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(54) Benævnelse: **Fremgangsmåde til fremstilling af 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazol og hydrogensulfatsaltet deraf**

(56) Fremdragne publikationer:
WO-A1-2013/150173
WENDY A. LOUGHLIN, IAN D. JENKINS, MARIA J. PETERSSON: "Cyclodehydration of N-(Aminoalkyl)benzamides under Mild Conditions with a Hendrickson Reagent Analogue", JOURNAL OF ORGANIC CHEMISTRY, vol. 78, no. 14, 27 June 2013 (2013-06-27) , pages 7356-7361, XP002788365, DOI: 10.1021/jo401082q
ANA M. REVERDITO; ISABEL A. PERILLO; ALEJANDRA SALERNO: "Synthesis and Synthetic Applications of 1-Aryl-2-alkyl-4,5-dihydro-1H-imidazoles", SYNTHETIC COMMUNICATIONS, vol. 42, no. 14, 27 October 2011 (2011-10-27), pages 2083-2097, XP002788366, DOI: 10.1080/00397911.2011.552155

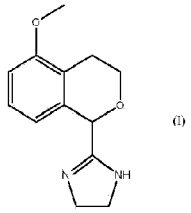
DESCRIPTION

TECHNICAL FIELD

[0001] The present disclosure relates to an improved process for the preparation of isochroman structured alpha2A adrenoceptor agonist, namely 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazole (I) and a pharmaceutically acceptable salts thereof, such as a sulfate salt (1a), and to a novel intermediate compound used in the process, namely *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamide monohydrate (V).

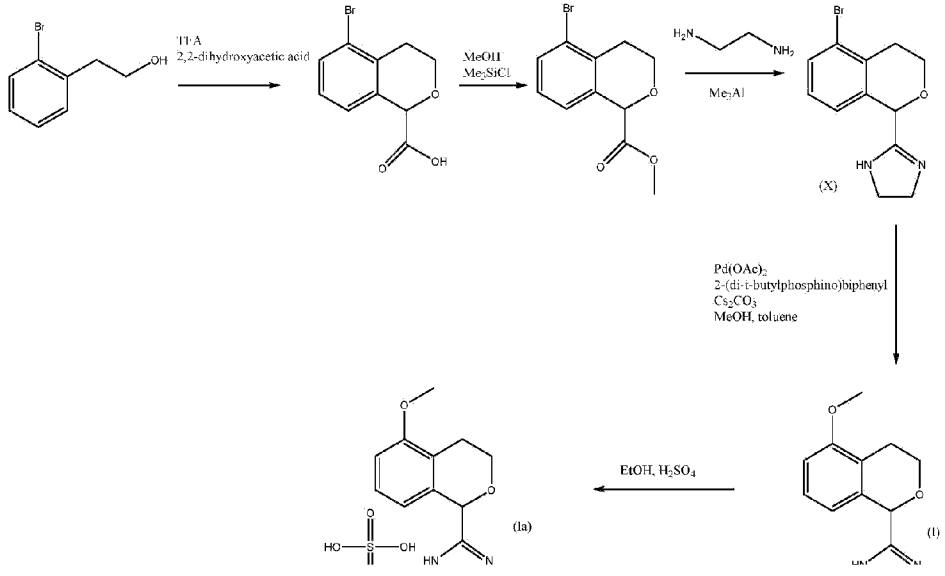
BACKGROUND OF THE INVENTION

[0002] The compound 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazole of formula (I) and a pharmaceutically acceptable salts thereof have been disclosed in WO 2013/150173. Compound of formula (I) exhibits agonistic activities on adrenergic alpha2 receptors, especially on alpha2A receptor, and can thus be used in the treatment of a disorder, condition or disease where an alpha2A agonist is indicated to be useful, particularly for use as a sedative or analgesic agent, and for use in the treatment of anxiety.



(I)

[0003] WO 2013/150173 discloses a process for the preparation of the compound of formula (I) and salts thereof through a 2-(5-bromoisochroman-1-yl)-4,5-dihydro-1H-imidazole intermediate of formula (X) as shown in scheme 1.

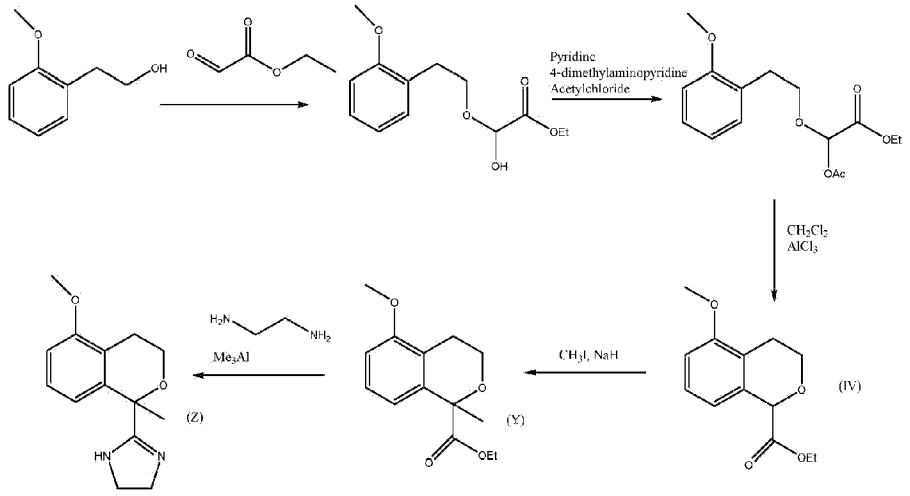


Scheme 1.

[0004] This process of scheme 1 comprises refluxing the mixture of 2-(2-bromophenyl)ethanol, TFA and 2,2-dihydroxyacetic acid to obtain 5-bromoisochroman-1-carboxylic acid which is further mixed with methanol and trimethylsilylchloride to form methyl 5-bromoisochroman-1-carboxylate. To a solution of ethylenediamine, trimethylaluminium and toluene is added the mixture of methyl 5-bromoisochroman-1-carboxylate and toluene to obtain 2-(5-bromoisochroman-1-yl)-4,5-dihydro-1H-imidazole of formula (X). Finally methanol and toluene is added to a mixture of 2-(5-bromoisochroman-1-yl)-4,5-dihydro-1H-imidazole of formula (X), 2-(di-t-butylphosphino)biphenyl, palladium(II)acetate and Cs_2CO_3, and formed 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazole of formula (I) is isolated from the reaction mixture.

[0005] The sulfate salt (Ia) of compound of formula (I) is prepared from isolated 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazole of formula (I) in ethanol by adding sulfuric acid in ethanol.

[0006] WO 2013/150173 discloses also another process for preparing derivatives of formula (I). In that process compound of formula (Y) is prepared through ethyl 5-methoxyisochroman-1-carboxylate intermediate of formula (IV) according to scheme 2.



Scheme 2.

[0007] This process of scheme 2 comprises reacting 2-(2-methoxyphenyl)ethanol with ethyl 2-oxoacetate in toluene to form ethyl 2-hydroxy-2-(2-methoxyphenethoxy)acetate which is further treated with pyridine, 4-dimethylaminopyridine and acetyl chloride to form ethyl 2-acetoxy-2-(2-methoxyphenethoxy)acetate. After several purification steps the isolated ethyl 2-acetoxy-2-(2-methoxyphenethoxy)acetate is dissolved in dichloromethane and treated with $AlCl_3$ to form ethyl 5-methoxyisochroman-1-carboxylate of formula (IV). The intermediate compound of formula (Y) is finally reacted with ethylenediamide in the presence of

trimethylauminium and toluene to form the 4,5-dihydroimidazole compound of formula (Z).

[0008] The above mentioned processes have several drawbacks. Due to the unfavorable reagents and the complex work-ups the purity and the yield of the product are very poor. Further, trimethylaluminum is a pyrophoric reagent which limits its usefulness. Moreover, the processes are very difficult to scale-up, i.e. those may not be readily adapted for use on industrial scale.

[0009] Thus, there is a need for a more practical and economical process that is suitable for the manufacture of the compound of formula (I) and a salt thereof in high yield and purity also being feasible for use in a large scale.

SUMMARY OF THE INVENTION

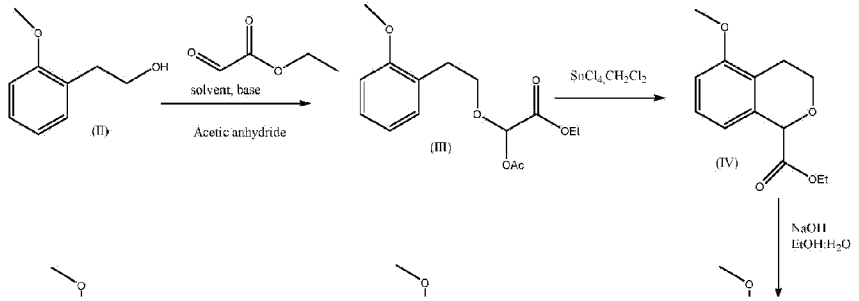
[0010] It has now been found that the compound of formula (I) can be prepared using a process which is more practical and economical and suitable for use in a large industrial scale. In particular, compound of formula (I) and a sulfate salt thereof prepared by simplified procedures together with the effective purification steps can be isolated in high yield and excellent purity. Moreover, the use of pyrophoric trimethylaluminum is avoided.

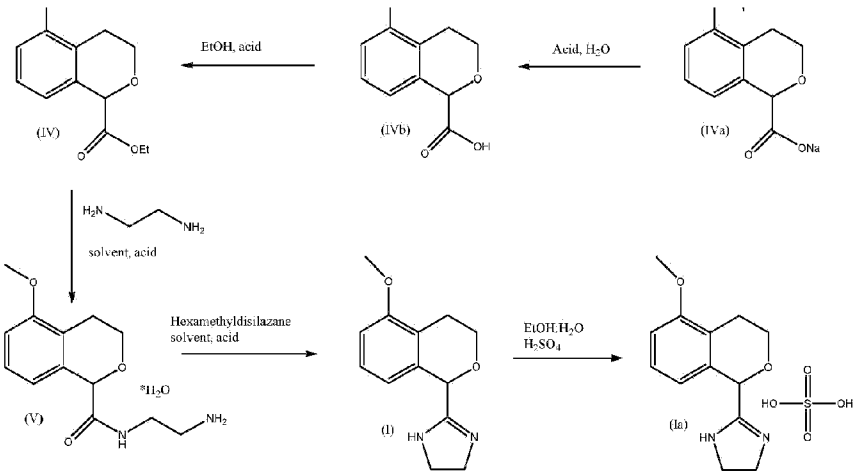
[0011] Thus, an object of the present disclosure is to provide a novel process for the preparation of 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazole of formula (I) and pharmaceutically acceptable salts thereof, such as 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazole hydrogensulfate of formula (Ia).

[0012] Another object of the present disclosure is to provide a process for the preparation of a novel intermediate *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamide monohydrate of formula (V) and a process for the preparation of 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazole of formula (I) and a sulfate salt thereof using said intermediate of formula (V).

[0013] Another object of the present disclosure is to provide a novel intermediate *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamide monohydrate of formula (V).

[0014] The process of the present disclosure can be summarized according to the following general reaction scheme 3 wherein, if not clearly otherwise stated, all abbreviations and expressions have the meanings well known to the person skilled in the art of organic chemistry.





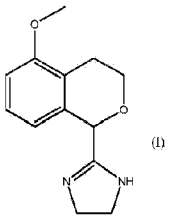
Scheme 3.

[0015] The foregoing as well as other feature and advantages of the present teachings will be more fully understood from the following description and claims.

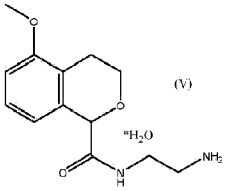
DETAILED DESCRIPTION OF THE INVENTION

[0016] The present disclosure relates to a novel process for the preparation of 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazole of formula (I) and a pharmaceutically acceptable salts thereof, such as 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazole hydrogensulfate of formula (Ia).

[0017] In one embodiment the present disclosure relates to a process for the preparation of 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazole of formula (I) or a pharmaceutically acceptable salt thereof

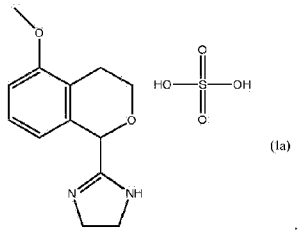


by reacting *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamide monohydrate of formula (V)



with hexamethyldisilazane under acidic conditions and in the presence of a non-reactive solvent, to obtain 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazole of formula (I), which is optionally converted to its pharmaceutically acceptable salt.

[0018] In one embodiment the present disclosure relates to above process, further comprising the step of converting the compound of formula (I) to 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazole hydrogensulfate of formula (Ia)



(Ia)

[0019] In one embodiment the present disclosure relates to a process for the preparation of compound of formula (I), comprising the steps of

1. a) reacting *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamide monohydrate of formula (V) in a non-reactive solvent, e.g. xylene, with hexamethyldisilazane, in the presence of catalytic amount of an acid, e.g. sulphuric acid; and
2. b) without isolating the formed 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazole of formula (I) from the reaction mixture, converting said 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazole to 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazole hydrogensulfate of formula (Ia).

[0020] In one embodiment the present disclosure relates to above process wherein, the step b) is carried out by treating the reaction mixture with ethanol-water solution and adding sulfuric acid.

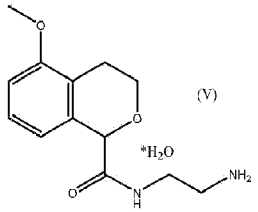
[0021] In one embodiment the present disclosure relates to a process for the preparation of compound of formula (I), comprising the steps of

1. a) reacting *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamide monohydrate of formula (V) in xylene with hexamethyldisilazane at an elevated temperature, e.g. above 80°C, in the presence of catalytic amount of sulphuric acid to obtain 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazole of formula (I);
2. b) without isolating the formed 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazole of formula (I) adding water and HCl to the reaction mixture to convert the compound of formula (I) to its hydrochloride salt;
3. c) isolating the water phase;
4. d) adding suitable extraction solvent, e.g. methylene chloride, and an inorganic base, e.g.NaOH;
5. e) isolating the organic phase;
6. f) adding ethanol-water solution and sulphuric acid to form 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazole hydrogensulfate of formula (Ia);
7. g) distilling the solvent off;

8. h) adding ethanol to the ethanol-water solution;
9. i) crystallizing 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazole hydrogensulfate of formula (Ia) by cooling and optionally seeding; and
10. j) isolating the crystalline compound of formula (Ia).

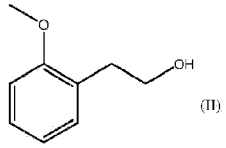
[0022] In one embodiment the present disclosure relates to process for the preparation of *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamide monohydrate of formula (V).

[0023] In one embodiment the present disclosure relates to a process for the preparation of *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamide monohydrate of formula (V)

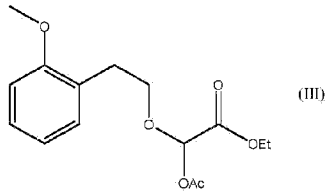


comprising the steps of

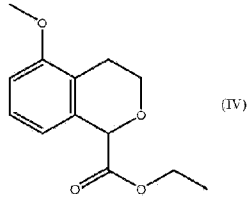
1. a) reacting 2-(2-methoxyphenyl)ethanol of formula (II)



with ethyl 2-oxoacetate in suitable organic solvent, e.g. dichloromethane or toluene, and the presence of a tertiary aliphatic amine, e.g. trimethylamine or triethylamine, and subsequently adding acetic anhydride to the reaction mixture to form ethyl 2-acetoxy-2-(2-methoxyphenethoxy)acetate of formula (III);



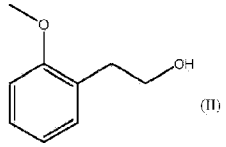
2. b) adding ethyl 2-acetoxy-2-(2-methoxyphenethoxy)acetate of formula (III) to the mixture of tin tetrachloride and chlorinated hydrocarbon solvent, e.g. dichloromethane, to form ethyl 5-methoxyisochroman-1-carboxylate of formula (IV); and



3. c) reacting the ethyl 5-methoxyisochroman-1-carboxylate of formula (IV) with ethylene diamine in suitable solvent, e.g. aliphatic or aromatic hydrocarbon solvent, such as toluene, and the presence of a catalytic amount of suitable acid, e.g. acetic acid, to form *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamide monohydrate of formula (V).

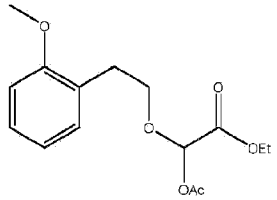
[0024] In one embodiment the present disclosure relates to a process for the preparation of *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamide monohydrate of formula (V), comprising the steps of

1. a) reacting 2-(2-methoxyphenyl)ethanol of formula (II)



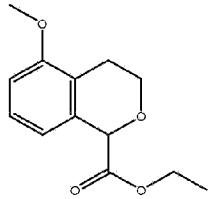
(II)

with ethyl 2-oxoacetate in suitable solvent, e.g. dichloromethane, and the presence of a tertiary aliphatic amine, e.g. trimethylamine or trimethylamine, and subsequently adding acetic anhydride to the reaction mixture to form ethyl 2-acetoxy-2-(2-methoxyphenethoxy)-acetate of formula (III);



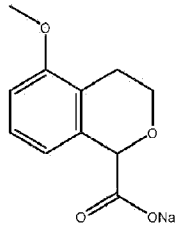
(III)

2. b) adding ethyl 2-acetoxy-2-(2-methoxyphenethoxy)acetate of formula (III) to the mixture of tin tetrachloride and a chlorinated hydrocarbon solvent to form ethyl 5-methoxyisochroman-1-carboxylate of formula (IV);



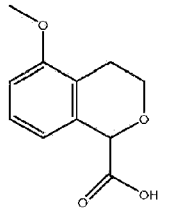
(IV)

3. c) without isolating the formed ethyl 5-methoxyisochroman-1-carboxylate of formula (IV) adding water, NaOH and ethanol to the reaction mixture to obtain sodium 5-methoxyisochroman-1-carboxylate of formula (IVa);



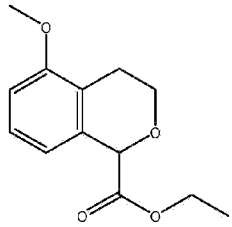
(IVa)

4. d) treating the sodium 5-methoxyisochroman-1-carboxylate of formula (IVa) with suitable acid, e.g. strong organic or inorganic acid, such as HCl, in water and isolating the formed 5-methoxyisochroman-1-carboxylic acid of formula (IVb);



(IVb)

5. e) reacting the 5-methoxyisochroman-1-carboxylic acid of formula (IVb) in suitable organic solvent, e.g. toluene, with ethanol in the presence of suitable acid, e.g. HCl, to form ethyl 5-methoxyisochroman-1-carboxylate of formula (IV); and



(IV)

6. f) reacting the ethyl 5-methoxyisochroman-1-carboxylate of formula (IV) with ethylene diamine in aliphatic or aromatic hydrocarbon solvent and the presence of a catalytic amount of suitable acid, e.g. acetic acid, to form *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamide monohydrate of formula (V).

[0025] In one embodiment the present disclosure relates to a process for the preparation of *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamide monohydrate of formula (V), comprising the steps of

1. a) reacting 2-(2-methoxyphenyl)ethanol of formula (II) with ethyl 2-oxoacetate in toluene and the presence of trimethylamine and subsequently adding acetic anhydride to the reaction mixture to form ethyl 2-acetoxy-2-(2-methoxyphenethoxy)acetate of formula (III);
2. b) adding ethyl 2-acetoxy-2-(2-methoxyphenethoxy)acetate of formula (III) in dichloromethane to the mixture of tin tetrachloride and dichloromethane to form ethyl 5-methoxyisochroman-1-carboxylate of formula (IV);
3. c) without isolating the formed ethyl 5-methoxyisochroman-1-carboxylate of formula (IV) from the reaction mixture adding water, NaOH and ethanol to the reaction mixture to obtain sodium 5-methoxyisochroman-1-carboxylate of formula (IVa);
4. d) treating the sodium 5-methoxyisochroman-1-carboxylate of formula (IVa) with HCl in water and isolating the formed 5-methoxyisochroman-1-carboxylic acid of formula (IVb);
5. e) reacting 5-methoxyisochroman-1-carboxylic acid of formula (IVb) in toluene with ethanol in the presence of HCl to form ethyl 5-methoxyisochroman-1-carboxylate of formula (IV) in toluene solution; and
6. f) reacting the ethyl 5-methoxyisochroman-1-carboxylate toluene solution obtained from step e) with ethylene diamine in the presence of a catalytic amount of acetic acid to form *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamide monohydrate of formula (V).

[0026] In one embodiment the present disclosure relates to a process for the preparation *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamide monohydrate of formula (V) according to the above processes further comprising the steps of

g) extracting the reaction mixture by adding water immiscible organic solvent, e.g. toluene, and

water and subsequently gradually adding suitable acid, e.g. acetic acid ; and

h) crystallizing *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamide monohydrate of formula (V) from the water phase by adding a suitable strong base, e.g. NaOH.

[0027] In one embodiment the present disclosure relates to a process for the preparation of 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazole of formula (I) or a pharmaceutically acceptable salt thereof comprising the steps of

1. a) reacting 2-(2-methoxyphenyl)ethanol of formula (II) with ethyl 2-oxoacetate in suitable solvent and the presence of an organic base and subsequently adding acetic anhydride to the reaction mixture to form ethyl 2-acetoxy-2-(2-methoxyphenethoxy)acetate of formula (III);
2. b) adding ethyl 2-acetoxy-2-(2-methoxyphenethoxy)acetate of formula (III) to the mixture of tin tetrachloride and a chlorinated hydrocarbon solvent to form ethyl 5-methoxyisochroman-1-carboxylate of formula (IV);
3. c) reacting the ethyl 5-methoxyisochroman-1-carboxylate of formula (IV) with ethylene diamine in aliphatic or aromatic hydrocarbon solvent and the presence of a catalytic amount of acid to form *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamide monohydrate of formula (V);
4. d) reacting *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamide monohydrate of formula (V) in suitable solvent with hexamethyldisilazane in the presence of catalytic amount of an acid; and
5. e) without isolating the formed 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazole of formula (I) from the reaction mixture, converting said 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazole to 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazole hydrogensulfate of formula (Ia).

[0028] In one embodiment the present disclosure relates to a novel compound of formula (V).

[0029] It was found that the compound of formula (I) and a sulfate salt thereof prepared according to the process described herein, can be obtained in high yield and excellent purity. Also the process for the preparation of compound of formula (V), as described herein, is very effective leading to high yield and is suitable for use in an industrial scale. The quality of the isolated compound of formula (V) is excellent. It is well characterized crystalline compound.

[0030] The conversion of the compound of formula (II) to the compound of formula (III) involves a presence of a base. It was found that by changing the base from pyridine to a tertiary aliphatic amine, such as trimethylamine, the extra purification steps can be avoided.

[0031] It was also found that when converting the compound of formula (III) to the compound

of formula (IV) changing the addition order of reagents and using $SnCl_4$ instead of $AlCl_3$ reduces the formation of impurities. Moreover, the purification of compound of formula (IV) can be carried out via its sodium salt of formula (IVa) instead of using many distillations to dryness which is a difficult operation to handle in a large scale. In addition, this purification method is more effective.

[0032] It was found that the conversion of the compound of formula (IV) to the compound of formula (I) can be carried out by safer two-step method. This new method avoids the use of pyrophoric $AlMe_3$ and the work-up and isolation of the new intermediate compound of formula (V) removes impurities effectively.

[0033] It was found that the conversion of the compound of formula (V) to the sulfate salt (Ia) of formula (I) is possible to carry out without isolation of the compound of formula (I).

[0034] The starting materials, such as compound of formula (II), are commercially available or can be prepared according to the methods known in the art.

[0035] The present disclosure will be explained in more detail by the following illustrative examples.

EXAMPLE 1: Preparation of ethyl 2-acetoxy-2-(2-methoxyphenethoxy)acetate (III)

[0036] A flask inserted with N_2 was charged with dichloromethane (900mL) followed by 2-(2-methoxyphenyl)ethanol (II) (150g, 1.0 equivalent). Then ethyl 2-oxoacetate in toluene (50%, 191g, 0.95 equivalent) and trimethylamine (199g, 2.0 equivalent) were subsequently added and the reaction mixture was stirred 1 hour. The bath temperature was adjusted to 0°C and acetic anhydride (161g, 1.6 equivalent) was added to the reaction mixture. The reaction mass was stirred 1h at 0±5°C. The reaction mixture was stirred 2 hours at 20-30°C.

[0037] Water (450 mL) was added to the reaction mixture. The reaction mixture was stirred 10 min and the organic layer was separated. Water (450 mL) and HCl (25mL, 30% aq, 0.24 equivalent) were added to the reaction mixture. The reaction mixture was stirred 10 min and the organic layer was separated. Water (450 mL) was added to the reaction mixture. The reaction mixture was stirred 10 min and the organic layer was separated.

[0038] The product was collected by distilling off the organic layer until the reaction mass reached 105-110°C. The reaction mixture was cooled to 30-50°C and the organic layer was distilled off at reduced pressure (100 mbar) until the reaction mass reached 100°C. The distill residue was the product and it was yellowish oil at 87.0 HPLC a-% purity.

EXAMPLE 2: Preparation of sodium 5-methoxyisochroman-1-carboxylate (IVa)

[0039] A flask inserted with N_2 was charged with dichloromethane (600mL) followed by tin(IV) chloride (63mL, 1.3 equivivalent). The reaction mixture was cooled to 0±3°C and ethyl 2-acetoxy-2-(2-methoxyphenethoxy)acetate (120g, 1 equivalent) in dichloromethane (840 mL) was added to the reaction mixture at 0±3°C over 1 hour. The reaction mixture was stirred 1 hour at 0±3°C and water (360 mL) was added to the reaction mixture at 0±3°C. The reaction mixture was stirred 10 min and the organic layer was separated. The organic layer was washed with water (360 mL). Ethanol (360 mL) was added to the reaction mixture. The organic layer was distilled off until the reaction mass reached 60°C (distillation residue 360 mL).

[0040] Water (192 mL) was added to the reaction and the reaction mixture was heated to 50±3°C. NaOH (50%, 39 mL, 1.8 equivalents) was added over 35 minutes and the temperature is maintained at 50±3°C during the addition. After the addition, the reaction mass was seeded with crystalline sodium 5-methoxyisochroman-1-carboxylate (100 mg). Ethanol (276 mL) was added over 50 minutes and the temperature is maintained at 50±3°C during the addition. The reaction mass was stirred 1 hour at 50±3°C and cooled to 0°C over 3 hours.

[0041] After stirring for 60 min at 0°C the product was collected by filtration and the cake was washed with *tert*-butylmethyl ether (96 mL). The product was dried in a vacuum oven at 60°C to give 75.7g (80.9%) of white solid at 99.2 HPLC a-% purity.

EXAMPLE 3: Preparation of 5-methoxyisochroman-1-carboxylic acid (IVb)

[0042] A flask inserted with N_2 was charged with water (1200 mL), ethanol (121 mL) and hydrogen chloride (30%, 103 mL, 1.3 equivalents). Sodium 5-methoxyisochroman-1-carboxylate (173 g, 1 equivalents) was added to the reaction mixture at 20±5°C followed by water (173 mL). The reaction mass was stirred 7 hour at 20±3°C. The reaction mass was cooled to 0±3°C over 5 hours and stirred 8 hours at 0±3°C.

[0043] The product was collected by filtration and the cake was washed with water (173 mL). The product was dried in a vacuum oven at 60°C to give 148.2g (94.7%) of white solid at 99.6 HPLC a-% purity.

EXAMPLE 4: Preparation of ethyl 5-methoxyisochroman-1-carboxylate (IV)

[0044] 5-Methoxyisochroman-1-carboxylic acid (13.2 g), ethanol (80 ml) and toluene (70 ml) were charged. The mixture was warmed to 60 ± 5°C. HCl in ethanol 20 % (7.9 ml) was added. The mixture was stirred for 3 hours at 60 ± 5°C. About 80 ml was distilled off under normal pressure. The mixture was cooled to room temperature. Water (50 ml) was added and the mixture was stirred for a few minutes. The phases were allowed to separate and the water phase was separated off. About 30 ml was distilled off under normal pressure. The toluene

solution was used as such for the next stage. The yield is practically quantitative. HPLC-purity (toluene excluded) was 99.0 %.

EXAMPLE 5: Preparation of *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamide monohydrate (V)

[0045] Ethyl 5-methoxyisochroman-1-carboxylate toluene solution from example 4 and ethylene diamine (13.0 ml) were charged. Acetic acid (0.30 ml) was added. The mixture was warmed to 97 ± 3°C. The mixture was stirred for 5 hours at 97 ± 3°C. The mixture was cooled to 10-20°C. Toluene (70 ml) and water (110 ml) were added at 10-20°C. Acetic acid (19 ml) was added gradually at 10-20°C. The mixture was heated to 80 ± 3°C and stirred for 0.5 hour at 80 ± 3°C. Phases were allowed to separate and the toluene phase was separated off. 50 % NaOH (21 ml) was added slowly at 45 ± 5°C. The mixture was cooled slowly (2-3 hours) to 10 ± 5°C and stirred for about 2 hours at 10 ± 5°C. The crystalline compound was filtered and washed with water (2 * 20 ml). The compound was dried under reduced pressure at 20 ± 5°C. The yield was 14.0 g (82 %). The HPLC-purity was 99.5 %.

[0046] ^{1}H-NMR ($CDCl_3$): 1.55 ppm 4 H (s broad), 2.75-2.85 ppm 4 H (m), 3.20-3.30 1 H (m), 3.32-3.42 ppm 1 H (m), 3.77-3.86 ppm 4 H (m+s), 4.20-4.28 ppm 1 H (m), 5.17 ppm 1 H (s), 6.76 ppm 1 H (d), 6.94 ppm 1 H (s), 7.17 ppm 1 H (tr), 7.33 ppm 1 H (d).

[0047] ^{13}C-NMR: 22.8, 41.5, 41.9, 55.4, 63.9, 77 (under $CDCl_3$), 108.5, 117.8, 121.9, 126.7, 133.3, 156.6, 171.0.

EXAMPLE 6: 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazole hydrogensulfate (Ia)

[0048] *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamide monohydrate (12 g) and xylene (60 ml) were charged. Sulfuric acid 93 % (0.3 ml) was added. Hexamethyldisilazane (26 ml) was added. The mixture was heated to 122°C and stirred for 4 hours at 122 ± 3°C. The mixture was cooled. Water (60 ml) and 30 % HCl (14 ml) were added slowly at 40 ± 5°C. The mixture was heated to 60 ± 3°C and stirred for 2 hours at 60 ± 3°C. The phases were allowed to separate and the organic phase was separated off. Methylene chloride (80 ml) was added to the water phase. 50 % NaOH (14 ml) was added gradually at 20 ± 5°C. The phases were allowed to separate. The water phase was separated off. Water (30 ml) was added to the organic phase. The mixture was stirred for a few minutes. The phases were allowed to separate. The water phase was separated off. Ethanol (80 ml), water (15 ml) and sulfuric acid 93 % (2.4 ml) were added to the methylene chloride solution. Methylene chloride was distilled off under normal pressure. The ethanol-water solution was cooled to 70 ± 5°C and ethanol (42 ml) was added. The solution was cooled to room temperature. Seed crystals were added

during the cooling. The mixture was stirred overnight at room temperature. The mixture was cooled to 0-5°C and stirred about 4 hours at 0-5°C. The crystalline compound was filtered and washed with cold ethanol (20 ml).The product was dried under reduced pressure at 60-70°C. The yield was 11.07 g (74.9 %). The HPLC-purity was 99.9 %.

[0049] ^{1}H-NMR (DMSO-d_6): 2.6-2.8 ppm 2 H (m), 3.82 ppm 3 H (s), 3.89 ppm 4 H (s), 3.8-3.9 ppm 1 H (m), 4.1-4.2 ppm 1 H (m), 5.78 ppm 1 H (s), 6.82 ppm 1 H (d), 6.99 ppm 1 H (d), 7.28 ppm 1 H (tr), 9.1-10.8 ppm 3 H (s+s, broad).

[0050] ^{13}C-NMR: 22.2, 44.8, 55.9, 63.6, 69.6, 110.4, 117.1, 122.7, 127.8, 130.9, 157.0, 169.8.

REFERENCES CITED IN THE DESCRIPTION

Cited references

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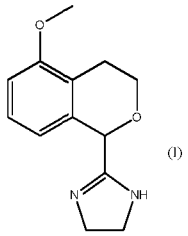
Patent documents cited in the description

- WO2013150173A [0002] [0003] [0006]

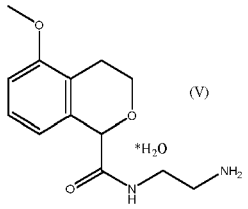
PATENTKRAV

1. Fremgangsmåde til fremstilling af 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazol med formlen (I) eller et farmaceutisk acceptabelt salt deraf



(I)

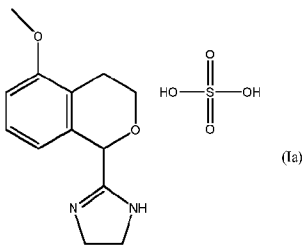
ved omsætning af *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamidmonohydrat med formlen (V)



(V)

med hexamethyldisilazan under sure betingelser og i tilstedeværelse af et ikke-reaktivt opløsningsmiddel for at opnå 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazol med formlen (I), der eventuelt omdannes til dets farmaceutisk acceptable salt.

2. Fremgangsmåde ifølge krav 1, der endvidere omfatter trinnet med omdannelse af forbindelsen med formlen (I) til 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazol-hydrogensulfat med formlen (Ia)



(Ia)

3. Fremgangsmåde ifølge et hvilket som helst af kravene 1 eller 2 omfattende følgende trin

a) omsætning af *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamidmonohydrat med formlen (V) i et ikke-reaktivt opløsningsmiddel med hexamethyldisilazan i tilstedeværelse af katalytisk mængde af en syre; og

b) uden isolering af det dannede 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazol med formlen (I) fra reaktionsblandingen omdannelse af 2-(5-methoxyisochroman-1-yl)-4,5 -dihydro-1H-imidazolet til 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazol-hydrogensulfat med formlen (Ia).

4. Fremgangsmåde ifølge krav 3 hvor trin b) udføres ved behandling af reaktionsblandingen med ethanolvandopløsning og tilsætning af svovlsyre.

5. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 4 omfattende følgende trin

a) omsætning af *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamidmonohydrat med formlen (V) i xylen med hexamethyldisilazan ved en forhøjet temperatur i tilstedeværelse af katalytisk mængde af svovlsyre for at opnå 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazol med formlen (I);

b) uden isolering af det dannede 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazol med formlen (I) tilsætning af vand og HCl til reaktionsblandingen for at omdanne forbindelsen med formlen (I) til dens hydrochloridsalt;

c) isolering af vandfasen;

d) tilsætning af egnet ekstraktionsopløsningsmiddel og en uorganisk base;

e) isolering af den organiske fase;

f) tilsætning af ethanol-vandopløsning og svovlsyre for at danne 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazol-hydrogensulfat med formlen (Ia);

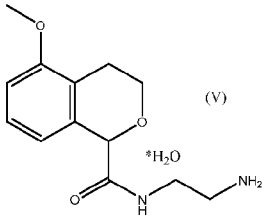
g) fradestillering af opløsningsmidlet;

h) tilsætning af ethanol til ethanol-vandopløsningen;

i) krystallisering af 2-(5-methoxyisochroman-1-yl)-4,5-dihydro-1H-imidazolhydrogensulfat med formlen (Ia) ved afkøling og eventuelt podning og

j) isolering af den krystallinske forbindelse med formlen (Ia).

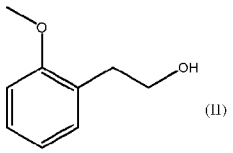
6. Fremgangsmåde til fremstilling af *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamidmonohydrat med formlen (V)



(V)

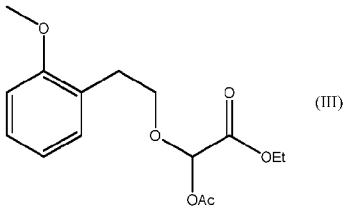
omfattende følgende trin

a) omsætning af 2-(2-methoxyphenyl)ethanol med formlen (II)



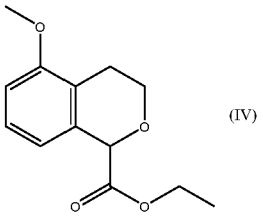
(II)

med ethyl 2-oxoacetat i egnet opløsningsmiddel og tilstedeværelse af et tertiært alifatisk amin og efterfølgende tilsætning af eddikesyreanhydrid til reaktionsblandingen for at danne ethyl 2-acetoxy-2-(2-methoxyphenethoxy)acetat med formlen (III);



(III)

b) tilsætning af ethyl 2-acetoxy-2-(2-methoxyphenethoxy)acetat med formlen (III) til blandingen af tintetrachlorid og et chloreret carbonhydridopløsningsmiddel for at danne ethyl 5-methoxyisochroman-1-carboxylat med formlen (IV); og



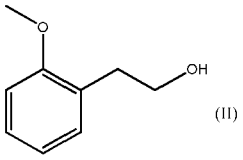
(IV)

c) omsætning af ethyl 5-methoxyisochroman-1-carboxylatet med formlen (IV) med ethylendiamin i alifatisk eller aromatisk carbonhydridopløsningsmiddel og

tilstedeværelse af en katalytisk mængde af syre for at danne *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamidmonohydrat med formlen (V).

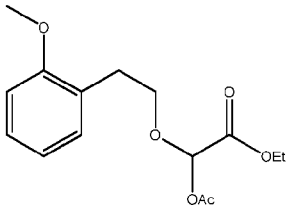
7. Fremgangsmåde ifølge krav 6 omfattende følgende trin

a) omsætning af 2-(2-methoxyphenyl)ethanol med formlen (II)



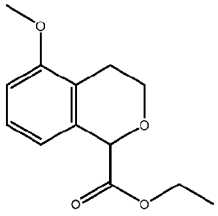
(II)

med ethyl 2-oxoacetat i egnet opløsningsmiddel og tilstedeværelse af et tertiært alifatisk amin og efterfølgende tilsætning af eddikesyreanhydrid til reaktionsblandingen for at danne ethyl 2-acetoxy-2-(2-methoxyphenethoxy)acetat med formlen (III);



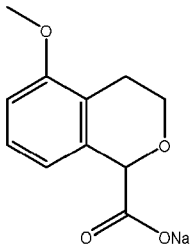
(III)

b) tilsætning af ethyl 2-acetoxy-2-(2-methoxyphenethoxy)acetat med formlen (III) til blandingen af tintetrachlorid og et chloreret carbonhydridopløsningsmiddel for at danne ethyl 5-methoxyisochroman-1-carboxylat med formlen (IV);



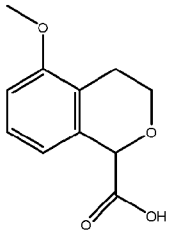
(IV)

c) uden isolering af det dannede ethyl 5-methoxyisochroman-1-carboxylat med formlen (IV) tilsætning af vand, NaOH og ethanol til reaktionsblandingen for at opnå natrium 5-methoxyisochroman-1-carboxylat med formlen (IVa);



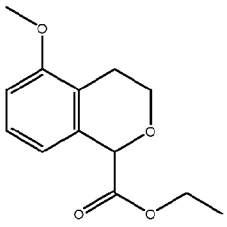
(IVa)

d) behandling af natrium 5-methoxyisochroman-1-carboxylat med formlen (IVa) med egnet syre i vand og isolering af den dannede 5-methoxyisochroman-1-carboxylsyre med formlen (IVb);



(IVb)

e) omsætning af 5-methoxyisochroman-1-carboxylsyren med formlen (IVb) i egnet organisk opløsningsmiddel med ethanol i tilstedeværelse af egnet syre for at danne ethyl 5-methoxyisochroman-1-carboxylat med formlen (IV); og



(IV)

f) omsætning af ethyl 5-methoxyisochroman-1-carboxylatet med formlen (IV) med ethylendiamin i alifatisk eller aromatisk carbonhydridopløsningsmiddel og tilstedeværelse af en katalytisk mængde af syre for at danne *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamidmonohydrat med formlen (V).

8. Fremgangsmåde ifølge krav 7 omfattende følgende trin

a) omsætning af 2-(2-methoxyphenyl)ethanol med formlen (II) med ethyl 2-oxoacetat i toluen og tilstedeværelse af trimethylamin og efterfølgende tilsætning af eddikesyreanhydrid til reaktionsblandingen for at danne ethyl 2-acetoxy-2-(2-methoxyphenethoxy)acetat med formlen (III);

b) tilsætning af ethyl 2-acetoxy-2-(2-methoxyphenethoxy)acetat med formlen (III) i diclormethan til blandingen af tintetrachlorid og dichlormethan for at danne ethyl 5-methoxyisochroman-1-carboxylat med formlen (IV);

c) uden isolering af det dannede ethyl 5-methoxyisochroman-1-carboxylat med formlen (IV) fra reaktionsblandingen tilsætning af vand, NaOH og ethanol til reaktionsblandingen for at opnå natrium 5-methoxyisochroman-1-carboxylat med formlen (IVa);

d) behandling af natrium 5-methoxyisochroman-1-carboxylatet med formlen (IVa) med HCl i vand og isolering af den dannede 5-methoxyisochroman-1-carboxylsyre med formlen (IVb);

e) omsætning af 5-methoxyisochroman-1-carboxylsyre med formlen (IVb) i toluen med ethanol i tilstedeværelse af HCl for at danne ethyl 5-methoxyisochroman-1-carboxylat med formlen (IV) i toluenopløsning; og

f) omsætning af ethyl 5-methoxyisochroman-1-carboxylatettoluenopløsning opnået fra trin e) med ethylendiamin i tilstedeværelse af en katalytisk mængde af eddikesyre for at danne *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamidmonohydrat med formlen (V).

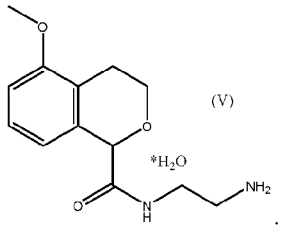
9. Fremgangsmåde ifølge et hvilket som helst af kravene 6 til 8, der endvidere omfatter følgende trin

g) ekstraktion af reaktionsblandingen ved tilsætning af et organisk opløsningsmiddel ikke blandbart med vand og vand og efterfølgende gradvis tilsætning af en egnet syre; og

h) krystallisering af *N*-(2-aminoethyl)-5-methoxyisochroman-1-carboxamidmonohydrat med formlen (V) fra vandfasen ved tilsætning af en egnet stærk base.

10. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 5, hvor forbindelsen med formlen (V) fremstille ifølge et hvilket som helst af kravene 6 til 9.

11. Forbindelse med formlen (V)



(V)