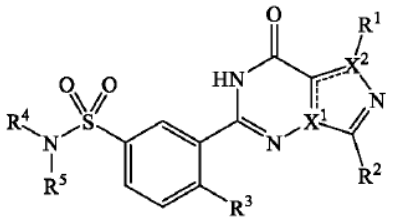
CLAIMS

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

X^1 is C or N;

X^2 is C or N;

R^1 is H or (C_1-C_5) alkyl;

R^2 is (C_1-C_5) alkyl;

R3 is O(C_1-C_5) alkyl;

R^4 is H or (C_1 -C_5) alkyl;

R^5 is carbocyclyl or heterocyclyl;

wherein the carbocyclyl or heterocyclyl is 4-membered; and

wherein the carbocyclyl or heterocyclyl is substituted with one or more independently selected R^6 substituents; or

R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a heterocyclyl;

wherein the heterocyclyl is 4-membered; and

wherein the heterocyclyl is substituted with one or more independently selected R^6 substituents;

each R6 is independently (C_1-C_5) alkyl, (C_1-C_5) alkylene-Z^1-(C_1-C_5) alkyl, (C_1-C_5) alkylene-(C_3-C_5) heterocyclyl, (C_1 -C_5) alkylene-(C_3-C_5) heterocyclylene-(C_1-C_5) alkyl, (C_2-C_{10}) alkenyl, (C_2-C_{10}) alkynyl, $NR^{1'}$-(C_1-C_{10}) alkyl, $NR^{1'}$-(C_1-C_5) alkylene-Z^1-(C_1-C_{10}) alkyl, $NR^{1'}$-(C_1-C_5) alkylene-Z^1-O(C_1-C_{10}) alkyl, OH, O(C_1-C_5) alkyl, O(C_1-C_5) alkylene-Z^1-(C_1-C_5) alkyl, ONO_2, (C_3-C_5) heterocyclyl, or (C_3-C_5) heterocyclylene-(C_1-C5) alkyl;

wherein each (C_1-C_5) alkyl, (C_1-C_5) alkylene-Z^1-(C_1-C_5) alkyl, (C_1-C_5) alkylene-(C_3-C_5) heterocyclyl, (C_2-C_{10}) alkenyl, (C_2-C_{10}) alkynyl, $NR^{1'}$-(C_1-C_{10}) alkyl, $NR^{1'}$-(C_1-C_5) alkylene-Z^1-(C_1-C_{10}) alkyl, $NR^{1'}$-(C_1-C_5) alkylene-Z^1-O(C_1-C_{10}) alkyl, O(C_1-C_5) alkyl, O(C_1-C_5) alkylene-Z^1-(C_1-C_5) alkyl, (C_3-C_5) heterocyclyl, and (C_3-C_5) heterocyclylene-(C_1-C_5) alkyl is optionally and independently substituted with one or more substituents independently selected from the group consisting of halogen, (C_1-C_3) alkyl, C(O)OH, NH_2, OH, O(C_1-C_3) alkyl, ONO, and ONO_2; and

wherein each (C_1-C_5) alkylene-(C_3-C_5) heterocyclylene-(C_1-C_5) alkyl is independently substituted with one or more substituents independently selected from the group consisting of halogen, (C_1-C_3) alkyl, C(O)OH, NH_2, OH, O(C_1-C_3) alkyl, ONO, and ONO_2;

$R^{1'}$ is H or (C_1-C_5) alkyl, wherein the (C_1-C_5) alkyl is optionally substituted with one or more substituents independently selected from the group consisting of NH_2, OH, and ONO_2; and

each Z^1 is independently -C(O)NH-, -C(O)O-, -NH-, -NHC(O)-, -O-, or -OC(O)-;

with the provisos that:

(1) at least one of X^1 and X^2 is N; and

(2) at least one R^6 substituent is substituted with NH_2, OH, ONO, or ONO_2.

2. The compound of claim 1, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

X^1 is N; and

X^2 is C.

3. The compound of claim 1, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

X^1 is C; and

X^2 is N.

4. The compound of claim 1, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein at least one R^6 substituent is substituted with ONO_2.

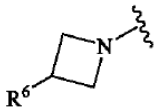
5. The compound of claim 1, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

R^4 is H; and

R^5 is azetidinyl, wherein the azetidinyl is substituted with one or more independently selected R^6 substituents.

6. The compound of claim 1, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$-NR^4R^5$ is:

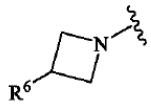


; and

R^6 is $(CH_2)_3$-OC(O)-$(CH_2)_2CH(ONO_2)CH_2ONO_2$ or $(CH_2)_3$-OC(O)-$(CH_2)_3CH(ONO_2)CH_2ONO_2$.

7. The compound of claim 1, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

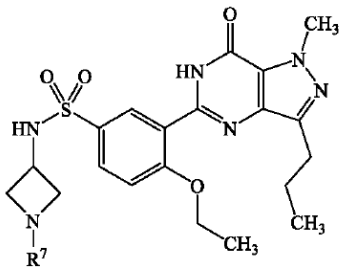
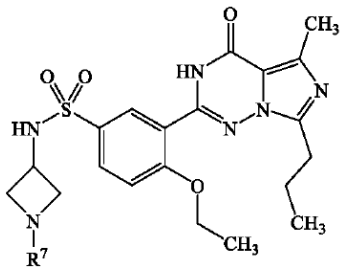
$-NR^4R^5$ is



; and

R^6 is NH-$(CH_2)_2$-OC(O)-$(CH_2)_3CH(ONO_2)CH_2ONO_2$ or N(CH_3)-$(CH_2)_2$-OC(O)-$(CH_2)_3CH(ONO_2)CH_2ONO_2$.

8. The compound of claim 5, wherein the compound is of formula (IIa) or formula (IIb):

(IIa) or (IIb)

or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

R^6 is R^7;

R^7 is H, R^{70}, or R^{71}-Z^2-R^{72};

R^{70} is $(C_1$-$C_5)$alkyl, $(C_2$-$C_{10})$alkenyl, $(C_2$-$C_{10})$alkynyl, or $O(C_1$-$C_5)$alkyl, wherein the $(C_1$-$C_5)$alkyl, $(C_2$-$C_{10})$alkenyl, $(C_2$-$C_{10})$alkynyl, or $O(C_1$-$C_5)$alkyl is optionally substituted with one or more substituents independently selected from the group consisting of NH_2, OH, and ONO_2;

R^{71} is $(C_1$-$C_5)$alkylene or $O(C_1$-$C_5)$alkylene, wherein the $(C_1$-$C_5)$ alkylene or $O(C_1$-$C_5)$ alkylene is optionally substituted with one or more substituents independently selected from the group consisting of NH_2, OH, and ONO_2;

Z^2 is -C(O)NH-, -C(O)O-, -NH-, -NHC(O)-, -O-, or -OC(O)-; and

R^{72} is $(C_1$-$C_5)$alkyl, wherein the $(C_1$-$C_5)$ alkyl, is optionally substituted with one or more substituents independently selected from the group consisting of NH_2, OH, and ONO_2.

9. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein:

R^6 is R^7;

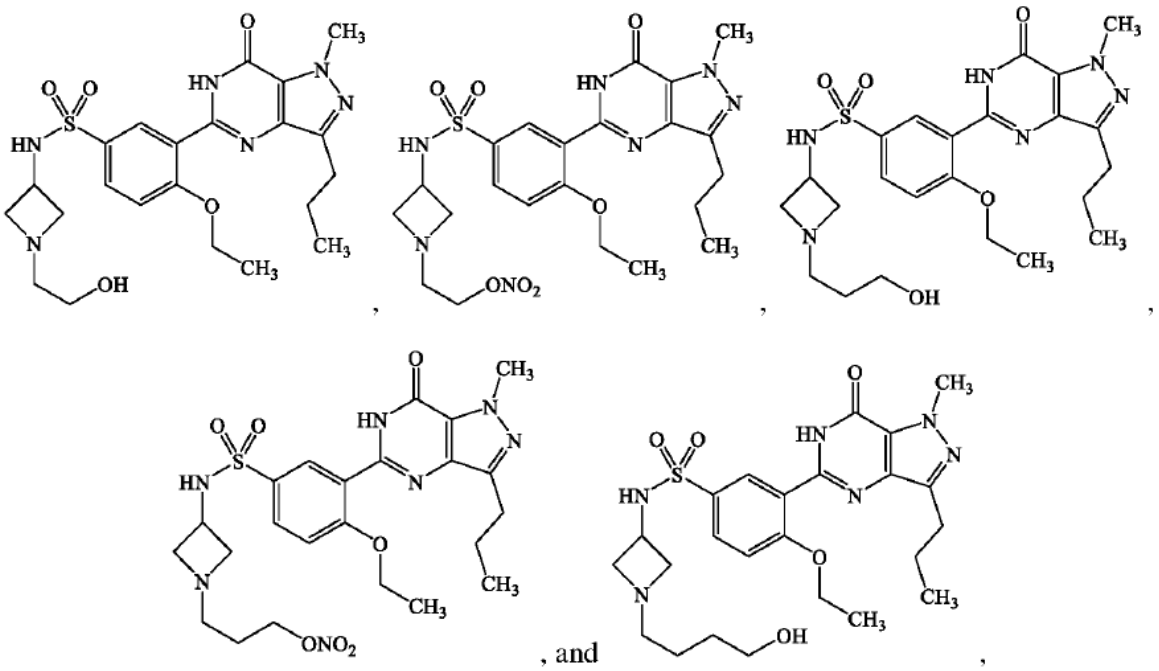
R^7 is R^{70};

R^{70} is $–(CH_2)_nOR^8$;

R^8 is H or NO_2; and

n is 1, 2, 3, 4, or 5.

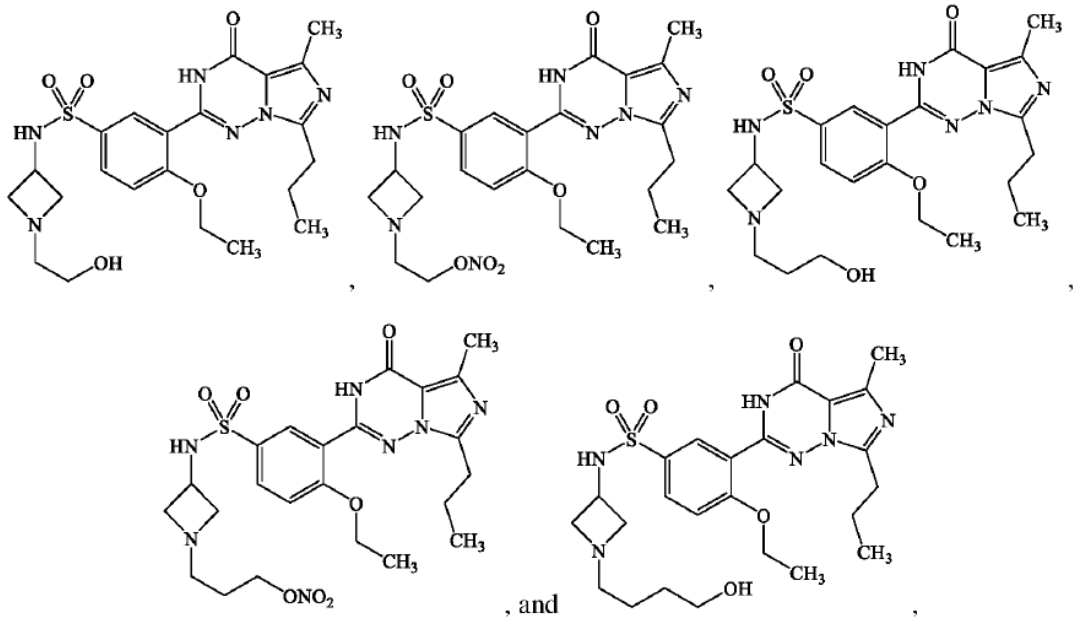
10. The compound of claim 9, wherein the compound is selected from the group consisting of:



, and

or a pharmaceutically acceptable salt thereof.

11. The compound of claim 9, wherein the compound is selected from the group consisting of:

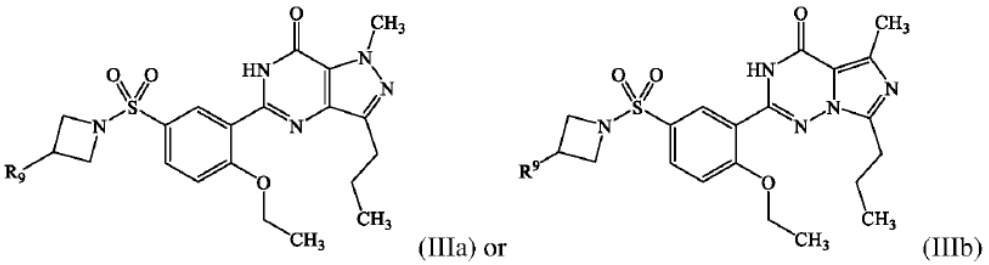


, and

Or a pharmaceutically acceptable salt thereof.

12. The compound of claim 1, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^4 and R^5, taken together with the nitrogen atom to which they are attached, form an azetidinyl, wherein the azetidinyl is substituted with one or more independently selected R^6 substituents.

13. The compound of claim 12, wherein the compound is of formula (IIIa) or formula (IIIb):



or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

R^6 is R^9;

R^9 is R^{90}, $NR^{10}R^{11}$, OR^{12}, or R^{91}-Z^3-R^{92};

R^{10} is (C_1-C_5) alkyl or (C_1-C_5) alkylene-Z^3-(C_1-C_5) alkyl, wherein the (C_1-C_5) alkyl or (C_1-C_5) alkylene-Z^3-(C_1-C_5) alkyl is optionally substituted with one or more substituents independently selected from the group consisting of NH_2, OH, and ONO_2;

R^{11} is H or (C_1-C_5) alkyl, wherein the (C_1-C_5) alkyl is optionally substituted with one or more substituents independently selected from the group consisting of NH_2, OH, and ONO_2;

R^{12} is H, (C_1-C_5) alkyl, (C_1-C_5) alkylene-Z^3-(C_1-C_5) alkyl, or NO_2, wherein the (C_1-C_5) alkyl or (C_1-C_5)alkylene-Z^3-(C_1-C_5) alkyl is optionally substituted with one or more substituents independently selected from the group consisting of NH_2, OH, and ONO_2;

R^{90} is (C_1-C_5) alkyl, (C_1 -C_5) alkylene-(C_3-C_5) heterocyclyl, (C_1-C_5) alkylene-(C_3-C_5) heterocyclylene(C_1-C_5) alkyl, (C_2-C_{10}) alkenyl, (C_2-C_{10}) alkynyl, O(C_1 -C_5) alkyl, or (C_3-C_5)heterocyclyl;

wherein the (C_1-C_5) alkyl, (C_1-C_5) alkylene-(C_3-C_5) heterocyclyl, (C_2-C_{10}) alkenyl, (C_2-C_{10}) alkynyl, O(C_1-C_5) alkyl, or (C_3-C_5) heterocyclyl is optionally substituted with one or more substituents independently selected from the group consisting of NH_2, OH, and ONO_2; and

wherein the (C_1 -C_5) alkylene-(C_3-C_5) heterocyclylene-(C_1-C_5) alkyl is substituted with one or more substituents independently selected from the group consisting of NH_2, OH, and ONO_2;

R^{91} is (C_1-C_5) alkylene or O(C_1-C_5) alkylene, wherein the (C_1-C_5) alkylene or O(C_1-C_5) alkylene is optionally substituted with one or more substituents independently selected from the group consisting of NH_2, OH, and ONO_2;

Z^3 is -C(O)NH-, -C(O)O-, -NH-, -NHC(O)-, -O-, or -OC(O)-; and

R^{92} is (C_1-C_5) alkyl, wherein the (C_1-C_5) alkyl is optionally substituted with one or more substituents independently selected from the group consisting of NH_2, OH, and ONO_2.

14. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein:

R^6 is R^9;

R^9 is R^{90}, $NR^{10}R^{11}$, OH, ONO_2, or OR^{12};

R^{90} is $-(CH_2)_nR^{13}$;

R^{10} is $-(CH_2)_{0\text{-}4}CH_2R^{15}$ or $-(CH_2)_{0\text{-}4}CH_2R^{16}$;

R^{11} is H, CH_3, or $-(CH_2)_mCH_2R^{17}$;

R^{12} is $-(CH_2)_{0\text{-}4}CH_2R^{14}$;

R^{13} is NH_2, OH, or ONO_2;

R^{14} is NH_2, OH, or ONO_2;

R^{15} is NH_2, OH, or ONO_2;

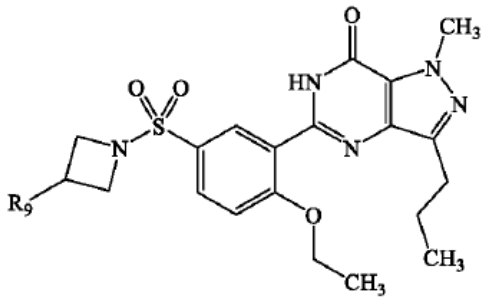
R^{16} is NH_2, OH, or ONO_2;

R^{17} is NH_2, OH, or ONO_2;

m is 0, 1, 2, 3, or 4; and

n is 1, 2, 3, 4, or 5.

15. The compound of claim 14, wherein the compound is of formula (IIIa):



(IIIa)

or a pharmaceutically acceptable salt thereof,

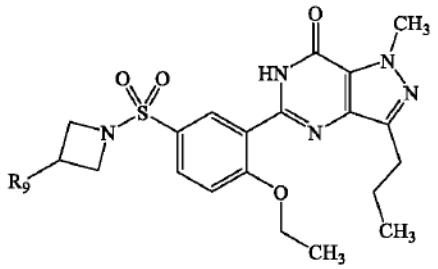
wherein:

R^6 is R^9;

R^9 is R^{90}, OH, or ONO_2; and

R^{90} is CH_2NH_2, CH_2OH, CH_2ONO_2, $(CH_2)_2OH$, $(CH_2)_2ONO_2$, $(CH_2)_3OH$, or $(CH_2)_3ONO_2$.

16. The compound of claim 14, wherein the compound is of formula (Illa):



(IIIa)

or a pharmaceutically acceptable salt thereof,

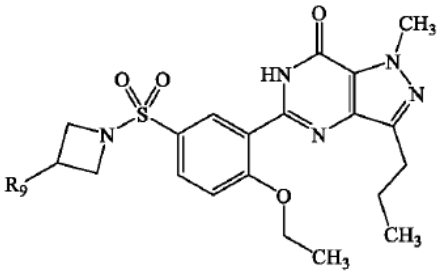
wherein:

R^6 is R^9;

R^9 is $NR^{10}R^{11}$; and

$NR^{10}R^{11}$ is $NH(CH_2)_2OH$, $NH(CH_2)_2ONO_2$, $N(CH_3)(CH_2)_2OH$, $N(CH_3)(CH_2)_2ONO_2$, $NH(CH_2)_3OH$, $NH(CH_2)_3ONO_2$, $N(CH_3)(CH_2)_3OH$, $N(CH_3)(CH_2)_3ONO_2$, $NH(CH_2)_4OH$, $N(CH_3)(CH_2)_4OH$, or $N(CH_3)(CH_2)_3ONO_2$.

17. The compound of claim 14, wherein the compound is of formula (IIIa):



(IIIa)

or a pharmaceutically acceptable salt thereof,

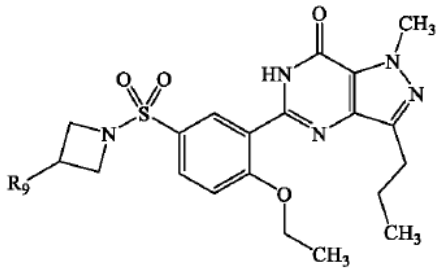
wherein:

R^6 is R^9;

R^9 is $NR^{10}R^{11}$; and

$NR^{10}R^{11}$ is $N[(CH_2)_3OH]_2$ or $N[(CH_2)_3ONO_2]$.

18. The compound of claim 14, wherein the compound is of formula (Illa):



(IIIa)

or a pharmaceutically acceptable salt thereof,

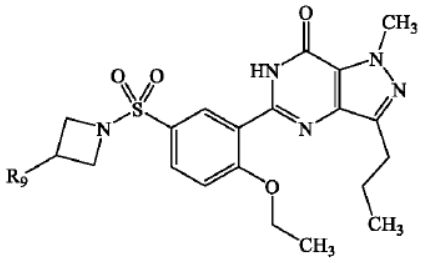
wherein:

R^6 is R^9;

R^9 is OR^{12}; and

R^{12} is $(CH_2)_2OH$, $(CH_2)_2ONO_2$, $(CH_2)_3OH$, $(CH_2)_3ONO_2$, $(CH_2)_4OH$, or $(CH_2)_4ONO_2$.

19. The compound of claim 13, wherein the compound is of formula (IIIa):



(IIIa)

or a pharmaceutically acceptable salt thereof,

wherein:

R^6 is R^9;

R^9 is R^{90}, $NR^{10}R^{11}$, or R^{91}-Z^3-R^{92};

R^{90} is $(CH_2)_{1-5}$-(azetidin-l,3-diyl)-$(CH_2)_{1-5}$-R^{18} or azetidin-l-yl-R^{18};

R^{18} is NH_2, OH, or ONO_2;

R^{91} -Z^3-R^{92} is $(CH_2)_{1-5}$-Z^3-$(CH_2)_{1-5}$-R^{19};

Z^3 is -OC(O)-;

R^{19} is NH_2, OH, or ONO_2;

R^{10} is $(CH_2)_{1-5}$-Z^3-$(CH_2)_{1-5}$-R^{20};

R^{20} is NH_2, OH, or ONO_2; and

R^{11} is H or CH_3.

20. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein:

R^6 is R^9;

R^9 is R^{90}; and

R^{90} is CH_2-(azetidin-l,3-diyl)-CH_2OH, CH_2-(azetidin-l,3-diyl)-CH_2ONO_2, CH_2-(azetidin-l,3-diyl)$(CH_2)_2OH$, 3-(CH_2OH)-azetidin-l-yl, 3-OH-azetidin-1-yl, or 3-ONO_2-azetidin-l-yl.

21. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein:

R^6 is R^9;

R^9 is $NR^{10}R^{11}$

R^{10} is $(CH_2)_{1-5}$-Z^3-$(CH_2)_{1-5}$-R^{20};

Z^3 is -OC(O)-;

R^{20} is NH_2, OH, or ONO_2;

R_{11} is H or CH_3; and

NR^{11} -$(CH_2)_{1-5}$-Z^3-$(CH_2)_{1-5}$-R^{20} is NH-$(CH_2)_2$-OC(O)-$(CH_2)_4$-ONO_2 or N(CH_3)-$(CH_2)_2$-OC(O)-$(CH_2)_5$-ONO_2.

22. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein:

R^6 is R^9;

R^9 is R^{91}-Z^3-R^{92};

R^{91}-Z^3-R^{92} is $(CH_2)_{1-5}$-Z^3-$(CH_2)_{1-5}$-R^{19};

Z^3 is -OC(O)-;

R^{19} is NH_2, OH, or ONO_2; and

$(CH_2)_{1-5}$-Z^3-$(CH_2)_{1-5}$-R^{19} is $(CH_2)_3$-OC(O)-$(CH_2)_3$-ONO_2, $(CH_2)_3$-OC(O)-$(CH_2)_4$-ONO_2, or $(CH_2)_3$-OC(O)-$(CH_2)_s$-ONO_2.

23. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein:

R^6 is R^9;

R^9 is R^{90}, $NR^{10}R^{11}$, OH, or ONO_2;

R^{90} is -$(CH_2)_nR^{13}$;

R^{10} is -$(CH_2)_{0-4}CH_2R^{15}$;

R^{11} is H, CH_3, or -$(CH_2)_mCH_2R^{17}$;

R^{13} is NH_2, OH, or ONO_2;

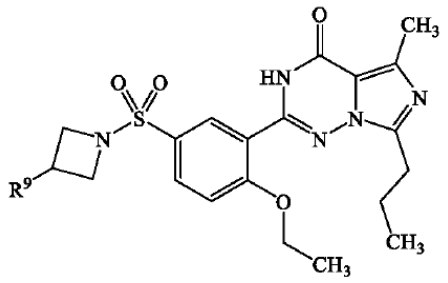
R^{15} is NH_2, OH, or ONO_2;

R^{17} is NH_2, OH, or ONO_2;

m is 0, 1, 2, 3, or 4; and

n is 1, 2, 3, 4, or 5.

24. The compound of claim 23, wherein the compound is of formula (IIIb):



(IIIb)

or a pharmaceutically acceptable salt thereof,

wherein:

R^6 is R^9;

R^9 is R^{90} or $NR^{10}R^{11}$;

R^{90} is $-(CH_2)_nR^{13}$;

R^{10} is $-(CH_2)_{0-4}CH_2R^{15}$;

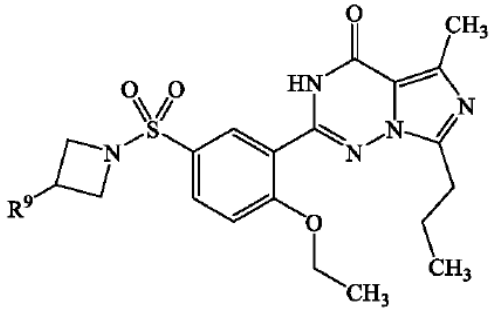
R^{11} is H or CH_3;

R^{13} is NH_2, OH, or ONO_2;

R^{15} is NH_2, OH, or ONO_2; and

n is 1, 2, 3, 4, or 5.

25. The compound of claim 23, wherein the compound is of formula (IIIb):



(IIIb)

or a pharmaceutically acceptable salt thereof,

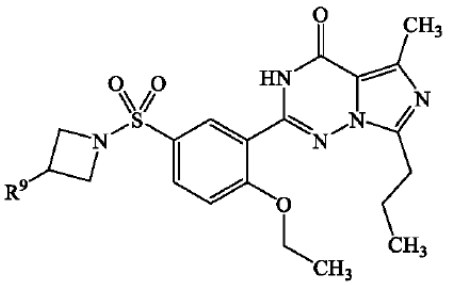
wherein:

R^6 is R^9;

R^9 is R^{90}, OH, or ONO_2; and

R^{90} is CH_2NH_2, CH_2OH, CH_2ONO_2, $(CH_2)_2OH$, $(CH_2)_2ONO_2$, $(CH_2)_3OH$, or $(CH_2)_3ONO_2$.

26. The compound of claim 23, wherein the compound is of formula (IIIb):



(IIIb)

or a pharmaceutically acceptable salt thereof,

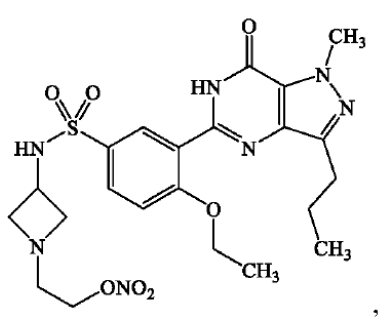
wherein:

R^6 is R^9;

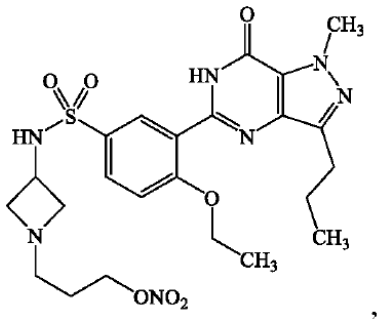
R^9 is $NR^{10}R^{11}$; and

$NR^{10}R^{11}$ is $NH(CH_2)_2OH$, $NH(CH_2)_2ONO_2$, $N(CH_3)(CH_2)_2OH$, $N(CH_3)(CH_2)_2ONO_2$, $NH(CH_2)_3OH$, $NH(CH_2)_3ONO_2$, $N(CH_3)(CH_2)_3OH$, $N(CH_3)(CH_2)_3ONO_2$, $NH(CH_2)_4OH$, $N(CH_3)(CH_2)4OH$, or $N(CH_3)(CH_2)_3ONO_2$.

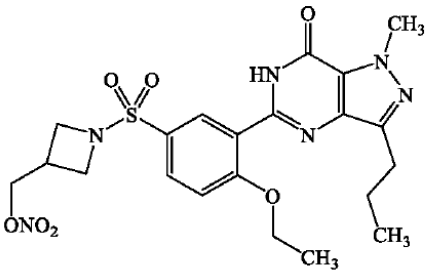
27. The compound of claim 1, wherein the compound is selected from the group consisting of:



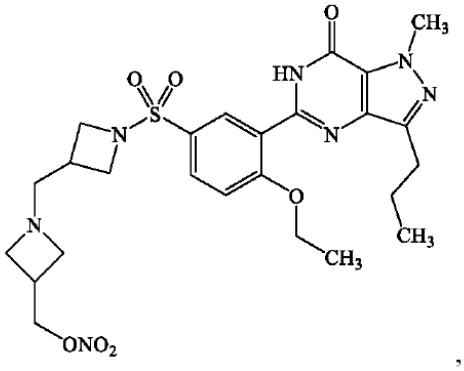
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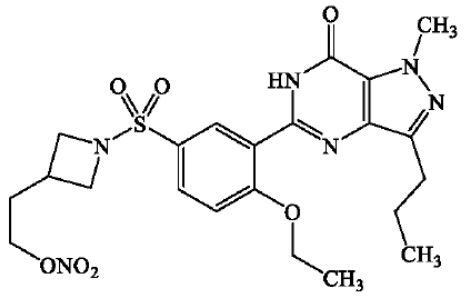
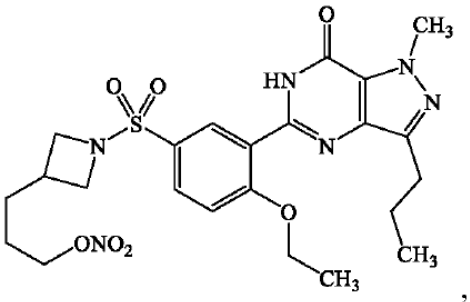
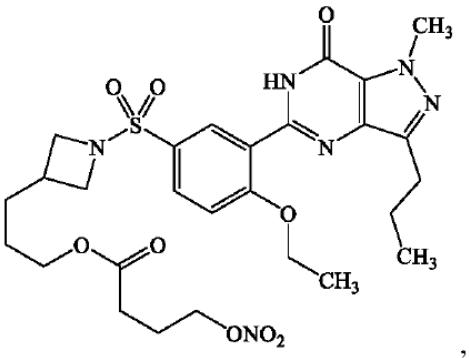
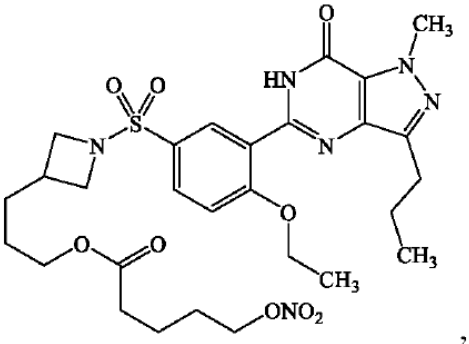
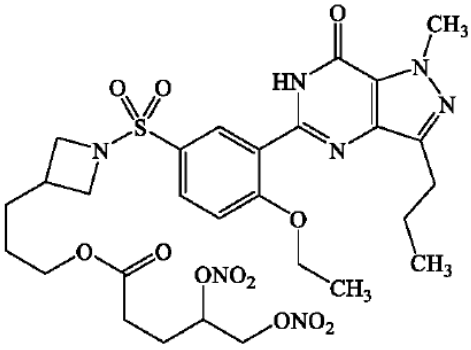
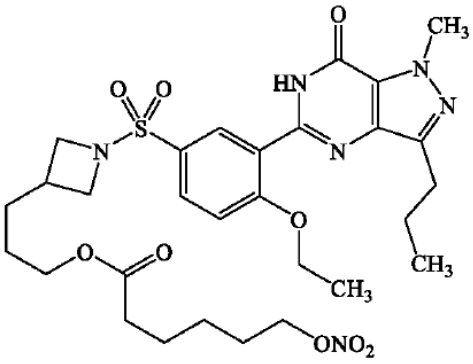
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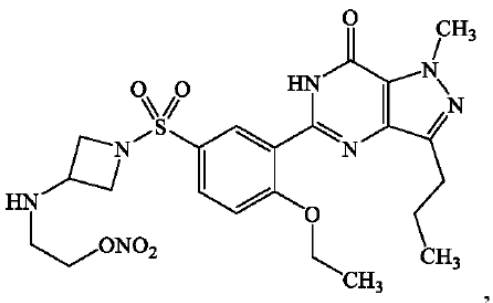
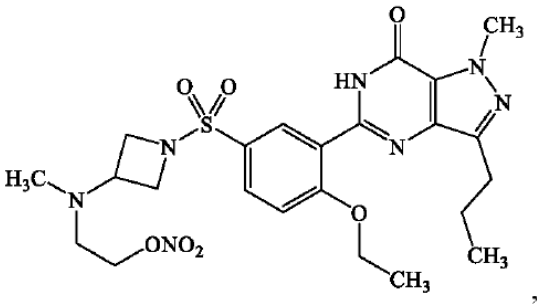
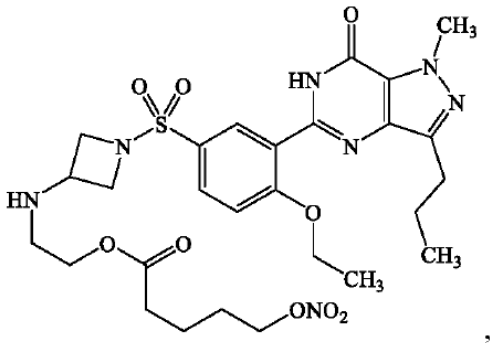
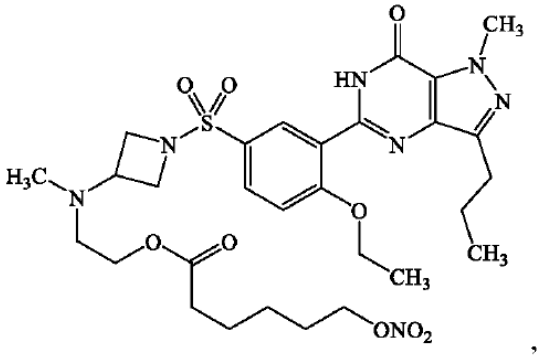
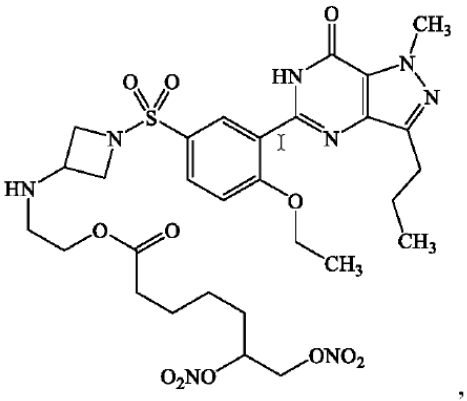
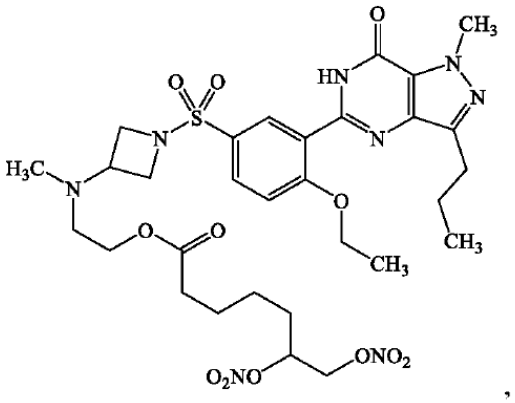
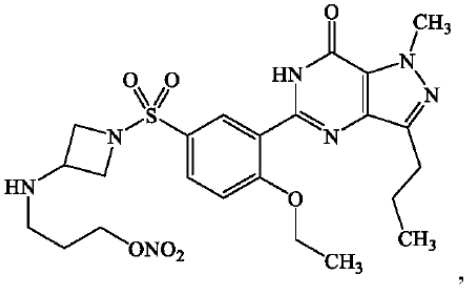
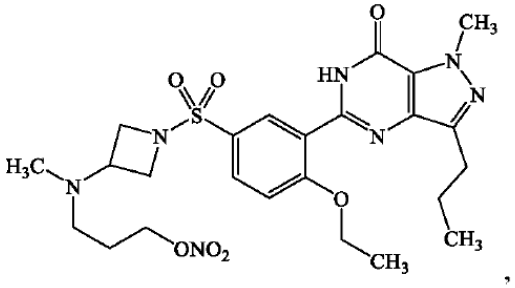


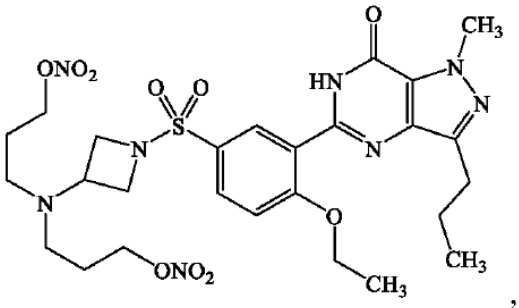
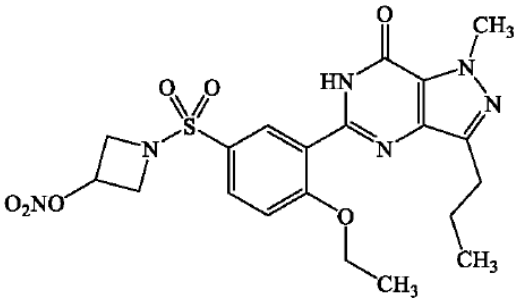
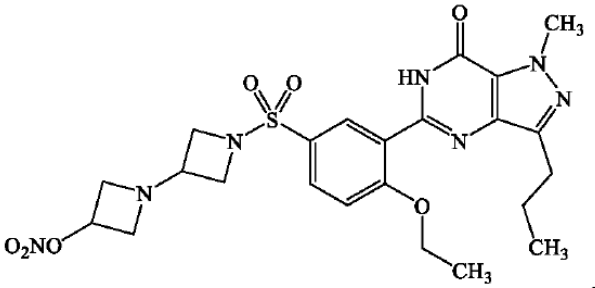
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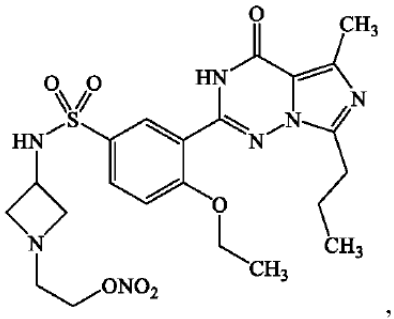
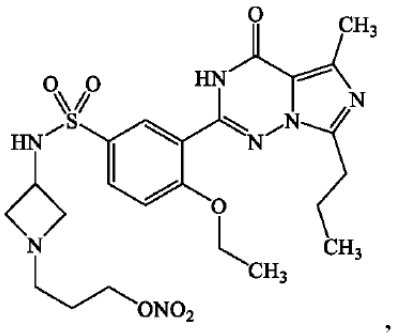
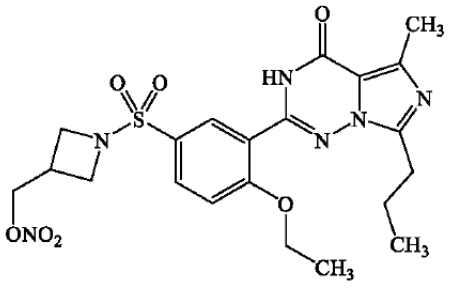
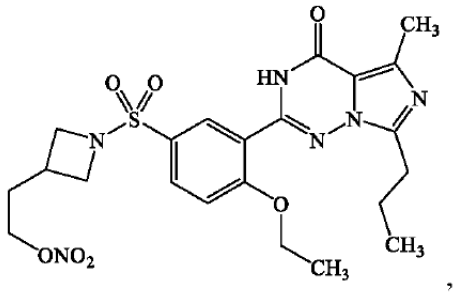

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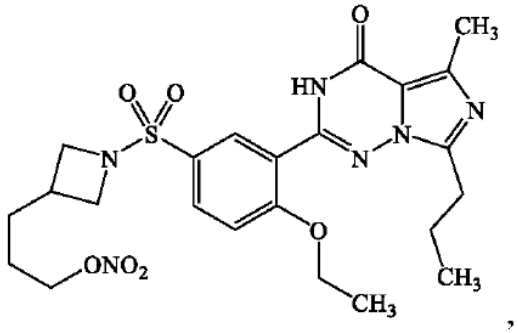
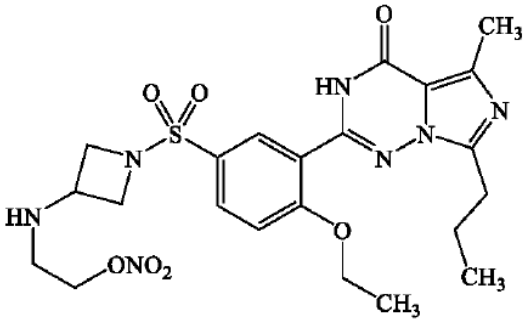
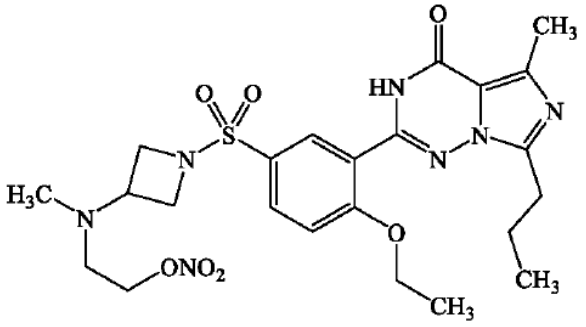
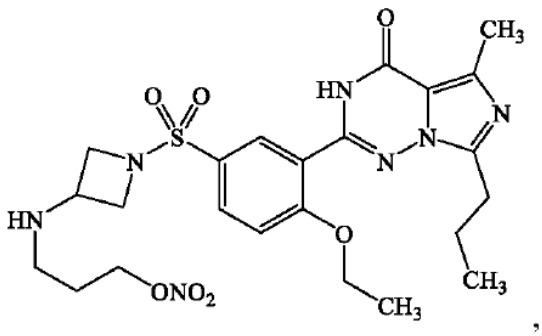
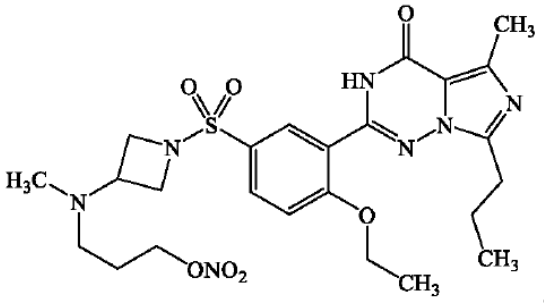
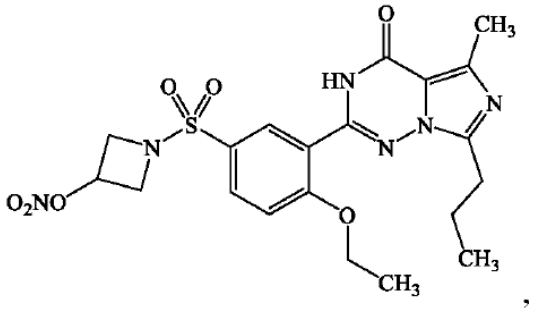

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or a pharmaceutically acceptable salt or stereoisomer thereof.

28. The compound of claim 1, wherein the compound is selected from the group consisting of:


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or a pharmaceutically acceptable salt thereof.

29. An ophthalmic composition comprising a physiologically compatible ophthalmic vehicle and a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or stereoisomer thereof.

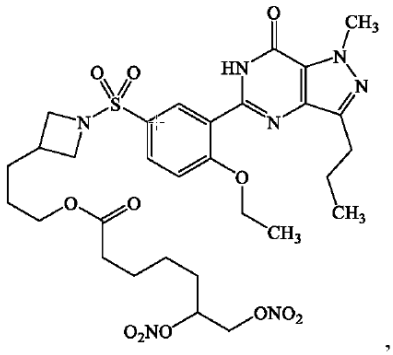
30. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or stereoisomer thereof.

31. A method for inhibiting phosphodiesterase-5 and/or phosphodiesterase-6 activity in a biological system, wherein the method comprises contacting the biological system with an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or stereoisomer thereof.

32. A method for treating an eye disease in a subject in need thereof, wherein the method comprises administering to an eye of the subject a therapeutically effective amount of the ophthalmic composition of claim 29.

33. The method of claim 32, wherein the eye disease is selected from the group consisting of age-related macular degeneration, a cataract, conjunctivitis, diabetic macular edema, diabetic retinopathy, dry eye syndrome, glaucoma, ischemic retinopathy, optic neuropathy, Sjogren's syndrome, Stevens-Johnson syndrome, trauma of the eye, uveitis, and xerophthalmia.

34. A compound:



or a pharmaceutically acceptable salt or stereoisomer thereof.