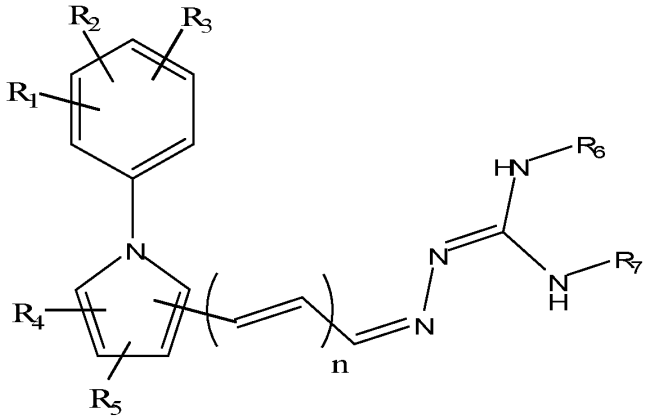
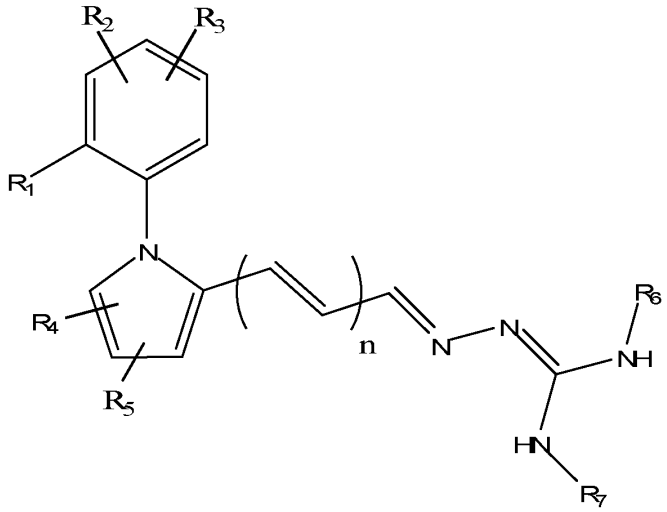
Claims

1. A composition comprising, separately or together, methotrexate (MTX), or a pro-drug thereof, and a compound of formula (I) or (Ia):



formula (I)



formula (Ia)

including tautomeric and isomeric forms, such as enantiomeric forms, diastereomeric forms and racemic forms, thereof;

wherein

n is 1, 2 or 3;

each R_1, R_2, R_3, R_4 and R_5 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted C_{3-6}-cycloalkyl, optionally substituted C_{2-6}-alkenyl, optionally substituted C_{4-6}-alkadienyl, optionally substituted C_{2-6}- alkynyl, hydroxy, optionally substituted C_{1-6}-alkoxy, optionally substituted C_{2-6}-alkenyloxy, carboxy, optionally substituted C_{1-6}-alkoxycarbonyl, optionally substituted C_{1-6}- alkylcarbonyl, formyl, C_{1-6}-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylcarbonyl, optionally substituted heteroarylamino, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally substituted heterocyclyloxycarbonyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylcarbonyl, optionally substituted heterocyclylamino, heterocyclylsulphonylamino, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkylamino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, amino-C_{1-6}-alkyl-carbonylamino, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-carbonylamino, cyano, guanidino, carbamido, C_{1-6}-alkanoyloxy, C_{1-6}-alkylsulphonyl, C_{1-6}-alkylsulphinyl, C_{1-6}-alkylsulphonyl- oxy, aminosulfonyl, mono- and di(C_{1-6}-alkyl)aminosulfonyl, nitro, optionally substituted C_{1-6}-alkylthio and halogen, where any nitrogen-bound C_{1-6}-alkyl is optionally substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino or guanidine;

each R_6 and R_7 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, optionally substituted C_{4-6}- alkadienyl, optionally substituted C_{2-6}-alkynyl, optionally substituted C_{1-6}-alkoxycarbonyl, optionally substituted C_{1-6}-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxycarbonyl,

optionally substituted arylcarbonyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino- C_{1-6}-alkyl-aminocarbonyl and mono- and di(C_{1-6}-alkyl)amino- C_{1-6}-alkyl-aminocarbonyl; or R_6 and R_7 may together form a five- or six-membered nitrogen-containing ring;

or a pharmaceutically acceptable derivative thereof;

for use in the treatment of an arthritic disease.

2. The composition for use according to claim 1, wherein n = 1.

3. The composition for use according to any of the preceding claims, wherein each R_1, R_2 and R_3 is independently selected from the group consisting of -H, $-CH_3$, $-CF_3$, $-CCl_3$, -O-C_{1-6} alkyl, -OH, $-OCH_3$, -NH-C_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, -S-C_{1-6} alkyl, -^{t}Bu, -CN, $-SO_3$-C_{1-6} alkyl, $-NH_2$, $-NO_2$, $-CO_2H$, $-CO_2$-C_{1-6} alkyl, -C(=O)-C_{1-6} alkyl, -CHO, morpholine, pyrrolidine, pyrrole, or halogen.

4. The composition for use according to any of the preceding claims, wherein R_1 and/or R_2 is an electron-withdrawing group.

5. The composition for use according to any of the preceding claims, wherein R_1 is selected from the group consisting of CF_3, CCl_3, F, Cl, CN and NO_2.

6. The composition for use according to any of the preceding claims, wherein R_2 and/or R_3 is hydrogen.

7. The composition for use according to any of the preceding claims, wherein each R_4 and R_5 is independently selected from the group consisting of -H, C_{1-6} alkyl, halogen, -O(C_{1-6} alkyl), -NH(C_{1-6} alkyl) and -C(=O)C_{1-6} alkyl.

8. The composition for use according to any of the preceding claims, wherein each R_6 and R_7 is independently selected from hydrogen, methyl, ethyl or propyl.

9. The composition for use according to any of the preceding claims, wherein R_6 and R_7 are hydrogen.

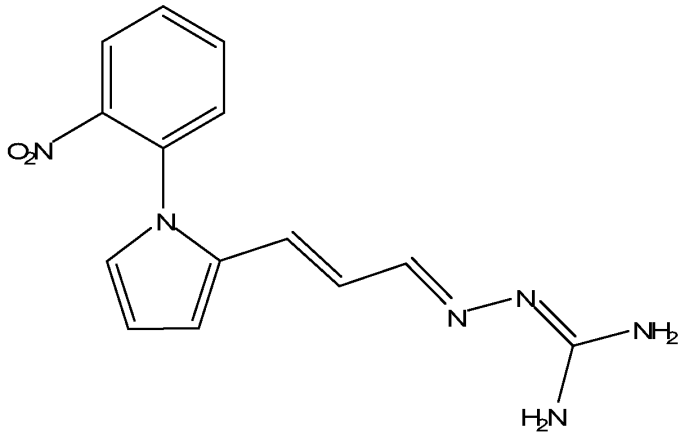
10. The composition for use according to any of the preceding claims, wherein R_2, R_3, R_4, R_5, R_6 and R_7 are hydrogen, and wherein R_1 is CF_3, CCl_3, F, Cl, NO_2 or CN.

11. The composition for use according to any of the preceding claims, wherein R_2, R_3, R_4, R_5, R_6 and R_7 are hydrogen, and wherein R_1 is CF_3, CCl_3, F, Cl, NO_2 or CN, and wherein n = 1.

12. The composition for use according to any of the preceding claims, wherein R_3 is located on the 4-position.

13. The composition for use according to any of the preceding claims, wherein R_3 is selected from F, Cl or Br.

14. The composition for use according to any of the preceding claims, wherein the compound is of formula (II)



formula (II)

including tautomeric and isomeric forms, such as enantiomeric forms, diastereomeric forms and racemic forms, thereof; or a pharmaceutically acceptable derivative thereof.

15. The composition for use according to any of the preceding claims, wherein said compound is selected from the group consisting of {3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine and (*E*)-*N*-*trans*-{3-[1-(2-nitrophenyl)-1H-

pyrrol-2-yl]-allylidene}-aminoguanidine, or a pharmaceutically acceptable derivative thereof, such as a pharmaceutically acceptable salt thereof.

16. The composition for use according to any of the preceding claims, wherein said pharmaceutically acceptable derivative is a pharmaceutically acceptable salt of an inorganic acid or of an organic acid.

17. The composition for use according to claim 16, wherein said organic acid is selected from the group consisting of: formic acid, acetic acid, trichloroacetic acid, trifluoroacetic acid, propionic acid, benzoic acid, cinnamic acid, citric acid, fumaric acid, glycolic acid, lactic acid, maleic acid, malic acid, malonic acid, mandelic acid, oxalic acid, picric acid, pyruvic acid, salicylic acid, succinic acid, methanesulfonic acid, ethanesulfonic acid, tartaric acid, ascorbic acid, pamoic acid, bismethylene salicylic acid, ethanedisulfonic acid, gluconic acid, citraconic acid, aspartic acid, stearic acid, palmitic acid, EDTA, glycolic acid, p-aminobenzoic acid, glutamic acid, benzenesulfonic acid and p-toluenesulfonic acid.

18. The composition for use according to any of claims 16 to 17, wherein said organic acid is acetic acid, succinic acid, tartaric acid or propionic acid.

19. The composition for use according to claim 16, wherein said inorganic acid is selected from the group consisting of hydrochloric acid, hydrobromic acid, hydroiodic acid, phosphoric acid, sulphuric acid and nitric acid.

20. The composition for use according to any of the preceding claims, wherein said pharmaceutically acceptable acid is acetic acid.

21. The composition for use according to any of the preceding claims, wherein said compound is selected from the group consisting of {3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}- aminoguanidinium acetate and (*E*)-*N*-*trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}- aminoguanidinium acetate.

22. The composition for use according to any of the preceding claims, wherein said compound is (*E*)-*N*-*trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate (AP1189).

23. The composition for use according to claim 1, wherein the arthritic disease is an auto-immune disease and/or an inflammatory disease that presents with joint inflammation.

24. The composition for use according to any of the preceding claims, wherein the arthritic disease is selected from the group consisting of inflammatory arthritis, degenerative arthritis, metabolic arthritis, reactive arthritis and infectious arthritis.

25. The composition for use according claim 24, wherein the inflammatory arthritis is selected from the group consisting of Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis.

26. The composition for use according to claim 24, wherein the degenerative arthritis is osteoarthritis.

27. The composition for use according to claim 24, wherein the metabolic arthritis is gouty arthritis.

28. The composition for use according to claim 24, wherein the reactive and/or infectious arthritis is a arthritis associated with infection with one or more of Hepatitis C, Chlamydia, gonorrhoea, salmonella or shigella.

29. The composition for use according to any of the preceding claims, wherein the arthritic disease is undifferentiated polyarthritis (UP).

30. The composition for use according to any of the preceding claims, wherein the arthritic disease is rheumatoid arthritis (RA).

31. The composition for use according to any of the preceding claims, wherein the arthritic disease is severe active rheumatoid arthritis (RA), such as newly diagnosed severe active RA.

32. The composition for use according to any of the preceding claims, wherein the arthritic disease is rheumatoid arthritis with a DAS28 score of above 5.1 and/or a CDAI > 22.

33. The composition for use according to any of the preceding claims, wherein the arthritic disease is rheumatoid arthritis with a DAS28 score of 5.1 or above (high disease activity), such as a DAS28-score of between 3.2 and ≤5.1 (moderate disease activity), such as a DAS28-score of between 2.6 to <3.2 (low disease activity).

34. The composition for use according to any of the preceding claims, wherein the arthritic disease is rheumatoid arthritis with a CDAI score of 22 or above (high disease activity), such as a CDAI-score of between 10 and ≤22 (moderate disease activity), such as a CDAI-score of between 2.8 to <10 (low disease activity).

35. The composition for use according to any of the preceding claims, wherein the rheumatoid arthritis is juvenile rheumatoid arthritis (JRA).

36. The composition for use according to claim 32, wherein the JRA is selected from the group consisting of pauciarticular JRA, systemic-onset JRA, polyarticular JRA, and seronegative spondylarthritis.

37. The composition for use according to any of the preceding claims, wherein the arthritic disease presents itself in association with synovitis.

38. The composition for use according to any of the preceding claims, wherein the arthritic disease affects one or more of joints in the hand, knee, hip, spine, wrist, ankle, hips, toe, and/or elbow.

39. The composition for use according to any of the preceding claims, wherein the arthritic disease presents with one or more further symptoms selected from the group consisting of: joint stiffness, joint tenderness, inability to use a hand, inability to walk, malaise, fatigue, weight loss, poor sleep, muscle aches, pain, muscle weakness, loss of flexibility and decreased aerobic fitness.

40. The composition for use according to any of the preceding claims, wherein the composition

    i) reduces joint inflammation,

    ii) reduces the number of tender joints and/or reduces the number of swollen joints,

iii) reduces the level of c-reactive protein (CRP) in the blood
iv) results in partial or complete remission of one or more arthritis symptoms,
v) results in improved physical function in the subject as determined by the Health Assessment Questionnaire Disability Index (HAQ-DI),
vi) results in improved function in the subject as determined by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue),
vii) reduces the DAS28 score, such as reduces the DAS28-score to between 3.2 and ≤5.1 (moderate disease activity), such as to between 2.6 to <3.2 (low disease activity), such as to between 0 and <2.6 (remission),
viii) reduces the CDAI score, such as reduces the CDAI score to between 10 and ≤22 (moderate disease activity), such as to between 2.8 to <10 (low disease activity), such as to between 0 and <2.8 (remission),
ix) reduces the CDAI score by 5 points or more, such as 10 points or more, such as 15 point or more,
x) results in a ≥20%, ≥50% or ≥70% improvement in ACR response rates.

41. The composition for use according to any of the preceding claims, wherein the subject tests positive for rheumatoid factor and/or anti-cyclic citrullinated peptide (CCP) IgG antibodies prior to the treatment.

42. The composition for use according to any of the preceding claims, for use in the treatment of an arthritic disease, such as RA, in an MTX non-responder.

43. The composition for use according to claim 42, wherein said MTX non-responder is selected from the group consisting of
a. a subject with non-response to treatment at 6 months
b. a subject with non-response to treatment at 6 months defined as “no response” using the EULAR response criteria,
c. a subject with non-response to treatment at 6 months evaluated as a Disease Activity Score in 28 joints (DAS28) improvement ≤ 0.6, or DAS28 improvement > 0.6 but ≤ 1.2 and 6-month DAS28 > 5.1,
d. a subject who discontinued MTX by 6 months, i.e. had stopped MTX and did not plan to restart, due to inefficacy,

e. a subject with one or more baseline predictors of non-response selected from RF (rheumatoid factor) negativity, higher HAQ (Health Assessment Questionnaire) score, higher tender joint count (TJC28), higher HADS (Hospital Anxiety and Depression Scale) anxiety score and lower disease activity (lower baseline DAS28-CRP),
f. an individual at high risk (or probability) of non-response, as determined by the model disclosed by Sergeant et al 2018,
g. a female,
h. a current smoker, and
i. a person with high BMI.

44. The composition for use according to any of the preceding claims, wherein methotrexate (MTX), or a prodrug thereof, is administered in an amount of about 1 to about 30 mg per week, for example about 10 to 25 mg once per week, such as about 5 to 15 mg per week.

45. The composition for use according to any of the preceding claims, wherein MTX, or a prodrug thereof, is administered once weekly.

46. The composition for use according to any of the preceding claims, wherein the compound of formula (I), (Ia) or (II) is administered in an amount of about 1 mg to about 1000 mg per day, for example about 50 to about 800 mg per day, such as 50 mg, 100mg, 200 mg, 400 mg, 600 mg or 800 mg per day.

47. The composition for use according to any of the preceding claims, wherein the compound of formula (I), (Ia) or (II) is administered daily, such as once daily, twice daily or three times daily.

48. The composition for use according to any of the preceding claims, wherein the composition is administered for 1 week such as more than 1 week, such as 2 weeks or more than 2 weeks, such as 3 weeks or more than 3 weeks, such as 4 weeks or more than 4 weeks,
such as for 1 month or more than 1 month, such as 2 months or more than 2 months, such as 3 months or more than 3 months, such as 4 months or more than 4 months, such as 5 months or more than 5 months, such as 6 months or more than 6 months,
such as for more than 1 year.

49. The composition for use according to any of the preceding claims, wherein the compound of formula (I) or (Ia) is administered prior to and/or simultaneously with and/or after MTX, or a prodrug thereof.

50. The composition for use according to any of the preceding claims, wherein the treatment with the compound of formula (I), (Ia) or (II) and MTX, or a prodrug thereof, is synergistic.

51. The composition for use according to any of the preceding claims, wherein the treatment with the compound of formula (I), (Ia) or (II) and MTX, or a prodrug thereof, is additive.

52. The composition for use according to any of the preceding claims, wherein the compound of formula (I),(Ia) or (II) is administered daily and the MTX, or a prodrug thereof, is administered once weekly.

53. The composition for use according to any of the preceding claims, wherein treatment with MTX is discontinued for a period of time, while treatment with the compound of formula (I), (Ia) or (II) is continued.

54. The composition for use according to any of the preceding claims, wherein MTX, or a prodrug thereof, is formulated for oral administration, such as in the form of tablets or capsules.

55. The composition for use according to any of the preceding claims, wherein MTX, or a prodrug thereof, is administered orally.

56. The composition for use according to any of the preceding claims, wherein MTX, or a prodrug thereof, is formulated as a liquid for injection.

57. The composition for use according to any of the preceding claims, wherein MTX, or a prodrug thereof, is administered by subcutaneous injection.

58. The composition for use according to any of the preceding claims, wherein the compound of formula (I), (Ia) or (II) is formulated for oral administration.

59. The composition for use according to any of the preceding claims, wherein the compound of formula (I), (Ia) or (II) is an oral solid dosage form, such as a tablet or a capsule.

60. The composition for use according to any of the preceding claims, wherein the compound of formula (I), (Ia) or (II) is a powder, such as an oral powder, such as an oral powder suitable for suspension in a liquid.

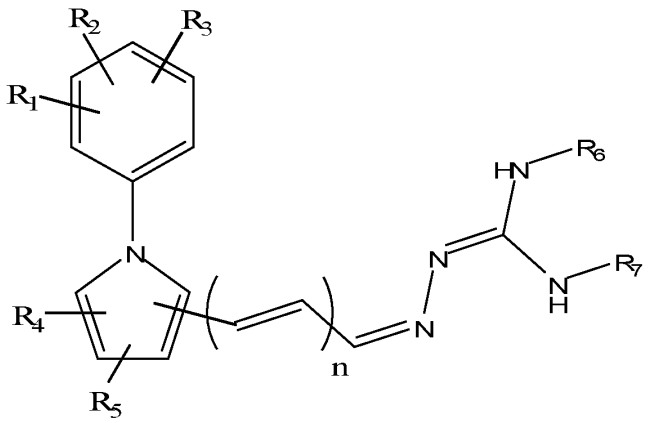
61. The composition for use according to any of the preceding claims, wherein the compound of formula (I), (Ia) or (II) is an an oral suspension, such as a suspension for oral administration.

62. The composition for use according to any of the preceding claims, wherein MTX has been administered for treatment of an arthritic disease prior to treatment with the compound of formula (I), (Ia) or (II).

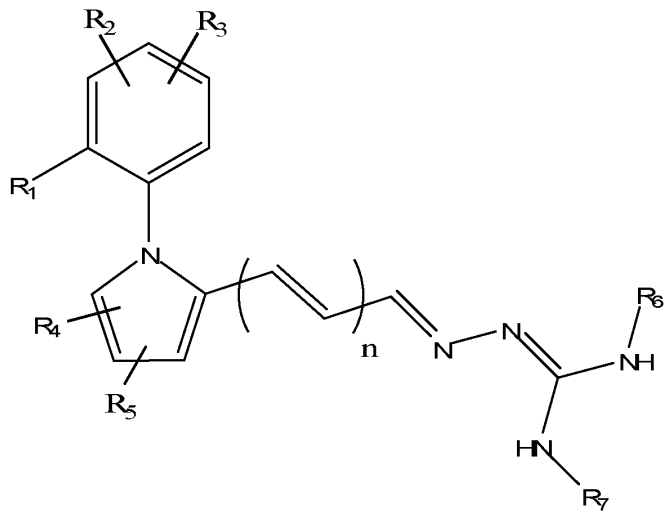
63. The composition for use according to claim 62, wherein prior MTX treatment of said arthritic disease has been suboptimal before initiation of treatment with the compound of formula(I), (Ia) or (II).

64. The composition for use according to any of the preceding claims, wherein the composition further comprises, separately or together, folic acid or an equivalent thereof.

65. A composition, such as a pharmaceutical composition comprising, separately or together, methotrexate (MTX), or a prodrug thereof, and a compound of formula (I) or (Ia):



formula (I)



formula (Ia)

including tautomeric and isomeric forms, such as enantiomeric forms, diastereomeric forms and racemic forms, thereof;

wherein

n is 1, 2 or 3;

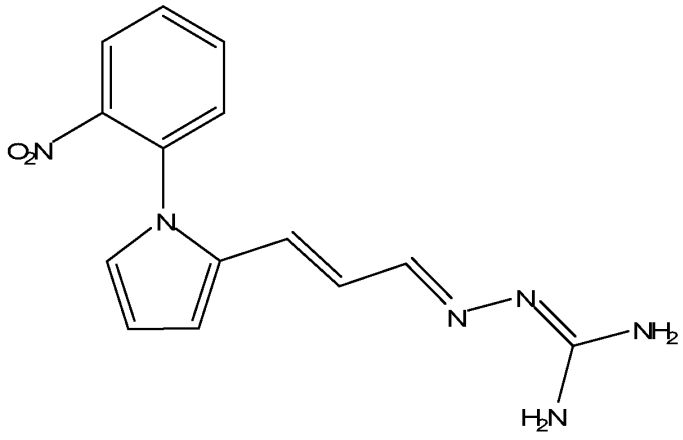
each R_1, R_2, R_3, R_4 and R_5 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted C_{3-6}-cycloalkyl, optionally substituted C_{2-6}-alkenyl, optionally substituted C_{4-6}-alkadienyl, optionally substituted C_{2-6}- alkynyl, hydroxy, optionally substituted C_{1-6}-alkoxy, optionally substituted C_{2-6}-alkenyloxy, carboxy, optionally substituted C_{1-6}-alkoxycarbonyl, optionally substituted C_{1-6}- alkylcarbonyl, formyl, C_{1-6}-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylcarbonyl, optionally

substituted heteroarylamino, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally substituted heterocyclyloxycarbonyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylcarbonyl, optionally substituted heterocyclylamino, heterocyclylsulphonylamino, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkylamino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, amino-C_{1-6}-alkyl-carbonylamino, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-carbonylamino, cyano, guanidino, carbamido, C_{1-6}-alkanoyloxy, C_{1-6}-alkylsulphonyl, C_{1-6}-alkylsulphinyl, C_{1-6}-alkylsulphonyl- oxy, aminosulfonyl, mono- and di(C_{1-6}-alkyl)aminosulfonyl, nitro, optionally substituted C_{1-6}-alkylthio and halogen, where any nitrogen-bound C_{1-6}-alkyl is optionally substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino or guanidine;

each R_6 and R_7 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, optionally substituted C_{4-6}- alkadienyl, optionally substituted C_{2-6}-alkynyl, optionally substituted C_{1-6}-alkoxycarbonyl, optionally substituted C_{1-6}-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino- C_{1-6}-alkyl-aminocarbonyl and mono- and di(C_{1-6}-alkyl)amino- C_{1-6}-alkyl-aminocarbonyl; or R_6 and R_7 may together form a five- or six-membered nitrogen-containing ring;

or a pharmaceutically acceptable derivative thereof.

66. The composition according to claim 65, wherein the compound is of formula (II)



formula (II)

including tautomeric and isomeric forms, such as enantiomeric forms, diastereomeric forms and racemic forms, thereof; or a pharmaceutically acceptable derivative thereof,

such as wherein said compound is selected from the group consisting of {3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine and (E)-N-trans-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine, or a pharmaceutically acceptable salt thereof,

such as wherein said compound is selected from the group consisting of {3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}- aminoguanidinium acetate and (E)-N-trans-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}- aminoguanidinium acetate.

67. The composition according to any of claims 62 to 63, wherein said composition further comprises folic acid, or an equivalent thereof.