry of 4-(bromomethyl)benzoic acid (500 mg, 2.33 mmol) in acetonitrile (10 mL) was added silver(I) nitrate (474 mg, 2.79 mmol) in one portion. The suspension was allowed to stir at 23°C for 12 h. The slurry was then vacuum filtered through a pad of Celite and concentrated *in vacuo* to provide the title compound as a white solid (361 mg, 79%), which was used without further purification.

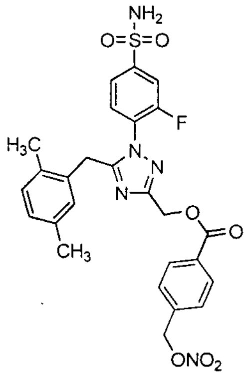
^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 13.09 (br s, 1 H) 7.98 (d, J=8.3 Hz, 2 H) 7.57 (d, J=7.9 Hz, 2 H) 5.65 (s, 2 H)

Step 2: 4-(1*H*-Imidazol-1-ylcarbonyl)benzyl Nitrate (e-3)



To a solution of 4-[(nitrooxy)methyl]benzoic acid (**e-2**; 210 mg, 1.07 mmol) in dichloromethane (10 mL) under nitrogen was added 1,1-carbonyldiimidazole (173 mg, 1.07 mmol) in one portion. The flask was purged with nitrogen and allowed to stir at 23 °C for 30 min. This solution was used as is for the following step.

Step 3: [1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1H-1,2,4-triazol-3-yl]methyl 4-[(nitrooxy)methyl] Benzoate (E-1)

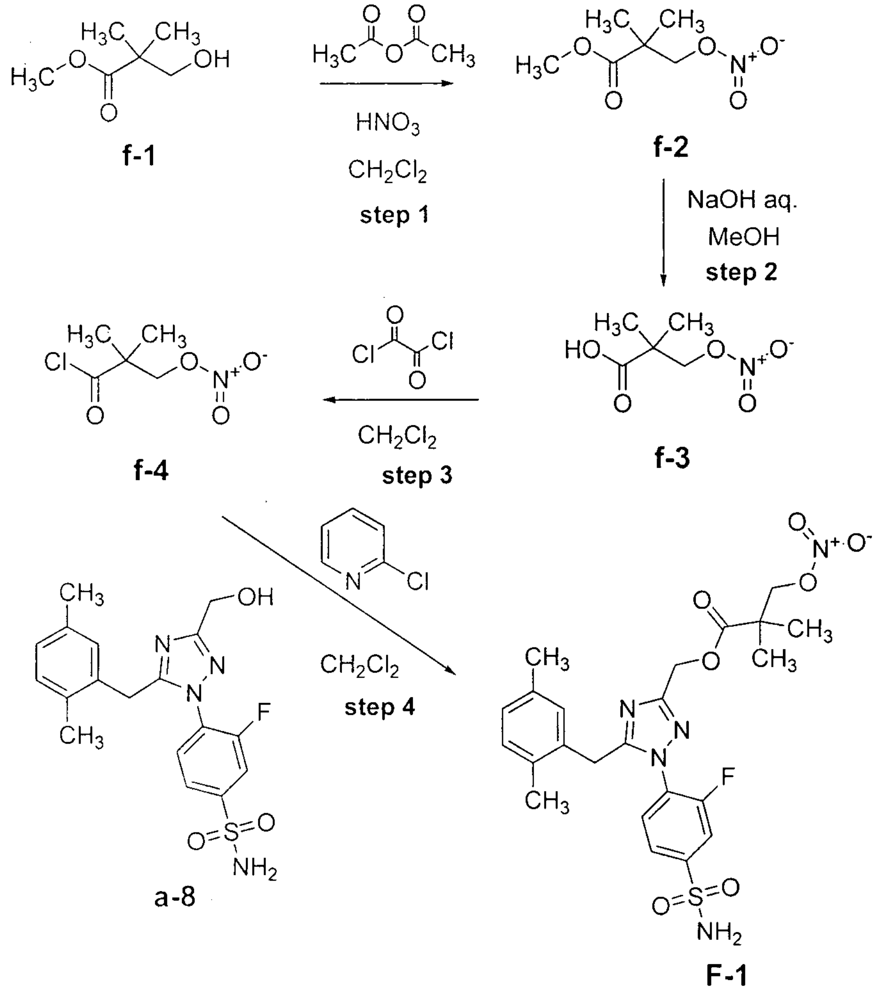


Using a method described by Greenwald, R.B.; et al; *J. Org. Chem.* **1998**, *63*, 7559-7562; to a solution of the alcohol (**a-8**; 208 mg, 0.533 mmol) in dichloromethane (10 mL) and N,N-dimethyl-acetamide (1 mL) was added N,N-dimethylaminopyridine (13 mg, 0.11 mmol) and scandium(III) triflate (26 mg, 0.053 mmol) sequentially. The flask was purged with nitrogen and the solution was cooled to 0°C in an ice bath. After 10 min a solution of 4-(1*H*-imidazol-1ylcarbonyl)benzyl nitrate (**e-3**) (10 mL, 1.07 mmol) was added in one portion. The solution was then allowed to warm to 23°C and stirred for 48 h. The solution was then diluted with dichloromethane (25 mL) and sequentially washed with aqueous sodium bisulfate (1N, 20 mL), deionized water (20 mL), and brine (20 mL). The organic layer was then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude solid was then purified by preparative reverse phase high performance liquid chromatography (40-90% MeCN/H_2O, 0.1% AcOH). The eluant was lyophilized to dryness to provide the title compound as a white solid (154 mg, 50%).

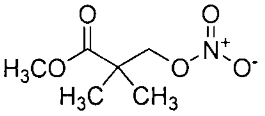
^1H NMR (300 MHz, DMSO-d_6) δ 8.03 (s, 1 H), 8.00 (s, 1 H), 7.74 - 7.90 (m, 3 H), 7.69 (br s, 2 H), 7.64 (s, 1 H), 7.61 (s, 1 H), 6.96 (d, J=7.6 Hz, 1 H), 6.88 (d, J=7.8 Hz, 1 H), 6.59 (s, 1 H), 5.67 (s, 2 H), 5.41 (s, 2 H), 4.06 (s, 2 H), 2.09 (s, 3 H), 2.02 (s, 3 H).

LC-MS (ESI), [M - H] = 568.0

Scheme F-1



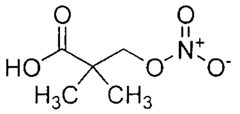
Step 1: Methyl 2,2-Dimethyl-3-(nitrooxy)propanoate (f-2)



To acetic anhydride (2.9 mL, 30.3 mmol), in methylene chloride at 0°C was added fuming nitric acid in 10 mL methylene chloride over 0.2 h, then stirred for 1h. Added methyl 3-hydroxy-2,2-dimethylpropanoate (2.5 g, 18.9 mmol), in 1 mL of methylene chloride over 0.1 h. After 1h, quenched with 20 g of ice then added 30 mL CH_2Cl_2 and partitioned with sat. $NaHCO_3$ (2 X 20 mL), and dried organic over Na_2SO_4. The organic layer was concentrated to afford product as a clear oil (2.54 g, 76%), which was used without further purification.

^{1}H NMR (400 MHz, CHLOROFORM-*d*), δ ppm 4.48 (s, 2 H), 3.71 (s, 3 H), 1.28 (s, 6 H).

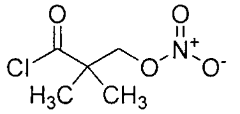
Step 2: 2,2-Dimethyl-3-(nitrooxy)propanoic Acid (f-3)



To methyl 2,2-dimethyl-3-(nitrooxy)propanoate (f-2; 1.3 g, 7.2 mmol), in methanol was added aq. sodium hydroxide solution (4.3 mL of 2N, 8.6 mmol). Allowed to stir for 2 hours, then concentrated to give white crystalline solid, which was dissolved in 20 mL methylene chloride and partitioned between aq. HCl (30 mL of 0.5 N). Separated organic layer dried over Na_2SO_4 then concentrated to afford product as a white solid (1.34 g, 80%), which was used without further purification.

^{1}H NMR (400 MHz, CHLOROFORM-*d*), δ ppm 4.53 (s, 2 H), 1.34 (s, 6 H).

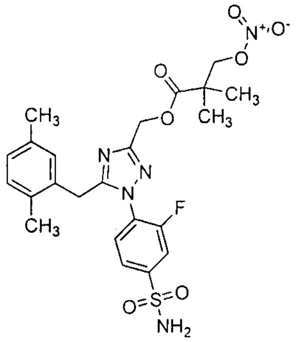
Step 3: 3-Chloro-2,2-dimethyl-3-oxopropyl Nitrate (f-4)



To nitrate ester f-3 (1.0 g, 6.1 mmol), in methylene chloride (10 mL), was added oxalyl chloride (0.82 mL, 9.2 mmol), and 0.05 mL of DMF. After 2 hours, concentrated under reduced pressure and the residue was azeotroped with toluene (2 X 4 mL), to afford product as a clear oil (0.56 g, 91%), which was used without further purification.

^{1}H NMR (400 MHz, CHLOROFORM-*d*), δ ppm; 4.58 (s, 2H), 1.43 (s, 6H).

Step 4: [1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1H-1,2,4-triazol-3-yl]methyl 2,2-Dimethyl-3-(nitrooxy)propanoate (F-1)



Prepared in a fashion similar to that of d-4, from 4-[5-2, 4-dimethylbenzyl-3-(hydroxymethyl)-1*H*-1,2,4-triazol-1-yl]-3-fluorobenzenesulfonamide (a-8; 1.10 g, 2.82 mmol), in DMA with 2-chloro pyridine and crude acid chloride f-4. Allowed to stir for 24 h at 60°C. Diluted with EtOAc (100 mL), and partitioned between HCl aq. (2 X 50 mL, 1N), $CuSO_4$ (2 x 25 mL, 10 % w/v), and $NaHCO_3$ (2 X 50 mL). The organic layer was dried over Na_2SO_4 and concentrated to give a clear oil. Purification with chromatography with silica gel eluting with EtOAc/Hexane (1:1). The residue was dissolved in EtOAc and added hexane to crystallize product as a white solid after drying under vacuum for 24 hours (1.43 g, 94%).

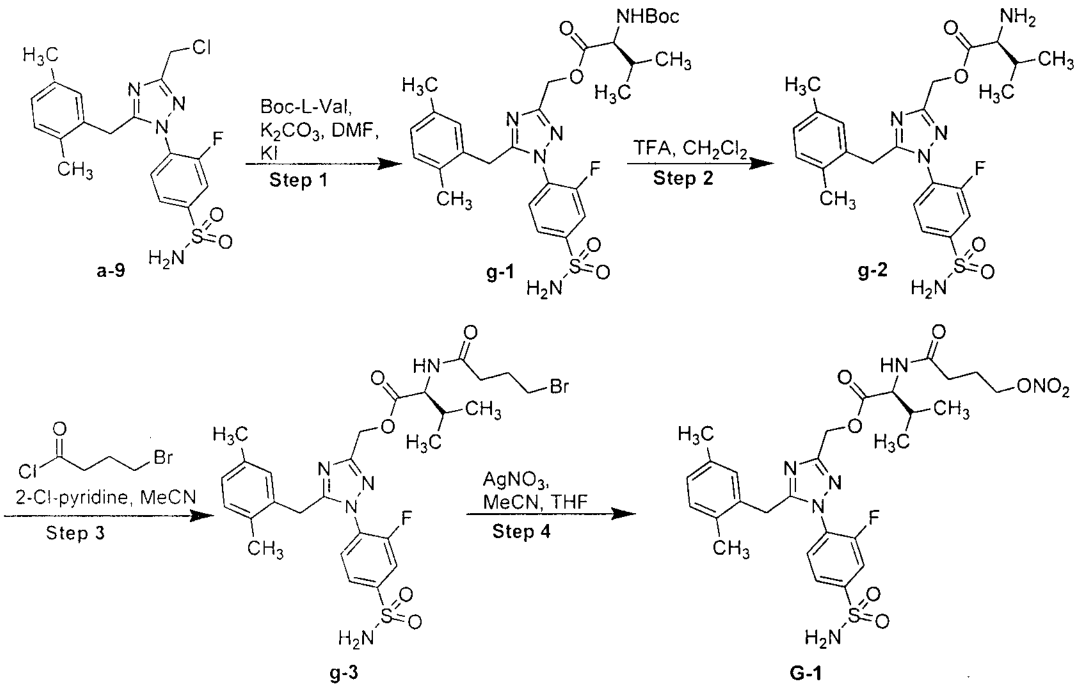
^1H NMR (400 MHz, CHLOROFORM-*d*), δ ppm; 7.74 (t, 2 H), 7.40 (t, *J*=7.8 Hz, 1 H), 6.85 - 6.98 (m, 2 H), 6.61 (s, 1 H), 5.27 (s, 2 H), 4.54 (s, 2 H), 4.04 (s, 2 H), 2.16 (s, 3 H), 2.04 (s, 3 H), 1.32 (s, 6 H).

LC/MS APCI m/z 433.1.

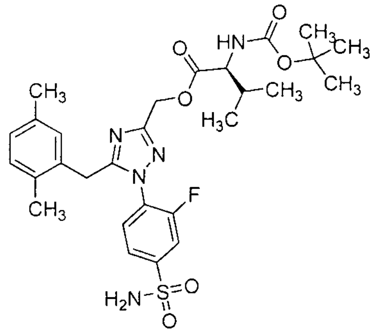
HRMS (ESI): Calcd for $C_{23}H_{27}FN_5O_7S$ *m/z*: 536.1615, Found: 536.3210.

Anal. Calcd for $C_{23}H_{26}FN_5O_7S{\bullet}0.7$ EtOAc: C, 51.89; H, 5.33; N, 11.73; Found: C, 51.91; H, 5.16; N, 11.61.

Scheme G



Step 1: [1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl *N*-(*tert*-butoxycarbonyl), L-Valinate (g-1)

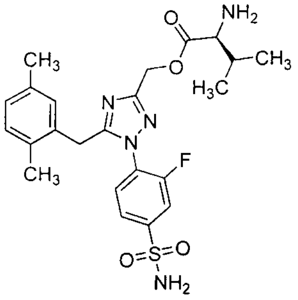


To a solution of 4-[3-(chloromethyl)-5-(2,5-dimethyl-benzyl)-1*H*-1,2,4-tria-zol-1-yl]-3-fluoro-benzene-sulfonamide (a-9; 400 mg, 0.987 mmol), in DMF (3 mL), was added sequentially BOC-L-valine (638 mg, 2.93 mmol), crushed K_2CO_3 (419 mg, 3.03 mmol), and KI (16 mg, 0.0978 mmol). The mixture stirred for 16 h, then heated to 60°C, and stirred for 2 h. The mixture was cooled to ambient temperature, diluted with EtOAc (50 mL), washed with H_2O (3 x 25 mL), and brine (25 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (25 - 60% EtOAc/hexanes), to give 1-[4-(aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl *N*-(*tert*-butoxycarbonyl)-L-valinate (437 mg, 74%), as a white solid, which was used without further purification.

^{1}H NMR (400 MHz, CHLOROFORM-*d*), δ ppm 7.71 - 7.79 (m, 2 H), 7.36 - 7.42 (m, 1 H), 6.95 (d, *J*=7.58 Hz, 1 H), 6.90 (d, *J*=7.58 Hz, 1 H), 6.60 (s, 1 H), 5.22 - 5.37 (m, 2 H), 5.07 (d, *J*=8.59 Hz, 1 H), 5.01 (s, 2 H), 4.34 (dd, *J*=8.84, 3.79 Hz, 1 H), 4.07 (s, 2 H), 2.17 - 2.28 (m, 1 H), 2.16 (s, 3 H), 2.05 (s, 3 H), 1.45 (s, 9 H), 0.97 (d, *J*=6.82 Hz, 3 H), 0.88 (d, *J*=6.82 Hz, 3 H).

LC/MS ESI m/z $(M+H)^+$ 590.2.

Step 2: [1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl L-Valinate (g-2)

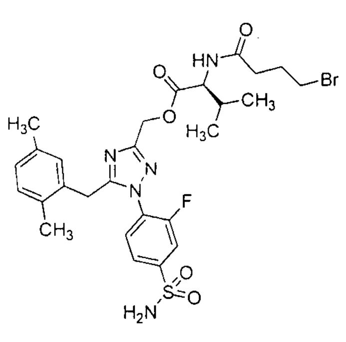


To a solution of the BOC-amine g-1 (437 mg, 0.741 mmol), in CH_2Cl_2 (2.5 mL), was added TFA (0.571 mL, 7.41 mmol). The reaction mixture was stirred for 4h, quenched with saturated aq. $NaHCO_3$ (50 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. [1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl L-valinate (237 mg, 65% yield), was obtained as a white foam and carried to the next step without purification.

^{1}H NMR (400 MHz, CHLOROFORM-*d*), δ ppm 7.70 - 7.80 (m, 2 H), 7.36 - 7.42 (m, 1 H), 6.95 (d, *J*=7.58 Hz, 1 H), 6.90 (d, *J*=7.83 Hz, 1 H), 6.60 (s, 1 H), 5.26 - 5.37 (m, 2 H), 4.99 (s, 2 H), 4.02 - 4.09 (m, 3 H), 2.24 - 2.37 (m, 1 H), 2.16 (s, 3 H), 2.05 (s, 3 H), 1.04 (d, *J*=6.82 Hz, 3 H), 0.90 (d, *J*=6.82 Hz, 3 H).

LC/MS ESI m/z $(M+H)^+$ 490.2.

Step 3: [1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl *N*-(4-bromobutanoyl), L-Valinate (g-3)



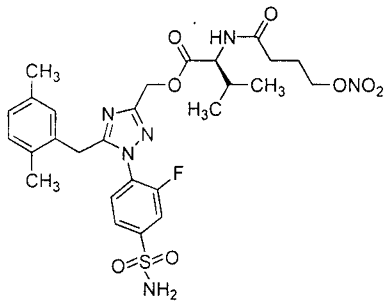
Amine g-2 (324 mg, 0.662 mmol), was dissolved in CH_3CN (3.3 mL), and 2-chloropyridine (0.188 mL, 1.99 mmol), and cooled to 0°C. 4-Bromobutyryl chloride (0.230 mL, 1.99 mmol), was added and allowed to warm to ambient temperature. After

3h, more 4-bromobutyryl chloride (0.080 mL), was added and stirred for another 1.5 h. The reaction mixture was diluted with EtOAc (50 mL), and washed with H_2O (2 x 30 mL), 1N HCl (30 mL), and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (35 – 80% EtOAc/hexanes), to obtain [1-[4-(aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl *N*-(4-bromobutanoyl)-L-valinate (286 mg, 68% yield), as a white solid, which was used without further purification.

^{1}H NMR (400 MHz, CHLOROFORM-*d*), δ ppm 7.72 - 7.79 (m, 2 H), 7.37 - 7.43 (m, 1 H), 6.94 - 6.97 (m, 1 H), 6.88 - 6.93 (m, 1 H), 6.61 (s, 1 H), 6.09 (d, *J*=8.6 Hz, 1 H), 5.23 - 5.36 (m, 2 H), 5.02 (s, 2 H), 4.69 (dd, *J*=8.8, 4.6 Hz, 1 H), 4.06 (s, 2 H), 3.41 - 3.54 (m, 2 H), 2.44 (t, *J*=6.8 Hz, 2 H), 2.17 - 2.30 (m, 3 H), 2.17 (s, 3 H), 2.05 (s, 3 H), 0.96 (d, *J*=7.1 Hz, 3 H), 0.91 (d, *J*=6.8 Hz, 3 H).

LC/MS ESI m/z $(M+H)^+$ 639.0.

Step 4: [1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl *N*-[4-(nitrooxy)butanoyl] L-Valinate (G-1)

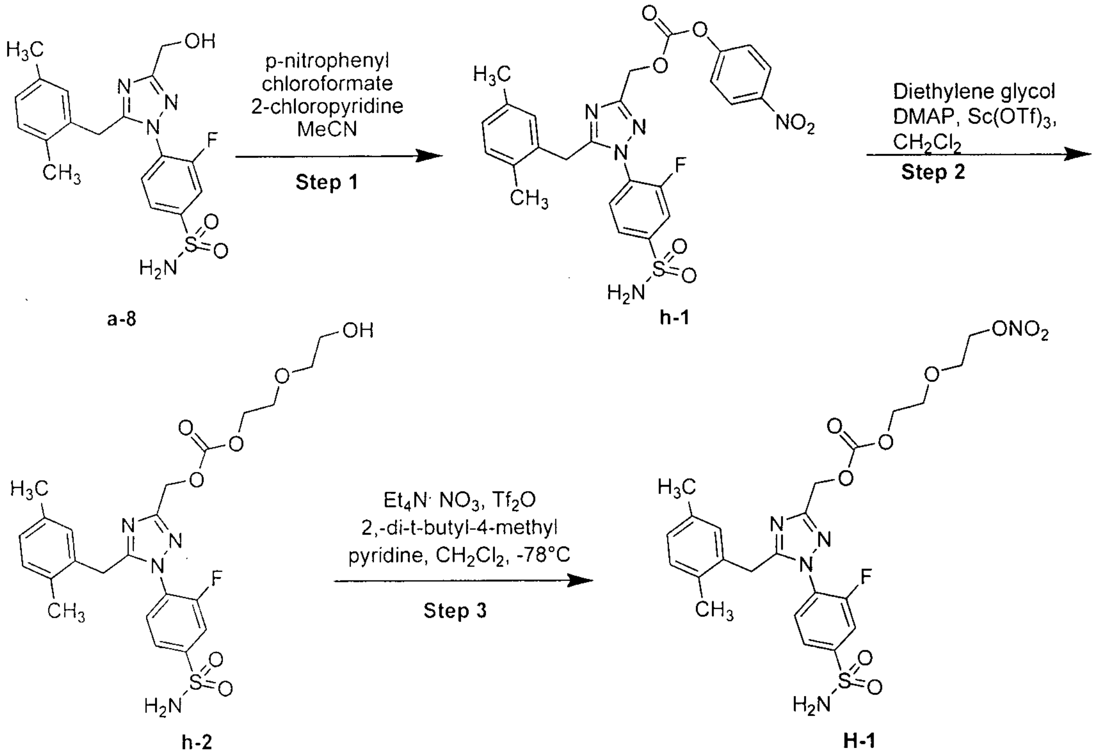


Silver nitrate (350 mg, 2.06 mmol), was added to a solution of bromide g-3 (350 mg, 0.688 mmol), in CH_3CN (5 mL), and THF (2 mL). The reaction mixture was heated at 60°C in the dark. After 1 h, the mixture was allowed to cool to ambient temperature, and then brine (1 mL), H_2O (1 mL), and CH_2Cl_2 (1 mL), were added. The precipitate was filtered off. The filtrate was diluted with H_2O (50 mL), and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The yellow residue was purified by column chromatography (45 - 75% EtOAc/hexanes), to obtain [1-[4-(aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl *N*-[4-(nitrooxy)butanoyl]-L-valinate (171 mg, 49% yield), as a white solid.

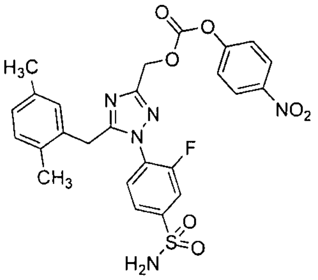
^{1}H NMR (400 MHz, CHLOROFORM-d), δ ppm 7.68 - 7.82 (m, 2 H), 7.40 (t, J=7.6 Hz, 1 H), 6.96 (d, J=7.8 Hz, 1 H), 6.91 (d, J=8.1 Hz, 1 H), 6.61 (s, 1 H), 6.10 (d, J=8.8 Hz, 1 H), 5.23 - 5.37 (m, 2 H), 5.02 (s, 2 H), 4.69 (dd, J=8.8, 4.80 Hz, 1 H), 4.52 (t, J=6.2 Hz, 2 H), 4.06 (s, 2 H), 2.38 (t, J=7.1 Hz, 2 H), 2.20 - 2.30 (m, 1 H), 2.17 (s, 3 H), 2.05 (s, 3 H), 2.04 - 2.14 (m, 2 H), 0.95 (d, J=6.8 Hz, 3 H), 0.90 (d, J=6.8 Hz, 3 H).

LC/MS ESI m/z $(M+H)^+$ 621.2.

Scheme H



Step 1: [1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl 4-nitrophenyl Carbonate (h-1)

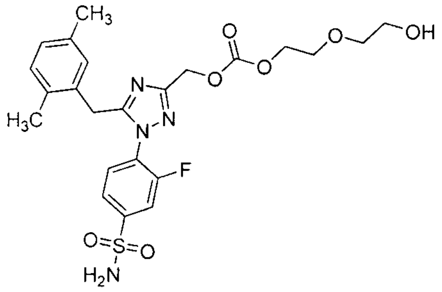


To a 0°C solution of the alcohol a-8 (500 mg, 1.28 mmol), in 2-chloropyridine (0.727 mL, 7.68 mmol), and CH_3CN (6 mL), was added 4-nitrophenyl chloroformate (1.29 mg, 6.40 mmol), and stirred for 1h. The mixture was allowed to warm to ambient temperature and stir for 2h. EtOAc (50 mL), was added to the mixture, washed with water (30 mL), 1N HCl (30 mL), and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (10 - 50% EtOAc/hexanes), to obtain [1-[4-(aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl 4-nitrophenyl carbonate (430 mg, 60%), as a clear oil, which was typically used without further purification.

^{1}H NMR (400 MHz, CHLOROFORM-*d*), δ ppm 8.27 - 8.31 (m, 2 H), 7.74 - 7.82 (m, 2 H), 7.39 - 7.45 (m, 3 H), 6.97 (d, *J*=7.6 Hz, 1 H), 6.92 (d, *J*=8.3 Hz, 1 H), 6.63 (s, 1 H), 5.43 (s, 2 H), 5.00 (s, 2 H), 4.09 (s, 2 H), 2.17 (s, 3 H), 2.07 (s, 3 H).

LC/MS ESI m/z $(M+H)^+$ 556.0.

Step 2: [1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1H-1,2,4-triazol-3-yl]methyl 2-(2-hydroxyethoxy)ethyl Carbonate (h-2)



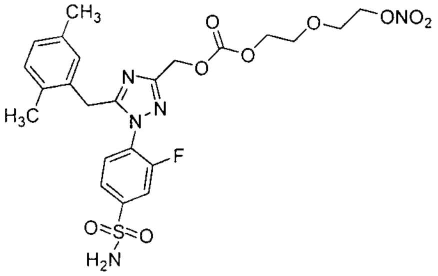
Similar to the preparation of Example E-1 and method cited therein; a solution of diethylene glycol (0.296 mL, 3.10 mmol), scandium (III) triflate (122 mg, 0.248 mmol), and DMAP (253 mg, 2.07 mmol), in CH_2Cl_2 (1.5 mL), was cooled to 0°C and stirred for 30 min. A suspension of the p-nitrophenyl carbonate h-1 (576 mg, 1.03 mmol), in CH_2Cl_2 (3 mL), was added to the reaction mixture and warmed to ambient temperature. After 4 h, the mixture was diluted with water (50 mL), and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with 0.1 N aq. HCl (50 mL), and brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (35-100% EtOAc/Hex), to obtain [1-[4-(aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl 2-(2-hydroxyethoxy)ethyl carbonate as a clear oil (206 mg, 38% yield), which was used without further purification.

^{1}H NMR (400 MHz, CHLOROFORM-*d*), δ ppm 7.69 - 7.78 (m, 2 H), 7.35 - 7.41 (m, 1 H), 6.94 (d, *J*=7.6 Hz, 1 H), 6.89 (d, *J*=7.6 Hz, 1 H), 6.60 (s, 1 H), 5.30 (s, 2 H), 5.17 (s, 2

H), 4.33 - 4.39 (m, 2 H), 4.07 (s, 2 H), 3.73 - 3.77 (m, 2 H), 3.69 - 3.73 (m, 2 H), 3.58 - 3.62 (m, 2 H), 2.16 (s, 3 H), 2.05 (s, 3 H).

LC/MS ESI m/z $(M+H)^+$ 523.0.

Step 3: [1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1H-1,2,4-triazol-3-yl]methyl 2-[2-(nitrooxy)ethoxy]ethyl Carbonate (H-1)



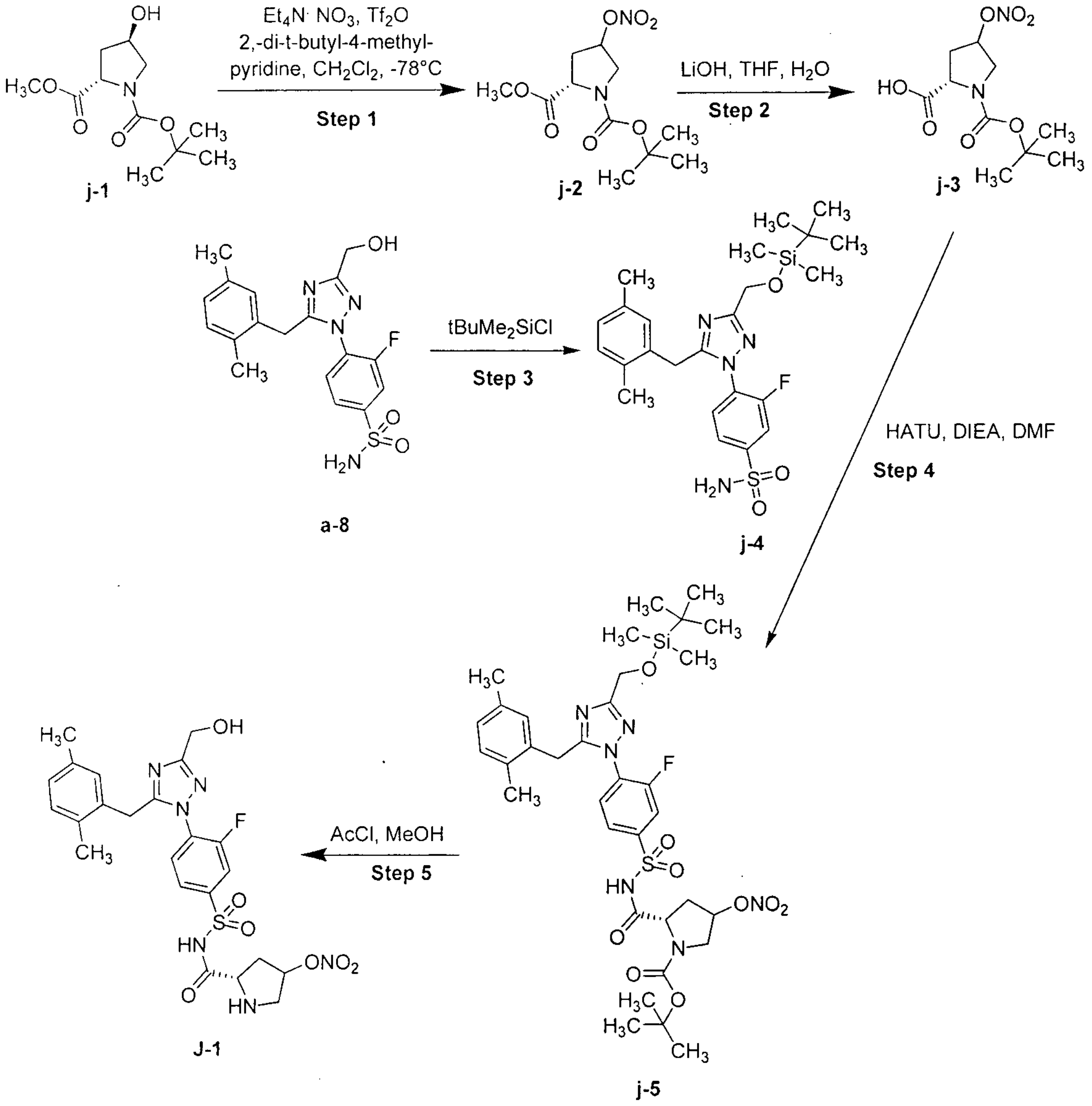
To a solution of the alcohol h-2 (206 mg, 0.380 mmol), in CH_2Cl_2 (2 ml), was added tetraethylammonium nitrate (205mg, 0.392 mmol), and 2,6-di-tert-butyl-4-methylpyridine (121 mg, 0.588 mmol). The reaction stirred at -78°C and a solution of trifluoromethanesulfonic anhydride (0.0693 ml, 0.412 mmol), in methylene chloride (0.5 mL), was slowly added. After 1h the temperature rose to ambient temperature and the mix was concentrated *in vacuo*. The residue was purified by flash chromatography (50% EtOAc/hexane), to obtain [1-[4-(aminosulfonyl)-2-fluoro-phenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl 2-[2-(nitrooxy)-ethoxy]-ethyl carbonate (170 mg, 76% yield), as a white foam.

^1H NMR (400 MHz, CHLOROFORM-*d*), δ ppm 7.70 - 7.78 (m, 2 H), 7.35 - 7.41 (m, 1 H), 6.95 (d, *J*=7.8 Hz, 1 H), 6.90 (d, *J*=7.6 Hz, 1 H), 6.60 (s, 1 H), 5.30 (s, 2 H), 4.99 (s, 2 H), 4.58 - 4.63 (m, 2 H), 4.32 - 4.37 (m, 2 H), 4.07 (s, 2 H), 3.76 - 3.80 (m, 2 H), 3.72 - 3.76 (m, 2 H), 2.16 (s, 3 H), 2.06 (s, 3 H).

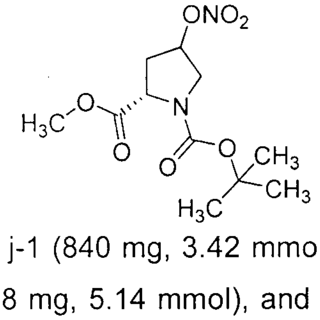
LC/MS ESI m/z $(M+H)^+$ 568.2.

Examples H-2, H-3 were prepared in a similar fashion to that of Example H-1, and their respective analytical and characterization data are provided in Table 1.

Scheme J



Step 1: 1-tert-Butyl 2-Methyl (2S)-4-(Nitrooxy)pyrrolidine-1,2-dicarboxylate (j-2)

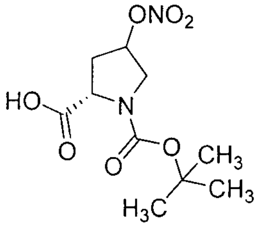


To a solution of proline alcohol j-1 (840 mg, 3.42 mmol), in CH_2Cl_2 (15 ml), was added tetraethylammonium nitrate (988 mg, 5.14 mmol), and 2,6-di-tert-butyl-4-methylpyridine (1.05 g, 5.14 mmol). Cooled to -78°C and a solution of trifluoromethanesulfonic anhydride (0.605 ml, 3.60 mmol), in CH_2Cl_2 (2 mL), was slowly added. After 2 h, the temperature rose to 25°C. The solution was treated with 5% aqueous NaH_2PO_4 (50 mL), and extracted with CH_2Cl_2 (3 x 75 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20-35% EtOAc/hexanes), to furnish 1-*tert*-butyl 2-methyl (2*S*)-4-(nitrooxy)pyrrolidine-1,2-dicarboxylate (535 mg, 54% yield), as a white foam.

^{1}H NMR (400 MHz, CHLOROFORM-*d*), δ ppm 5.48 (s, 1 H), 4.43 - 4.50 (m, 0.4 H), 4.38 (t, *J*=8.0 Hz, 0.6 H), 3.85 (d, *J*=3.3 Hz, 2 H), 3.77 (s, 3 H), 2.45 - 2.61 (m, 1 H), 2.28 - 2.41 (m, 1 H), 1.47 (s, 3 H), 1.43 (s, 6 H).

LC/MS ESI m/z $(M-C_4H_9)^+$ 235.2 and $(M-BOC)^+$ 191.2.

Step 2: 1-(*tert*-Butoxycarbonyl)-4-(nitrooxy)-L-proline (j-3)

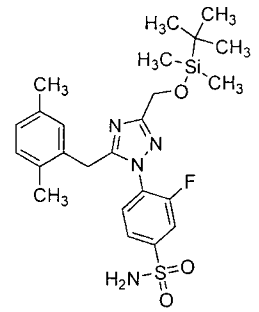


LiOH (225 mg, 5.36 mmol), and H_2O (3 mL), were added to a solution of the methyl ester (519 mg, 1.79 mmol), in THF (3 mL), and stirred for 2 h. The mixture was acidified to pH~4 using 1 N and 6 N aqueous HCl and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 1-(*tert*-butoxycarbonyl)-4-(nitrooxy)-L-proline (490 mg, 99%), that was carried forward to the next step without further purification.

^{1}H NMR (400 MHz, CHLOROFORM-*d*), δ ppm 5.48 (s, 1 H), 4.53 (t, *J*=7.7 Hz, 1 H), 4.42 (t, *J*=8.0 Hz, 1 H), 3.66 - 3.93 (m, 2 H), 2.34 - 2.81 (m, 2 H), 1.51 (s, 6 H), 1.45 (s, 3 H).

LC/MS ESI m/z $(M-C_4H_9)^+$ 221.2 and $(M-BOC)^+$ 177.2

Step 3: {[({4-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-5-(2,5-dimethylbenzyl)-1H-1,2,4-triazol-1-yl]-3-fluorophenyl}sulfonamide (j-4)

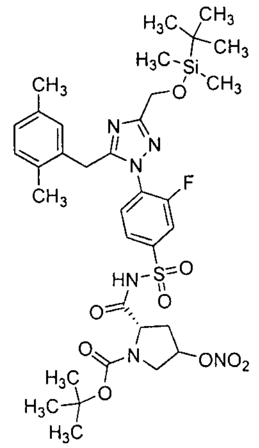


To a suspension of alcohol **a-8** (1.00g, 2.56 mmol) was added t-butyldimethylsilyl chloride (425 mg, 2.82 mmol), and imidazole (192 mg, 2.82 mmol). After 16 h, H_2O (75 mL) was added to the mixture and extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (75 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. 4-[3-({[*tert*-butyl-dimethyl)-silyl]oxy}-methyl)-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-1-yl]-3-fluorobenzenesulfonamide (1.30 g, 100%) was isolated as a yellow solid, which was typically used without further purification.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.68 - 7.76 (m, 2 H) 7.34 - 7.39 (m, 1 H) 6.92 - 6.95 (m, 1 H) 6.85 - 6.90 (m, 1 H) 6.60 (s, 1 H) 4.98 (s, 2 H) 4.83 (s, 2 H) 4.08 (s, 2 H) 2.15 (s, 3 H) 2.06 (s, 3 H) 0.93 (s, 9 H) 0.14 (s, 6 H).

LC/MS ESI m/z $(M+H)^+$ 505.2.

Step 4: tert-Butyl (2S)-2-{[({4-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-5-(2,5-dimethylbenzyl)-1H-1,2,4-triazol-1-yl]-3-fluorophenyl}sulfonyl)amino]carbonyl}-4-(nitrooxy)pyrrolidine-1-carboxylate (j-5)

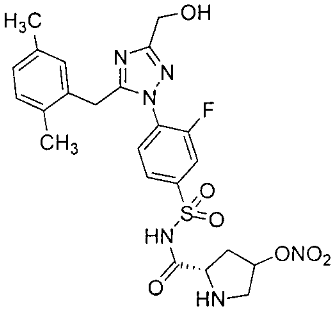


To a solution of the sulfonamide j-4 (300 mg, 0.594 mmol), and proline acid j-3 (164 mg, 0.594 mmol), in DMF (2 mL), was added *i*-Pr_2NEt (0.207 mL, 1.19 mmol), and HATU (271 mg, 0.713 mmol). After 3 h, EtOAc (50 mL), was added, then washed with H_2O (3 x 30 mL), and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (80 – 100 % EtOAc/hexanes), to obtain *tert*-butyl (2*S*)-2-{[({4-[3-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-1-yl]-3-fluorophenyl}sulfonyl)amino]carbonyl}-4-(nitrooxy)pyrrolidine-1-carboxylate (409 mg, 90% yield), which was used without further purification.

^1H NMR (400 MHz, CHLOROFORM-*d*), δ ppm 10.89 (s, 1 H), 7.78 - 7.94 (m, 2 H), 7.34 - 7.41 (m, 1 H), 6.93 (d, *J*=7.6 Hz, 1 H), 6.88 (d, *J*=8.3 Hz, 1 H), 6.60 (s, 1 H), 5.43 (s, 1 H), 4.82 (s, 2 H), 4.38 - 4.50 (m, 1 H), 4.07 (s, 2 H), 3.55 - 3.98 (m, 4 H), 2.14 (s, 3 H), 2.05 (s, 3 H), 1.63 (s, 9 H), 0.93 (s, 9 H), 0.13 (s, 6 H).

LC/MS ESI m/z $(M+H)^+$ 763.2

Step 5: *N*-({4-[5-(2,5-Dimethylbenzyl)-3-(hydroxymethyl)-1*H*-1,2,4-triazol-1-yl]-3-fluorophenyl}sulfonyl)-4-(nitrooxy)-L-prolinamide (J-1)

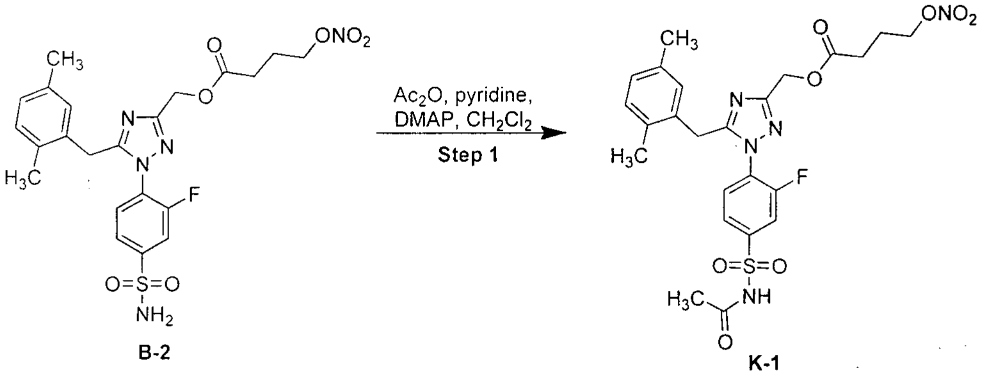


To a solution of the silyl-BOC protected substrate j-5 (405, 0.531 mmol), in MeOH (2 mL), was added dropwise acetyl chloride (0.226 mL, 3.19 mmol). After 18 h, the mixture was concentrated, and suspended in THF (4 mL). Triethylamine (0.11 mL), was added. After 2 h, presumed triethylammonium salt was filtered off and the filtrate was purified by column chromatography (7 - 10 % MeOH/CH_2Cl_2), to give a greenish white solid, which was suspended in CH_2Cl_2, filtered, and washed with CH_2Cl_2 to give *N*-({4-[5-(2,5-dimethylbenzyl)-3-(hydroxymethyl)-1*H*-1,2,4-triazol-1-yl]-3-fluorophenyl}sulfonyl)-4-(nitrooxy)-L-prolinamide (158 mg, 53%), as a white solid.

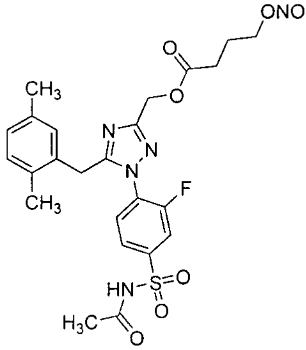
^1H NMR (400 MHz, DMSO-*d*$_6$), δ ppm 8.97 (s, 1 H), 7.71 - 7.81 (m, 2 H), 7.60 - 7.69 (m, *J*=7.7, 7.7 Hz, 1 H), 6.97 (d, *J*=7.6 Hz, 1 H), 6.89 (d, *J*=7.3 Hz, 1 H), 6.64 (s, 1 H), 5.61 (t, *J*=5.1 Hz, 1 H), 5.35 (t, *J*=6.2 Hz, 1 H), 4.43 (d, *J*=6.1 Hz, 2 H), 4.06 (dd, *J*=10.4, 7.8 Hz, 1 H), 3.97 (s, 2 H), 3.56 - 3.64 (m, 1 H), 3.45 (d, *J*=13.6 Hz, 1 H), 2.17 - 2.28 (m, 1 H), 2.13 (s, 3 H), 2.03 (s, 3 H).

LC/MS ESI m/z $(M+H)^+$ 549.1.

Scheme K



Step 1: [1-{4-[(Acetylamino)sulfonyl]-2-fluorophenyl}-5-(2,5-dimethylbenzyl)-1H-1,2,4-triazol-3-yl]methyl 4-(Nitrooxy)butanoate (K-1)



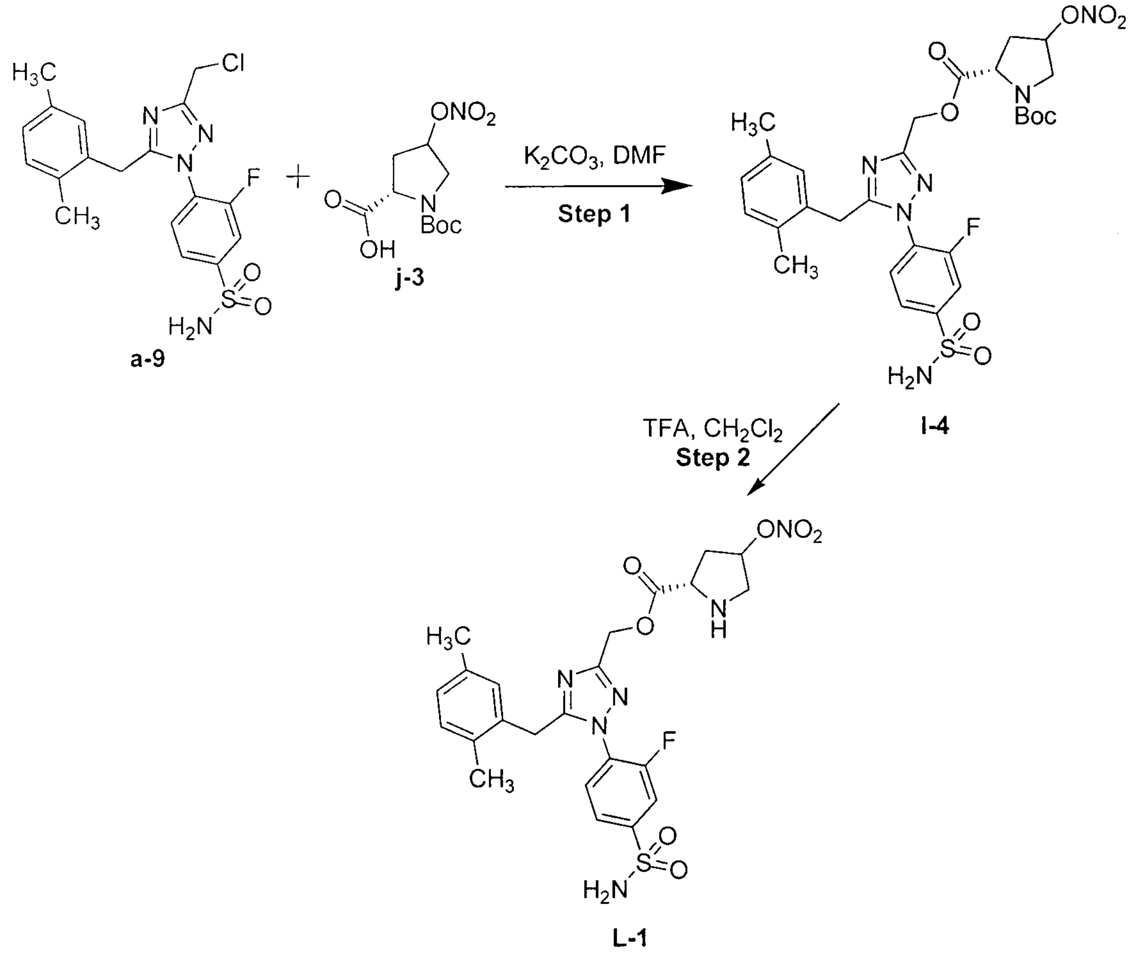
To a solution of sulfonamide **B-2** (260 mg, 0.499 mmol), in CH_2Cl_2 (2 ml), was added pyridine (0.202 mL, 2.49 mmol), acetic anhydride (0.141 mL, 1.50 mmol), and DMAP (6.09 mg, 0.050 mmol). After 3 h, the resultant suspension was diluted with EtOAc (20 mL), and washed with H_2O (10 mL), 1N HCl (10 mL), and brine (10 mL). The EtOAc layer was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (40 - 65% EtOAc/Hexanes), to provide [1-{4-[(acetylamino)sulfonyl]-2-fluorophenyl}-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl 4-(nitrooxy)butanoate (198 mg, 71% yield), as a white solid.

^{1}H NMR (400 MHz, CHLOROFORM-*d*), δ ppm 8.34 (s, 1 H), 7.92 (dd, *J*=8.7, 1.89 Hz, 1 H), 7.88 (d, *J*=8.3 Hz, 1 H), 7.41 (dd, *J*=8.3, 6.8 Hz, 1 H), 6.94 (d, *J*=7.6 Hz, 1 H), 6.90 (s, 1 H), 6.61 (s, 1 H), 5.26 (s, 2 H), 4.53 (t, *J*=6.3 Hz, 2 H), 4.08 (s, 2 H), 2.57 (t, *J*=7.1 Hz, 2 H), 2.16 (s, 3 H), 2.07 - 2.13 (m, 5 H), 2.05 (s, 3 H).

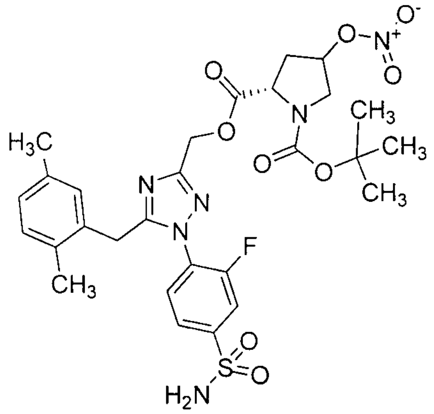
LC/MS ESI m/z $(M+H)^+$ 564.0.

Examples K-2, K3 were prepared in a similar manner to that of K-1 and their respective analytical and characterization data are provided in Table 1.

Scheme L



Step 1: 2-{[1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl} 1-*tert*-Butyl (2*S*)-4-(nitrooxy)pyrrolidine-1,2-dicarboxylate (l-4)

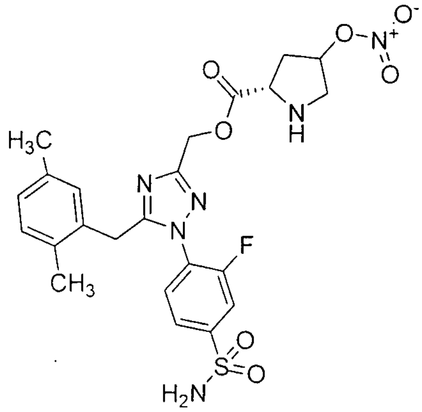


To a solution of the chloride **a-9** (300 mg, 0.734 mmol, 1.0 equiv), compound **j-3** (243 mg, 0.880 mmol, 1.20 equiv), crushed K_2CO_3 (314 mg, 2.27 mmol, 3.1 equiv), and KI (16 mg, 0.0978 mmol, 0.1 equiv) were added. The reaction mixture was heated up to

60°C and stirred for 4 h. After cooling to ambient temperature, EtOAc was added and washed with H_2O 3x, and brine, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by column chromatography (30% to 60% EtOAc/Hexanes) and obtained ester **I-4** (251 mg, 53% yield), which was used without further characterization.

LCMS $(M+H)^+$: 649.2.

Step 2: [1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl 4-(Nitrooxy)-L-prolinate (L-1)

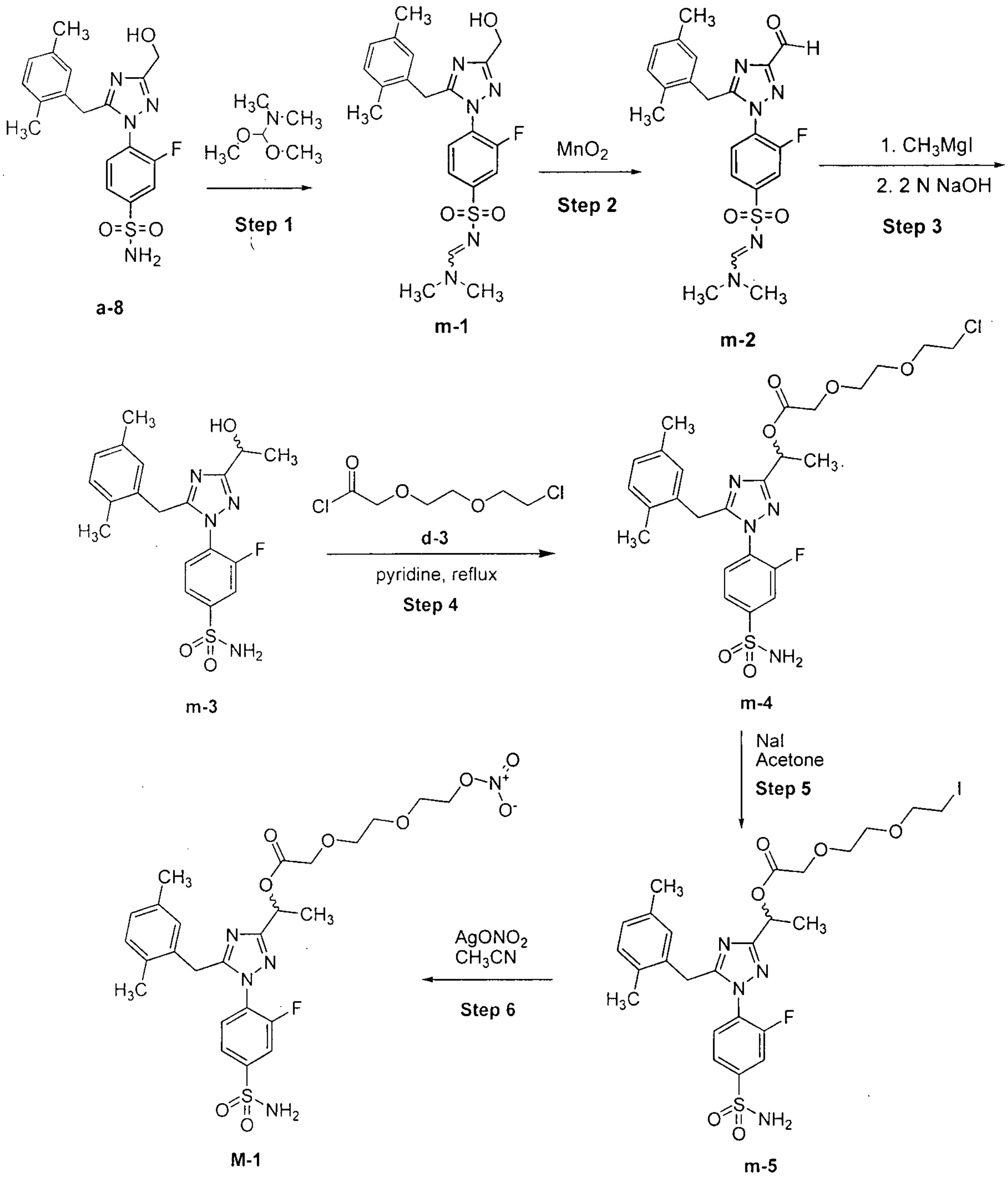


To a solution of the BOC-protected amine **I-4** (251 mg, 0.387 mmol) in CH_2Cl_2 (1.3 mL) was added TFA (0.298 mL, 3.87 mmol). The reaction mixture stirred for 4 h, was quenched with saturated $NaHCO_3$ (30 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (60 – 100% EtOAc/Hexanes) and 1-[4-(aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl 4-(nitrooxy)-L-prolinate (75 mg, 35%) was obtained as a white solid.

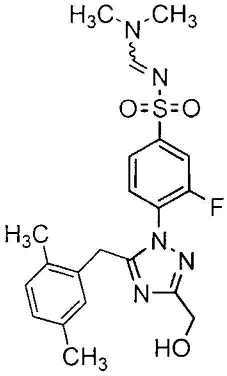
^1H NMR (400 MHz, CHLOROFORM-*d*) δ 7.73 - 7.83 (m, 2 H), 7.40 - 7.47 (m, 1 H), 6.95 - 6.99 (m, 1 H), 6.89 - 6.95 (m, 1 H), 6.64 (s, 1 H), 5.42 - 5.47 (m, 1 H), 5.35 - 5.41 (m, 1 H), 4.99 (s, 2 H), 4.79 (t, *J*=7.6 Hz, 1 H), 4.68 (t, *J*=7.6 Hz, 1 H), 4.05 (d, *J*=3.0 Hz, 2 H), 3.95 (d, *J*=3.8 Hz, 1 H), 2.53 - 2.61 (m, 2 H), 2.18 (s, 3 H), 2.05 (s, 3 H).

LCMS $(M+H)^+$: 549.2.

Scheme M


a-8
Step 1
m-1
MnO2
Step 2
m-2
1. CH3MgI
2. 2 N NaOH
Step 3
m-3
d-3
pyridine, reflux
Step 4
m-4
NaI
Acetone
Step 5
m-5
AgONO2
CH3CN
Step 6
M-1

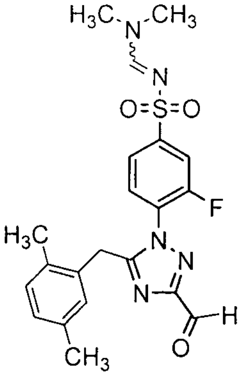
Step 1: (E,Z)-N'-(4-(5-(2,5-Dimethylbenzyl)-3-(hydroxymethyl)-1H-1,2,4-triazol-1-yl)-3-fluorophenylsulfonyl)-N,N-dimethylformamidine (m-1)



To a solution of the alcohol a-8 (1.63 g, 4.17 mmol) in acetonitrile (50 mL), was added N,N dimethylformamide dimethyl acetal (1.66 mL, 12.5 mmol). The solution stirred at ambient temperature for 1h. The volatiles were removed and the residue triturated in ether to give the product as a white solid (1.8 g, 99 %), which was used without any further purification.

LCMS, APCI pos mode M+1= 446.51

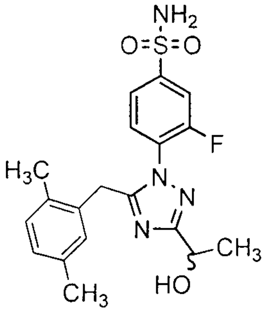
Step 2: (E,Z)-N'-(4-(5-(2,5-Dimethylbenzyl)-3-formyl-1H-1,2,4-triazol-1-yl)-3-fluorophenylsulfonyl)-N,N-dimethylformamidine (m-2)



To a solution of the alcohol m-1 (1.87 g, 4.8 mmol) in THF (20 mL) was added MnO_2 (4.1g, 48.1 mmol). The mixture was stirred at ambient temperature for 8h. The MnO_2 was filtered through a bed of Celite and the cake was washed with acetone (3 x 50 mL). The solvent was removed to give the product as a yellow solid (1.5 g, 71 %), which was used without further purification.

^1H NMR (400 MHz, DMSO-d_6) δ 2.02 (s, 3 H), 2.09 (s, 3 H), 2.96 (s, 3 H), 3.19 (s, 3 H), 4.15 (s, 2 H), 6.57 (s, 1 H), 6.82 - 6.91 (m, 1 H), 6.92 - 6.99 (m, 1 H), 7.75 - 7.86 (m, 2 H), 7.86 - 7.95 (m, 1 H), 8.29 (s, 1 H), 9.93 (s, 1 H).

Step 3: **4-(5-(2,5-Dimethylbenzyl)-3-(1-hydroxyethyl)-1H-1,2,4-triazol-1-yl)-3-fluorobenzenesulfonamide (m-3)**



To a solution of aldehyde m-2 (200 mg, 0.451 mmol) in THF at -40°C was added methylmagnesium iodide in diethyl ether (0.600 mL of 3M in diethyl ether, 1.8 mmol). The reaction was allowed to warm up to ambient temperature over a 2h period. The reaction was quenched with aqueous sat NH_4Cl (20 mL) and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The product was purified by HPLC using MeCN/H_2O/ acetic acid.

^1H NMR (400 MHz, METHANOL-d_4) δ 1.56 (d, J=6.8 Hz, 3 H), 2.02 (s, 3 H), 2.10 (s, 3 H), 4.12 (s, 2 H), 4.92 (q, J=6.6 Hz, 1 H), 6.54 (s, 1 H), 6.82 - 6.88 (m, 1 H), 6.88 - 6.94 (m, 1 H), 7.51 (t, J=7.8 Hz, 1 H), 7.67 - 7.78 (m, 2 H).

LCMS (APCI, pos Mode) M+1= 404.1.

HRMS Calcd for $C_{19}H_{21}FN_4O_3S$ $(M+H)^+$: 404.13. Found: 406.14067

Elemental Anal. Calcd for $C_{19}H_{21}FN_4O_3S$, C, 56.42; H, 5.23; F, 4.70; N, 13.85; O, 11.87; S, 7.93. Found C 54.38, H 5.40, N 13.5, F 4.45, S 7.61.

4-(5-(2,5-Dimethylbenzyl)-3-(1-hydroxyethyl)-1H-1,2,4-triazol-1-yl)-3-fluorobenzenesulfonamide Enantiomers (m-3a) and (m-3b)

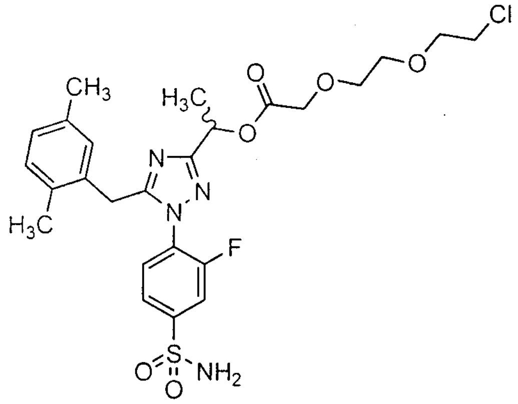
The enantiomeric mixture T-1 was resolved via preparative chiral SFC using a ChiralPak OJ-H, 20% MeOH @ 140 bar, 2.5 mL/min.

^1H NMR (400 MHz, MeOD) δ 1.57 (d, J=6.8 Hz, 3 H), 2.02 (s, 3 H), 2.10 (s, 3 H), 4.12 (s, 2 H), 4.92 (q, J=6.6 Hz, 2 H), 6.55 (s, 1 H), 6.85 (s, 1 H), 6.89 - 6.97 (m, 1 H), 7.51 (t, J=7.7 Hz, 1 H), 7.73 (s, 2 H).

The slower eluting enantiomer

^{1}H NMR (400 MHz, MeOD) δ 1.57 (d, J=6.8 Hz, 3 H), 2.02 (s, 3 H), 2.10 (s, 3 H), 4.12 (s, 2 H), 4.92 (q, J=6.6 Hz, 2 H), 6.55 (s, 1 H), 6.85 (s, 1 H), 6.89 - 6.97 (m, 1 H), 7.51 (t, J=7.7 Hz, 1 H), 7.73 (s, 2 H).

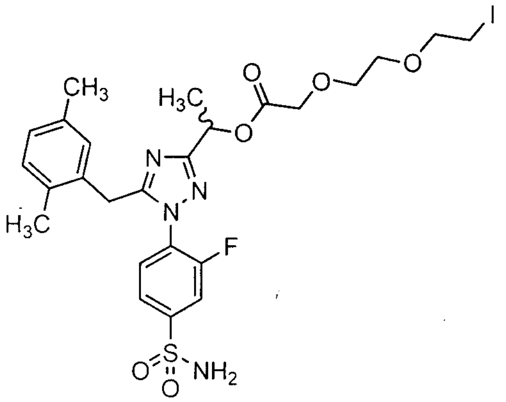
Step 4: 1-[1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1H-1,2,4-triazol-3-yl]ethyl [2-(2-chloroethoxy)ethoxy]acetate (m-4)



To 4-{5-(2,5-dimethylbenzyl)-3-[(1*R*)-1-hydroxyethyl]-1*H*-1,2,4-triazol-1-yl}-3-fluoro-benzene-sulfonamide (**m-3**; 0.57 g, 1.41 mmol) and 2-chloropyridine (0.68 mL, 7.2 mmol) in dichloromethane (10 mL) was added [2-(2-chloroethoxy)ethoxy]acetyl chloride (**d-3**; 0.29 g, 1.4 mmol) and stirred for 24 h. Diluted mixture with EtOAc (70 mL) and partitioned with sat. aq. $NaHCO_3$ (2 X 50 mL). The organic layer was dried over Na_2SO_4 then concentrated. Purification with silica (M + 25 Biotage cartridge) elution with EtOAc/Hexane (1:1), combined purified fractions, and concentrated *in vacuo*. The residue was dissolved in EtOAc (2 mL) and added hexane (2 mL) to afford crystallize product as white solid (0.35 g, 44.8%), which was used without further purification.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ : 7.66 - 7.77 (m, 2 H), 7.31 - 7.39 (m, 1 H), 6.86 - 6.97 (m, 2 H), 6.54 (s, 1 H), 6.03 - 6.20 (m, 1 H), 4.28 - 4.37 (m, 2 H), 4.20 - 4.25 (m, 2 H), 4.18 - 4.20 (m, 2 H), 3.71 - 3.82 (m, 4 H), 3.63 - 3.70 (m, 2 H), 2.14 (s, 3 H), 2.02 - 2.06 (m, 3 H), 1.71 (d, *J*=6.8 Hz, 3 H). LC/MS ESI m/z $(M+H)^+$; 569.1.

Step 5: **1-[1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1H-1,2,4-triazol-3-yl]ethyl [2-(2-Iodoethoxy)ethoxy]acetate (m-5)**

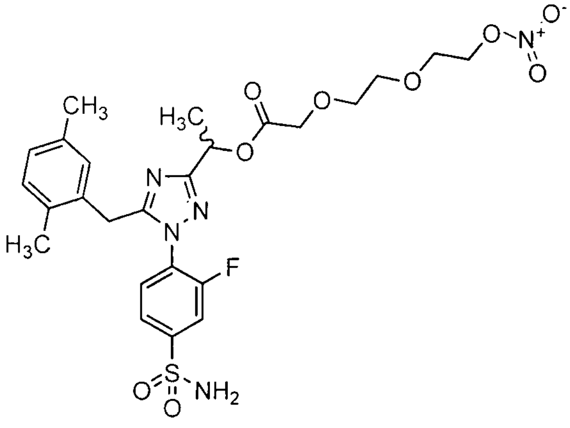


Dissolved (1*R*)-1-[1-[4-(aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]ethyl [2-(2-chloroethoxy)ethoxy]acetate (**m-4**; 0.35 g, 0.63 mmol) and potassium iodide (0.32 g, 1.89 mmol) in acetone (15 mL) then warmed to 60°C for 60h. Diluted with EtOAc (70 mL) partitioned with sat. aq. $NaHCO_3$ (2 X 50 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford a clear oil. Purification with silica (M + 25, a Biotage cartridge), elution with EtOAc/Hexane (1:1), then combined purified fractions, concentrated, and dried under high vacuum for 2h to afford a white solid (0.33 g, 79%), which was used without further purification.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ: 7.62 - 7.77 (m, 2 H), 7.34 (t, 1 H), 6.81 - 6.97 (m, 2 H), 6.54 (s, 1 H), 6.12 (q, *J*=6.8 Hz, 1 H), 5.16 (bs, 2 H), 4.55 - 4.66 (m, 2 H), 4.17 - 4.25 (m, 2 H), 4.07 (s, 2 H), 3.76 - 3.83 (m, 2 H), 3.66 - 3.76 (m, 4 H), 2.14 (s, 3 H), 2.04 (s, 3 H), 1.71 (d, *J*=6.6 Hz, 3 H).

LC/MS ESI m/z $(M+H)^+$; 661.0.

Step 4: **1-[1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1H-1,2,4-triazol-3-yl]ethyl {2-[2-(Nitrooxy)ethoxy]ethoxy}acetate (M-1)**

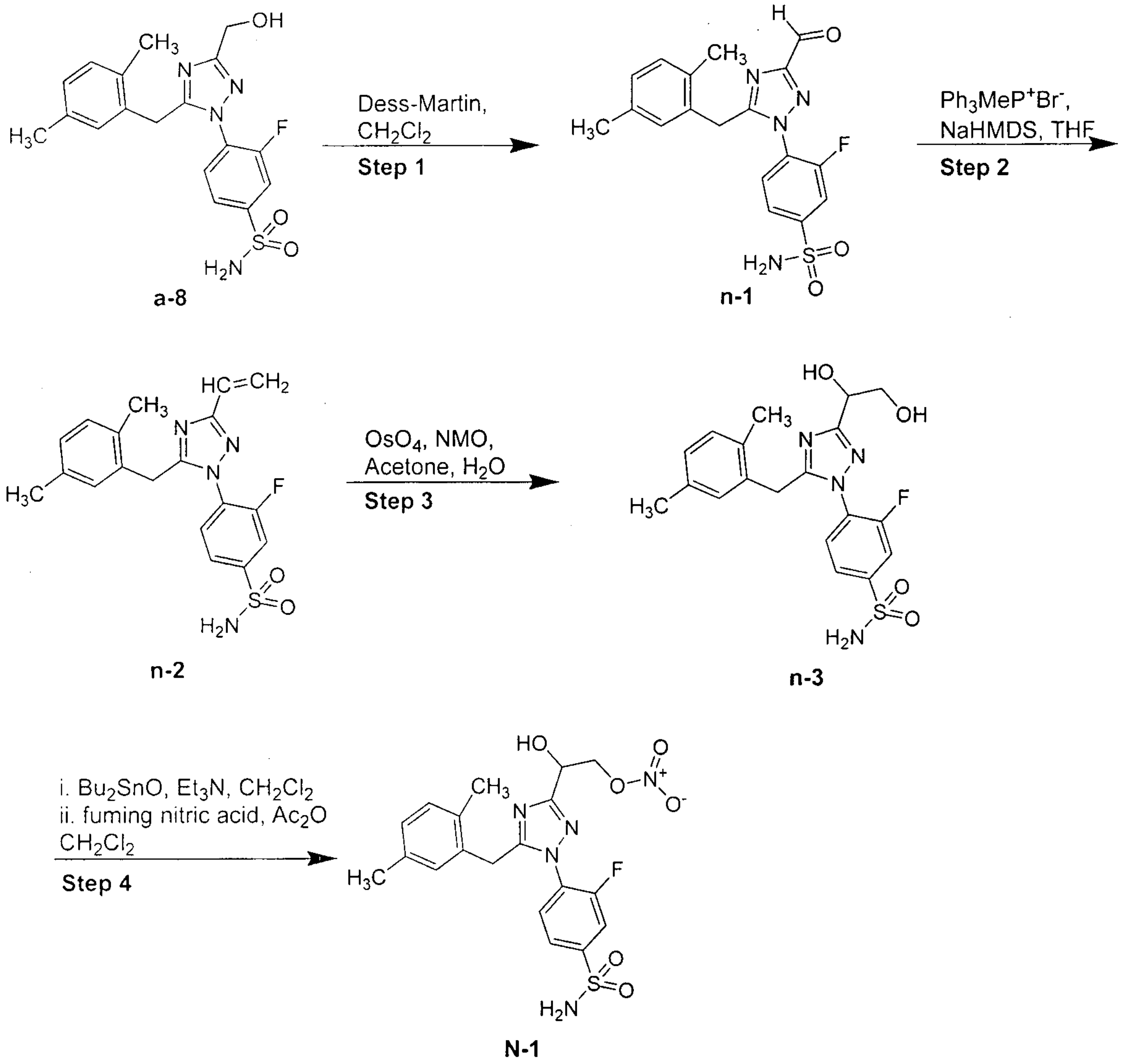


To a solution of iodo-triazole (1*R*)-1-[1-[4-(aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]ethyl [2-(2-iodoethoxy)ethoxy]acetate (**m-5**; 0.34 g, 0.53 mmol) in acetonitrile (25 ml) was added silver(I) nitrate (0.25 g, 1.58 mmol) in one portion at 60°C. The heterogeneous mixture was allowed to cool to 23°C and diluted with sat. aq. NaCl (25 mL) and ethyl acetate (50 mL). The mixture was vigorously stirred at 23°C for 30 min to consume excess silver(I) nitrate. The layers were separated and the aqueous layer was extracted with EtOAc (1 x 30 mL). The combined organic layers were dried over $MgSO_4$. and concentrated in vacuo. The crude oil was purified by flash chromatography (Biotage, 25 + S) eluting with EtOAc/Hex (60-100% over 10 CV). The purified oil was then azeotroped with dichloromethane (2 x 10 mL), dissolved in a minimal amount of deionized water, and lyophilized to dryness to provide the desired nitrate ester as a hygroscopic gum (0.23 g, 74%).

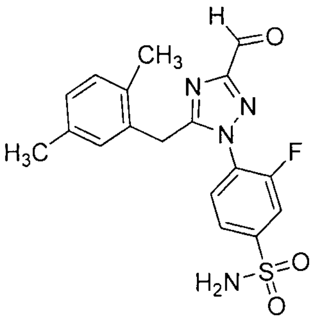
^1H NMR (300 MHz, DMSO-d_6) δ : 7.73 - 7.87 (m, 3 H), 7.70 (br. s., 2 H), 6.96 (d, J=7.5 Hz, 1 H), 6.88 (d, J=7.7 Hz, 1 H), 6.55 (s, 1 H), 5.95 (q, J=6.5 Hz, 1 H), 4.60 - 4.68 (m, 2 H), 4.15 (d, J=4.3 Hz, 2 H), 4.05 (s, 2 H), 3.67 - 3.73 (m, 2 H), 3.53 - 3.62 (m, 4 H), 2.09 (s, 3 H), 2.02 (s, 3 H), 1.56 (d, J=6.6 Hz, 3 H).

HRMS (ESI) $C_{25}H_{30}FN_5O_9S$ (M + H+) m/z: Calc. 596.1821, Found: 596.1821.

Scheme N



Step 1: 4-(5-(2,5-Dimethylbenzyl)-3-formyl-1H-1,2,4-triazol-1-yl)-3-fluorobenzenesulfonamide (n-1)

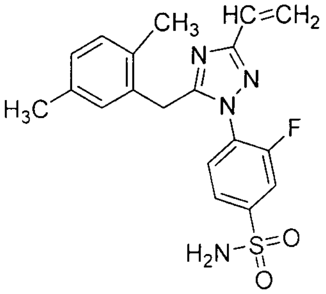


To a suspension of alcohol **a-8** (10.3 g, 26.4 mmol) in CH_2Cl_2 (130 mL), Dess-Martin periodinane (12.31 g, 29.0 mmol) was added. The reaction mixture was stirred for 3 h and diluted with 5% aq. $Na_2S_2O_3$ (350 mL), and saturated sodium bicarbonate (400 mL) and extracted with CH_2Cl_2 (3 x 150 mL). The combined organic layers were washed with brine and dried with $MgSO_4$, treated with charcoal, filtered, concentrated under reduced pressure. The aldehyde **n-1** (9.42 g, 92 % yield) was isolated as an off-white solid and was taken to the next step without further purification.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1 H), 7.94 - 8.00 (m, 1 H), 7.79 - 7.87 (m, 2 H), 7.73 (s, 2 H), 6.96 - 7.00 (m, 1 H), 6.88 - 6.94 (m, 1 H), 6.63 (s, 1 H), 5.76 (s, 1 H), 4.15 (s, 2 H), 2.12 (s, 3 H), 2.03 (s, 3 H).

LCMS $(M+H)^+$: 389.0

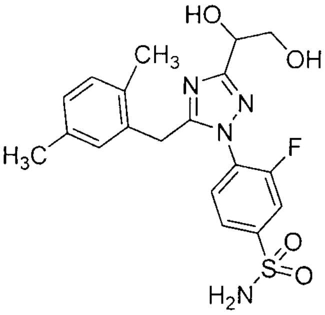
Step 2: 4-(5-(2,5-Dimethylbenzyl)-3-vinyl-1H-1,2,4-triazol-1-yl)-3-fluorobenzenesulfonamide (n-2)



A solution of sodium hexamethyldisilazane (60 mL of 1.0 M solution in THF) was added dropwise to a suspension of Methyltriphenylphosphonium bromide (26.0 g, 72.8 mmol) in THF (300 mL). After 10 min, the reaction mixture was cooled to -70°C and a suspension of aldehyde **n-1** (9.42 g, 24.3 mmol) in THF (50 mL) was slowly added. The mixture was stirred at -70°C for 10 min and warmed to ambient temperature and stirred overnight. The reaction mixture was poured onto sat. aq. NH_4Cl (400 mL) and EtOAc (200 mL) was added and the phases were separated. The aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with water (200 mL) and brine (200 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel plug eluting 50 % heptane/ethyl acetate and obtained alkene **n-2** (4.28 g, 46% yield) as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.69 - 7.79 (m, 2 H), 7.33 - 7.40 (m, 1 H), 6.91 - 6.97 (m, 1 H), 6.89 (d, J=7.33 Hz, 1 H), 6.73 (dd, J=17.56, 10.99 Hz, 1 H), 6.59 (s, 1 H), 6.35 (d, J=17.68 Hz, 1 H), 5.61 (d, J=11.12 Hz, 1 H), 4.96 (s, 2 H), 4.11 (s, 2 H), 2.15 (s, 4 H), 2.08 (s, 3 H).

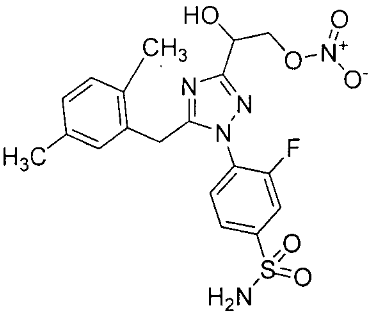
LCMS $(M+H)^+$: 387.0

Step 3: 4-(5-(2,5-Dimethylbenzyl)-3-(1,2-dihydroxyethyl)-1H-1,2,4-triazol-1-yl)-3-fluorobenzene-sulfonamide (n-3)



To a solution of olefin **n-2** (4.38 g, 11.1 mmol) in acetone (180 mL) and water (27 mL), was added successively NMO (1.43 g, 12.2 mmol) and osmium tetroxide solution (5.1 mL, 2.5 wt % solution in 2-methyl-2-propanol) and stirred at ambient temperature overnight. The reaction mixture was poured onto saturated aq. NH_4Cl (400 mL) and extracted with EtOAc (3 x 30 mL). The organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel plug eluting 50 % heptane/ethyl acetate and obtained diol **n-3** as a white solid (3.32 g, 71% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 7.76 - 7.82 (m, 3 H), 7.70 (s, 2 H), 6.93 - 6.98 (m, 1 H), 6.86 - 6.90 (m, 1 H), 6.59 (s, 1 H), 5.43 (d, *J*=5.6 Hz, 1 H), 4.70 (t, *J*=5.9 Hz, 1 H), 4.53 - 4.58 (m, 1 H), 4.02 (s, 2 H), 3.59 - 3.70 (m, 2 H), 2.10 (s, 3 H), 2.03 (s, 3 H). LCMS $(M-1)^-$: 419.2.

Step 4: 2-[1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]-2-hydroxyethyl Nitrate (N-1)



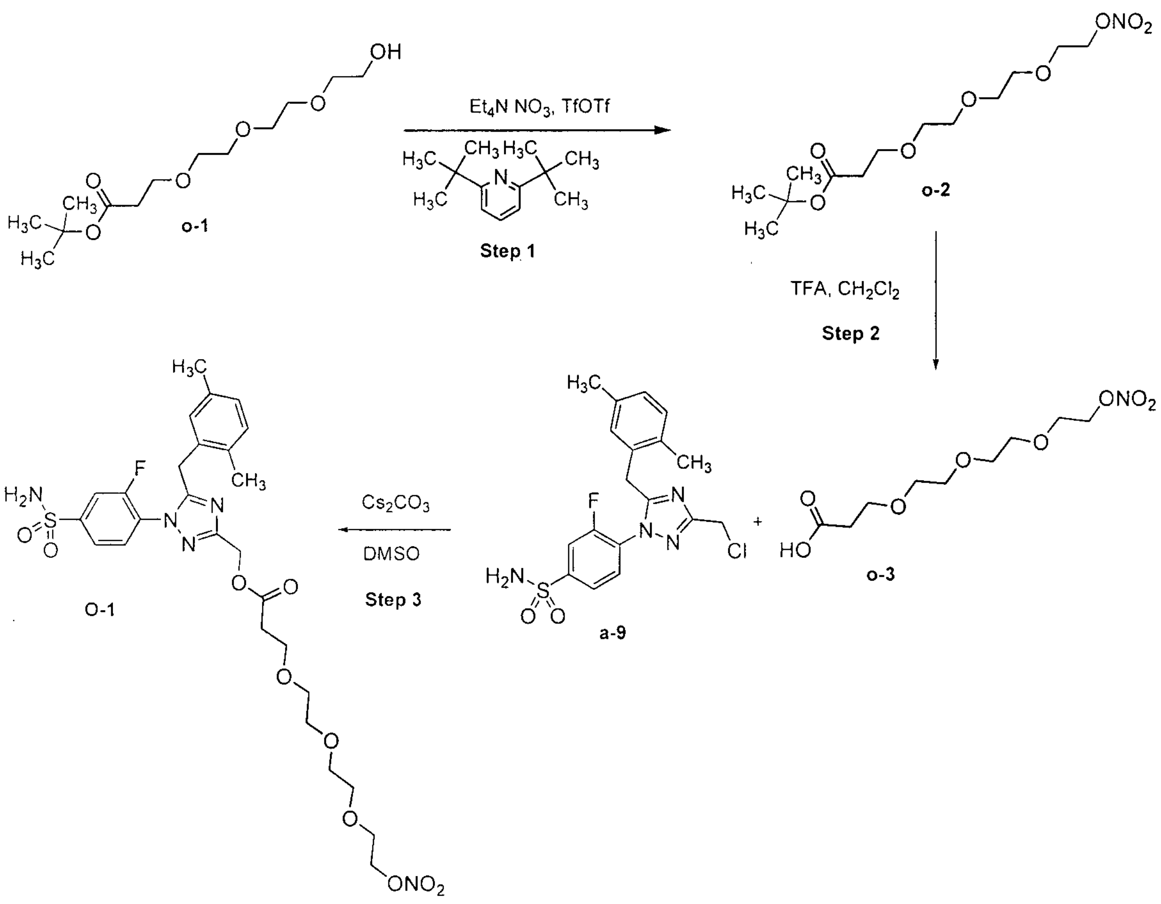
Dichloromethane (10 mL) and acetic anhydride (2.97 mL. 31.4 mmol) was added to a 50 mL round-bottom flask. The solution was cooled to 0°C and fuming nitric acid (1.22 mL, 27.2 mmol) in dichloromethane (10 mL) was added via syringe. The reaction mixture was continued to stir at 0°C for 1h. In a separate 500 mL round-bottom flask, the diol **n-3** (4.40 g, 10.4 mmol), THF (100mL), dibutyltinoxide (0.05 g, 0.20 mmol), and Et_3N (1.45

mL, 10.5 mmol) were added. After stirring at ambient temperature for 30 min, dichloromethane (80 mL) was added followed by the acetic anhydride and fuming nitric acid solution. The reaction mixture was stirred overnight at ambient temperature and then poured onto ice-cold water (80 mL). EtOAc (400 mL) and sat. aq. $NaHCO_3$ (20 mL) were added and partitioned. The aqueous layer was extracted with EtOAc (120 mL). The combined organic layers was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel plug eluting 50 % heptane/ethyl acetate, then 33% heptane/ethyl acetate to give the nitrate ester **N-1** (3.50 g, 72% yield) as a white solid.

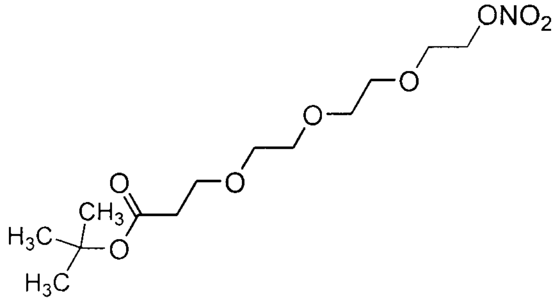
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 - 7.85 (m, 5 H), 6.93 - 6.99 (m, 1 H), 6.85 - 6.91 (m, 1 H), 6.58 (s, 1 H), 6.17 (d, J=6.1 Hz, 1 H), 4.90 - 4.99 (m, 1 H), 4.76 - 4.86 (m, 2 H), 4.05 (s, 2 H), 2.10 (s, 3 H), 2.02 (s, 3 H).

LCMS $(M+H)^+$: 466.2.

Scheme O



Step 1: tert-Butyl 3-(2-{2-[2-(Nitrooxy)ethoxy]ethoxy}ethoxy)propanoate (o-2)



To a -50°C solution of *tert*-butyl 12-hydroxy-4,7,10-trioxadodecanoate (2.50 g, 8.98 mmol) in dichloromethane (45 mL) was added tetraethylamonium nitrate (3.45 g, 18.00 mmol) followed by 2,6-di-tert-butylpyridine (2.98 mL, 13.50 mmol). Trifluoromethanesulfonic anhydride (1.66 mL, 9.88 mmol) in methylene chloride (0.5 mL) was slowly added and the reaction mixture was stirred at -50°C for 1h then let warm to ambient temperature over 18h.

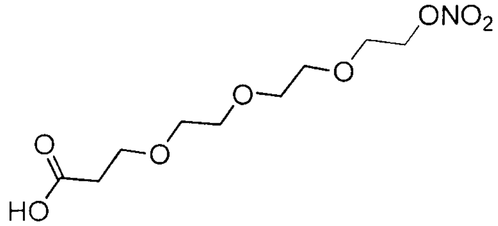
The reaction mixture was diluted in dichloromethane (45 mL) and 1N aq. HCl (45 mL). The organic layer was washed with brine (45 mL), dried (MgSO$_4$), and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate-hexane 10-100%) to give the title compound (2.68 g, 92%) as a colorless oil.

^{1}H NMR (300 MHz, DMSO- *d*$_6$) δ 1.41 (s, 9 H), 2.43 (t, J=6.2 Hz, 2 H), 3.48 - 3.56 (m, 8 H), 3.60 (t, J=6.2 Hz, 2 H), 3.68 - 3.77 (m, 2 H), 4.60 - 4.73 (m, 2 H).

HRMS (TOF): calcd for $C_{13}H_{26}NO_8$ $[MH]^+$: 324.16529, found: 324.16601.

Anal. Calcd for $C_{13}H_{25}NO_8$: C, 48.29; H, 7.79; N, 4.33. Found: C, 48.21; H, 7.96; N, 4.39.

Step 2: 3-(2-{2-[2-(Nitrooxy)ethoxy]ethoxy}ethoxy)propanoic Acid (o-3)



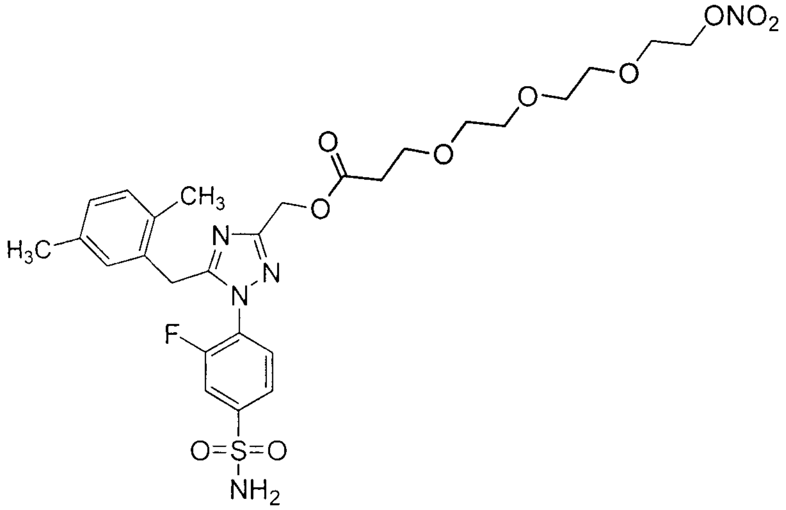
To a 0°C solution of **o-2** (1.0 g , 3.1 mmol) in dichloromethane (7.5 mL) was added trifluoroacetic acid (7.5 mL). The reaction mixture was stirred at 0°C to ambient temperature over 3h. The mixture was diluted with toluene (2 mL) and concentrated under reduced pressure to give the title compound (0.87 g, 100%) as a colorless oil.

^{1}H NMR (300 MHz, DMSO- *d*$_6$) δ 2.46 (t, J=6.3 Hz, 2 H), 3.49 - 3.58 (m, 8 H), 3.62 (t, J=6.4 Hz, 2 H), 3.70 - 3.76 (m, 2 H), 4.59 - 4.73 (m, 2 H).

LC/MS (ESI) m/z 268.1 [MH]$^+$.

HRMS (TOF): calcd for $C_9H_{18}NO_8$ [MH]$^+$: 268.10269, found: 268.10435.

Step 3: {1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1H-124-triazol-3-yl}methyl 3-(2-{2-[2-(Nitrooxy)ethoxy]ethoxy}ethoxy)propanoate (O-1)



To a solution of **a-9** (323 mg, 0.790 mmol) and **o-3** (211 mg, 0.790 mmol) in DMSO (4 mL) was added cesium carbonate (283 mg, 0.869 mmol). The reaction mixture was stirred at ambient temperature for 18h, then at 50°C for 1h. The reaction mixture was diluted in ethyl acetate (15 mL) and water (5 mL). The organic layer was washed with water (5 mL), dried (MgSO4) and concentrated under reduced pressure.

The residue was purified by column chromatography (ethyl acetate-hexane, 25-100%) to yield the title product (290 mg, 57%) as a colorless oil.

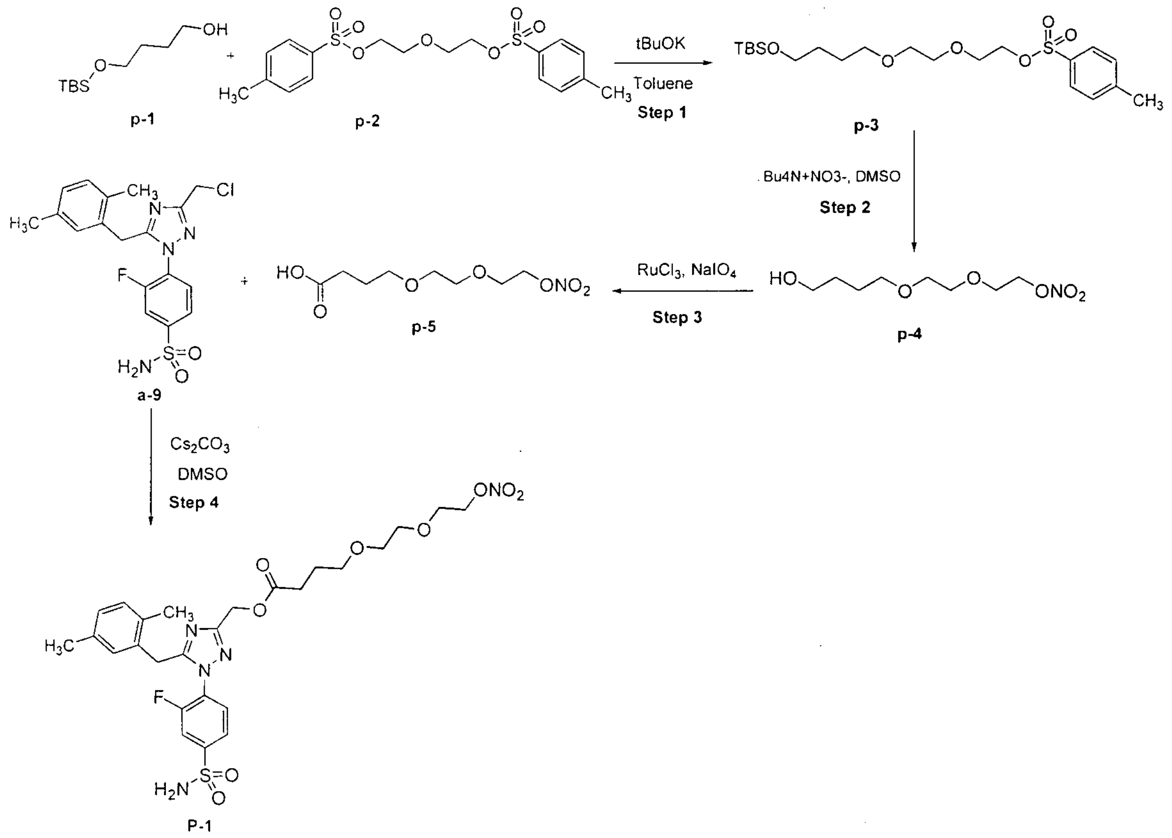
^{1}H NMR (300 MHz, DMSO- *d*$_6$) δ 2.05 (s, 3 H), 2.13 (s, 3 H), 2.62 (t, J=6.1 Hz, 2 H), 3.48 - 3.57 (m, 8 H), 3.66 (t, J=6.1 Hz, 2 H), 3.69 - 3.73 (m, 2 H), 4.07 (s, 2 H), 4.63 - 4.69 (m, 2 H), 5.13 (s, 2 H), 6.62 (s, 1 H), 6.91 (d, J=7.5 Hz, 1 H), 6.98 (d, J=7.5 Hz, 1 H), 7.72 (s, 2 H), 7.77 - 7.92 (m, 3 H).

LC/MS (ESI) m/z 640.2 [MH]$^+$.

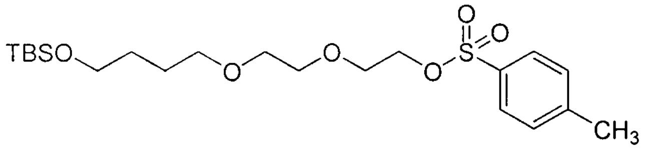
HRMS (TOF): calcd for $C_{27}H_{35}FN_5O_{10}S$ [MH]$^+$: 640.20832, found: 640.20929.

Anal. Calcd for $C_{27}H_{34}FN_5O_{10}S+0.1H_2O$: C, 50.21; H, 5.44; N, 10.70. Found: C, 50.56; H, 5.37; N, 10.92.

Scheme P



Step 1: 12,12,13,13-Tetramethyl-3,6,11-trioxa-12-silatetradec-1-yl 4-Methylbenzenesulfonate (p-3)



To a solution of 4-(*tert*-butyldimethylsilyl)oxy-1-butanol (3.2 g, 15.7 mmol) in toluene (24.5 mL) was added potassium *t*-butoxide (18.1 mL, 18.1 mmol, 1 M in THF). After 30 min 2,2'-oxydiethyl ditosylate (5.00 g, 12.1 mmol) was added and the mixture was stirred for 48 h at ambient temperature, then diluted in ethyl acetate (200 mL) and water (50 mL). The organic layer was washed with brine (50 mL), dried (MgSO4) and concentrated under reduced pressure.The residue was purified by column chromatography (ethyl acetate-hexane, 15-50%) to yield the title product (0.73 g, 14%) as a colorless oil.

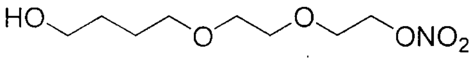
^{1}H NMR (300 MHz, DMSO- d_6) δ -0.00 (s, 6 H), 0.79 - 0.87 (m, 9 H), 1.39 - 1.52 (m, 4 H), 2.40 (s, 3 H), 3.32 - 3.45 (m, 6 H), 3.52 - 3.58 (m, 4 H), 4.06 - 4.11 (m, 2 H), 7.46 (d, J=8.5 Hz, 2 H), 7.76 (d, J=8.3 Hz, 2 H).

LC/MS (ESI) m/z 447.2 $[MH]^+$.

HRMS (TOF): calcd for $C_{21}H_{39}O_6SSi$ $[MH]^+$: 447.22311, found: 447.22222.

Anal. Calcd for $C_{21}H_{38}O_6SSi+1.5H_2O$: C, 53.25; H, 8.72. Found: C, 53.21; H, 8.57.

Step 2: 2-[2-(4-Hydroxybutoxy)ethoxy]ethyl Nitrate (p-4)



To a solution of tosylate **p-3** (825 mg, 1.85 mmol) in DMSO (9.25 mL) was added tetraethylammonium nitrate (710 mg, 3.69 mmol). The reaction mixture was stirred at 75°C for 18h. The crude reaction mixture was purified by preparative reverse phase HPLC (water:acetonitrile, 85-35%) to yield the title product (0.113 g, 27.4%) as a yellow oil.

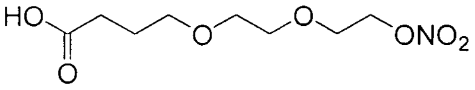
^{1}H NMR (300 MHz, DMSO- d_6) δ 1.37 - 1.60 (m, 4 H), 3.38 - 3.44 (m, 4 H), 3.46 - 3.52 (m, 2 H), 3.54 - 3.59 (m, 2 H), 3.70 - 3.76 (m, 2 H), 4.38 (t, J=5.2 Hz, 2 H), 4.65 - 4.70 (m, 2 H).

LC/MS (ESI) m/z 224.0 $[MH]^+$.

HRMS (TOF): calcd for $C_8H_{18}NO_6$ $[MH]^+$: 224.11286, found: 224.11253.

Anal. Calcd for $C_8H_{17}NO_6$-$0.2H_2O$: C, 42.36; H, 7.73; N, 6.18. Found: C, 42.19; H, 7.83; N, 5.95.

Step 3: 4-{2-[2-(Nitrooxy)ethoxy]ethoxy}butanoic Acid (p-5)



To a solution of alcohol **p-4** (95 mg, 0.43 mmol) in a biphasic mixture of water (1.2 mL), CCl_4 (0.81 mL), and acetonitrile (0.81 mL) was added ruthenium trichloride hydrate (2 mg, 0.01 mmol) and sodium metaperiodate (228 mg, 1.06 mmol). The reaction mixture was stirred at ambient temperature for 18h then diluted with brine (5 mL) and extracted with dichloromethane (3x10 mL). The combined organic extracts were dried ($MgSO_4$), and the solvents were removed under reduced pressure. The crude reaction mixture was purified by preparative reverse phase HPLC (water:acetonitrile, 85-35%) to yield the title product (0.03 g, 30%) as a colorless oil.

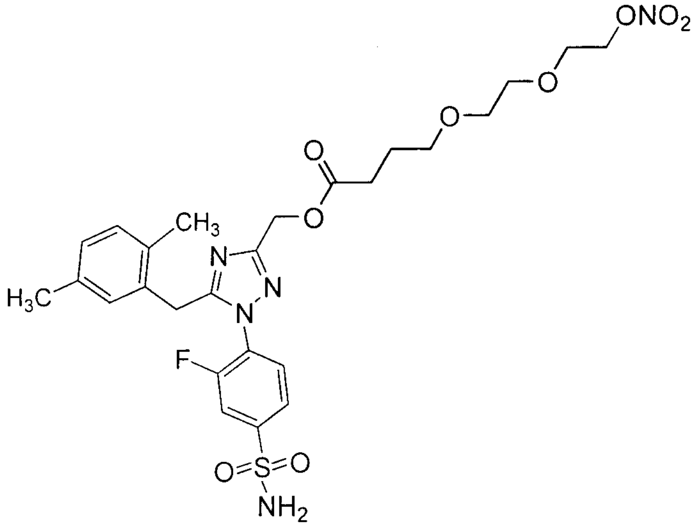
^{1}H NMR (300 MHz, DMSO- d_6): δ 1.67 - 1.78 (m, 2 H), 2.26 (t, J=7.4 Hz, 2 H), 3.40 (t, J=6.5 Hz, 2 H), 3.46 - 3.52 (m, 2 H), 3.53 - 3.59 (m, 2 H), 3.70 - 3.76 (m, 2 H), 4.58 - 4.72 (m, 2 H), 12.06 (br. s., 1 H).

LC/MS (ESI) m/z 238.0 $[MH]^+$.

HRMS (TOF): calcd for $C_8H_{16}NO_7$ $[MH]^+$: 238.09213, found: 238.09230.

Anal. Calcd for $C_8H_{15}NO_7$-$0.15H_2O$: C, 40.05; H, 6.43; N, 5.84. Found: C, 39.97; H, 6.49; N, 5.70.

Step 4: {1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1H-124-triazol-3-yl}methyl 4-{2-[2-(Nitrooxy)ethoxy]ethoxy}butanoate (P-1)



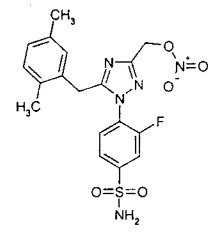
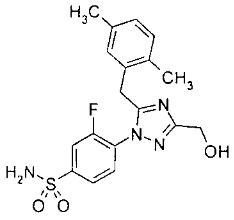
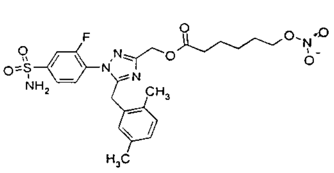
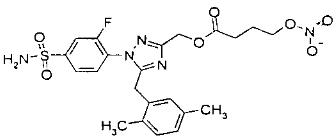
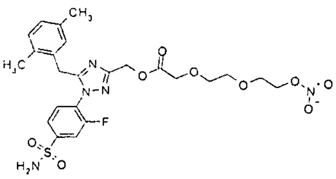
To a solution of chloride **a-9** (190 mg, 0.464 mmol) and acid **p-5** (110 mg, 0.464 mmol) in DMSO (2.3 mL) was added cesium carbonate (159 mg, 0.487 mmol). The reaction mixture was stirred at ambient temperature for 18h, then at 50°C for 1.5h. The reaction mixture was diluted in ethyl acetate (15 mL) and water (7.5 mL). The organic layer was washed with water (7.5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate-hexane, 25-100%) to yield the title product as a colorless oil (52 mg, 18%).

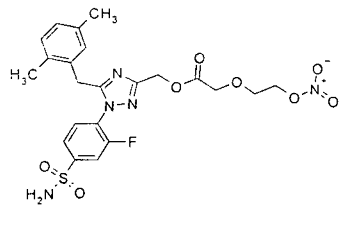
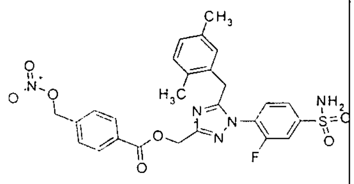
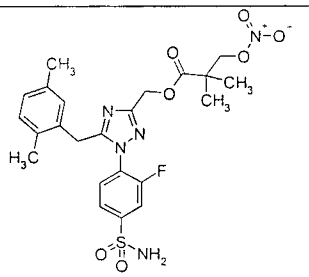
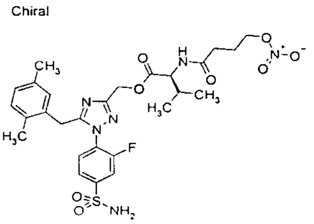
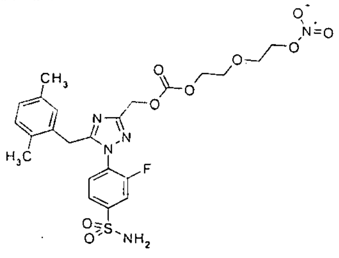
^{1}H NMR (300 MHz, DMSO- d_6) δ 1.72 - 1.84 (m, 2 H), 2.05 (s, 3 H), 2.13 (s, 3 H), 2.41 (t, J=7.4 Hz, 2 H), 3.38 - 3.43 (m, 2 H), 3.45 - 3.49 (m, 2 H), 3.51 - 3.56 (m, 2 H), 3.69 - 3.74 (m, 2 H), 4.05 - 4.08 (m, 2 H), 4.63 - 4.68 (m, 2 H), 5.13 (s, 2 H), 6.62 (s, 1 H), 6.91 (d, J=7.5 Hz, 1 H), 6.98 (d, J=7.5 Hz, 1 H), 7.72 (s, 2 H), 7.77 - 7.92 (m, 3 H).

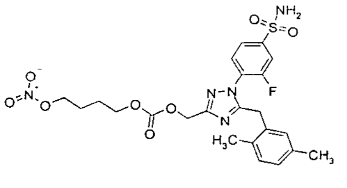
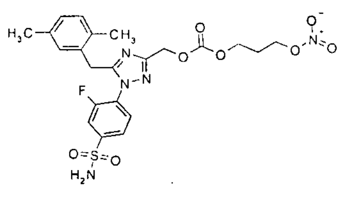
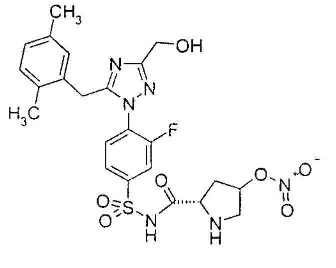
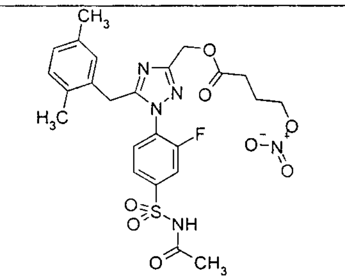
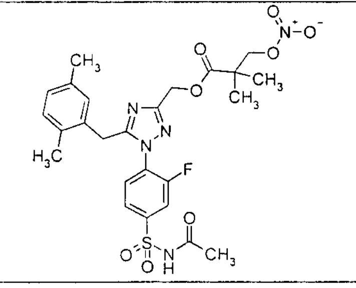
LC/MS (ESI) m/z 610.1 $[MH]^+$.

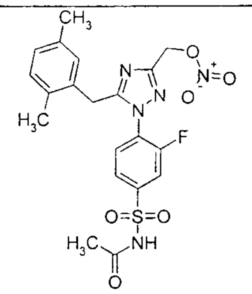
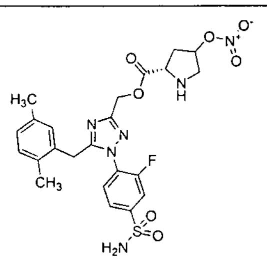
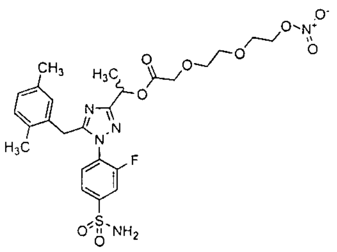
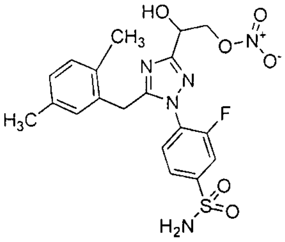
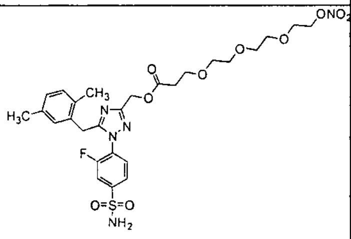
HRMS (TOF): calcd for $C_{26}H_{33}FN_5O_9S$ $[MH]^+$: 610.19775, found: 610.20081.

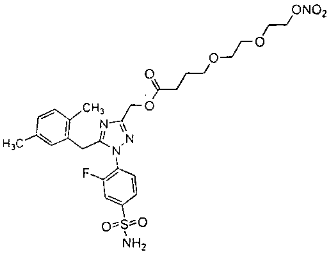
Table 1

Example #	Structure	Chemical Name	^{1}HNMR	MS
A-1		[1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl Nitrate	(300 MHz, DMSO-d_6): δ 2.03 (s, 3 H), 2.13 (s, 3 H), 4.07–4.14 (m, 2 H), 5.69–5.74 (m, 2 H), 6.64 (m, 1 H), 6.88–7.02 (m, 2 H), 7.70–7.91 (m, 5 H).	436.2
A-8		4-[5-2, 4-Dimethylbenzyl-3-(hydroxymethyl)-1*H*-1,2,4-triazol-1-yl]-3-fluorobenzenesulfonamide	(400 MHz, DMSO-*d*6), δ ppm 2.03 (s, 3 H), 2.12 (s, 3 H), 4.01 (s, 2 H), 4.44 (d, *J*=6.32 Hz, 2 H), 5.39 (t, *J*=6.06 Hz, 1 H), 6.63 (s, 1 H), 6.86 - 6.91 (m, 1 H), 6.93 - 7.00 (m, 1 H), 7.70 (s, 2 H), 7.76 - 7.82 (m, 2 H), 7.82 - 7.87 (m, 1 H).	391.1
B-1		[1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl 6-(Nitrooxy)-hexanoate	(400 MHz, CHLOROFORM-d), δ ppm 1.42-1.53 (m, 2 H), 1.67-1.78 (m, 4 H), 2.05 (s, 3 H), 2.16 (s, 3 H), 2.44 (t, J=7.33 Hz, 2 H), 4.07 (s, 2 H), 4.42 (t, J=6.57 Hz, 2 H), 5.10 (s, 2 H), 5.23 (s, 2 H), 6.60 (s, 1 H), 6.88-6.96 (m, 2 H), 7.35-7.41 (m, 1 H), 7.70-7.77 (m, 2 H).	550
B-2		[1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl 4-(Nitrooxy)-butanoate	(400 MHz, CHLOROFORM-d), δ ppm 2.05 (s, 3 H), 2.06-2.14 (m, J=6.76, 6.76, 6.76, 6.76 Hz, 2 H), 2.16 (s, 3 H), 2.57 (t, J=7.07 Hz, 2H), 4.07 (s, 2 H), 4.53 (t, J=6.44 Hz, 2 H), 5.03 (s, 2 H), 5.26 (s, 2 H), 6.61 (s, 1 H), 6.88-6.92 (m, 1 H), 6.92-6.98 (m, 1 H), 7.36-7.43 (m, 1 H),7.71-7.78 (m, 2 H)	522
C-1		[1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl [2-(Nitrooxy)ethoxy]acetate	(400 MHz, DMSO-d_6), δ ppm 2.03 (s, 3 H), 2.11 (s, 3 H), 3.76-3.85 (m, 2 H), 4.05 (s, 2 H), 4.25 (s, 2 H), 4.54-4.75 (m, 2 H), 5.18 (s, 2 H), 6.61 (s, 1 H), 6.83-6.93 (m, 1 H), 6.92-7.02 (m, 1 H), 7.70 (s, 2 H), 7.82 (m, 3 H).	582.1

Example #	Structure	Chemical Name	^{1}HNMR	MS
D-1		[1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl {2-[2-(Nitrooxy)ethoxy]ethoxy}acetate	(400 MHz, DMSO-d_6), δ ppm 2.02 (s, 3 H), 2.11 (s, 3 H), 3.58 (m, 4 H), 3.71 (m, 2 H), 4.06 (s, 2 H), 4.17 (s, 2 H), 4.57-4.69 (m, 2 H), 5.18 (s, 2 H), 6.61 (s, 1 H), 6.89 (m, 1 H), 6.93-7.00 (m, 1 H), 7.71 (s, 2 H), 7.82 (m, 3 H).	538.1
E-1		[1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1H-1,2,4-triazol-3-yl]methyl 4-[(nitrooxy)methyl] Benzoate	(300 MHz, DMSO-d_6), □ ppm 8.03 (s, 1 H), 8.00 (s, 1 H), 7.74 - 7.90 (m, 3 H), 7.69 (br. s., 2 H), 7.64 (s, 1 H), 7.61 (s, 1 H), 6.96 (d, J=7.55 Hz, 1 H), 6.88 (d, J=7.78 Hz, 1 H), 6.59 (s, 1 H), 5.67 (s, 2 H), 5.41 (s, 2 H), 4.06 (s, 2 H), 2.09 (s, 3 H), 2.02 (s, 3 H)	568
F-1		[1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1H-1,2,4-triazol-3-yl]methyl 2,2-Dimethyl-3-(nitrooxy)propanoate	(400 MHz, CHLOROFORM-*d*), δ ppm; 7.74 (t, 2 H), 7.40 (t, *J*=7.8 Hz, 1 H), 6.85 - 6.98 (m, 2 H), 6.61 (s, 1 H), 5.27 (s, 2 H), 4.54 (s, 2 H), 4.04 (s, 2 H), 2.16 (s, 3 H), 2.04 (s, 3 H), 1.32 (s, 6 H)	
G-1		[1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl *N*-[4-(nitrooxy)butanoyl] L-Valinate	(400 MHz, CHLOROFORM-d), δ ppm 7.68 - 7.82 (m, 2 H), 7.40 (t, J=7.6 Hz, 1 H), 6.96 (d, J=7.8 Hz, 1 H), 6.91 (d, J=8.1 Hz, 1 H), 6.61 (s, 1 H), 6.10 (d, J=8.8 Hz, 1 H), 5.23 - 5.37 (m, 2 H), 5.02 (s, 2 H), 4.69 (dd, J=8.8, 4.80 Hz, 1 H), 4.52 (t, J=6.2 Hz, 2 H), 4.06 (s, 2 H), 2.38 (t, J=7.1 Hz, 2 H), 2.20 - 2.30 (m, 1 H), 2.17 (s, 3 H), 2.05 (s, 3 H), 2.04 - 2.14 (m, 2 H), 0.95 (d, J=6.8 Hz, 3 H), 0.90 (d, J=6.8 Hz, 3 H).	
H-1		[1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1H-1,2,4-triazol-3-yl]methyl 2-[2-(nitrooxy)ethoxy]ethyl Carbonate	(400 MHz, CHLOROFORM-*d*), δ ppm 7.70 - 7.78 (m, 2 H), 7.35 - 7.41 (m, 1 H), 6.95 (d, *J*=7.8 Hz, 1 H), 6.90 (d, *J*=7.6 Hz, 1 H), 6.60 (s, 1 H), 5.30 (s, 2 H), 4.99 (s, 2 H), 4.58 - 4.63 (m, 2 H), 4.32 - 4.37 (m, 2 H), 4.07 (s, 2 H), 3.76 - 3.80 (m, 2 H), 3.72 - 3.76 (m, 2 H), 2.16 (s, 3 H), 2.06 (s, 3 H).	

Example #	Structure	Chemical Name	^{1}HNMR	MS
H-2		[1-[4-(aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl 4-(nitrooxy)butyl carbonate	1H NMR (400 MHz, DMSO-d6), δ ppm 7.77-7.88 (m, 3 H), 7.71 (s, 2 H), 6.93-6.99 (m, 1 H), 6.87-6.91 (m, 1 H), 6.60 (s, 1 H), 5.17 (s, 2 H), 4.53 (t, J=6.06 Hz, 2 H), 4.15 (t, J=5.94 Hz, 2 H), 3.33 (s, 1 H), 2.11 (s, 3 H), 2.02 (s, 3 H), 1.65-1.75 (m, 4 H)	551
H-3		[1-[4-(aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl 3-(nitrooxy)propyl carbonate	1H NMR (400 MHz, DMSO-d6), δ ppm 7.77-7.88 (m, 3 H), 7.70 (s, 2 H), 6.94-6.98 (m, 1 H), 6.87-6.92 (m, 1 H), 6.61 (s, 1 H), 5.18 (s, 2 H), 4.57 (t, J=6.32 Hz, 2 H), 4.20 (t, J=6.19 Hz, 2 H), 4.05 (s, 2 H), 2.11 (s, 3 H), 2.00-2.07 (m, 5 H)	537
J-1		*N*-({4-[5-(2,5-Dimethylbenzyl)-3-(hydroxymethyl)-1*H*-1,2,4-triazol-1-yl]-3-fluorophenyl}sulfonyl)-4-(nitrooxy)-L-prolinamide	(400 MHz, DMSO-d_6), δ ppm 8.97 (s, 1 H), 7.71 - 7.81 (m, 2 H), 7.60 - 7.69 (m, *J*=7.7, 7.7 Hz, 1 H), 6.97 (d, *J*=7.6 Hz, 1 H), 6.89 (d, *J*=7.3 Hz, 1 H), 6.64 (s, 1 H), 5.61 (t, *J*=5.1 Hz, 1 H), 5.35 (t, *J*=6.2 Hz, 1 H), 4.43 (d, *J*=6.1 Hz, 2 H), 4.06 (dd, *J*=10.4, 7.8 Hz, 1 H), 3.97 (s, 2 H), 3.56 - 3.64 (m, 1 H), 3.45 (d, *J*=13.6 Hz, 1 H), 2.17 - 2.28 (m, 1 H), 2.13 (s, 3 H), 2.03 (s, 3 H).	
K-1		1-{4-[(Acetylamino)sulfonyl]-2-fluorophenyl}-5-(2,5-dimethylbenzyl)-1H-1,2,4-triazol-3-yl]methyl 4-(Nitrooxy)butanoate	(400 MHz, CHLOROFORM-*d*), δ ppm 8.34 (s, 1 H), 7.92 (dd, *J*=8.7, 1.89 Hz, 1 H), 7.88 (d, *J*=8.3 Hz, 1 H), 7.41 (dd, *J*=8.3, 6.8 Hz, 1 H), 6.94 (d, *J*=7.6 Hz, 1 H), 6.90 (s, 1 H), 6.61 (s, 1 H), 5.26 (s, 2 H), 4.53 (t, *J*=6.3 Hz, 2 H), 4.08 (s, 2 H), 2.57 (t, *J*=7.1 Hz, 2 H), 2.16 (s, 3 H), 2.07 - 2.13 (m, 5 H), 2.05 (s, 3 H).	564.0
K-2		[1-{4-[(Acetylamino)sulfonyl]-2-fluorophenyl}-5-(2,5-dimethylbenzyl)-1*H*-1,2,4-triazol-3-yl]methyl 2,2-Dimethyl-3-(nitrooxy)propanoate	(400 MHz, CHLOROFORM-*d*), δ ppm; 7.83 - 7.98 (m, 2 H), 7.43 (dd, *J*=8.2, 7.0 Hz, 1 H), 7.25 - 7.28 (m, 1 H), 6.85 - 6.98 (m, 2 H), 5.28 (s, 2 H), 4.55 (s, 2 H), 4.07 (s, 2 H), 2.16 (s, 3 H), 2.10 (s, 3 H), 2.04 (s, 3 H), 1.29 - 1.34 (m, 6 H).	578.6

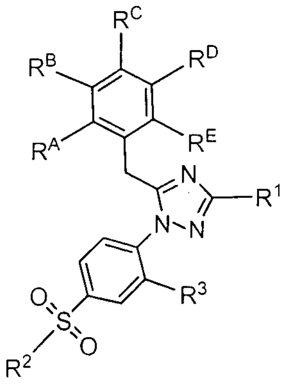
Example #	Structure	Chemical Name	¹HNMR	MS
K-3		[1-{4-[(Acetylamino)sulfonyl]-2-fluorophenyl}-5-(2,5-dimethylbenzyl)-1H-1,2,4-triazol-3-yl]methyl Nitrate	^{1}H NMR (300 MHz, DMSO-d_6): δ 2.00 (s, 3 H), 2.02 (s, 3 H), 2.10 (s, 3 H), 4.11-4.14 (m, 2 H), 5.72 – 5.70 (m, 2 H), 6.59 – 6.63 (m, 1 H), 6.86 – 6.92 (m, 2 H), 6.94 – 6.99 (m, 2 H), 7.87 – 7.99 (m, 3 H), 12.44 (br s, 1 H).	478.2
L-1		[1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1H-1,2,4-triazol-3-yl]methyl 4-(Nitrooxy)-L-prolinate	(400 MHz, CHLOROFORM-d) δ 7.73 - 7.83 (m, 2 H), 7.40 - 7.47 (m, 1 H), 6.95 - 6.99 (m, 1 H), 6.89 - 6.95 (m, 1 H), 6.64 (s, 1 H), 5.42 - 5.47 (m, 1 H), 5.35 - 5.41 (m, 1 H), 4.99 (s, 2 H), 4.79 (t, J=7.6 Hz, 1 H), 4.68 (t, J=7.6 Hz, 1 H), 4.05 (d, J=3.0 Hz, 2 H), 3.95 (d, J=3.8 Hz, 1 H), 2.53 - 2.61 (m, 2 H), 2.18 (s, 3 H), 2.05 (s, 3 H).	549.2
M-1		1-[1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1H-1,2,4-triazol-3-yl]ethyl {2-[2-(Nitrooxy)ethoxy]ethoxy}acetate	(300 MHz, DMSO-d_6) δ 7.73 - 7.87 (m, 3 H), 7.70 (br. s., 2 H), 6.96 (d, J=7.5 Hz, 1 H), 6.88 (d, J=7.7 Hz, 1 H), 6.55 (s, 1 H), 5.95 (q, J=6.5 Hz, 1 H), 4.60 - 4.68 (m, 2 H), 4.15 (d, J=4.3 Hz, 2 H), 4.05 (s, 2 H), 3.67 - 3.73 (m, 2 H), 3.53 - 3.62 (m, 4 H), 2.09 (s, 3 H), 2.02 (s, 3 H), 1.56 (d, J=6.6 Hz, 3 H).	391.1
N-1		2-[1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1H-1,2,4-triazol-3-yl]-2-hydroxyethyl Nitrate	(400 MHz, DMSO-d_6) □ 7.66 - 7.85 (m, 5 H), 6.93 - 6.99 (m, 1 H), 6.85 - 6.91 (m, 1 H), 6.58 (s, 1 H), 6.17 (d, J=6.1 Hz, 1 H), 4.90 - 4.99 (m, 1 H), 4.76 - 4.86 (m, 2 H), 4.05 (s, 2 H), 2.10 (s, 3 H), 2.02 (s, 3 H).	466.2
O-1		{1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1H-124-triazol-3-yl}methyl 3-(2-{2-[2-(Nitrooxy)ethoxy]ethoxy}ethoxy)propanoate	(300 MHz, DMSO- d_6) δ 2.05 (s, 3 H), 2.13 (s, 3 H), 2.62 (t, J=6.1 Hz, 2 H), 3.48 - 3.57 (m, 8 H), 3.66 (t, J=6.1 Hz, 2 H), 3.69 - 3.73 (m, 2 H), 4.07 (s, 2 H), 4.63 - 4.69 (m, 2 H), 5.13 (s, 2 H), 6.62 (s, 1 H), 6.91 (d, J=7.5 Hz, 1 H), 6.98 (d, J=7.5 Hz, 1 H), 7.72 (s, 2 H), 7.77 - 7.92 (m, 3 H).	640.2

Example #	Structure	Chemical Name	^{1}HNMR	MS
P-1		{1-[4-(Aminosulfonyl)-2-fluorophenyl]-5-(2,5-dimethylbenzyl)-1H-124-triazol-3-yl}methyl 4-{2-[2-(Nitrooxy)ethoxy]ethoxy}butanoate	(300 MHz, DMSO- d_6) δ 1.72 - 1.84 (m, 2 H), 2.05 (s, 3 H), 2.13 (s, 3 H), 2.41 (t, J=7.4 Hz, 2 H), 3.38 - 3.43 (m, 2 H), 3.45 - 3.49 (m, 2 H), 3.51 - 3.56 (m, 2 H), 3.69 - 3.74 (m, 2 H), 4.05 - 4.08 (m, 2 H), 4.63 - 4.68 (m, 2 H), 5.13 (s, 2 H), 6.62 (s, 1 H), 6.91 (d, J=7.5 Hz, 1 H), 6.98 (d, J=7.5 Hz, 1 H), 7.72 (s, 2 H), 7.77 - 7.92 (m, 3 H).	610.1

While the invention has been illustrated by reference to specific and preferred embodiments, those skilled in the art will recognize that variations and modifications may be made through routine experimentation and practice of the invention. Thus, the invention is intended not to be limited by the foregoing description, but to be defined by the appended claims and their equivalents.

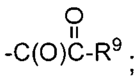
We Claim:

1. A compound of formula (I):



(I)

wherein:

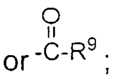
R^1 is H, $(C_1\text{-}C_{10})$alkyl, $-OR^5$, $-C(O)R^5$, $-C(O)OR^5$, or  $-C(O)C(=O)\text{-}R^9$;

R^2 is $(C_1\text{-}C_6)$alkyl or NR^6R^7;

R^3 is H or halo;

each R^A, R^B, R^C, R^D, and R^E is independently H, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $-OR^5$, or $-C(O)R^5$;

each R^5 is independently H, -OH, $-NO_2$, $-ONO_2$, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_6\text{-}C_{10})$aryl, or $(C_6\text{-}C_{10})$heteroaryl, wherein each of said $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_6\text{-}C_{10})$aryl, and $(C_6\text{-}C_{10})$heteroaryl moieties of said R^5 groups is optionally substituted by one or more R^9 moieties;

each R^6 and R^7, which may be the same or different, is independently H, -OH, -C(O)R^8, or  $-C(=O)\text{-}R^9$;

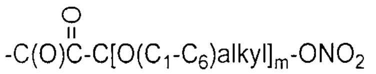
each R^8 is independently $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, or $(C_6\text{-}C_{10})$heteroaryl, wherein each of said $(C_3\text{-}C_{10})$cycloalkyl, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, and $(C_6\text{-}C_{10})$heteroaryl moieties of said R^8 groups are optionally substituted by $-NO_2$ or $-ONO_2$;

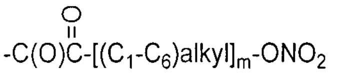
each R^9 is independently $-NO_2$, $-ONO_2$, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_{10})$cycloalkyl, $[(C_1\text{-}C_6)\text{alkyl}(O)]_m$, $-C[O(C_1\text{-}C_6)\text{alkyl}]_m$, $-[O(C_1\text{-}C_6)\text{alkyl}]_m$, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_1\text{-}C_6)\text{alkyl}(NH)_nC(=O)$, $-(NH)_n(C_1\text{-}C_6)$alkoxy, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, or $(C_6\text{-}C_{10})$heteroaryl, wherein each of said $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $[(C_1\text{-}C_6)alkyl(O)]_m$, $-C[O(C_1\text{-}C_6)alkyl]_m$, $-[O(C_1\text{-}C_6)alkyl]_m$, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_1\text{-}C_6)alkyl(NH)_nC(=O)$, $-(NH)_n(C_1\text{-}C_6)$alkoxy, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, and $(C_6\text{-}C_{10})$heteroaryl moieties of said R^9 groups are optionally substituted by $-NO_2$, $-ONO_2$, $[(C_1\text{-}C_{10})alkoxy]NO_2$, $[(C_1\text{-}C_{10})alkoxy]ONO_2$, $[(C_1\text{-}C_6)alkyl]ONO_2$, or $[(C_1\text{-}C_6)alkyl]NO_2$; and

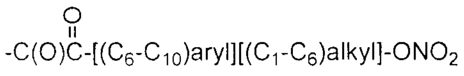
m and n are each independently an integer from 1 to 4;

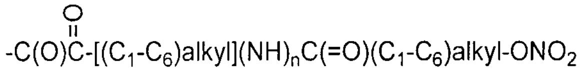
or a pharmaceutically acceptable salt or solvate thereof.

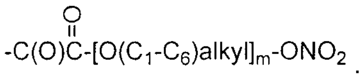
2. A compound according to claim 1 wherein R^1 is $-COH$, $-C(O)NO_2$,


$-C(O)\overset{O}{\overset{\|}{C}}\text{-}C[O(C_1\text{-}C_6)alkyl]_m\text{-}ONO_2$,

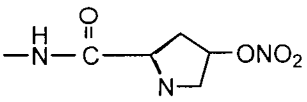

$-C(O)\overset{O}{\overset{\|}{C}}\text{-}[(C_1\text{-}C_6)alkyl]_m\text{-}ONO_2$,


$-C(O)\overset{O}{\overset{\|}{C}}\text{-}[(C_6\text{-}C_{10})aryl][(C_1\text{-}C_6)alkyl]\text{-}ONO_2$,

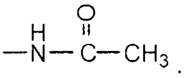

$-C(O)\overset{O}{\overset{\|}{C}}\text{-}[(C_1\text{-}C_6)alkyl](NH)_nC(=O)(C_1\text{-}C_6)alkyl\text{-}ONO_2$, or


$-C(O)\overset{O}{\overset{\|}{C}}\text{-}[O(C_1\text{-}C_6)alkyl]_m\text{-}ONO_2$.

3. A compound according to claim 1 wherein R^2 is NH_2 ,



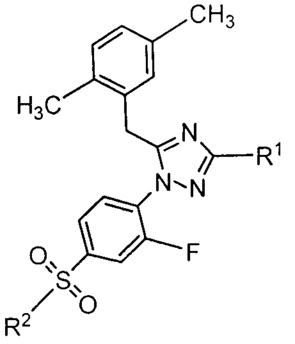
, or


$-\overset{H}{N}-\overset{O}{\overset{\|}{C}}-CH_3$.

4. A compound according to claim 1 wherein R^3 is selected from Br, Cl, F, and I.

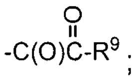
5. A compound according to claim 1 wherein each R^A, R^B, R^C, R^D, and R^E is independently H or $(C_1\text{-}C_6)$alkyl.

6. A compound of formula (IIa):



(IIa)

wherein:

R^1 is H, $(C_1\text{-}C_{10})$alkyl, $-OR^5$, $-C(O)R^5$, $-C(O)OR^5$, or  $-C(O)\overset{O}{\overset{\|}{C}}-R^9$;

R^2 is $(C_1\text{-}C_6)$alkyl or NR^6R^7;

each R^5 is independently H, -OH, $-NO_2$, $-ONO_2$, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_6\text{-}C_{10})$aryl, or $(C_6\text{-}C_{10})$heteroaryl, wherein each of said $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_6\text{-}C_{10})$aryl, and $(C_6\text{-}C_{10})$heteroaryl moieties of said R^5 groups is optionally substituted by one or more R^9 moieties;

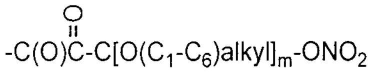
each R^6 and R^7, which may be the same or different, is independently H, -OH, $-C(O)R^8$,

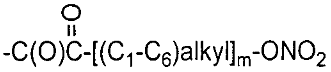
each R^8 is independently $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, or $(C_6\text{-}C_{10})$heteroaryl, wherein each of said $(C_3\text{-}C_{10})$cycloalkyl, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, and $(C_6\text{-}C_{10})$heteroaryl moieties of said R^8 groups are optionally substituted by $-NO_2$ or $-ONO_2$;

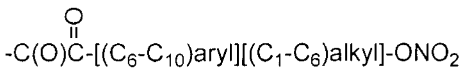
each R^9 is independently $-NO_2$, $-ONO_2$, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_{10})$cycloalkyl, $[(C_1\text{-}C_6)alkyl(O)]_m$, $-C[O(C_1\text{-}C_6)alkyl]_m$, $-[O(C_1\text{-}C_6)alkyl]_m$, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_1\text{-}C_6)alkyl(NH)_nC(=O)$, $-(NH)_n(C_1\text{-}C_6)$alkoxy, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, or $(C_6\text{-}C_{10})$heteroaryl, wherein each of said $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $[(C_1\text{-}C_6)alkyl(O)]_m$, $-C[O(C_1\text{-}C_6)alkyl]_m$, $-[O(C_1\text{-}C_6)alkyl]_m$, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_1\text{-}C_6)alkyl(NH)_nC(=O)$, $-(NH)_n(C_1\text{-}C_6)$alkoxy, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, and $(C_6\text{-}C_{10})$heteroaryl moieties of said R^9 groups are optionally substituted by $-NO_2$, $-ONO_2$, $[(C_1\text{-}C_{10})alkoxy]NO_2$, $[(C_1\text{-}C_{10})alkoxy]ONO_2$, $[(C_1\text{-}C_6)alkyl]ONO_2$, or $[(C_1\text{-}C_6)alkyl]NO_2$; and m and n are each independently an integer from 1 to 4;

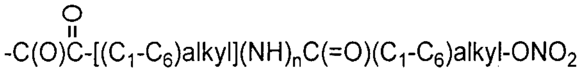
or a pharmaceutically acceptable salt or solvate thereof.

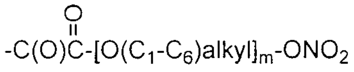
7. A compound according to claim 6 wherein R^1 is –COH, -C(O)NO$_2$,


$-C(O)\overset{\underset{\|}{O}}{C}-C[O(C_1-C_6)alkyl]_m-ONO_2$,

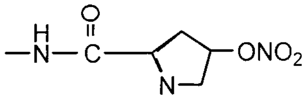

$-C(O)\overset{\underset{\|}{O}}{C}-[(C_1-C_6)alkyl]_m-ONO_2$,


$-C(O)\overset{\underset{\|}{O}}{C}-[(C_6-C_{10})aryl][(C_1-C_6)alkyl]-ONO_2$,

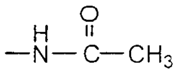

$-C(O)\overset{\underset{\|}{O}}{C}-[(C_1-C_6)alkyl](NH)_nC(=O)(C_1-C_6)alkyl-ONO_2$, or


$-C(O)\overset{\underset{\|}{O}}{C}-[O(C_1-C_6)alkyl]_m-ONO_2$.

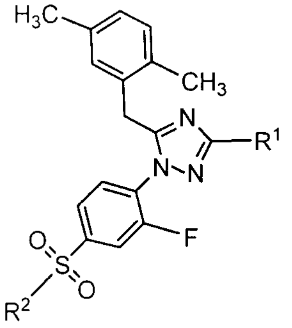
8. A compound according to claim 6 wherein R^2 is NH_2 ,



, or


$-\overset{H}{N}-\overset{\underset{\|}{O}}{C}-CH_3$.

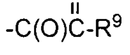
9. A compound of formula (IIb):



(IIb)

wherein:

R^1 is H, (C_1-C_{10})alkyl, $-OR^5$, $-C(O)R^5$, $-C(O)OR^5$, or


$-C(O)\overset{\underset{\|}{O}}{C}-R^9$;

R^2 is (C_1-C_6)alkyl or NR^6R^7;

each R^5 is independently H, -OH, $-NO_2$, $-ONO_2$, (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, (C_1-C_6)alkoxy, (C_3-C_{10})cycloalkoxy, (C_6-C_{10})aryl, or (C_6-C_{10})heteroaryl, wherein each of said (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, (C_1-C_6)alkoxy, (C_3-C_{10})cycloalkoxy, (C_6-C_{10})aryl, and (C_6-C_{10})heteroaryl moieties of said R^5 groups is optionally substituted by one or more R^9 moieties;

each R^6 and R^7, which may be the same or different, is independently H, -OH, -C(O)R^8, or $-\overset{\text{O}}{\overset{\|}{\text{C}}}-R^9$;

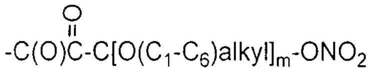
each R^8 is independently (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_{10})cycloalkyl, (C_4-C_{10})heterocycloalkyl, (C_6-C_{10})aryl, or (C_6-C_{10})heteroaryl, wherein each of said (C_3-C_{10})cycloalkyl, (C_4-C_{10})heterocycloalkyl, (C_6-C_{10})aryl, and (C_6-C_{10})heteroaryl moieties of said R^8 groups are optionally substituted by -NO_2 or -ONO_2;

each R^9 is independently -NO_2, -ONO_2, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_{10})cycloalkyl, [(C_1-C_6)alkyl(O)]$_m$, -C[O(C_1-C_6)alkyl]$_m$, -[O(C_1-C_6)alkyl]$_m$, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_3-C_{10})cycloalkoxy, (C_1-C_6)alkyl(NH)$_n$C(=O), -(NH)$_n$(C_1-C_6)alkoxy, (C_4-C_{10})heterocycloalkyl, (C_6-C_{10})aryl, or (C_6-C_{10})heteroaryl, wherein each of said (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_{10})cycloalkyl, (C_1-C_6)alkoxy, [(C_1-C_6)alkyl(O)]$_m$, -C[O(C_1-C_6)alkyl]$_m$, -[O(C_1-C_6)alkyl]$_m$, (C_3-C_{10})cycloalkoxy, (C_1-C_6)alkyl(NH)$_n$C(=O), -(NH)$_n$(C_1-C_6)alkoxy, (C_4-C_{10})heterocycloalkyl, (C_6-C_{10})aryl, and (C_6-C_{10})heteroaryl moieties of said R^9 groups are optionally substituted by -NO_2, -ONO_2,. [(C_1-C_{10})alkoxy]NO_2, [(C_1-C_{10})alkoxy]ONO_2, [(C_1-C_6)alkyl]ONO_2, or [(C_1-C_6)alkyl]NO_2; and

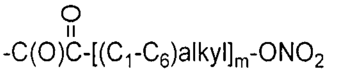
m and n are each independently an integer from 1 to 4;

or a pharmaceutically acceptable salt or solvate thereof.

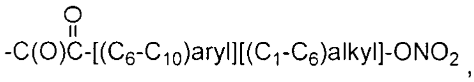
10. A compound according to claim 9 wherein R^1 is –COH, -C(O)NO_2,



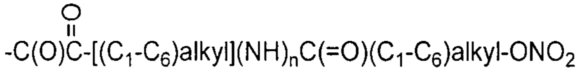
$-C(O)\overset{\text{O}}{\overset{\|}{\text{C}}}-C[O(C_1-C_6)alkyl]_m-ONO_2$,



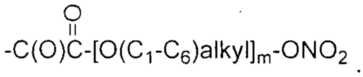
$-C(O)\overset{\text{O}}{\overset{\|}{\text{C}}}-[(C_1-C_6)alkyl]_m-ONO_2$,



$-C(O)\overset{\text{O}}{\overset{\|}{\text{C}}}-[(C_6-C_{10})aryl][(C_1-C_6)alkyl]-ONO_2$,

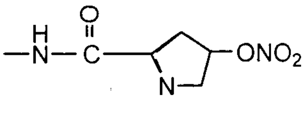


$-C(O)\overset{\text{O}}{\overset{\|}{\text{C}}}-[(C_1-C_6)alkyl](NH)_nC(=O)(C_1-C_6)alkyl-ONO_2$, or

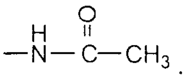


$-C(O)\overset{\text{O}}{\overset{\|}{\text{C}}}-[O(C_1-C_6)alkyl]_m-ONO_2$.

11. A compound according to claim 9 wherein R^2 is NH_2 ,

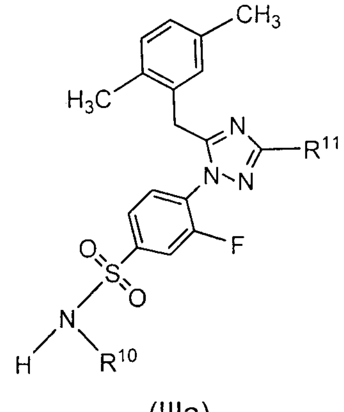


, or



$-\overset{\text{H}}{\text{N}}-\overset{\text{O}}{\overset{\|}{\text{C}}}-CH_3$.

12. A compound of formula (IIIa):



(IIIa)

wherein:

R^{10} is H or $\overset{\overset{\displaystyle O}{\|}}{C}\text{-}R^{13}$;

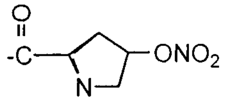
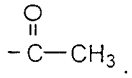
R^{11} is H, $(C_1\text{-}C_{10})$alkyl, $-OR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, or $-C(O)\overset{\overset{\displaystyle O}{\|}}{C}\text{-}R^{13}$;

each R^{12} is independently H, -OH, $-NO_2$, $-ONO_2$, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_6\text{-}C_{10})$aryl, or $(C_6\text{-}C_{10})$heteroaryl, wherein each of said $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_6\text{-}C_{10})$aryl, and $(C_6\text{-}C_{10})$heteroaryl moieties of said R^{12} groups is optionally substituted by one or more R^{13} moieties;

R^{13} is independently $-NO_2$, $-ONO_2$, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_{10})$cycloalkyl, $[(C_1\text{-}C_6)alkyl(O)]_m$, $-C[O(C_1\text{-}C_6)alkyl]_m$, $-[O(C_1\text{-}C_6)alkyl]_m$, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_1\text{-}C_6)alkyl(NH)_nC(=O)$, $-(NH)_n(C_1\text{-}C_6)$alkoxy, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, or $(C_6\text{-}C_{10})$heteroaryl, wherein each of said $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $[(C_1\text{-}C_6)alkyl(O)]_m$, $-C[O(C_1\text{-}C_6)alkyl]_m$, $-[O(C_1\text{-}C_6)alkyl]_m$, $(C_3\text{-}C_{10})$cycloalkoxy, $(C_1\text{-}C_6)alkyl(NH)_nC(=O)$, $-(NH)_n(C_1\text{-}C_6)$alkoxy, $(C_4\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, and $(C_6\text{-}C_{10})$heteroaryl moieties of said R^9 groups are optionally substituted by $-NO_2$, $-ONO_2$, $[(C_1\text{-}C_{10})alkoxy]NO_2$, $[(C_1\text{-}C_{10})alkoxy]ONO_2$, $[(C_1\text{-}C_6)alkyl]ONO_2$, or $[(C_1\text{-}C_6)alkyl]NO_2$; and

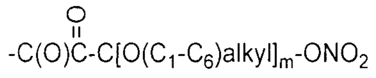
m and n are each independently an integer from 1 to 4;

or a pharmaceutically acceptable salt or solvate thereof.

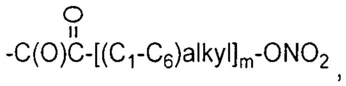
13. A compound according to claim 12 wherein R^{10} is H,  , or 

$-\overset{\overset{O}{\|}}{C}-CH_3$.

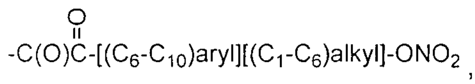
14. A compound according to claim 12 wherein R^{11} is –COH, $-C(O)NO_2$,



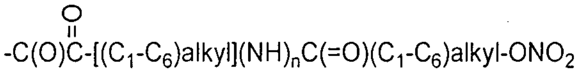
$-C(O)\overset{\overset{O}{\|}}{C}-C[O(C_1-C_6)\text{alkyl}]_m-ONO_2$,



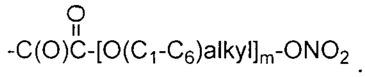
$-C(O)\overset{\overset{O}{\|}}{C}-[(C_1-C_6)\text{alkyl}]_m-ONO_2$,



$-C(O)\overset{\overset{O}{\|}}{C}-[(C_6-C_{10})\text{aryl}][(C_1-C_6)\text{alkyl}]-ONO_2$,

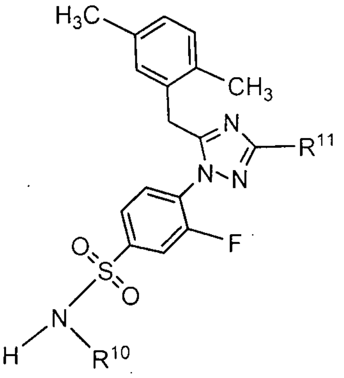


$-C(O)\overset{\overset{O}{\|}}{C}-[(C_1-C_6)\text{alkyl}](NH)_nC(=O)(C_1-C_6)\text{alkyl}-ONO_2$, or



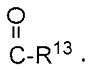
$-C(O)\overset{\overset{O}{\|}}{C}-[O(C_1-C_6)\text{alkyl}]_m-ONO_2$.

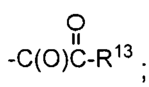
15. A compound of formula (IIIb):



(IIIb)

wherein:

R^{10} is H or  $\overset{\overset{O}{\|}}{C}-R^{13}$;

R^{11} is H, (C_1-C_{10})alkyl, $-OR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, or  $-C(O)\overset{\overset{O}{\|}}{C}-R^{13}$;

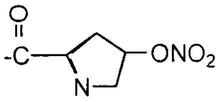
each R^{12} is independently H, -OH, $-NO_2$, $-ONO_2$, (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, (C_1-C_6)alkoxy, (C_3-C_{10})cycloalkoxy, (C_6-C_{10})aryl, or (C_6-C_{10})heteroaryl, wherein each of said (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, (C_1-C_6)alkoxy, (C_3-C_{10})cycloalkoxy, (C_6-C_{10})aryl, and (C_6-C_{10})heteroaryl moieties of said R^{12} groups is optionally substituted by one or more R^{13} moieties;

R^{13} is independently -NO_2, -ONO_2, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_{10})cycloalkyl, [(C_1-C_6)alkyl(O)]$_m$, -C[O(C_1-C_6)alkyl]$_m$, -[O(C_1-C_6)alkyl]$_m$, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_3-C_{10})cycloalkoxy, (C_1-C_6)alkyl$(NH)_n$C(=O), -$(NH)_n$(C_1-C_6)alkoxy, (C_4-C_{10})heterocycloalkyl, (C_6-C_{10})aryl, or (C_6-C_{10})heteroaryl, wherein each of said (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_{10})cycloalkyl, (C_1-C_6)alkoxy, [(C_1-C_6)alkyl(O)]$_m$, -C[O(C_1-C_6)alkyl]$_m$, -[O(C_1-C_6)alkyl]$_m$, (C_3-C_{10})cycloalkoxy, (C_1-C_6)alkyl$(NH)_n$C(=O), -$(NH)_n$(C_1-C_6)alkoxy, (C_4-C_{10})heterocycloalkyl, (C_6-C_{10})aryl, and (C_6-C_{10})heteroaryl moieties of said R^9 groups are optionally substituted by -NO_2, -ONO_2, [(C_1-C_{10})alkoxy]NO_2, [(C_1-C_{10})alkoxy]ONO_2, [(C_1-C_6)alkyl]ONO_2, or [(C_1-C_6)alkyl]NO_2; and

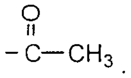
m and n are each independently an integer from 1 to 4;

or a pharmaceutically acceptable salt or solvate thereof.

16. A compound according to claim 15 wherein R^{10} is H,

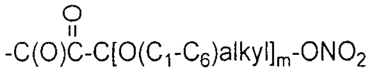


, or

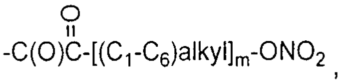


$-\overset{\overset{O}{\|}}{C}-CH_3$.

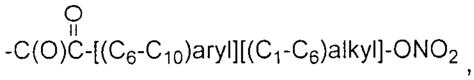
17. A compound according to claim 15 wherein R^{11} is –COH, -C(O)NO_2,



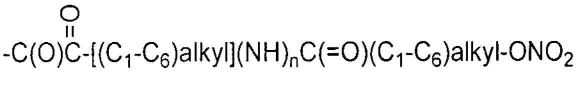
$-C(O)\overset{\overset{O}{\|}}{C}\text{-C[O(}C_1\text{-}C_6\text{)alkyl]}_m\text{-}ONO_2$,



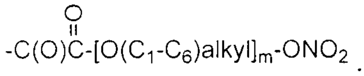
$-C(O)\overset{\overset{O}{\|}}{C}\text{-[(}C_1\text{-}C_6\text{)alkyl]}_m\text{-}ONO_2$,



$-C(O)\overset{\overset{O}{\|}}{C}\text{-[(}C_6\text{-}C_{10}\text{)aryl][(}C_1\text{-}C_6\text{)alkyl]-}ONO_2$,

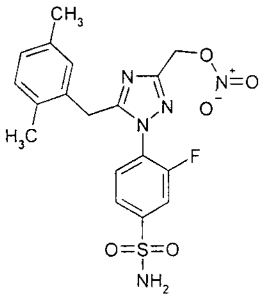


$-C(O)\overset{\overset{O}{\|}}{C}\text{-[(}C_1\text{-}C_6\text{)alkyl](NH)}_n\text{C(=O)(}C_1\text{-}C_6\text{)alkyl-}ONO_2$, or



$-C(O)\overset{\overset{O}{\|}}{C}\text{-[O(}C_1\text{-}C_6\text{)alkyl]}_m\text{-}ONO_2$.

18. A compound selected from the group consisting of:



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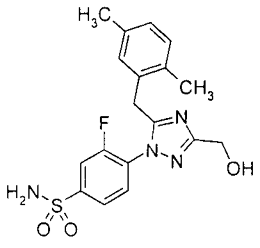

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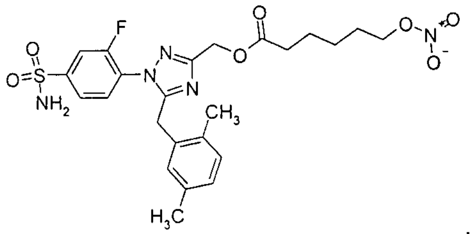

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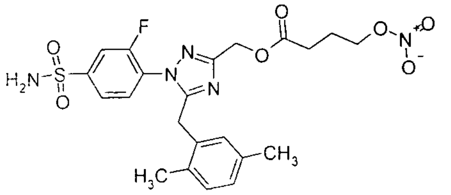

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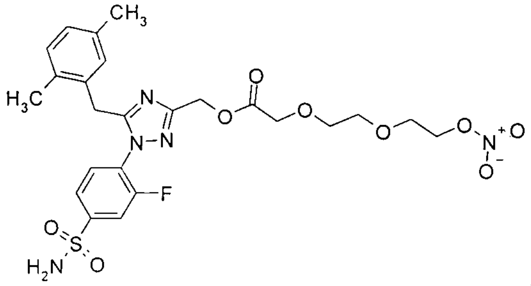

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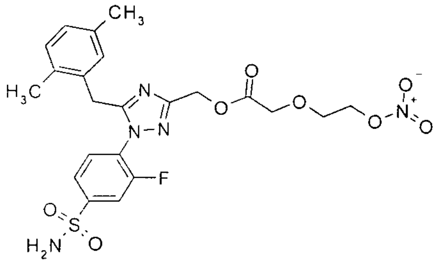

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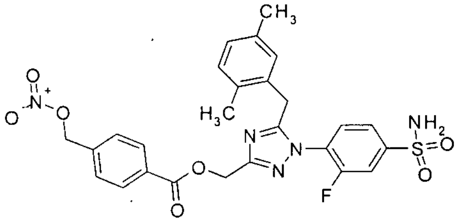

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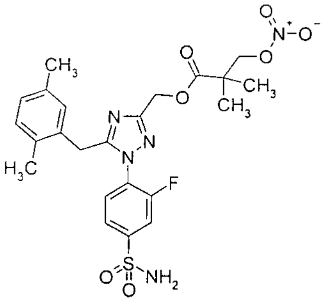
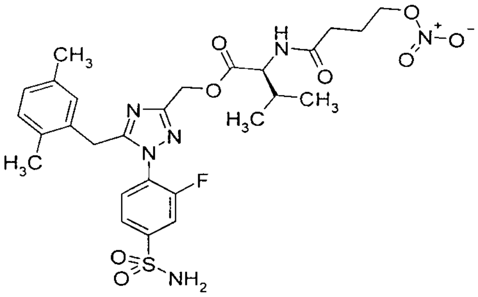


,

Chiral



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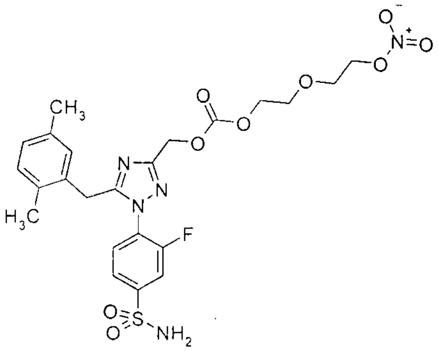

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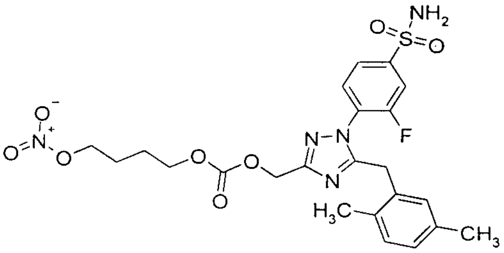

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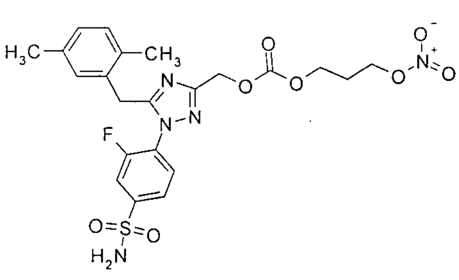

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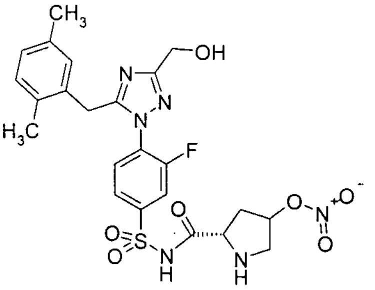

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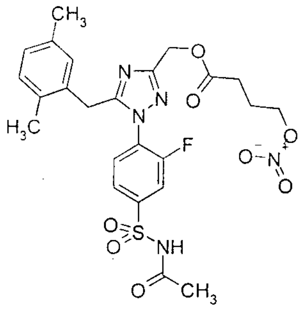

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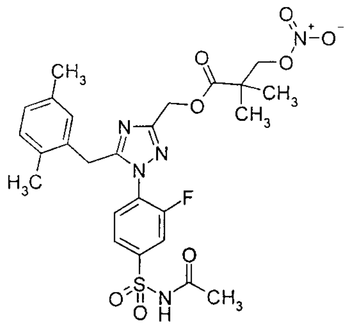
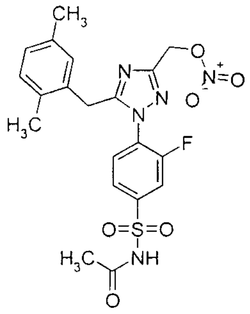


and



,

or a pharmaceutically acceptable salt or solvate thereof.

19. The use of a compound according to any one of claims 1 to 18 for the preparation of a medicament for treating glaucoma or ocular hypertension.

20. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound according to any one of claims 1 to 18.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2007/003831

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D249/08 A61K31/4196 A61P27/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2006/042215 A (JANSSEN PHARMACEUTICA NV [BE]) 20 April 2006 (2006-04-20) claims 1,42	1-20
A	US 5 681 834 A (MAY JESSE A [US] ET AL) 28 October 1997 (1997-10-28) column 1, line 58 - column 2, line 20	1-20

☐ 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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search 19 May 2008	Date of mailing of the international search report 27/05/2008
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Cortés, José

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2007/003831

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006042215 A	20-04-2006	AU 2005295016 A1 CA 2583150 A1 CN 101084200 A EP 1797049 A1 KR 20070061907 A	20-04-2006 20-04-2006 05-12-2007 20-06-2007 14-06-2007
US 5681834 A	28-10-1997	NONE	

Form PCT/ISA/210 (patent family annex) (April 2005)