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(54) **Title**: PROCESS FOR THE PREPARATION OF NEPAFENAC

(57) **Abstract**: Described herein are processes for the preparation of nepafenac and related intermediates, particularly wherein 2-aminobenzophenone is treated with a 2-(alkylthio)acetamide in the presence of sulfuryl chloride to afford a 2-(2-amino-3-benzoyl-phenyl)-2-(alkylthio)acetamide, which upon reduction affords nepafenac. Described herein are also processes for the purification of nepafenac, particularly for the removal of structurally similar impurities.

"PROCESS FOR THE PREPARATION OF NEPAFENAC"

Cross-Reference to Related Applications:

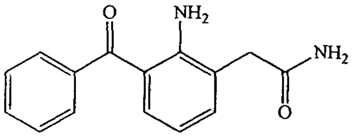
This application claims the benefit of priority to IN 2823/CHE/2013, filed June 27, 2013 and IN 4979/CHE/2013, filed November 4, 2013, which are hereby expressly incorporated by reference in their entirety.

Field:

Processes for the preparation of nepafenac and intermediates thereof, as well as processes for the purification of nepafenac.

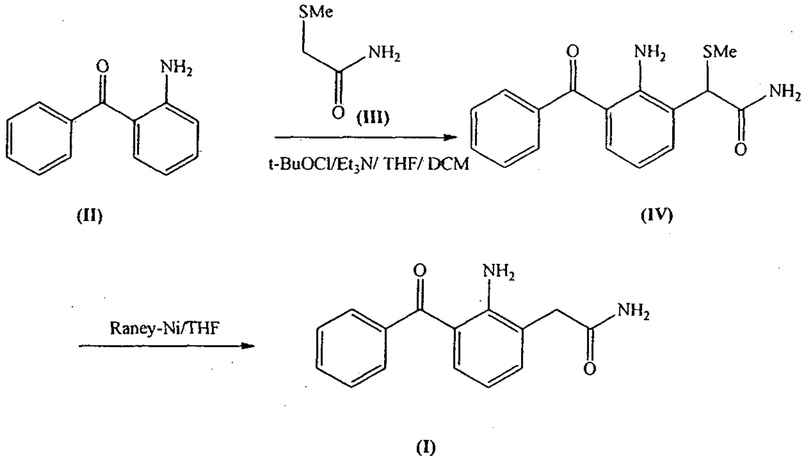
Description of the Related Art:

Nepafenac is a non-steroidal anti-inflammatory drug (NSAID) approved for ophthalmic use. Nepafenac is sometimes referred to as 2-amino-3-benzoylbenzeneacetamide and is structurally represented by Formula (I).



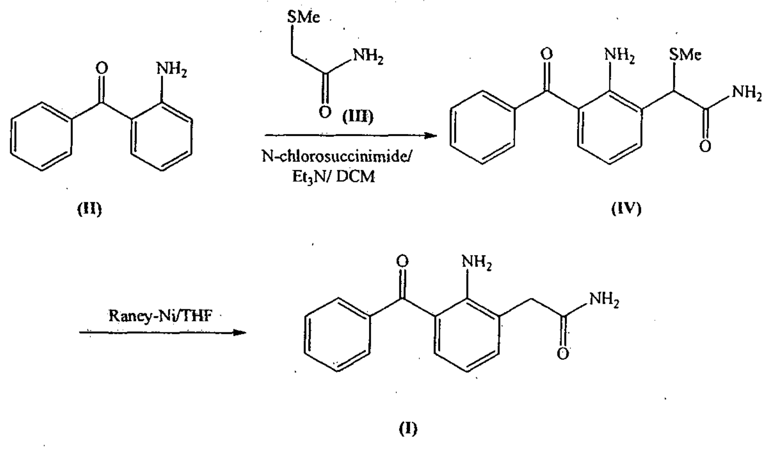
Formula (I)

U.S. Patent No. 4,313,949 discloses nepafenac and its preparation by treating 2-aminobenzophenone (II) with 2-(methylthio)acetamide (III) in the presence of *t*-butylhypochlorite to afford 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide (IV), which is subsequently reduced in the presence of Raney nickel and crystallized from isopropyl alcohol to afford nepafenac. This process is represented below in Scheme I.



Scheme I

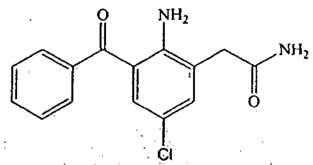
U.S. Patent No. 8,278,484 discloses a process for the preparation of nepafenac in which 2-aminobenzophenone (II) is treated with 2-(methylthio)acetamide (III) in the presence of *N*-chlorosuccinimide to afford 2-(2-amino-3-benzoylpheny1)-2-(methylthio)acetamide (IV), which is subsequently reduced in the presence of Raney nickel to afford nepafenac. This process is represented below in Scheme II.



Scheme II

Indian Publication No. 148/MUM/2011 discloses a process for the preparation of nepafenac in which 2-aminobenzophenone (II) is treated with 2-(methylthio)acetamide (III) in the presence of *N*-chlorophthalimide to afford 2-(2-amino-3-benzoylpheny1)-2-(methylthio)acetamide (IV), which is subsequently reduced in the presence of Raney nickel under hydrogen pressure to afford nepafenac.

A structurally similar impurity is also formed during the preparation of nepafenac. This impurity is known as 2-amino-3-benzoyl-5-chlorobenzeneacetamide and is represented below by Formula (Ia).



2-Amino-3-benzoyl-5-chlorobenzene acetamide

Formula (Ia)

This impurity is difficult to remove by conventional purification methods. Moreover, U.S. Patent No. 8,278,484 describes this impurity as causing "reproducibility problems" during the synthesis of nepafenac and also characterizes the formation of this impurity as a "drawback" suffered by the synthesis described in U.S. Patent No. 4,313,949. Accordingly, there is a continuing need for new and improved processes for the preparation of nepafenac, as well as methods for removing, reducing, or eliminating the chlorinated impurities formed during the preparation of nepafenac from nepafenac compositions.

Summary of the Disclosure:

Some aspects of the present disclosure are to provide a process for the preparation of nepafenac.

One aspect provides a process for the preparation of 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide (IV), comprising: treating 2-aminobenzophenone (II) with 2-(methylthio)acetamide (III) in the presence of sulfuryl chloride to afford 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide (IV).

One aspect provides a process for the preparation of nepafenac, comprising:

a) treating 2-aminobenzophenone (II) with 2-(methylthio)acetamide (III) in the presence of sulfuryl chloride and a base to afford 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide (IV), and
b) removing the thiomethyl moiety from the 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide (IV) to afford nepafenac.

In some embodiments, the removing of the thiomethyl moiety is conducted under reducing conditions. In some embodiments, the reducing conditions comprise hydrogen gas and a catalyst. In some embodiments, the catalyst is Raney nickel, palladium on carbon, palladium oxide, or platinum oxide. In some embodiments, the catalyst is Raney nickel. In some embodiments, the catalyst is palladium on carbon. In some embodiments, the catalyst is platinum oxide. In some embodiments, the catalyst is palladium oxide. In some embodiments, the reducing conditions further comprise a solvent selected from the group consisting of diethyl ether, tetrahydrofuran, and diisopropylether. In some embodiments, the base is a trialkylamine, a dialkylamine, a cycloamine, or an N-alkylcycloamine. In some embodiments, the base is selected from the group consisting of: triethylamine, diisopropylamine, methylisopropylamine, N-methylmorpholine and mixtures thereof. In some embodiments, the base is triethylamine. In some embodiments, the base is diisopropylethylamine. In some embodiments, the treating of 2-aminobenzophenone (II) with 2-(methylthio)acetamide (III) occurs in a solvent selected from the group consisting of dichloromethane, dichloroethane, chloroform, diethyl ether, tetrahydrofuran, diisopropylether and mixtures thereof.

Some embodiments are directed to a process for the purification of a nepafenac composition containing a halogenated impurity, comprising: subjecting a nepafenac composition containing a halogenated impurity to reducing conditions, wherein the reducing conditions convert the halogenated impurity to nepafenac, and optionally crystallizing the resultant nepafenac composition. In some embodiments, the halogenated impurity is 2-amino-3-benzoyl-5-chlorobenzeneacetamide. In some embodiments, the reducing conditions comprise hydrogen gas and a catalyst. In some embodiments, the catalyst is Raney nickel, palladium on carbon, palladium oxide, or platinum oxide. In some embodiments, the reducing conditions further include a base. In some embodiments, the base is selected from the group consisting of sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, diisopropylamine, methylisopropylamine and triethylamine. In some embodiments, the resultant nepafenac composition is crystallized and the crystallization is performed in a solvent comprising an alcohol. In some embodiments, the alcohol is methanol, ethanol, isopropanol or mixtures thereof. In some embodiments, the resultant nepafenac is crystallized from an isopropanol-water (9:1) mixture.

Some embodiments are directed to a process for the preparation of 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide (IV), comprising: treating 2-aminobenzophenone (II) with 2-(methylthio)acetamide (III) in the presence of sulfuryl chloride and a base to afford 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide (IV). In some embodiments, the base is a trialkylamine, a dialkylamine, a cycloamine, or an N-alkylcycloamine. In some embodiments, the treating occurs at about -30° C.

Some embodiments are directed to a process for the preparation of nepafenac, comprising:

a) treating 2-aminobenzophenone (II) with 2-(methylthio)acetamide (III) in the presence of sulfuryl chloride and a base to afford 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide (IV);
b) removing the thiomethyl moiety from the 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide (IV) to afford a nepafenac composition containing a halogenated impurity;
c) subjecting the nepafenac composition containing the halogenated impurity to reducing conditions, wherein the reducing conditions convert the halogenated impurity to nepafenac; and
d) optionally crystallizing the resultant nepafenac composition.

Some embodiments are directed to a process for the preparation of nepafenac, comprising:

a) treating 2-aminobenzophenone (II) with 2-(methylthio)acetamide (III) in the presence of sulfuryl chloride to afford 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide (IV), and
b) removing the thiomethyl moiety from the 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide (IV) to afford nepafenac.

Some embodiments are directed to a process for the preparation of nepafenac, comprising:

a) treating 2-aminobenzophenone (II) with 2-(methylthio)acetamide (III) in the presence of sulfuryl chloride to afford 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide (IV), and
b) reducing the 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide (IV) to afford nepafenac.

Some embodiments are directed to a process for the purification of a nepafenac composition containing a halogenated impurity, comprising: subjecting a nepafenac composition containing a halogenated impurity to reducing conditions, wherein the reducing conditions convert the halogenated impurity to nepafenac.

Some embodiments are directed to a process for the purification of a nepafenac composition containing a chlorinated impurity, comprising: hydrogenating a nepafenac composition containing a chlorinated impurity, wherein the hydrogenating converts the chlorinated impurity to nepafenac.

Some embodiments are directed to a process for the purification of a nepafenac composition containing a chlorinated impurity, comprising:

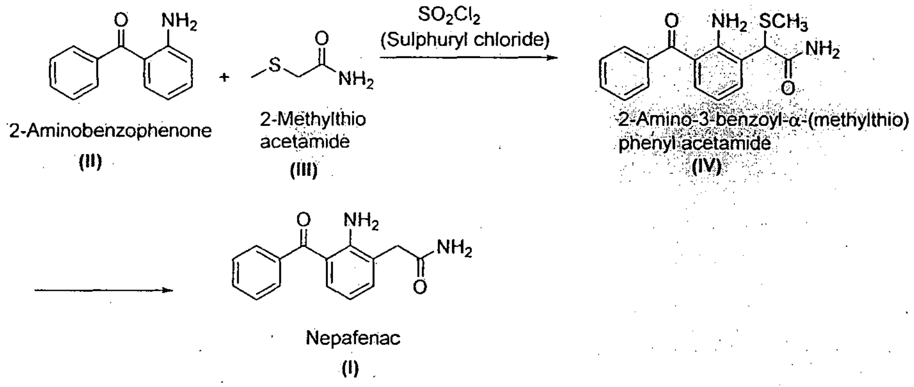
a) hydrogenating a nepafenac composition containing a chlorinated impurity, wherein the hydrogenating converts the chlorinated impurity to nepafenac, and
b) optionally crystallizing the step a) product in an alcohol and water solvent to afford nepafenac.

Some embodiments are directed to a process for the purification of a nepafenac composition containing a chlorinated impurity, comprising:

a) hydrogenating a nepafenac composition containing a chlorinated impurity in the presence of a catalyst and a base,

b) optionally crystallizing the step a) product in an alcohol and water solvent, and isolating pure nepafenac.

Scheme III below represents other embodiments in the present disclosure.



Scheme III

Detailed Description of the Disclosure:

The present disclosure is directed to a process for the preparation of nepafenac, wherein 2-aminobenzophenone of Formula (II) is treated with 2-(methylthio)acetamide of Formula (III) in the presence of sulfuryl chloride to yield 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide of Formula (IV), which upon reduction affords nepafenac, represented by Formula (I). *See*, *e.g.*, Scheme III above.

The present disclosure also relates to a process for the purification of nepafenac to remove a structurally similar impurity, wherein the nepafenac containing the structurally similar impurity compound is subjected to hydrogenation in the presence of a catalyst and a base, followed by isolation, to afford nepafenac. The obtained nepafenac of formula (I) is optionally subjected to crystallization in a mixture of alcohol and water to obtain a purified nepafenac. In some embodiments, the structurally similar impurity is a halogenated impurity, particulary one which contains a halogenated aromatic ring. In some embodiments, the halogenated impurity is 2-amino-3-benzoyl-5-chlorobenzeneacetamide.

One embodiment of the present disclosure is to provide an improved process for the preparation of nepafenac comprising the steps of:

a) reacting 2-aminobenzophenone of Formula (II) with 2-(methylthio)acetamide of Formula (III) in the presence of sulfuryl chloride to afford a 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide (IV), and
b) reducing the compound of formula (IV) to obtain nepafenac.

The reaction of 2-aminobenzophenone of Formula (II) with 2-(methylthio)acetamide of Formula (III) is carried out in the presence of sulfuryl chloride and a base, preferably an organic base in a chlorinated solvent, at a temperature in the range of about -40° to about 0° C, preferably about -30° C, for a period of about 30 minutes to about 2 hours to afford a 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide of formula (IV). The 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide of formula (IV) is then reduced in the presence of a catalyst under hydrogen pressure in a suitable solvent, such as an ether and water solvent, at a temperature in the range of about 20° C to about 35° C and the reaction mixture is stirred for a period of 10 minutes to 60 minutes to afford nepafenac of formula (I). One of skill in the art will readily understand that a 2-(alkylthio)acetamide may be utilized in place of the specifically exemplified 2-(methylthio)acetamide. Moreover, a skilled artisan will readily recognize that alternative sources of hydrogen may be utilized in place of hydrogen gas in the reduction reaction described above. Such alternative sources include, but are not limited to, hydrazine, dihydronapthalene, dihydroanthracene, isopropanol, formic acid, and the like. Alternative hydrogen sources for reduction reactions are well-known in the synthetic arts.

According to the present disclosure, the base that is utilized in the reaction of 2-aminobenzophenone of Formula (II) with 2-(methylthio)acetamide of Formula (III) in the presence of sulfuryl chloride may be selected form organic amines such as trialkylamines, dialkylamines, monoalkylamines, cycloamines, and *N*-alkylcycloamines. As used herein, "alkyl" refers to C_1-C_6 linear and branched alkyl groups. As used herein, "cycloamine" refers to dialkylamines in which two of the alkyl groups are taken together to form a nitrogen-containing heterocyle (such as morpholine, piperidine, piperazine, pyrrolidine, imidazole, and pyridine). Non-limiting examples of trialkylamines include triethylamine and diisopropylethylamine. Non-limiting examples of dialkylamines include diisopropylamine and methylisopropylamine. Non-limiting examples of *N*-alkylcycloamines include *N*-methylmorpholine, *N,N*-dimethylpiperazine, *N*-methylpiperazine, and *N*-methylpyrollidine. A skilled artisan will readily understand that mixtures of the aforementioned bases can be utilized.

According to the present disclosure, the solvent for the reaction of 2-aminobenzophenone of Formula (II) with 2-(methylthio)acetamide of Formula (III) in the presence of sulfuryl chloride may be selected from chlorinated solvents such as dichloromethane (or "DCM"), dichloroethane, or chloroform, as well as ether solvents such as diethyl ether, tetrahydrofuran or diisopropylether. Additional solvents include those suitable for aromatic acylation reactions.

According to the present disclosure, the catalyst for the reduction of 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide may be a metal catalyst such as Raney nickel, Palladium on carbon, Palladium oxide, or Platinum oxide. The solvent used in the reduction of 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide may be selected from an ether solvent such as without limitation, diethyl ether, tetrahydrofuran, or diisopropylether. Other solvents include those that are compatible with catalytic reductions, mixtures thereof, and aqueous mixtures thereof. Such solvents include, but are not limited to, alcohols exemplified by methanol, ethanol, isopropanol and *n*-butanol.

Another embodiment of the present disclosure relates to an improved process for the purification of nepafenac containing the structurally similar impurity comprising the steps of:

a) hydrogenating nepafenac containing 2-amino-3-benzoyl-5-chlorobenzeneacetamide as a chlorinated impurity in the presence of a catalyst and a base;
b) optionally crystallizing the step a) product in a mixture of alcohol and water solvent; and
c) isolating nepafenac.

According to the present disclosure, impure nepafenac, which is containing 2-amino-3-benzoyl-5-chlorobenzene acetamide as a halogenated impurity in the range of, for example, about 0.3% to about 0.7%, is hydrogenated in the presence of a catalyst and a base in a solvent at about 40-45° C under 5-7 psi hydrogen pressure until effective reaction completion, or for about about 6-15 hours, about 8-10 hours, or about 12-13 hours. After the effective completion of the reaction, the catalyst is filtered and the filtrate is concentrated to afford nepafenac. This is then optionally subjected to further purification by crystallization from an appropriate solvent. Crystallization solvents include, but are not limited to, alcohols such as methanol, ethanol, isopropanol, *n*-butanol, or mixtures thereof, as well as alcohol-water mixtures. A 9:1 ratio of alcohol to water has proven useful in practice, with 9:1 isopropanol:water being particularly preferred.

According to the present disclosure, the catalyst for use during the removal of the halogenated impurity may be selected from metal catalyst such as without limitation, palladium on carbon, or platinum oxide. Palladium on carbon is particularly preferred. The base for use during the removal of the halogenated impurity is one that is suitable for use during catalytic reductions, and may be selected without limitation from bases such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, diisopropylamine, methylisopropylamine and triethylamine. Organic amines such as trialkylamines, dialkylamines, monoalkylamines, cycloalkylamines, and *N*-alkylcycloamines as previously described above are particularly preferred. Moreover, a skilled artisan will readily recognize that alternative sources of hydrogen as described above may be utilized in place of hydrogen gas in the reduction reaction.

According to the present disclosure, the solvent for for use during the removal of the halogenated impurity includes, but is not limited to those that are suitable for use during catalytic reductions. These include alcohols such as methanol, ethanol, isopropanol and n-butanol, ethers such as diethyl ether and tetrahydrofuran, and esters such as ethyl acetate.

Additional Aspects of the Detailed Disclosure

Additional aspects of the detailed disclosure are repeated and further enumerated as follows:

1. A process for the preparation of nepafenac, comprising:
   a) treating 2-aminobenzophenone (II) with 2-(methylthio)acetamide (III) in the presence of sulfuryl chloride and a base to afford 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide (IV), and
   b) removing the thiomethyl moiety from the 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide (IV) to afford nepafenac.
2. A process for the preparation of nepafenac, comprising:
   a) treating 2-amino-benzophenone (II) with 2-(methylthio)acetamide (III) in the presence of sulfuryl chloride and a base to afford 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide (IV);
   b) removing the thiomethyl moiety from the 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide (IV) to afford a nepafenac composition containing a halogenated impurity;
   c) subjecting the nepafenac composition containing the halogenated impurity to reducing conditions, wherein the reducing conditions convert the halogenated impurity to nepafenac; and
   d) optionally crystallizing the resultant nepafenac composition.
3. A process for the purification of a nepafenac composition containing a halogenated impurity, comprising: subjecting a nepafenac composition containing a halogenated impurity to reducing conditions, wherein the reducing conditions convert the

halogenated impurity to nepafenac, and optionally crystallizing the resultant nepafenac composition.

4. A process for the preparation of 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide (IV), comprising: treating 2-aminobenzophenone (II) with 2-(methylthio)acetamide (III) in the presence of sulfuryl chloride and a base to afford 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide (IV).
5. The process of any one of aspects 1-4, wherein the removing of the thiomethyl moiety is conducted under reducing conditions.
6. The process of any one of aspects 1-5, wherein the reducing conditions comprise a hydrogen source and a catalyst.
7. The process of any one of aspects 1-6, wherein the catalyst is Raney nickel, palladium on carbon, palladium oxide, or platinum oxide.
8. The process of any one of aspects 1-7, wherein the reducing conditions further comprise a solvent selected from the group consisting of diethyl ether, tetrahydrofuran, and diisopropylether.
9. The process of any one of aspects 1-8, wherein the hydrogen source is hydrogen gas.
10. The process of any one of aspects 1-9, wherein the base is a trialkylamine, a dialkylamine, a cycloalkylamine, or an N-alkylcycloamine.
11. The process of any one of aspects 1-10, wherein the base is selected from the group consisting of: triethylamine, diisopropylamine, methylisopropylamine, N-methylmorpholine and mixtures thereof.
12. The process of any one of aspects 1-11, wherein the treating of 2-aminobenzophenone (II) with 2-(methylthio)acetamide (III) occurs in a solvent selected from the group consisting of dichloromethane, dichloroethane, chloroform, diethyl ether, tetrahydrofuran, diisopropylether and mixtures thereof.
13. The process of any one of aspects 1-12, wherein the halogenated impurity is 2-amino-3-benzoyl-5-chlorobenzeneacetamide.
14. The process of any one of aspects 1-13, wherein the reducing conditions further include a base.
15. The process of any one of aspects 1-14, wherein the base is selected from the group consisting of sodium hydroxide, potassium hydroxide, sodium carbonate, potassium

carbonate, diisopropylamine, methylisopropylamine and triethylamine and the hydrogen source is hydrogen gas.

16. The process of any one of aspects 1-15, wherein the resultant nepafenac composition is crystallized and the crystallization is performed in a solvent comprising an alcohol.
17. The process of any one of aspects 1-16, wherein the alcohol is methanol, ethanol, isopropanol or mixtures thereof.
18. The process of any one of aspects 1-17, wherein the resultant nepafenac is crystallized from an isopropanol-water (9:1) mixture.
19. The process of any one of aspects 1-18, wherein treating the 2-aminobenzophenone (II) with the 2-(methylthio)acetamide (III) in the presence of sulfuryl chloride and a base is conducted at a temperature between -40° C and 0° C.
20. The process of any one of aspects 1-19, wherein treating the 2-aminobenzophenone (II) with the 2-(methylthio)acetamide (III) in the presence of sulfuryl chloride and a base is conducted at a temperature of about -30° C.

Examples

In view of the above description and the examples below, one of ordinary skill in the art will be able to practice the invention as claimed without undue experimentation. The foregoing will be better understood with reference to the following examples that detail certain procedures for the preparation of molecules, compositions and formulations according to the present invention. All references made to these examples are for the purposes of illustration. The following examples should not be considered exhaustive, but merely illustrative of only a few of the many aspects and embodiments contemplated by the present disclosure.

Example-1: Preparation of 2-amino-3-benzoyl-α-(methylthio)phenylacetamide (also referred to as 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide)

To a suspension of 2-aminobenzophenone (75 g) and 2-(methylthio)acetamide (22 g) in methylene dichloride (450 mL) was added dropwise a solution of sulfuryl chloride (25 g) in methylene chloride (300 mL) at -30° C over a period of 30 min. The resulting mixture was stirred for 30 min at -30° C; followed by the slow addition of triethylamine (76 g) at -30° C and the reaction mixture was maintained for 60 minutes at the same temperature. The reaction mixture temperature was then raised to room temperature and the reaction was quenched with water (500 mL). The aqueous layer was separated and extracted twice with methylene chloride (2 x 200 mL). The combined organic layer was concentrated under reduced pressure to afford a residue that was subsequently dissolved in isopropyl alcohol (1940 mL) at 65°-70° C. The solution was allowed to cool to room temperature and stirred for 30 min. The resultant solid was filtered, washed with isopropyl alcohol (150 mL) and dried at 50-55° C in a hot air oven to afford 2-amino-3-benzoyl-α-(methylthio)phenylacetamide (26 g) as a yellow solid.

Example-2: Preparation of nepafenac

To a solution of 2-amino-3-benzoyl-α-(methylthio)phenylacetamide (26 gm) in tetrahydrofuran (340 mL) and water (80 mL), Raney nickel (wet 208 g) was added at room temperature. The mixture was stirred for 15 min and filtered through a hyflo bed. The filtrate was concentrated under reduced pressure and the obtained solid was dissolved in isopropyl alcohol (780 mL) at about 75°-80° C. The solution was allowed to cool to room temperature and the resultant precipitate was filtered and dried at about 50-55° C under reduced pressure to afford nepafenac as a yellow solid (13 g).

Example 3: Purification of nepafenac

To a solution of nepafenac (17 g) containing 0.33% of 2-amino-3-benzoyl-5-chlorobenzeneacetamide in methanol (2550 mL) was added potassium carbonate (17 g) and 10 % palladium on carbon (1.7 g). Hydrogen gas was then applied to the mixture at about 40-45° C and 5-7 psi pressure for about 8-10 hours. After completion, the reaction mass was filtered and the filtrate was concentrated to afford nepafenac with 0.06 % 2-amino-3-benzoyl-5-chlorobenzeneacetamide. This product was further purified by crystallization from an isopropanol-water mixture (9:1) to afford nepafenac as a yellow solid (8.0 g, purity 99.86% with 0.03% 2-amino-3-benzoyl-5-chlorobenzeneacetamide).

Example 4: Purification of nepafenac

To a solution of nepafenac (0.50 g) containing 0.67% of 2-amino-3-benzoyl-5-chlorobenzeneacetamide in methanol (75 mL) was added potassium carbonate (0.50 mg) and 10% palladium on carbon (50 mg). Hydrogen gas was then applied to the mixture at about 40-45° C and 5-7 psi pressure for 12-13 hours. After completion, the reaction mass was filtered and the filtrate was concentrated to afford nepafenac with 0.08% 2-amino-3-benzoyl-5-chlorobenzeneacetamide. This product was further purified by crystallization from an isopropanol–water mixture (9:1) to afford nepafenac as a yellow solid (0.3 g, purity 99.84%, with 0.03% 2-amino-3-benzoyl-5-chlorobenzeneacetamide).

Example 5: Purification of nepafenac

To a solution of nepafenac (17 g) containing 0.33% 2-amino-3-benzoyl-5-chlorobenzeneacetamide in methanol (2550 mL) was added triethylamine (17 g) and 10% palladium on carbon (1.7 g). Hydrogen gas was then applied to the mixture at about 40-45° C and 5-7 psi pressure for 8-10 hours. After completion, the reaction mass was filtered and the filtrate was concentrated to afford nepafenac (yield 11 g, purity 99.86% with 0.06% 2-amino-3-benzoyl-5-chlorobenzeneacetamide).

Example 6: Purification of nepafenac

To a solution of nepafenac (1 g) containing 0.67% 2-amino-3-benzoyl-5-chlorobenzeneacetamide in methanol (150 mL) was added triethylamine (1 g) and 10 % palladium on carbon (100 mg). Hydrogen gas was then applied to the mixture at about 40-45° C and 5-7 psi pressure for 8-10 hours. After completion, the reaction mass was filtered and the filtrate was concentrated to afford nepafenac (yield 0.67 g, purity 99.89% with 0.01% 2-amino-3-benzoyl-5-chlorobenzeneacetamide).

We claim:

1. A process for the preparation of nepafenac, comprising:
   a) treating 2-aminobenzophenone (II) with 2-(methylthio)acetamide (III) in the presence of sulfuryl chloride and a base to afford 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide (IV), and
   b) removing the thiomethyl moiety from the 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide (IV) to afford nepafenac.
2. The process of Claim 2, wherein the removing of the thiomethyl moiety is conducted under reducing conditions.
3. The process of Claim 3, wherein the reducing conditions comprise a hydrogen source and a catalyst.
4. The process of Claim 4, wherein the catalyst is Raney nickel, palladium on carbon, palladium oxide, or platinum oxide.
5. The process of Claim 5, wherein the reducing conditions further comprise a solvent selected from the group consisting of diethyl ether, tetrahydrofuran, and diisopropylether and the hydrogen source is hydrogen gas.
6. The process of Claim 1, wherein the base is a trialkylamine, a dialkylamine, a cycloamine, or an N-alkylcycloamine.
7. The process of Claim 6, wherein the base is selected from the group consisting of: triethylamine, diisopropylamine, methylisopropylamine, *N*-methylmorpholine and mixtures thereof.
8. The process of Claim 7, wherein the treating of 2-aminobenzophenone (II) with 2-(methylthio)acetamide (III) occurs in a solvent selected from the group consisting of dichloromethane, dichloroethane, chloroform, diethyl ether, tetrahydrofuran, diisopropylether and mixtures thereof.
9. A process for the purification of a nepafenac composition containing a halogenated impurity, comprising: subjecting a nepafenac composition containing a halogenated impurity to reducing conditions, wherein the reducing conditions convert the halogenated impurity to nepafenac, and optionally crystallizing the resultant nepafenac composition.

10. The process of Claim 9, wherein the halogenated impurity is 2-amino-3-benzoyl-5-chlorobenzeneacetamide.
11. The process of Claim 10, wherein the reducing conditions comprise a hydrogen source and a catalyst.
12. The process of Claim 11, wherein the catalyst is Raney nickel, palladium on carbon, palladium oxide, or platinum oxide.
13. The process of Claim 12, wherein the reducing conditions further include a base.
14. The process of Claim 13, wherein the base is selected from the group consisting of sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, diisopropylamine, methylisopropylamine and triethylamine and the hydrogen source is hydrogen gas.
15. The process of Claim 9, wherein the resultant nepafenac composition is crystallized and the crystallization is performed in a solvent comprising an alcohol.
16. The process of Claim 15, wherein the alcohol is methanol, ethanol, isopropanol or mixtures thereof.
17. The process of Claim 9, wherein the resultant nepafenac is crystallized from an isopropanol-water (9:1) mixture.
18. A process for the preparation of 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide (IV), comprising: treating 2-amino-benzophenone (II) with 2-(methylthio)-acetamide (III) in the presence of sulfuryl chloride and a base to afford 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide (IV).
19. The process of Claim 18, wherein the base is a trialkylamine, a dialkylamine, a cycloalkylamine or an N-alkylcycloamine.
20. The process of Claim 18, wherein the base is an organic amine.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2014/000429

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C231/12 C07C237/20 C07C319/20
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	CN 101 906 055 A (SHANGHAI HUIKU BIOLOGY TECHNOLOGY CO LTD) 8 December 2010 (2010-12-08) See WPI abstract or automated translation; the whole document -----	1-20
X	CYBULSKI MARCIN ET AL: "Development and a Practical Synthesis of Nepafenac Intermediate via Modified Gassman Reaction", LETTERS IN ORGANIC CHEMISTRY, BENTHAM SCIENCE PUBLISHERS LTD, NL, vol. 9, no. 7, 1 September 2012 (2012-09-01), pages 461-464, XP008168099, ISSN: 1570-1786, DOI: 10.2174/157017812802139582 the whole document ----- -/--	1-8, 18-20

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search 15 October 2014	Date of mailing of the international search report 23/10/2014
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Bedel, Christian

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	US 2009/312575 A1 (SUAREZ GABRIEL TOJO [ES] ET AL) 17 December 2009 (2009-12-17) cited in the application the whole document -----	1-8, 18-20
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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		WO 2009150524 A1	17-12-2009