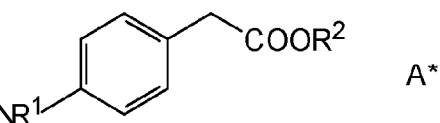


Claims

1. Method for synthesizing N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]acetamide according to the following steps:

Step A:

Reacting compound A of the following general formula A*



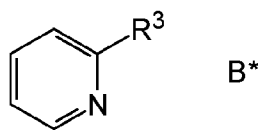
wherein

R¹ represents a leaving group and

R² represents an alkyl residue with 1 to 6 carbon atoms or a cycloalkyl residue with 3 to 6 carbon atoms

with a boronic acid derivative, borolane, borinane or diboronic acid reagent under elimination of R¹-H or R¹-B(OR)₂ and formation of an intermediate boronic acid derivative of compound A,

wherein the intermediate boronic acid derivative is then reacted with the pyridine compound B of the following general formula B*



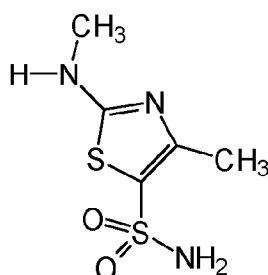
wherein

R³ represents a leaving group

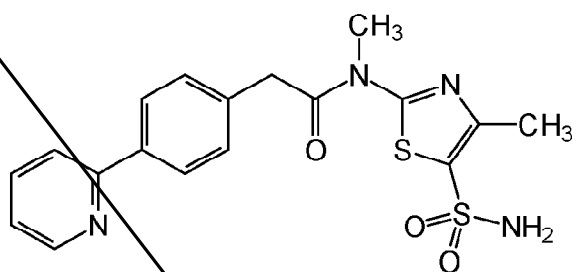
under basic conditions in order to directly obtain (4-pyridin-2-ylphenyl)acetic acid which is then purified.

Step B:

Reacting (4-pyridin-2-ylphenyl)acetic acid obtained from step A with 4-methyl-2-(methylamino)-1,3-thiazole-5-sulfonamide

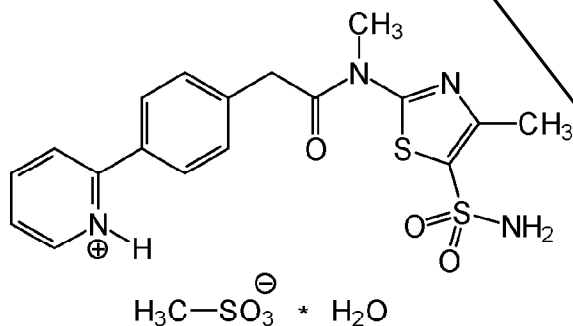


in order to obtain N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]acetamide of the formula



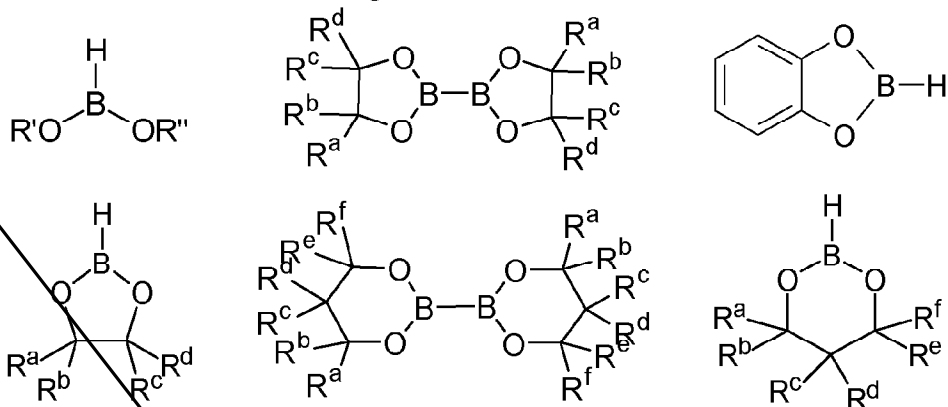
2. Method according to claim 1 further comprising step C:

Converting N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]acetamide with methanesulfonic acid in a mixture of an organic solvent and water to crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]acetamide methanesulfonic acid monohydrate of the formula



3. Method according to claim 1, wherein R^1 and R^3 are independently of each other selected from $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{OMs}$, $-\text{OTf}$ and $-\text{OTs}$.

4. Method according to claim 1, wherein the boronic acid derivative, borolane, borinane or diboronic acid reagent is selected from:



wherein

- 5 R', R'', R^a, R^b, R^c, R^d, R^e and R^f represent independently of each other a substituted or unsubstituted, linear or branched alkyl group with 1 to 10 carbon atoms or cycloalkyl group with 3 to 10 carbon atoms.
- 10 5. Method according to claim 1, wherein for the preparation of the intermediate boronic acid derivative or borolane reagent, the reagents palladium acetate, triethylamine and triphenylphosphine or PdCl₂(PPh₃)₂ and triethylamine are used.
- 15 6. Method according to claim 1, wherein Step B is carried out with EDC x HCl as coupling agent in a THF / NMP solvent mixture.
- 20 7. Method according to claim 2, wherein the mixture of N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]acetamide in an organic solvent and water yields a supersaturated solution upon addition of methanesulfonic acid at elevated temperatures from which the N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]-acetamide methanesulfonic acid monohydrate crystallizes after either extended stirring, seeding or cooling.
- 25 8. Method according to any one of claims 1 – 7 further comprising step D: Preparing a pharmaceutical composition of the crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]-acetamide methanesulfonic acid monohydrate with at least one pharmaceutically acceptable carrier, excipient, solvent and/or diluent.

9. Crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide methanesulfonic acid monohydrate.
- 5 10. Crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide methanesulfonic acid monohydrate according to claim 9, wherein the crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide methanesulfonic acid monohydrate is a polymorph of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide methanesulfonic acid monohydrate, characterised in that the X-Ray diffraction pattern of the polymorph comprises 2-Theta angle values of 6.5, 12.9, 16.8, 18.9, 19.3, 19.5, 20.0, 22.4, 22.5, 23.2, 23.8, 25.5, 25.9, 28.8, 30.5, 32.7, and 35.7 degrees.
- 10 11. Crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide methanesulfonic acid monohydrate according to claim 9 exhibiting a polymorphic form as described by Fig 1A and/or an X-ray diffraction pattern as described by Fig. 1D.
- 15 12. Crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide methanesulfonic acid monohydrate according to claim 9, 10 or 11 in combination with acetylsalicylic acid, trifluridine, idoxuridine, foscarnet, cidofovir, ganciclovir, aciclovir, penciclovir, valaciclovir and/or famciclovir.
- 20 13. Crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide methanesulfonic acid monohydrate according to claim 9, 10, 11 or 12 used for treatment and/or prophylaxis of infectious diseases and/or prevention of transmission of infectious diseases.
- 25 14. Crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide methanesulfonic acid monohydrate according to claim 13, wherein the infectious disease is a herpes simplex virus infection.
- 30 15. Pharmaceutical composition containing crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]acetamide methane-sulfonic acid monohydrate according to claim 9, 10 or 11 together with at least one pharmaceutically acceptable carrier, excipient, solvent and/or diluent.
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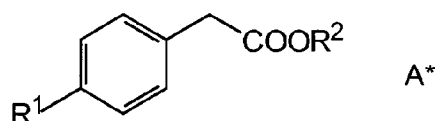
Claims

1. Method for synthesizing N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]acetamide according to the following steps:

5

Step A:

Reacting compound A of the following general formula A*



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wherein

R¹ represents a leaving group and

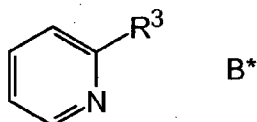
R² represents an alkyl residue with 1 to 6 carbon atoms or a cycloalkyl residue with 3 to 6 carbon atoms

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with a boronic acid derivative, borolane, borinane or diboronic acid reagent under elimination of R¹-H or R¹-B(OR)₂ and formation of an intermediate boronic acid derivative of compound A,

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wherein the intermediate boronic acid derivative is then reacted with the pyridine compound B of the following general formula B*



wherein

R³ represents a leaving group

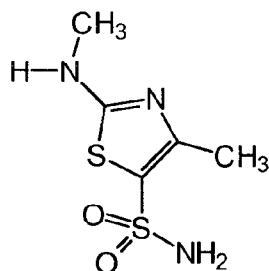
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under basic conditions in order to directly obtain (4-pyridin-2-ylphenyl)acetic acid which is then purified.

Step B:

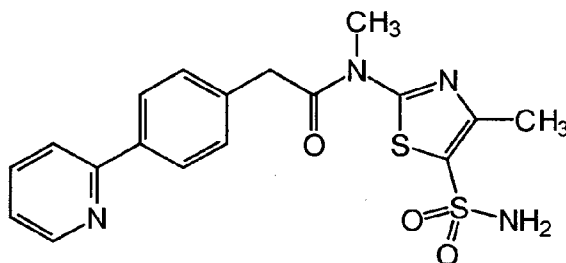
Reacting (4-pyridin-2-ylphenyl)acetic acid obtained from step A with 4-methyl-2-(methylamino)-1,3-thiazole-5-sulfonamide

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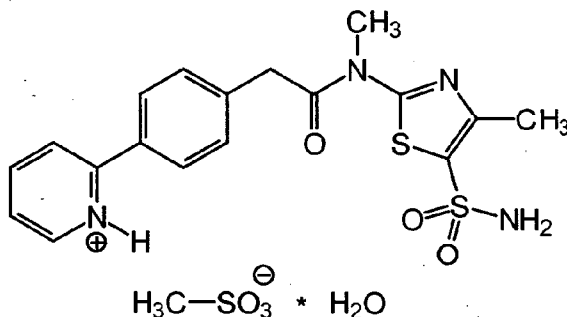
in order to obtain N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]acetamide of the formula

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2. Method according to claim 1 further comprising step C:
 10 Converting N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]acetamide with methanesulfonic acid in a mixture of an organic solvent and water to crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]acetamide methanesulfonic acid monohydrate of the formula

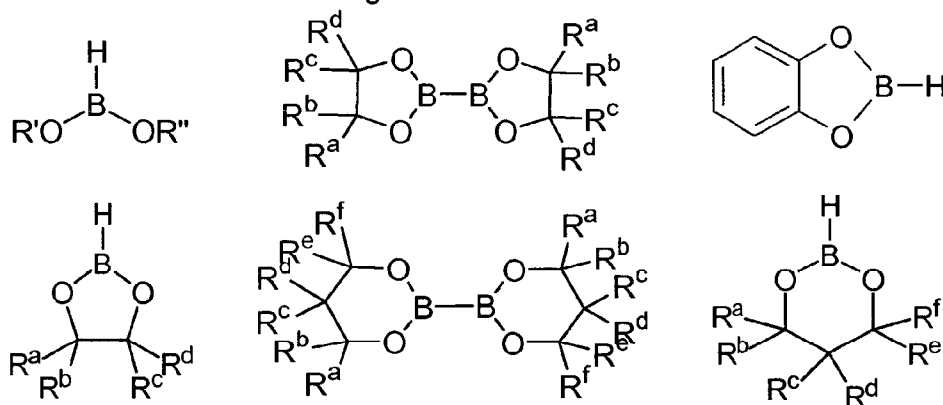
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3. Method according to claim 1, wherein R^1 and R^3 are independently of each other selected from $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{OMs}$, $-\text{OTf}$ and $-\text{OTs}$.

4. Method according to claim 1, wherein the boronic acid derivative, borolane, borinane or diboronic acid reagent is selected from:



wherein

- 5 R' , R'' , R^a , R^b , R^c , R^d , R^e and R^f represent independently of each other a substituted or unsubstituted, linear or branched alkyl group with 1 to 10 carbon atoms or cycloalkyl group with 3 to 10 carbon atoms.
- 10 5. Method according to claim 1, wherein for the preparation of the intermediate boronic acid derivative or borolane reagent, the reagents palladium acetate, triethylamine and triphenylphosphine or $PdCl_2(PPh_3)_2$ and triethylamine are used.
- 15 6. Method according to claim 1, wherein Step B is carried out with EDC x HCl as coupling agent in a THF / NMP solvent mixture.
- 20 7. Method according to claim 2, wherein the mixture of of N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]acetamide in an organic solvent and water yields a supersaturated solution upon addition of methanesulfonic acid at elevated temperatures from which the N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]-acetamide methanesulfonic acid monohydrate crystallizes after either extended stirring, seeding or cooling.
- 25 8. Method according to any one of claims 1 – 7 further comprising step D: Preparing a pharmaceutical composition of the crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]-acetamide methanesulfonic acid monohydrate with at least one pharmaceutically acceptable carrier, excipient, solvent and/or diluent.