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(54) Benevnelse **NOVEL METHOD FOR THE SYNTHESIS OF 7-METHOXY-NAPHTHALENE-1-CARBALDEHYDE AND USE THEREOF IN THE SYNTHESIS OF AGOMELATINE**

(56) Anførte publikasjoner

FR-A1- 2 918 369, KANDAGATLA, B. ET AL: "A facile synthesis of melatonergic antidepressant agomelatine", TETRAHEDRON LETTERS, vol. 53, 26 octobre 2012 (2012-10-26), pages 7125-7127, XP002727615, cité dans la demande, GARIGIPATI R S ET AL: "Novel frameworks for

trifluoromethyl ketone and phosphonate TSA inhibitors of type II PLA2", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 7, no. 11, 3 juin 1997 (1997-06-03), pages 1421-1426, XP004136229, ISSN: 0960-894X, DOI: 10.1016/S0960-894X(97)00246-1

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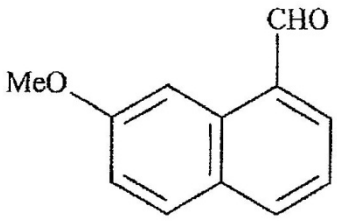
Description

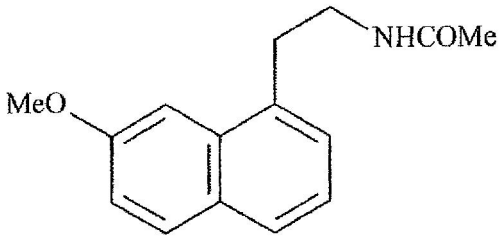
The present invention relates to a new process for the industrial synthesis of 7-methoxy-naphthalene-1-carbaldehyde and the application thereof to the industrial production of agomelatine or *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide.

More specifically, the present invention relates to a process for the industrial synthesis of the compound of formula (I):



(I)

The compound of formula (I) obtained in accordance with the process of the invention can be used in the synthesis of agomelatine or *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide of formula (II):



(II)

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

It has the double feature of being on the one hand an agonist of the receptors of the melatoninergic system and on the other hand an antagonist of the 5-HT_{2C} receptor. These properties impart thereto an 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 patents EP 0 447 285 and EP 1 564 202.

In view of the pharmaceutical value of this compound, it was important to be able to obtain it by means of an efficient synthesis process which can easily be transposed to the industrial scale and yields agomelatine with a good yield and excellent purity, starting from inexpensive and readily accessible starting materials.

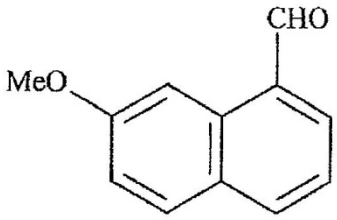
Patent EP 0 447 285 describes access to agomelatine in eight steps starting from 7-methoxy-1-tetralone. However, when transposed to the industrial scale, difficulties in implementing this process quickly became apparent.

The literature describes access to 7-methoxy-naphthalene-1-carbaldehyde in 5 steps starting from 8-amino-naphthalen-2-ol (Kandagatla *et al*. *Tetrahedron Lett.* **2012**, 53, 7125-7127) or in 3 steps starting from 2-(7-methoxy-1-naphthyl)ethanol (FR 2 918 369). The preparation of 7-methoxy-naphthalene-1-carbaldehyde in 4 steps starting from 7-methoxy-tetralone has also been described (Garipati *et al*. *Bioorg. Med. Chem. Lett.* **1997**, 7, 1421-1426). However, 7-methoxy-1-tetralone and 8-amino-naphthalen-2-ol are expensive raw materials and, consequently, the search for new synthesis routes, especially starting from less expensive reagents, is still current.

The applicant has continued his investigations and has developed a new industrial synthesis which yields agomelatine in a reproducible manner and without the need for laborious purification, with a purity which is compatible with its use as a pharmaceutical active ingredient, starting from a less expensive and more easily accessible starting material.

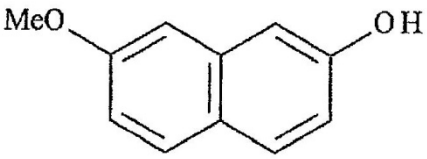
In particular, the applicant has now developed a new process for industrial synthesis which allows 7-methoxy-naphthalene-1-carbaldehyde to be obtained in a reproducible manner and without the need for laborious purification, using 7-methoxy-naphthalen-2-ol as starting material. This new starting material has the advantage of being simple and readily accessible in large quantities at lower costs. 7-Methoxy-naphthalen-2-ol also has the advantage of having a naphthalene nucleus in its structure, which avoids the inclusion of an aromatisation step in the synthesis, a step which is always tricky from an industrial point of view.

More specifically, the present invention relates to a process for the industrial synthesis of the compound of formula (I):



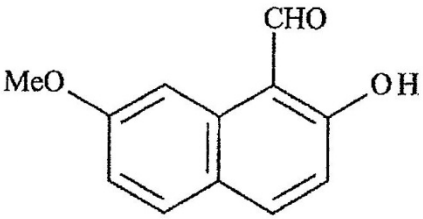
(I)

characterised in that 7-methoxy-naphthalen-2-ol of formula (III):



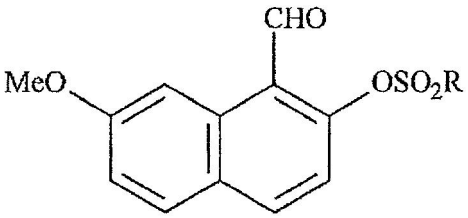
(III)

is reacted, wherein a formylation reaction is carried out at position 1 of the compound of formula (III) to yield the compound of formula (IV):



(IV)

which compound of formula (IV) is subjected to a sulfonylation reaction to yield the compound of formula (V):



(V)

wherein R represents a group $–CH_3$, $-(CH_2)_2-CH_3$, $-CF_3$ or toluyl;

which compound of formula (V) is subjected to a deoxygenation reaction in the presence of a transition metal and a reducing agent to yield the compound of formula (I), which is isolated in the form of a solid.

The compound of formula (III) is commercial or readily accessible to the person skilled in the art by conventional chemical reactions or chemical reactions described in the literature.

R preferably represents a group $-CH_3$ or toluyl.

In the process according to the invention, the conversion of the compound of formula (III) into the compound of formula (IV) consists in the action of ethyl orthoformate in the presence of aniline followed by hydrolysis of the intermediate imine obtained.

In the process according to the invention, the conversion of the compound of formula (IV) into the compound of formula (V) consists in a step of sulfonylation carried out by the action of a sulfonyl chloride, a sulfonic anhydride or a sulfonimide. According to a preferred embodiment, this sulfonylation step is carried out by the action of a sulfonyl chloride and especially of tosyl chloride or mesyl chloride.

In the process according to the invention, the conversion of the compound of formula (V) into the compound of formula (I) consists in a step of deoxygenation in the presence of a transition metal and a reducing agent.

Preferably, the transition metal is nickel, palladium or platinum. The transition metal may either be in the form of a salt or in the form of an element. Preferably, the transition metal salt is a nickel salt or a palladium salt, more preferably a palladium salt.

Advantageously, the reducing agent is a hydride such as sodium borohydride or lithium aluminium hydride; or an aminoborane such as dimethylamineborane; or an alkoxysilane such as dimethoxymethylsilane; or an alkylsilane such as triethylsilane; or an alkaline earth metal such as magnesium; or dihydrogen. Preferably, the reducing agent is dihydrogen, which is used directly in its gaseous form or alternatively is obtained indirectly by decomposition of an ammonium formate. The reducing agent is preferably dihydrogen obtained by decomposition of an ammonium formate.

According to another preferred embodiment, the conversion of the compound of formula (V) into the compound of formula (I) consists in a step of deoxygenation in the presence of nickel, especially a nickel salt, and of a hydride, preferably sodium borohydride.

According to another preferred embodiment, the conversion of the compound of formula (V) into the compound of formula (I) consists in a step of deoxygenation in the presence of palladium and dihydrogen.

According to another preferred embodiment, the conversion of the compound of formula (V) into the compound of formula (I) consists in a step of deoxygenation in the presence of palladium and an alkaline earth metal, preferably magnesium.

Advantageously, the reaction for converting the compound of formula (V) into the compound of formula (I) is carried out in dimethylformamide, dioxane, tetrahydrofuran and toluene and, more preferably, dimethylformamide.

Preferably, the reaction for converting the compound of formula (V) into the compound of formula (I) is carried out between 25°C and 110°C, more especially between 40°C and 95°C.

According to another preferred embodiment, the conversion of the compound of formula (V) into the compound of formula (I) consists in a step of deoxygenation in the presence of a transition metal, a reducing agent and a ligand.

The ligand may be either a phosphine ligand or a diaminocarbene ligand, more preferably a phosphine ligand, and more especially 1,3-bis(diphenylphosphino)-propane or (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphane).

An advantageous variant of the process for industrial synthesis consists in that the conversion of the compound of formula (IV) into the compound of formula (I) is carried out directly, said sulfonylation reaction and said deoxygenation reaction in the presence of a transition metal being carried out as a "one-pot" process.

This process is especially valuable for the following reasons:

- it allows the compound of formula (I) to be obtained on an industrial scale with good yields starting from a starting material that is simple and inexpensive;
- it allows an aromatisation reaction to be avoided, since the naphthalene nucleus is present in the starting substrate;
- it allows agomelatine to be obtained starting from 7-methoxy-naphthalen-2-ol with a reduced number of steps.

The compounds of formula (V) obtained in accordance with the process of the invention are new and can be used as an intermediate for the synthesis of agomelatine and of the compound of formula (I).

The preferred compounds of formula (V) are the following:

- 1-formyl-7-methoxynaphthalen-2-yl 4-methylbenzenesulfonate;
- 1-formyl-7-methoxynaphthalen-2-yl methanesulfonate.

The compound of formula (I) so obtained is, where appropriate, subjected to a series of conventional chemical reactions (for example: reduction of the aldehyde to the primary alcohol, cyanation, reduction and acetylation of the primary amine obtained) to yield agomelatine of formula (II).

The examples below illustrate the invention but do not limit it in any way.

In order to validate the reaction routes, the synthesis intermediates were systematically isolated and characterised. However, it is possible to optimise the processes considerably by limiting the number of intermediates isolated.

The structures of the described compounds were confirmed by the usual spectroscopic techniques: proton NMR (s = singlet; d = doublet; dd = doublet of doublets); carbon NMR (s = singlet; d = doublet; q = quadruplet).

EXAMPLE 1: 7-Methoxynaphthalene-1-carbaldehyde

Step A: 2-Hydroxy-7-methoxynaphthalene-1-carbaldehyde

7-Methoxy-naphthalen-2-ol (3.5 g; 20.11 mmol), ethyl orthoformate (3.51 mL; 21.12 mmol) and aniline (1.83 mL; 20.11 mmol) are introduced into a flask equipped with a condenser. After stirring for 20 hours at reflux and cooling, the solid is ground in 2M ethanolic hydrochloric acid solution (20 ml). At the end of 30 minutes' stirring at 60°C and cooling, the solid is collected by filtration and is then washed with water and azeotropically dried with ethanol and used directly without being purified further (2.95 g; 73%).

^{1}H NMR spectroscopic analysis ($CDCl_3$, δ in ppm): 13.17 (s, 1H); 10.74 (s, 1H); 7.88 (d, J = 9.1 Hz, 1H); 7.69 (d, J = 8.9 Hz, 1H); 7.65 (d, J = 2.4 Hz, 1H); 7.07 (dd, J = 8.9 and 2.4 Hz, 1H); 6.97 (d, J = 9.1 Hz, 1H); 3.95 (s, 3H).

Step B: 1-Formyl-7-methoxynaphthalen-2-yl 4-methylbenzenesulfonate

Triethylamine (826 μL; 5.94 mmol) and tosyl chloride (0.99 g; 5.2 mmol) are added to a solution of the product of the preceding Step A (1 g; 4.95 mmol) in dichloromethane (20 mL). At the end of 24 hours' stirring, the solvent is evaporated off and then the residue is taken up in a water/ethyl acetate mixture. The organic phase is washed with dilute hydrochloric acid solution, water and brine and then dried over sodium sulfate and filtered. Evaporation of the solvents provides a crude product which is purified by recrystallisation in hot ethyl acetate to yield the title product (1.132 g; 65%).

Melting point: 147-148°C

^{1}H NMR spectroscopic analysis ($CDCl_3$, δ in ppm): 10.41 (s, 1H); 8.68 (d, J = 2.6 Hz, 1H); 7.95 (d, J = 8.9 Hz, 1H); 7.74 (d, J = 8.2 Hz, 2H); 7.72 (d, J = 8.9 Hz, 1H); 7.33 (d, J = 8.2 Hz, 2H); 7.19 (dd, J = 8.9 and 2.6 Hz, 1H); 7.15 (d, J = 8.9 Hz, 1H); 3.93 (s, 3H); 2.45 (s, 3H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, δ in ppm): 190.3 (d); 161.5 (s); 154.3 (s); 146.4 (s); 136.4 (d); 132.8 (s); 131.5 (s); 130.3 (2 x d); 129.9 (d); 128.6 (2 x d); 127.8 (s); 121.5 (s); 120.1 (d); 118.6 (d); 104.1 (d); 55.6 (q); 21.9 (q).

Step C: 7-Methoxynaphthalene-1-carbaldehdye

The product of the preceding Step B (356 mg; 1 mmol), palladium acetate (4.5 mg; 0.02 mmol), 1,3-bis(diphenylphosphino)propane (8.2 mg; 0.02 mmol), dimethylformamide (2 mL), triethylamine (556 μL; 4 mmol) and formic acid (150 μL; 4 mmol) are introduced into a flask which has been placed in an oven and purged with argon. The flask is placed in a bath heated at 90°C for 1.5 hours. After cooling, the mixture is diluted in ethyl acetate and the organic phase is washed with 1M aqueous hydrochloric acid solution and with brine, dried over sodium sulfate and filtered. After evaporation of the solvent, the crude product is purified by filtration over neutral alumina to give the title product (139 mg; 75%).

Melting point: 65-67°C

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 10.29 (s, 1H); 8.75 (d, J = 2.6 Hz, 1H); 7.99 (d, J = 8.1 Hz, 1H); 7.9 (d, J = 7.1 Hz, 1H); 7.77 (d, J = 8.9 Hz, 1H); 7.45 (dd, J = 8.1 and 7.1 Hz, 1H); 7.23 (dd, J = 8.9 and 2.6 Hz, 1H); 3.98 (s, 3H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 194.1 (d); 160.7 (s); 138.3 (d); 135.1 (d); 132.2 (s); 130.2 (s); 129.9 (d); 129.3 (s); 122.5 (d); 119.8 (d); 103.6 (d); 55.6 (q).

EXAMPLE 2: 7- Methoxynaphthalene-1-carbaldehyde

Step A: 1-Formyl-7-methoxynaphthalen-2-yl methanesulfonate

Triethylamine (250 μL; 1.782 mmol) and mesyl chloride (120 μL) are added to a solution of the compound obtained in Step A of Example 1 (300 mg; 1.485 mmol) in dichloromethane (5 mL). After one hour's stirring, the solvent is evaporated off and the residue is taken up in an ethyl acetate/water mixture. The organic fraction is washed twice with water and then with brine, dried over sodium sulfate and filtered. Evaporation of the solvent gives the clean title product (416 mg; 95%) without the need for purification.

^{1}H NMR spectroscopic analysis ($CDCl_3$, δ in ppm): 10.74 (s, 1H); 8.72 (d, J = 2.4 Hz, 1H); 8.03 (d, J = 8.9 Hz, 1H); 7.75 (d, J = 8.9 Hz, 1H); 7.36 (d, J = 8.9 Hz, 1H); 7.22 (dd, J = 8.9 and 2.4 Hz, 1H); 3.97 (s, 3H); 3.32 (s, 3H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, δ in ppm): 190.4 (d); 161.6 (s); 153.2 (s); 136.8 (d); 133.1 (s); 130.0 (d); 128.0 (s); 121.6 (s); 120.3 (d); 118.2 (d); 104.0 (d); 55.7 (q); 38.5 (q).

Step B: 7-Methoxynaphthalene-1-carbaldehyde

The title product (84%) is obtained in accordance with the process described in Step C of Example 1, starting from the product of the preceding Step A and with a reaction time of 4 hours at 90°C instead of 1.5 hours.

Melting point: 65-67°C

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 10.29 (s, 1H); 8.75 (d, J = 2.6 Hz, 1H); 7.99 (d, J = 8.1 Hz, 1H); 7.9 (d, J = 7.1 Hz, 1H); 7.77 (d, J = 8.9 Hz, 1H); 7.45 (dd, J = 8.1 and 7.1 Hz, 1H); 7.23 (dd, J = 8.9 and 2.6 Hz, 1H); 3.98 (s, 3H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 194.1 (d); 160.7 (s); 138.3 (d); 135.1 (d); 132.2 (s); 130.2 (s); 129.9 (d); 129.3 (s); 122.5 (d); 119.8 (d); 103.6 (d); 55.6 (q).

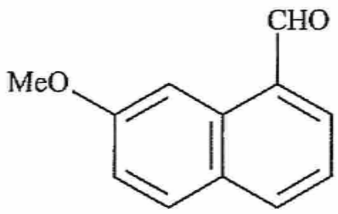
EXAMPLE 3: 7-Methoxynaphthalene-1-carbaldehyde

In a flask purged with argon, sodium hydride (60%; 17 mg; 0.415 mmol) is added in several portions to a solution of 7-methoxy-naphthalen-2-ol (70 mg; 0.35 mmol) in anhydrous dimethylformamide (1 mL). At the end of 30 minutes' stirring at ambient temperature, tosyl chloride is then added in several portions (190.5 mg;

0.36 mmol). After 4 hours' stirring at ambient temperature, 1,3-bis(diphenylphosphino)propane (7.1 mg; 0.017 mmol), palladium acetate (3.9 mg; 0.073 mmol), triethylamine (192 μL; 1.38 mmol) and formic acid (150 μL; 4 mmol) are added and the reaction mixture is heated at 90°C for 1.5 hours. After cooling, the mixture is diluted in ethyl acetate and the organic phase is washed with 1 M aqueous hydrochloric acid solution and then with brine, dried over sodium sulfate and filtered. After evaporation of the solvent, the crude product is filtered over neutral alumina (eluant: ethyl acetate) to give the title product (61.6 mg; 95%).
Melting point: 65-67°C

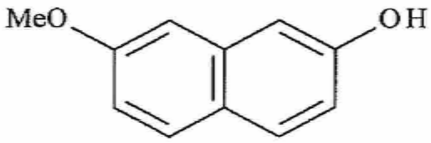
Patentkrav

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



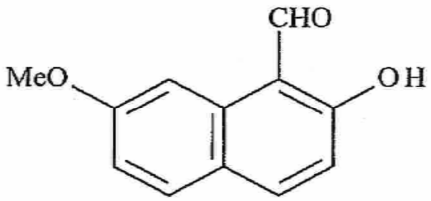
(I)

karakterisert ved at 7-metoksy-naftalen-2-ol av formel (III):



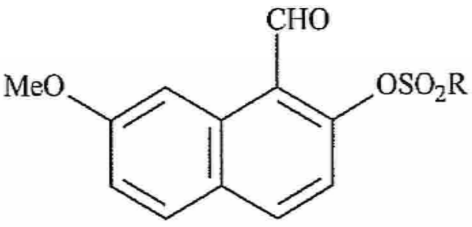
(III)

reageres, hvor en formylgruppe introduseres ved posisjon 1, for å gi forbindelsen av formel (IV):



(IV)

hvilken forbindelse av formel (IV) usettes for en sulfonyleringsreaksjon for å gi forbindelsen av formel (V):



(V)

hvor R representerer en gruppe $–CH_3$, $-(CH_2)_2-CH_3$, $-CF_3$ eller toluyl;
hvilken forbindelse av formel (V) utsettes for en deoksygeneringsreaksjon ved nærvær av et overgangsmetall og et reduksjonsmiddel for å gi forbindelsen av formel (I) , hvilken isoleres for å danne et faststoff.

2. Fremgangsmåte for industriell syntese av forbindelsen av formel (I) ifølge krav 1, **karakterisert ved** at R representerer en gruppe $–CH_3$ eller toluyl.

3. Fremgangsmåte for industriell syntese av forbindelsen av formel (I) ifølge krav 1, **karakterisert ved** at omdannelsen av forbindelsen av formel (IV) til forbindelsen av formel (V) utføres ved virkning av et sulfonylklorid, et sulfonsyreanhydrid eller et sulfonamid.

4. Fremgangsmåte for industriell syntese av forbindelsen av formel (I) ifølge krav 3, **karakterisert ved** at omdannelsen av forbindelsen av formel (IV) til forbindelsen av formel (V) utføres under virkning av et sulfonylklorid.

5. Fremgangsmåte for industriell syntese av forbindelsen av formel (I) ifølge krav 1, **karakterisert ved** at, ved omdannelsen av forbindelsen av formel (V) til forbindelsen av formel (I), overgangsmetallet er nikkel, palladium eller platina.

6. Fremgangsmåte for industriell syntese av forbindelsen av formel (UI) ifølge krav 1, **karakterisert ved** at, ved omdannelsen av forbindelsen av formel (V) til forbindelsen av formel (I), overgangsmetallet er et palladiumsalt.

7. Fremgangsmåte for industriell syntese av forbindelsen av formel (I) ifølge krav 1, **karakterisert ved** at omdannelsen av forbindelsen av formel (V) til forbindelsen av formel (I) utføres i dimetylformamid, dioksan, tetrahydrofuran eller toluen.

8. Fremgangsmåte for industriell syntese av forbindelsen av formel (I) ifølge krav 7, **karakterisert ved** at omdannelsen av forbindelsen av formel (V) til forbindelsen av formel (I) utføres i dimetylformamid.

9. Fremgangsmåte for industriell syntese av forbindelsen av formel (I) ifølge krav 1, **karakterisert ved** at omdannelsen av forbindelsen av formel (V) til forbindelsen av formel (I) utføres ved mellom 25°C og 110°C.

10. Fremgangsmåte for industriell syntese av forbindelsen av formel (I) ifølge krav 9, **karakterisert ved** at omdannelsen av forbindelsen av formel (V) til forbindelsen av formel (I) utføres ved mellom 40°C og 95°C.

11. Fremgangsmåte for industriell syntese av forbindelsen av formel (I) ifølge krav 1, **karakterisert ved** at, ved omdannelsen av forbindelsen av formel (V) til forbindelsen av formel (I), er reduksjonsmiddelet dihydrogen.

12. Fremgangsmåte for industriell syntese av forbindelsen av formel (I) ifølge krav 11, **karakterisert ved** at dihydrogenet blir fremstilt ved nedbrytning av ammoniumformat.

13. Fremgangsmåte for industriell syntese av forbindelsen av formel (I) ifølge krav 1, **karakterisert ved** at ved omdannelsen av forbindelsen av formel (V) til forbindelsen av formel (I) utføres ved nærvær av palladium og dihydrogen.

14. Fremgangsmåte for industriell syntese av forbindelsen av formel (I) ifølge krav 1, **karakterisert ved** at ved omdannelsen av forbindelsen av formel (V) til forbindelsen av formel (I) utføres ved nærvær av (9,9-dimetyl-9*H*-xanten-4,5-diyl)bis(difenylfosfan) eller 1,3-bis(di-fenylfosfino)propan.

15. Forbindelse av formel (V) ifølge krav 1 for anvendelse som et intermediat for syntese av forbindelsen av formel (I).

16. Forbindelse av formel (V) ifølge krav 15 for anvendelse som et intermediat for syntese av agomelatin av formel (II).

17. Forbindelse av formel (V) ifølge krav 15 og 16 valgt fra de følgende forbindelser:

- 1-formyl-7-metoksynaftalen-2-yl 4-metylbenzensulfonat;
- 1-formyl-7-metoksynaftalen-2-yl metansulfonat.

18. Anvendelse av forbindelse av formel (V) ifølge krav 15 til 17 ved syntese av forbindelsen av formel (I).

19. Anvendelse av forbindelsen av formel (V) ifølge krav 18 ved syntese av agomelatin av formel (II).

20. Anvendelse av forbindelse av formel (III) ifølge krav 1 ved syntese av forbindelsen av formel (I).

21. Anvendelse av forbindelse av formel (III) ifølge krav 20 ved syntese av agomelatin av formel (II).

22. Fremgangsmåte for syntese av agomelatin fra forbindelsen av formel (V), **karakterisert ved** at forbindelsen av formel (V) fremstilles ved syntheseprosessen ifølge et hvilket som helst av kravene 1 til 4.