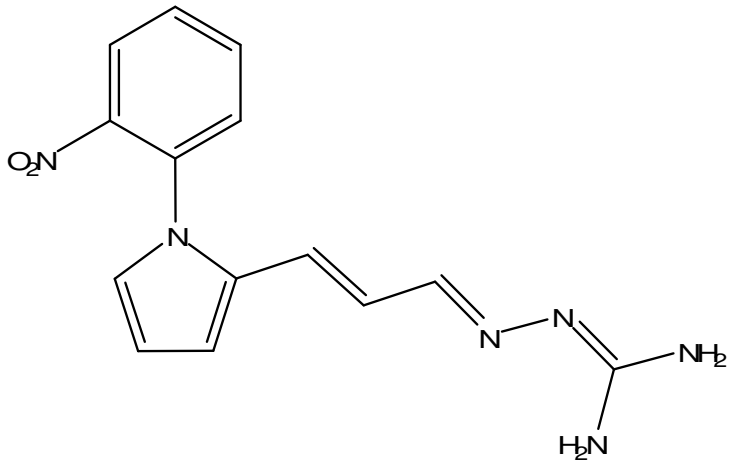
MC3R that does not provoke canonical cAMP generation (and hence no MC1R-induced melanogenesis) but instead appear to induce alternative pathways including ERK1/2-phosphorylation and Ca^{2+} mobilization (Montero-Melendez et al. 2015).

Summary

The present inventors have found that the phenyl pyrrole aminoguanidine derivative AP1189 (*(E)-N-trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidium acetate), when used in combination with the current standard-care methotrexate (MTX), exhibits significantly superior anti-arthritic effects compared to either of the compounds when administered alone. By provision of a new anti-arthritic combination treatment as disclosed herein, the present inventors provide a therapeutically effective alternative to current anti-arthritic treatments, and an attractive means for potentially reducing MTX toxicity and providing a novel therapeutic management of patients with a low response rate to MTX, such as MTX non-responders.

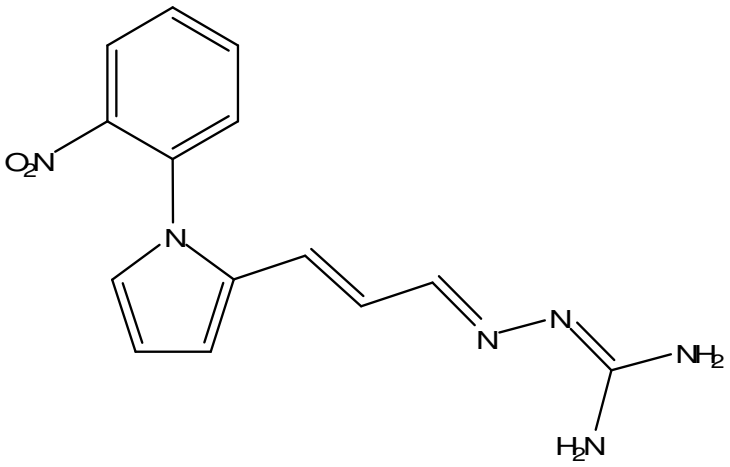
In one aspect, the present disclosure refers to a use of a compound of formula (II)



formula (II)

including tautomeric forms, enantiomeric forms, diastereoisomeric forms, and racemic forms thereof; or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in combinatorial therapy for treating an arthritic disease in a subject, wherein said medicament is to be administered in combination with methotrexate (MTX), wherein said arthritic disease is rheumatoid arthritis with a Clinical Disease Activity Index (CDAI) score of 22 or above (severe disease).

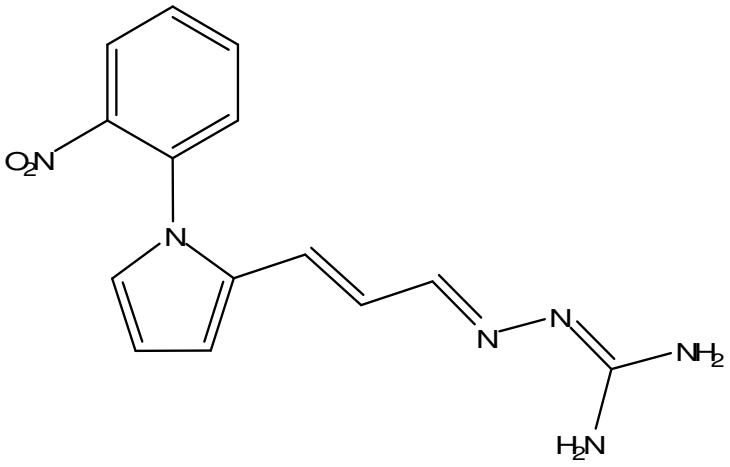
In another aspect, the present disclosure refers to a use of methotrexate (MTX) and a compound of formula (II)



formula (II)

including tautomeric forms, enantiomeric forms, diastereoisomeric forms, and racemic forms thereof; or a pharmaceutically acceptable salt thereof; in the manufacture of a medicament for combination therapy to treat an arthritic disease in a subject, wherein said arthritic disease is rheumatoid arthritis with a Clinical Disease Activity Index (CDAI) score of 22 or above (severe disease).

In another aspect, the present disclosure refers to a use of a compound of formula (II)



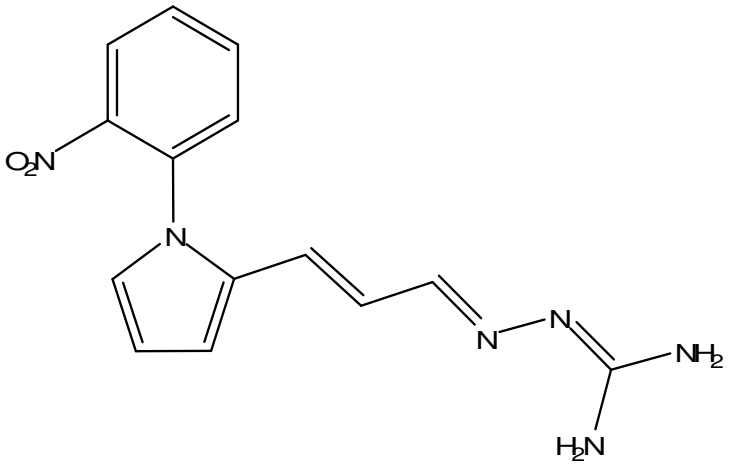
formula (II)

including tautomeric forms, enantiomeric forms, diastereoisomeric forms, and racemic forms thereof; or a pharmaceutically acceptable salt thereof in the manufacture of a first medicament and use of methotrexate (MTX) in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat an arthritic disease in a subject, wherein said arthritic disease is rheumatoid arthritis with a Clinical Disease Activity Index (CDAI) score of 22 or above (severe disease).

In yet another aspect, the present disclosure refers to a composition, such as a pharmaceutical composition, comprising methotrexate (MTX) and a compound of

Claims

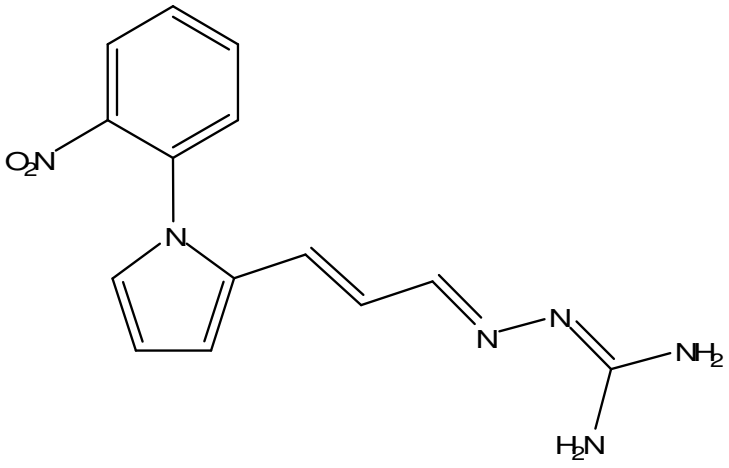
1. Use of a compound of formula (II)



formula (II)

including tautomeric forms, enantiomeric forms, diastereoisomeric forms, and racemic forms thereof; or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in combinatorial therapy for treating an arthritic disease in a subject, wherein said medicament is to be administered in combination with methotrexate (MTX),
wherein said arthritic disease is rheumatoid arthritis with a Clinical Disease Activity Index (CDAI) score of 22 or above (severe disease).

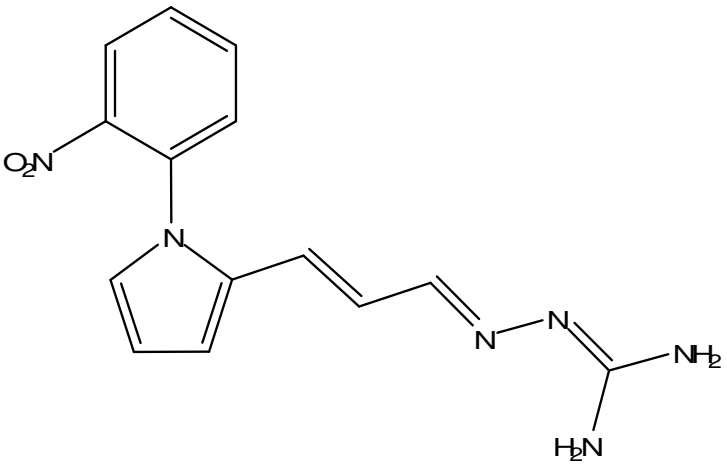
2. Use of methotrexate (MTX) and a compound of formula (II)



formula (II)

including tautomeric forms, enantiomeric forms, diastereoisomeric forms, and racemic forms thereof; or a pharmaceutically acceptable salt thereof;
in the manufacture of a medicament for combination therapy to treat an arthritic disease in a subject,
wherein said arthritic disease is rheumatoid arthritis with a Clinical Disease Activity Index (CDAI) score of 22 or above (severe disease).

3. Use of a compound of formula (II)



formula (II)

including tautomeric forms, enantiomeric forms, diastereoisomeric forms, and racemic forms thereof; or a pharmaceutically acceptable salt thereof in the manufacture of a first medicament and use of methotrexate (MTX) in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat an arthritic disease in a subject,
wherein said arthritic disease is rheumatoid arthritis with a Clinical Disease Activity Index (CDAI) score of 22 or above (severe disease).

4. The use according to claim 1 or 3, wherein the compound of formula (II) is to be administered prior to MTX.

5. The use according to any one of claims 1 to 3, wherein the compound of formula (II) is to be administered simultaneously with MTX.

6. The use according to claim 1 or 3, wherein the compound of formula (II) is to be administered after MTX.

7. The use according to any one of claims 1 to 6, wherein said subject's CDAI score during and/or after said treatment reduces the CDAI score by 5 points or more, such as 10 points or more, such as 15 points or more.

8. The use according to any one of claims 1 to 7, wherein said subject's CDAI score during and/or after said treatment reduces the CDAI score by 10 points or more.

~~7.~~9. The use according to any one of claims 1 to ~~8~~6, 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 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 (AP1189).

~~8.~~10. The use according to any one of claims 1 to ~~9~~7, wherein said pharmaceutically acceptable salt is a pharmaceutically acceptable salt of an inorganic acid, such as an inorganic acid selected from the group consisting of hydrochloric acid, hydrobromic acid, hydroiodic acid, phosphoric acid, sulphuric acid and nitric acid; or of an organic acid, such as an organic acid 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, preferably an organic acid selected from the group consisting of acetic acid, succinic acid, tartaric acid, and propionic acid, more preferably said organic acid is acetic acid.

~~9.~~11. The use according to any one of claims 1 to 10~~8~~, wherein said compound is (*E*)-*N*-*trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}- aminoguanidinium acetate (AP1189).

~~10. The use according to any one of claims 1 to 9, wherein the arthritic disease is an auto-immune disease and/or an inflammatory disease that presents with joint inflammation.~~

~~11. The use according to any one of claims 1 to 10, wherein the arthritic disease is selected from the group consisting of inflammatory arthritis, such as Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis; degenerative arthritis, such as osteoarthritis; metabolic arthritis, such as gouty arthritis ; reactive arthritis and/or infectious arthritis, such as arthritis associated with infection with one or more of Hepatitis C, Chlamydia, gonorrhoea, salmonella or shigella; and undifferentiated polyarthritis (UP).~~

12. The use according to any one of claims 1 to 11, wherein ~~the arthritic disease is~~ said rheumatoid arthritis ~~(RA), such as rheumatoid arthritis (RA)~~is selected from the group consisting of severe active rheumatoid arthritis (RA), newly diagnosed severe active RA, and juvenile rheumatoid arthritis (JRA), such as pauciarticular JRA, systemic-onset JRA, polyarticular JRA, or seronegative spondylarthritis.

~~13. The use according to any one of claims 1 to 12, 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) and/or 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).~~

~~14.~~13. The use according to any one of claims 1 to 12~~13~~, wherein the medicament

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), orsuch as to between 2.6 to <3.2 (low disease activity), orsuch 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), orsuch as to between 2.8 to <10 (low disease activity), orsuch 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, and/or~~

~~x)~~ix) results in a ≥20%, ≥50% or ≥70% improvement in ACR response rates.

~~15.~~14. The use according to any one of claims 1 to 13~~14~~, wherein the treatment of ~~an arthritic disease, such as RA,~~rheumatoid arthritis is in an MTX non-responder, such as in an MTX non-responder 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 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. has 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 higher risk (or probability) of non-response, as determined by the model disclosed by Sergeant et al 2018,

g. a female,

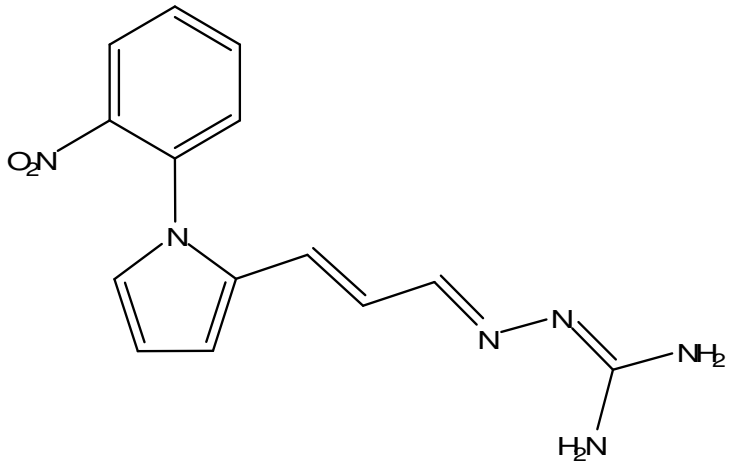
h. a current smoker, and

i. a person with high BMI.

~~16.~~15. The use according to any one of claims 1 to 14~~15~~, wherein methotrexate (MTX) is to be administered in an amount of 1 to 30 mg per week, for example 10 to 25 mg once per week, such as 5 to 15 mg per week; and the compound of formula (II) is to be administered in an amount of 1 mg to 1000 mg per day, for example 50 to 800 mg per day, such as 50 mg, 100 mg, 200 mg, 400 mg, 600 mg, or 800 mg per day.

~~17.~~16. The use according to any one of claims 1 to 15~~16~~, wherein the compound of formula (II) is to be administered daily, such as once daily, twice daily or three times daily, and the MTX is to be administered once weekly.

~~18.~~17. A composition, such as a pharmaceutical composition, comprising methotrexate (MTX) and a compound of formula (II)



formula (II)

including tautomeric forms, enantiomeric forms, diastereoisomeric forms, and racemic forms, thereof; 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}-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;

preferably wherein said compound is (E)-N-trans-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}- aminoguanidinium acetate (AP1189).

~~19.~~18. The use according to any one of claims 1 to 16~~17~~, or the composition according to claim 17~~18~~, wherein the medicament or the composition further ~~comprising~~ comprises folic acid.