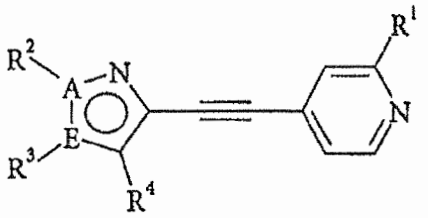
Claims

1. A pharmaceutical composition comprising a compound of formula I

formula I



(I)

wherein

one of A or E is N and the other is C;

R^1 is halogen or cyano;

R^2 is lower alkyl;

R^3 is aryl or heteroaryl, each of which is optionally substituted by one, two or three substituents chosen from halogen, lower alkyl, lower alkoxy, cycloalkyl, lower haloalkyl, lower haloalkoxy, cyano, or NR'R'',

or by

1-morpholinyl,

1-pyrrolidinyl, optionally substituted by $(CH_2)_mOR$,

piperidinyl, optionally substituted by $(CH_2)_mOR$,

1,1-dioxo-thiomorpholinyl,

piperazinyl, optionally substituted by lower alkyl or $(CH_2)_m$-cycloalkyl;

R is hydrogen, lower alkyl or $(CH_2)_m$-cycloalkyl;

R' and R'' are each independently hydrogen, lower alkyl, $(CH_2)_m$-cycloalkyl or $(CH_2)_nOR$;

m is 0 or 1;

n is 1 or 2; and

R^4 is CHF_2, CF_3, C(O)H, or CH_2R^5, wherein R^5 is hydrogen, OH, C_1-C_6-alkyl or C_3-C_{12}-cycloalkyl;

and pharmaceutically acceptable salts thereof, a rate-controlling polymer, selected from the group consisting of polyvinyl pyrrolidine, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, vinyl acetate/crotonic acid copolymers, poly(meth)acrylates, polyvinylacetate, ethyl cellulose, maleic anhydride/methyl vinyl ether copolymers, polyvinylacetate/polidone copolymers and mixtures thereof and containing a pH responding polymer, selected from the group consisting of

hydroxyproplymethyl cellulose phthalate, cellulose acetate phthalate, hydroxypropylmethyl cellulose acetate succinate, cellulose acetate trimellitate, ionic poly(meth)acrylates, polyvinyl phthalate, and mixtures thereof.

2. A composition according to claim 1, in tablet form.

3. A composition according to claim 1, encapsulated in a capsule.

4. The capsule according to claim 3, wherein the composition comprises a hard gelatin capsule.

5. The capsule according to claim 3, wherein the composition comprises a hypermellose capsule.

6. The composition according to any of claims 1 to 5, wherein the particles are further coated with a soluble or insoluble polymer.

7. The composition according to any one of claims 1 to 6, wherein the compound of formula I is present in an amount from about 0.005 % to about 5 % by weight.

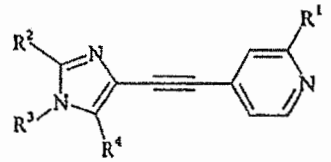
8. The composition according to any one of claims 1 to 7, wherein the compound of formula I is present in an amount from about 0.5 % to about 5 %.

9. The composition according to any one of claims 1 to 8, wherein the particle size of the compound of formula I is 50 microns or less.

10. The composition according to any one of claims 1 to 9, wherein the particle size of the compound of formula I is 20 microns or less.

11. The composition according to any one of claims 1 to 10, wherein the particle size of the compound of formula I is 10 microns or less.

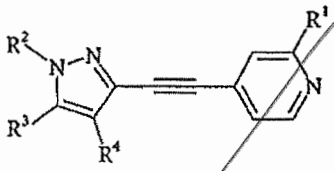
12. The composition according to any one of claims 1 to 11, wherein the metabotropic glutamate 5 receptor antagonist is a compound of formula Ia



(Ia)

wherein the substituents are described in claim 1.

13. The composition according to any one of claims 1 to 11, wherein the metabotropic glutamate 5 receptor antagonist is a compound of formula Ib



(Ib)

wherein the substituents are described in claim 1.

14. The composition according to any one of claims 1 to 11, wherein the metabotropic glutamate 5 receptor antagonist is a compound selected from the group consisting of
2-[4-(2-Chloro-pyridin-4-ylethynyl)-2,5-dimethyl-1H-imidazol-1-yl]-5-methyl-pyridine;
2-Chloro-5-[4-(2-Chloro-pyridin-4-ylethynyl)-2,5-dimethyl-1H-imidazol-1-yl]-pyridine;
2-[4-(2-Chloro-pyridin-4-ylethynyl)-2,5-dimethyl-1H-imidazol-1-yl]-6-methyl-4-trifluoromethyl-pyridine;
2-[4-(2-Chloro-pyridin-4-ylethynyl)-2,5-dimethyl-1H-imidazol-1-yl]-pyrazine;
2-[4-(2-Chloro-pyridin-4-ylethynyl)-2,5-dimethyl-1H-imidazol-1-yl]-6-methyl-pyridine;
2-[4-(2-Chloro-pyridin-4-ylethynyl)-2,5-dimethyl-1H-imidazol-1-yl]-6-(trifluoromethyl)-pyridine;
3-[4-(2-Chloro-pyridin-4-ylethynyl)-2,5-dimethyl-1H-imidazol-1-yl]-5-fluoro-pyridine.
2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;

2-Chloro-4-[1-(2,4-difluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;
2-Chloro-4-[1-(3,5-difluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;
2-Chloro-4-[1-(4-fluoro-2-methyl-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;
2-Chloro-4-[1-(4-fluoro-3-methyl-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;
2-Chloro-4-(2,5-dimethyl-1-p-tolyl-1H-imidazol-4-ylethynyl)-pyridine;
2-Chloro-4-[1-(3-chloro-4-methyl-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;
2-Chloro-4-[1-(3-fluoro-4-methoxy-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;
2-Chloro-4-[1-(4-methoxy-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;
2-Chloro-4-[2,5-dimethyl-1-(4-trifluoromethoxy-phenyl)-1H-imidazol-4-ylethynyl]-pyridine;
2-Chloro-4-[2,5-dimethyl-1-(3-trifluoromethoxy-phenyl)-1H-imidazol-4-ylethynyl]-pyridine;
2-Chloro-4-[2,5-dimethyl-1-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylethynyl]-pyridine;
2-Chloro-4-[2,5-dimethyl-1-(3-methyl-4-trifluoromethoxy-phenyl)-1H-imidazol-4-ylethynyl]-pyridine;
2-Chloro-4-[1-(4-chloro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;
2-Chloro-4-[1-(3-chloro-2-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;
2-Chloro-4-[2,5-dimethyl-1-(3-trifluoromethyl-phenyl)-1H-imidazol-4-ylethynyl]-pyridine;
2-Chloro-4-[1-(3-chloro-4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;
2-Chloro-4-[2,5-dimethyl-1-(2-methyl-4-trifluoromethoxy-phenyl)-1H-imidazol-4-ylethynyl]-pyridine;
2-Chloro-4-[5-difluoromethyl-1-(4-fluoro-phenyl)-2-methyl-1H-imidazol-4-ylethynyl]-pyridine;
[5-(2-Chloro-pyridin-4-ylethynyl)-3-(4-fluoro-phenyl)-2-methyl-3H-imidazol-4-yl]-methanol;

2-Chloro-4-[1-(4-methoxy-3-trifluoromethyl-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;

2-Chloro-4-[1-(3,5-difluoro-4-methoxy-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;

2-Chloro-4-[1-(4-methoxy-3-trifluoromethoxy-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;

2-Chloro-4-[1-(3-methoxy-4-trifluoromethoxy-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;

4-{3-[4-(2-Chloro-pyridin-4-ylethynyl)-2,5-dimethyl-imidazol-1-yl]-5-fluoro-phenyl}-morpholine;

2-Chloro-4-[1-(4-fluoro-2-trifluoromethoxy-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;

2-Chloro-4-[1-(2-fluoro-4-trifluoromethoxy-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;

2-Chloro-4-[2,5-dimethyl-1-(4-methyl-3-trifluoromethyl-phenyl)-1H-imidazol-4-ylethynyl]-pyridine;

2-Chloro-4-[2,5-dimethyl-1-(3-methyl-4-trifluoromethyl-phenyl)-1H-imidazol-4-ylethynyl]-pyridine;

2-Chloro-4-[2,5-dimethyl-1-(3-methyl-5-trifluoromethyl-phenyl)-1H-imidazol-4-ylethynyl]-pyridine;

2-Chloro-4-[1-(3-methoxy-5-trifluoromethyl-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;

2-Chloro-4-[1-(3-methoxy-4-trifluoromethyl-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;

2-Chloro-4-[1-(3,5-dichloro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;

2-Chloro-4-[1-(3-chloro-5-methyl-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;

2-Chloro-4-[1-(3-fluoro-5-methyl-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;

2-Chloro-4-[1-(3-chloro-5-methoxy-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;

2-Chloro-4-[1-(3-fluoro-5-methoxy-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine; and

2-Chloro-4-[5-(4-fluoro-phenyl)-1,4-dimethyl-1H-pyrazol-3-ylethynyl]-pyridine.

15. The composition according to any one of claims 1 to 11 and 14, wherein the metabotropic glutamate 5 receptor antagonist is 2-chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

16. The composition according to any of claims 1 to 15, in the form of a matrix tablet which comprises a compound of formula I dispersed in a gel-forming cellulose ether.

17. The composition according to any one of claims 1 to 16, wherein the rate controlling polymer is present in an amount from about 5 % to about 50 % by weight of the composition.

18. The composition according to any one of claims 1 to 17, wherein the rate controlling polymer is present in an amount from about 10 % to about 35 % by weight of the composition.

19. The composition according to any one of claims 1 to 18, wherein the rate controlling polymer is present in an amount from about 10 % to about 2 5% by weight of the composition.

20. The composition according to any one of claims 1 to 19, wherein the pH responding polymer is present in an amount from about 5 % to about 50 % by weight of the composition.

21. The composition according to any one of claims 1 to 20, wherein the pH responding polymer is present in an amount from about 10 % to about 35 % by weight of the composition.

22. The composition according to any of claims 1 to 21, wherein the pH responding polymer is present in an amount from about 10 % to about 25 % by weight of the composition.

23. The composition according to any of claims 1 to 22, wherein the composition further comprises a filler, surfactant, glidant, lubricant and/or binder.

24. The composition according to any one of claims 1 to 23, which comprises

Composition (mg)	**Amount (mg/tablet)**
2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-	1.3

1H-imidazol-4-ylethynyl]-pyridine	
HPMC	50.0
Poly(meth)acrylate	50.0
Lactose monohydrate	83.2
Povidone	10.0
Talc	4.0
Magnesium stearate	1.5
Film-coat	5.0
Total tablet Weight	205.0

25. The composition according to any one of claims 1 to 15, in the form of a matrix pellet composition which comprises a compound of formula I dispersed within formed matrix pellets.

26. The composition according to any one of claims 1 to 15 and 25, wherein the pH responding polymer comprises an ionic polymer.

27. The composition according to any one of claims 1 to 15, 25 and 26, wherein the ionic polymer is poly(meth)acrylate.

28. The composition according to any one of claims 1 to 15 and 25 to 27, wherein the pH responding polymer is present in an amount from about 5 % to about 50 % by weight of the composition.

29. The composition according to any one of claims 1 to 15 and 25 to 28, wherein the pH responding polymer is present in an amount from about 10 % to about 40 % by weight of the composition.

30. The composition according to any one of claims 1 to 15 and 25 to 29, wherein the pH responding polymer is present in an amount from about 25 % to about 35 % by weight of the composition.

31. The composition according to any one of claims 1 to 15 and 25 to 30, wherein the matrix pellets have a particle size of less than 3000 microns.

32. The composition according to any one of claims 1 to 15 and 25 to 31, wherein the matrix pellets have a particle size of less than 2000 microns.

33. The composition according to any one of claims 1 to 15 and 25 to 32, wherein the matrix pellets have an average particle size of from about 400 microns to about 1500 microns.

34. The composition according to any one of claims 1 to 15 and 25 to 33, which further comprises an insoluble polymer selected from the group consisting of ethyl cellulose, polyvinylacetate, or polyvinylacetate/povidone copolymer.

35. The composition according to any one of claims 1 to 15 and 25 to 34, wherein the insoluble polymer is present in an amount from about 5 % to about 50 % by weight of the composition.

36. The composition according to any one of claims 1 to 15 and 25 to 35, wherein the insoluble polymer is present in an amount from about 10 % to about 35 % by weight of the composition.

37. The composition according to any one of claims 1 to 15 and 25 to 36, wherein the insoluble polymer is present in an amount from about 5 % to about 2 5% by weight of the composition.

38. The composition according to any one of claims 1 to 15 and 25 to 37, wherein the composition further comprises a filler, disintegrant, surfactant, glidant, lubricant spheronization enhancer, release modifier and/or binder.

39. The composition according to any one of claims 1 to 15 and 25 to 38, which comprises

Composition (mg)	**mg/Capsule**
2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine	1.3
Microcrystalline cellulose	128.2
Poly(meth)acrylate	60.0
HPMC	10.0
Talc	0.5
Total fill weight (mg) in a capsule	200.0
Hard Gelatin Capsules (Size #2)	61.0

Claims

1. A pharmaceutical modified release composition for a poorly water soluble drug, comprising:

- a compound 2-chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine and pharmaceutically acceptable salts thereof;

- an insoluble rate-controlling polymer selected from the group consisting of polyvinylacetate, ethylcellulose, polyvinylacetate/povidone copolymers, microcrystalline cellulose and mixtures thereof; and

- a pH responding polymer such as ionic poly(meth)acrylates,

wherein the composition is in the form of a matrix pellet composition, whereby the compound is dispersed within formed matrix pellets.

2. A pharmaceutical modified release composition according to claim 1, wherein the drug has a solubility at alkaline conditions of 0.0003 mg/ml at pH7.

3. The composition according to claim 1, wherein the compound is present in an amount from 0.005 % to 5 % by weight.

4. The composition according to any one of claims 1 or 3, wherein the compound is present in an amount from 0.5 % to 5 %.

5. The composition according to claim 1, wherein the particle size of the compound is 50 microns or less.

6. The composition according to any one of claim 1 or 5, wherein the particle size of the compound is 20 microns or less.

7. The composition according to any one of claims 1, 5 or 6, wherein the particle size of the compound is 10 microns or less.

8. The composition according to claim 1, wherein the pH responding polymer is present in an amount from 5 % to 50 % by weight of the composition.

9. The composition according to any one of claims 1 and 8, wherein the pH responding polymer is present in an amount from 10 % to 40 % by weight of the composition.

10. The composition according to any one of claims 1, 8 or 9, wherein the pH responding polymer is present in an amount from 25 % to 35 % by weight of the composition.

11. The composition according to claim 1, wherein the matrix pellets have a particle size of less than 3000 microns.

12. The composition according to any one of claims 1 or 11, wherein the matrix pellets have a particle size of less than 2000 microns.

13. The composition according to any one of claims 1, 11 or 12, wherein the matrix pellets have an average particle size of from 400 microns to 1500 microns.

14. The composition according to claim 1, wherein the insoluble rate-controlling polymer is present in an amount from 5 % to 50 % by weight of the composition.

15. The composition according to any one of claims 1 or 14, wherein the insoluble rate-controlling polymer is present in an amount from 10 % to 35 % by weight of the composition.

16. The composition according to any one of claims 1, 14 or 15, wherein the insoluble polymer is present in an amount from 5 % to 25 % by weight of the composition.

17. The composition according to claim 1, wherein the composition further comprises a filler, disintegrant, surfactant, glidant, lubricant, spheronization enhancer, release modifier and/or binder.

18. A composition according to claim 1, which comprises

Compositions (mg) (1 mg dose)	**Excipient Functionality**	**Matrix pellets**
2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine	Active ingredient	1.3
Avicel RC591® (MCC and Sodium CMC blend)	Rate controlling and matrix forming polymer (MCC) and pH responding polymer (Sodium CMC)	138.7
Eudragit L100-55®	pH responding polymer	60.0
Talc	Glidant	3.2
Total fill weight (mg) in a capsule		203.2

19. A composition according to claim 1, which comprises

Compositions (mg) (1 mg dose)	**Excipient Functionality**	**Matrix pellets**
2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine	Active ingredient	1.3
Avicel 101®	Rate controlling and matrix forming polymer	128.2
Eudragit L100-55®	pH responding polymer	60.0
Pharmacoat 603®	Binder	10.0
Talc	Glidant	0.5
Total fill weight (mg) in a capsule		203