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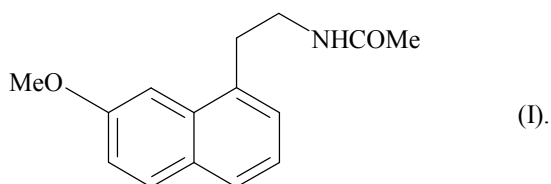
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(54)	Benevnelse	METHOD AND INTERMEDIATE PRODUCTS FOR THE PREPARATION OF AGOMELATINE
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Description

The present invention relates to a new process for the industrial synthesis of agomelatine, or *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide, of formula (I):



5

Agomelatine, or *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide, has valuable pharmacological properties.

It has, in fact, the double characteristic of being, on the one hand, an agonist of receptors of the melatonergic system and, on the other hand, an antagonist of the 5-HT_{2C} receptor. These properties provide it with activity in the central nervous system and, more especially, in the treatment of major depression, seasonal affective disorder, sleep disorders, cardiovascular pathologies, pathologies of the digestive system, insomnia and fatigue due to jet-lag, appetite disorders and obesity.

Agomelatine, its preparation and its use in therapeutics have been described in European patent specifications EP 0 447 285 and EP 1 564 202.

15

In view of the pharmaceutical value of this compound, it has been important to be able to produce it using an effective industrial synthesis process which is readily transferable to the industrial scale and which provides agomelatine in a good yield and with excellent purity.

Patent specification EP 0 447 285 describes production of agomelatine in eight steps starting from 7-methoxy-1-tetralone.

20

In patent specification EP 1 564 202, the Applicant developed a new, much more effective and industrialisable synthesis route in only four steps starting from 7-methoxy-1-tetralone that makes it possible to obtain agomelatine in highly reproducible manner in a well-defined crystalline form.

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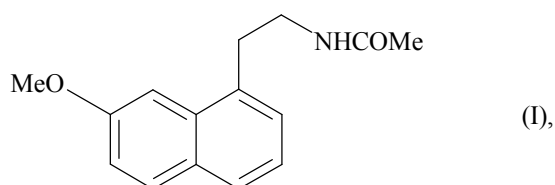
However, the search for new synthesis routes, especially starting from starting materials that are less costly than 7-methoxy-1-tetralone, is currently still relevant.

The Applicant has continued his investigations and has developed a new process for the synthesis of agomelatine starting from allyl cyanide and a xanthate compound: these new starting materials have the advantage of being simple and readily obtainable in large quantities at less cost.

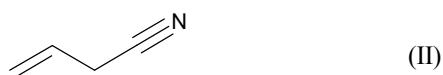
5 This synthesis route is based on carrying out free radical reactions that are not very commonly used but are nevertheless very effective. Converting these reactions to the industrial scale using continuous-flow reactors is promising as it becomes simpler to control propagation of the chain reaction.

This new process moreover makes it possible to obtain agomelatine in reproducible
10 manner and without requiring laborious purification, with a purity that is compatible with its use as a pharmaceutical active ingredient. Indeed, agomelatine can accordingly be synthesised in 6 steps in the course of which only two of the intermediates are isolated.

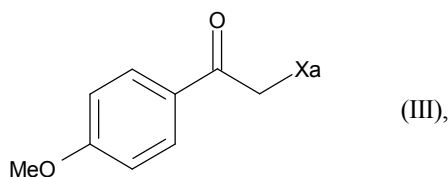
More specifically, the present invention relates to a process for the industrial syn-
15 thesis of the compound of formula (I):



which process is characterised in that allyl cyanide of formula (II):



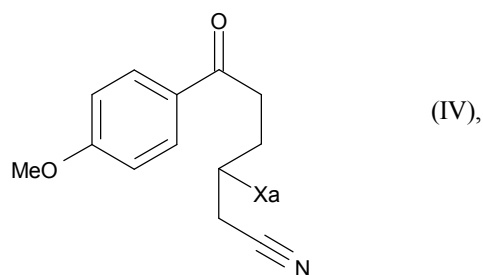
is reacted, in the presence of a free radical initiator, with a compound of formula (III):



wherein Xa represents a group -S-C(S)-OR in which R represents a linear or
20 branched (C₁-C₆)alkyl group,

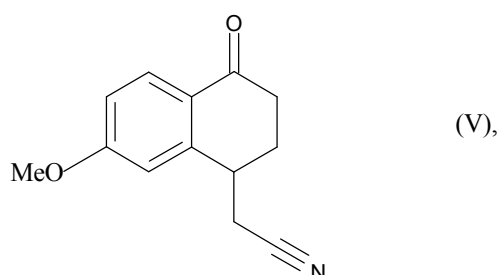
to yield the compound of formula (IV):

3



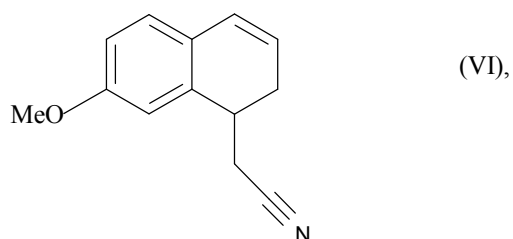
wherein Xa is as defined hereinbefore,

it being possible for this latter compound optionally to be isolated, before being subjected to a cyclisation reaction in the presence of a free radical initiator in order to form the compound of formula (V):

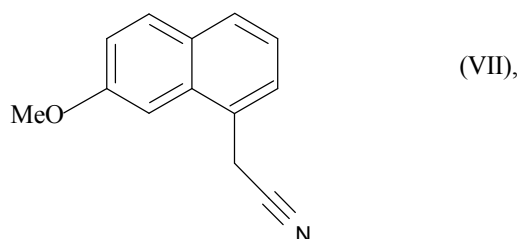


5 which compound of formula (V) also optionally may be isolated,

which is subjected to a reduction-dehydration reaction to yield the compound of formula (VI):

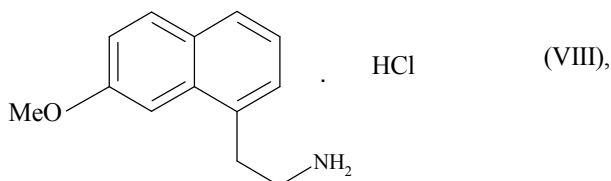


which is then subjected to an aromatisation reaction to yield the compound of formula (VII):



10 which is subjected to reduction using hydrogen in the presence of Raney nickel in a polar protic medium and to a reaction with acetic anhydride to yield the compound of formula (I), which is isolated in the form of a solid.

In a preferred embodiment of the invention, the compound of formula (VII) is then subjected to reduction using hydrogen in the presence of Raney nickel in an ammoniacal ethanol medium and then converted into a salt using hydrochloric acid to yield the compound of formula (VIII):



which is successively subjected to the action of sodium acetate and then acetic anhydride to yield the compound of formula (I), which is isolated in the form of a solid.

Alternatively, the compound of formula (VII) may be subjected to reduction using hydrogen in the presence of Raney nickel in a medium comprising acetic anhydride in a polar protic medium to yield the compound of formula (I), which is isolated in the form of a solid.

In a preferred compound of formula (III), Xa represents a group $-S-C(S)-OC_2H_5$.

In the processes according to the invention, initiation of the free radical reactions is carried out by thermal means. Preferably, the reaction mixture is heated to a temperature of from 50°C to 140°C. Even more preferably, cyclisation is carried out at a temperature of from 130 to 135°C.

Peroxides are free radical initiators that are especially suitable for carrying out the step of addition of the compound of formula (II) to the compound of formula (III), or for performing cyclisation of the compound of formula (IV) to form the compound of formula (V). By way of example, there may be mentioned, especially, diisobutyl peroxide, cumyl peroxyneodecanoate, *tert*-amyl peroxyneodecanoate, di(2-ethylhexyl) peroxydicarbonate, *tert*-butyl peroxyneodecanoate, dibutyl peroxydicarbonate, dicetyl peroxydicarbonate, dimyristyl peroxydicarbonate, *tert*-butyl peroxyneoheptanoate, *tert*-amyl peroxy-pivalate, didecanoyl peroxide, *tert*-amyl peroxy-2-ethylhexanoate, *tert*-butyl peroxyisobutyrate, 1,4-di(*tert*-butylperoxycarbo)cyclohexane, *tert*-butyl peroxyacetate, *tert*-butyl peroxybenzoate, di-*tert*-amyl peroxide, *tert*-butyl cumyl peroxide, bis(*tert*-butyl) peroxide, di-

cumyl peroxide, dilauroyl peroxide (DLP) or di(4-*tert*-butylcyclohexyl) peroxydicarbonate.

Preferably, the reaction is initiated in the presence of dilauroyl peroxide.

The amount of dilauroyl peroxide used in the cyclisation is preferably from 1 to 2.5
5 equivalents.

In a preferred embodiment of the invention, dilauroyl peroxide is added to the medium in stages.

The addition and/or cyclisation reactions are carried out in a solvent customarily used in free radical chemistry such as 1,2-dichloroethane, dichloromethane, benzene, toluene, trifluoromethylbenzene, chlorobenzene, hexane, cyclohexane, heptane, octane, ethyl acetate, *tert*-butyl alcohol, and mixtures thereof.
10

Preference is given to using ethyl acetate in the step of addition of the compound of formula (II) to the compound of formula (III), whilst cyclisation of the compound of formula (IV) to form the compound of formula (V) is advantageously carried out in chlorobenzene, ethyl acetate or ethyl butyrate. In this latter reaction, chlorobenzene is more especially preferred.
15

Conversion of the compound of formula (V) into the compound of formula (VI) is advantageously carried out in the presence of a Lewis acid such as aluminium isopropoxide or samarium isopropoxide. This conversion is moreover preferably carried out in an alcohol (primary or secondary), and even more preferably in isopropanol.
20

Preferably, a catalytic amount of *p*-toluenesulphonic acid is added to the mixture once all the tetralone (V) has been consumed at the end of conversion of the compound of formula (V) into the compound of formula (VI).

Aromatisation of compound (VI) is carried out in the presence of a quinone, preferably in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or tetrachlorobenzoquinone (TCQ). Even more preferably, aromatisation is carried out in the presence of TCQ at the reflux of toluene.
25

The compound of formula (II) is accessible to the person skilled in the art by means of conventional chemical reactions and/or chemical reactions described in the literature.

This process is especially valuable for the following reasons:

- 5 - it makes it possible to obtain the compound of formula (I) on an industrial scale in good yields, starting from a simple, low-cost starting material;
- only the intermediates of formulae (VI) and (VII) require a purification and isolation step.

10 The compounds of formulae (V) and (VI) obtained according to the process of the invention are new and useful as intermediates in the synthesis of agomelatine.

The Examples hereinbelow illustrate the invention without limiting it in any way. For the purpose of validating the reaction route, the synthesis intermediates were systematically isolated and characterised. However, it is possible to considerably optimise the procedures by limiting the number of intermediates isolated. Accord-
15 ingly, Example 2 given hereinbelow corresponds to the same reaction route as that used in Example 1 but with the difference that only (7-methoxy-1,2-dihydro-1-naphthyl)acetonitrile and (7-methoxy-1-naphthyl)acetonitrile were isolated.

Example 1: N-[2-(7-Methoxy-1-naphthyl)ethyl]acetamide

20 **Step A: S-[1-(cyanomethyl)-4-(4-methoxyphenyl)-4-oxobutyl]-O-ethyl dithiocarbonate**

A solution of allyl cyanide (4.8 mL, 60.0 mmol) and S-[2-(4-methoxyphenyl)-2-oxoethyl]-O-ethyl dithiocarbonate¹ (8.1 g, 30.0 mmol) in ethyl acetate (30 mL) is heated at reflux for 15 minutes under a nitrogen atmosphere. There is added, first-
25 ly, an amount of dilauroyl peroxide (10 mol%) to the solution under reflux. After 1 hour 30 minutes, another amount of dilauroyl peroxide (5 mol%) is also introduced. When the reagents have been completely consumed, the mixture is cooled to ambi-

¹ S-[2-(4-methoxyphenyl)-2-oxoethyl]-O-ethyl dithiocarbonate is obtained according to the protocol described in Batanero, B. *et al.*, *J. Org. Chem.* **2001**, 66, 320.

ent temperature and concentrated under reduced pressure. The crude mixture is then purified by flash column chromatography (petroleum ether-ethyl acetate: 95-5 to 80-20) to yield the title compound in the form of an oil in a yield of 98%.

¹H NMR (δ, ppm) 7.93 (m, 2H, CH-4), 6.93 (m, 2H, CH-3), 4.67-4.57 (m, 2H, CH₂-13), 3.99 (m, 1H, CH-9), 3.87 (s, 3H, CH₃-1), 3.15 (t, 2H, *J* = 7.3 Hz, CH₂-7), 2.95 (dd, 2H, *J* = 17.0, 6.0 Hz, CH₂-10), 2.41-2.31 (m, 1H, CH₂-8), 2.19-2.08 (m, 1H, CH₂-8), 1.41 (t, 3H, *J* = 7.1 Hz, CH₃-14).

Step B: (7-Methoxy-4-oxo-1,2,3,4-tetrahydro-1-naphthyl)acetonitrile

- 5 The compound of Step A, used directly without having been purified, is redissolved in chlorobenzene (900 mL) and the solution is refluxed for 15 minutes under a nitrogen atmosphere. Dilauroyl peroxide is then gradually added to the solution under reflux (10 mol% every 10 minutes). When the reaction is complete, the mixture is cooled to ambient temperature and concentrated under reduced pressure. Acetonitrile is then introduced in order to cause a large part of the dilauroyl peroxide compounds to precipitate out. The mixture is then filtered, concentrated under reduced pressure and purified by flash column chromatography (petroleum ether-ethyl acetate: 60-40) to yield the title compound in solid form in a yield of 40%.

HRMS (EI, *m/z*) Calc. for C₁₃H₁₃NO₂: 215.0946; found: 215.0946.

Step C: (7-Methoxy-1,2-dihydro-1-naphthyl)acetonitrile

- 15 Aluminium isopropoxide (2.05 g, 10.0 mmol) is added to a solution of the compound obtained in Step B (680 mg, 3.15 mmol) in isopropanol (15 mL) at ambient temperature. The reaction mixture is refluxed. When the reagents have been completely consumed, a few crystals of *p*-toluenesulphonic acid monohydrate are added and a Dean-Stark apparatus is mounted on top of the flask. The mixture is again
20 refluxed for 1 hour, during which the isopropanol is gradually replaced with toluene by means of the Dean-Stark apparatus. A 1N HCl solution is then added and the resulting phases are separated. The aqueous phase is extracted with ethyl acetate, the organic phases being washed with saturated NaHCO₃ solution and with saturated NaCl solution, then dried over MgSO₄, filtered and concentrated under reduced
25 pressure. The residue is purified by column chromatography (petroleum ether-ethyl acetate: 80-20) to yield the title product in the form of an oil in a yield of 85%.

HRMS (EI, *m/z*) Calc. for C₁₃H₁₃NO: 199.0997; found: 199.1001.

Step D: (7-Methoxy-1-naphthyl)acetonitrile**Method A:**

To a solution of the compound obtained in Step C (1.0 g, 5.0 mmol) in dichloromethane (50 mL) at ambient temperature there is added DDQ (1.4 g, 6.0 mmol).

- 5 The reaction mixture is stirred for 2 days and is then washed with saturated NaHCO₃ solution. The aqueous phase is extracted with ethyl acetate, the organic phase being washed with saturated NaCl solution, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue is purified by column chromatography (petroleum ether-ethyl acetate: 80-20) to yield the title product in solid form
- 10 in a yield of 55%.

Method B:

To a solution of TCQ (615 mg, 2.5 mmol) in toluene (1.5 mL) heated to 80°C there is added the compound obtained in Step C (462 mg, 2.3 mmol) dissolved in toluene (3.5 mL). The mixture is then refluxed for 2.5 hours and is then diluted with water

15 and extracted with petroleum ether. The organic phase is washed with NaOH solution (30% by weight) and with water and is then dried over MgSO₄, filtered and concentrated under reduced pressure. The residue is purified by column chromatography (petroleum ether-ethyl acetate: 80-20) to yield the title product in solid form in a yield of 61%.

HRMS (EI, m/z) Calc. for C₁₃H₁₁NO: 197.0841; found: 197.0838.

20 **Step E: N-[2-(7-Methoxy-1-naphthyl)ethyl]acetamide**

The reaction was carried out on a larger batch in order to optimise the yield obtained:

- 136 g of Raney nickel, 2.06 L of ethanol and 0.23 L of water are introduced into an 8 L reactor. Whilst stirring at 70°C and under 30 bars of hydrogen, the compound obtained in Step D (0.8 kg) dissolved in acetic anhydride (2.4 L) is slowly added. At the
- 25 end of the addition, the reaction mixture is stirred for 1 hour under hydrogen at 30 bar, the reactor is then decompressed and the liquors are filtered. After concentration of the mixture, the residue is crystallised from a mixture of ethanol/water 35/65 to yield the title product in a yield of 89% and with a chemical purity greater than 99%.

30 **Melting point:** 108°C

Example 2: *N*-[2-(7-Methoxy-1-naphthyl)ethyl]acetamide**Step A: (7-Methoxy-1,2-dihydro-1-naphthyl)acetonitrile**

A solution of allyl cyanide (6.75 mL, 84.0 mmol) and *S*-[2-(4-methoxyphenyl)-2-oxoethyl]-*O*-ethyl dithiocarbonate¹ (11.3 g, 42.0 mmol) in ethyl acetate (45 mL) is
 5 heated at reflux for 15 minutes under a nitrogen atmosphere. There is added, first-
 ly, an amount of dilauroyl peroxide (10 mol%) to the solution under reflux. After 1
 hour 30 minutes, another amount of dilauroyl peroxide (5 mol%) is also introduced.
 When the reagents have been completely consumed, the mixture is cooled to ambi-
 ent temperature and concentrated under reduced pressure. The crude mixture is
 10 redissolved in chlorobenzene (640 mL) and the solution is refluxed for 15 minutes
 under a nitrogen atmosphere. Dilauroyl peroxide is then gradually added to the
 solution under reflux (10 mol% every 10 minutes). When the reaction is complete,
 the mixture is cooled to ambient temperature and concentrated under reduced
 pressure. Acetonitrile is then introduced in order to cause a large part of the dilau-
 15 royl peroxide compounds to precipitate out. The mixture is then filtered and con-
 centrated under reduced pressure. Half the crude oil thereby obtained is redissolved
 in isopropanol (100 mL) at ambient temperature in the presence of aluminium iso-
 propoxide (13.6 g, 66.6 mmol). The reaction mixture is refluxed. When the rea-
 gents have been completely consumed, a few crystals of *p*-toluenesulphonic acid
 20 monohydrate are added and a Dean-Stark apparatus is mounted on top of the
 flask. The mixture is again refluxed for 2 hours, during which the isopropanol is
 gradually replaced with toluene by means of the Dean-Stark apparatus. A 1N HCl
 solution is then added and the resulting phases are separated. The aqueous phase
 is extracted with ethyl acetate, the organic phases being washed with saturated
 25 NaHCO₃ solution and with saturated NaCl solution, then dried over MgSO₄, filtered
 and concentrated under reduced pressure. The residue is purified by column chro-
 matography (petroleum ether-ethyl acetate: 80-20) to yield the title product in the
 form of an oil in a yield of 24%.

HRMS (EI, *m/z*) Calc. for C₁₃H₁₃NO : 199.0997; found: 199.1001.

Step B: (7-Methoxy-1-naphthyl)acetonitrile

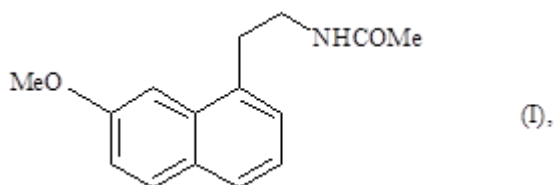
30 The procedure is analogous to Step D of Example 1.

Step C: *N*-[2-(7-Methoxy-1-naphthyl)ethyl]acetamide

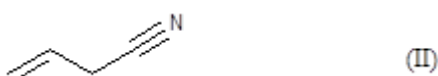
The procedure is analogous to Step E of Example 1.

Patentkrav

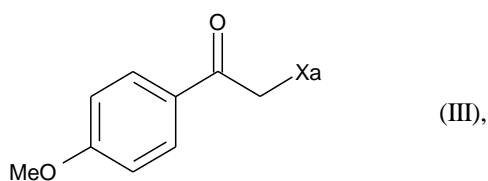
1. Fremgangsmåte for industriell syntese av forbindelsen med formel (I):



5 karakterisert ved at allylcyanid med formel (II):

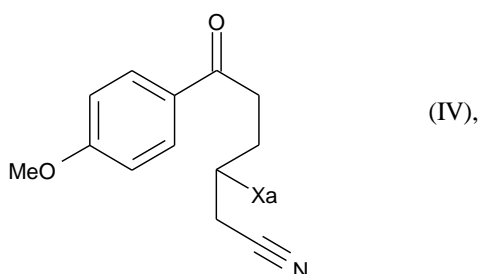


omsettes, i nærvær av en fri radikal-initiator, med en forbindelse med formel (III):



hvor Xa representerer en gruppe -S-C(S)-ELLER hvor R representerer en rettkjedet eller forgrenet (C₁-C₆)alkylgruppe,

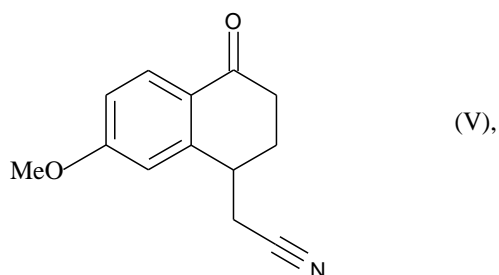
10 for å gi forbindelsen med formel (IV):



hvor Xa har ovennevnte betydning,

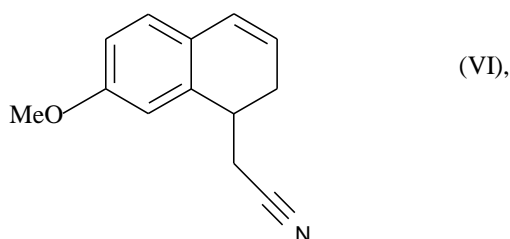
hvor det er mulig for denne sistnevnte forbindelse å valgfritt isoleres, før den underkastes en cyclisasjonsreaksjon i nærvær av en fri radikal-initiator for å danne
15 forbindelsen med formel (V):

2



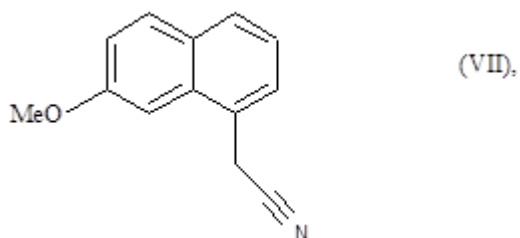
hvilken forbindelse med formel (V) også valgfritt kan isoleres,

som underkastes en reduksjon-dehydrerings-reaksjon for å gi forbindelsen med formel (VI):



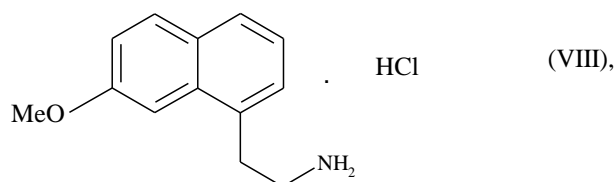
5

som deretter underkastes en aromatiseringsreaksjon for å gi forbindelsen med formel (VII):



10 som underkastes reduksjon ved bruk av hydrogen i nærvær av Raney-nikkel i et polart protisk medium og en omsetning med eddiksyreanhydrid for å gi forbindelsen med formel (I), som isoleres i form av et fast stoff.

2. Fremgangsmåte for syntese av forbindelsen med formel (I) ifølge krav 1, karakterisert ved at forbindelsen med formel (VII) deretter underkastes reduksjon ved bruk av hydrogen i nærvær av Raney-nikkel i et ammoniakk-etanoll-
15 medium og deretter omvandles til et salt ved bruk av saltsyre, for å gi forbindelsen med formel (VIII):



som suksessivt underkastes virkningen av natriumacetat og deretter eddiksyreanhydrid for å gi forbindelsen med formel (I), som isoleres i form av et fast stoff.

- 5 3. Fremgangsmåte for syntese av forbindelsen med formel (I) ifølge krav 1, karakterisert ved at forbindelsen med formel (VII) underkastes reduksjon ved bruk av hydrogen i nærvær av Raney-nikkel i et medium som omfatter eddiksyreanhydrid, i et polart protisk medium, for å gi forbindelsen med formel (I), som isoleres i form av et fast stoff.
- 10 4. Fremgangsmåte for syntese av forbindelsen med formel (I) ifølge krav 1, karakterisert ved at gruppen Xa = -S-C(S)-OC₂H₅.
5. Fremgangsmåte for syntese av forbindelsen med formel (I) ifølge krav 1, karakterisert ved at fri radikal-reaksjonene initieres med varme ved en temperatur fra 50 til 140°C.
- 15 6. Fremgangsmåte for syntese av forbindelsen med formel (I) ifølge krav 1, karakterisert ved at cycliseringen av forbindelsen med formel (IV) utføres ved en temperatur fra 130 to 135°C.
7. Fremgangsmåte for syntese av forbindelsen med formel (I) ifølge krav 1, karakterisert ved at trinnet med tilsetning av forbindelsen med formel (II) til forbindelsen med formel (III) og trinnet med cyclisering av forbindelsen med formel (IV) initieres i nærvær av dilauroylperoksid.
- 20 8. Fremgangsmåte for syntese av forbindelsen med formel (I) ifølge krav 1, karakterisert ved at trinnet med tilsetning av forbindelsen med formel (II) til forbindelsen med formel (III) utføres i klorbenzen.
- 25 9. Fremgangsmåte for syntese av forbindelsen med formel (I) ifølge krav 1, karakterisert ved at trinnet med cyclisering av adduktet med formel (IV) for å danne forbindelsen med formel (V), utføres i etylacetat.

10. Syntesefremgangsmåte ifølge krav 1, k a r a k t e r i s e r t v e d a t omvandlingen av forbindelsen med formel (V) til forbindelsen med formel (VI) utføres i nærvær av aluminiumisopropoksid.
- 5 11. Syntesefremgangsmåte ifølge krav 1, k a r a k t e r i s e r t v e d a t omvandlingen av forbindelsen med formel (V) til forbindelsen med formel (VI) utføres i isopropanol.
12. Syntesefremgangsmåte ifølge krav 1, k a r a k t e r i s e r t v e d a t en katalytisk mengde *p*-toluensulfonsyre tilsettes til blandingen etter avsluttet omvandling av forbindelsen med formel (V) til forbindelsen med formel (VI).
- 10 13. Syntesefremgangsmåte ifølge krav 1, k a r a k t e r i s e r t v e d a t aromatiseringen av forbindelsen med formel (VI) utføres i nærvær av et kinon.
14. Syntesefremgangsmåte ifølge krav 1, k a r a k t e r i s e r t v e d a t aromatiseringen av forbindelsen med formel (VI) utføres i nærvær av tetraklorbenzokinon-TCQ ved tilbakeløpstemperaturen for toluen.
- 15 15. Forbindelse med formel (V) ifølge krav 1 for anvendelse som et mellomprodukt ved syntese av agomelatin med formel (I) ifølge krav 1.
16. Anvendelse av forbindelsen med formel (V) ifølge krav 15 ved syntese av agomelatin med formel (I) ifølge krav 1.
17. Forbindelse med formel (VI) ifølge krav 1 for anvendelse som
20 mellomprodukt ved syntese av agomelatin med formel (I) ifølge krav 1.
18. Anvendelse av forbindelsen med formel (VI) ifølge krav 17 ved syntese av agomelatin med formel (I) ifølge krav 1.