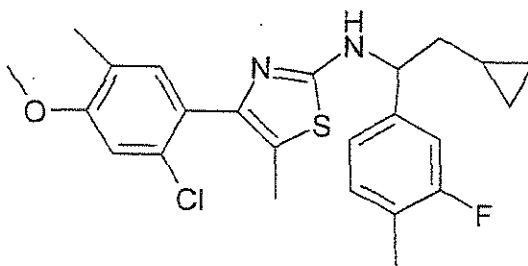


PROCESS FOR THE PREPARATION OF
[4-(2-CHLORO-4-METHOXY-5-METHYLPHENYL)-5-METHYL-THIAZOLO-2-YL]-[2-CYCLOPROPYL-1-(3-FLUORO-4-METHYLPHENYL)-ETHYL]-AMINE

The subject of the present invention is novel process for the preparation of the [4-(2-chloro-4-methoxy-5-methylphenyl)-5-methyl-thiazolo-2-yl]-[2-cyclopropyl-1-(3-fluoro-4-methylphenyl)-ethyl]-amine of formula (I)

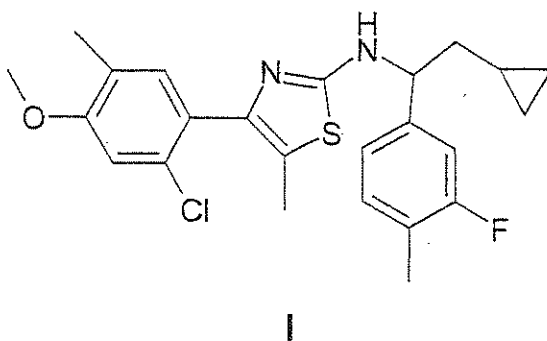


I

and the new intermediates of the preparation process.

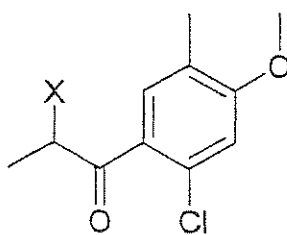
SUMMARY

In a first aspect, there is provided a process for the preparation of the [4-(2-chloro-4-methoxy-5-methylphenyl)-5-methyl-thiazolo-2-yl]-[2-cyclopropyl-1-(3-fluoro-4-methylphenyl)-ethyl]-amine of formula (I)



characterized in that

a.) the compound of the general formula (II)

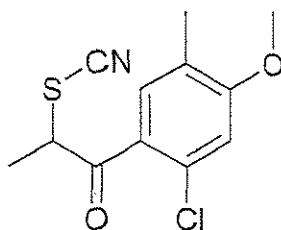


— where X means halogen — is reacted with an alkali metal-thiocyanate, in the presence of a phase transfer catalyst,

and

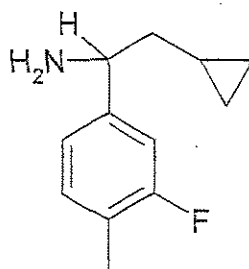
b.) the thus obtained 2-thioyanato-1-(2-chloro-4-methoxy-5-methylphenyl)-propan-1-one of formula (III)

1b



III

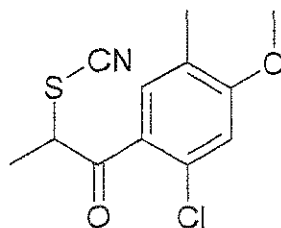
or a tautomeric form of it is reacted with the 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)-ethyl-amine



IV

of formula (IV).

In a second aspect, there is provided the 2-thiocyanato-1-(2-chloro-4-methoxy-5-methylphenyl)-propan-1-one

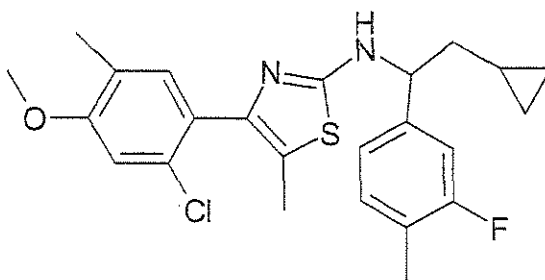


III

of formula (III) and its tautomers.

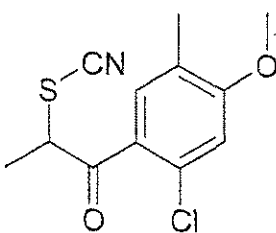
In a third aspect, there is provided a process for the preparation of the [4-(2-chloro-4-methoxy-5-methylphenyl)-5-methyl-thiazol-2-yl]-[2-cyclopropyl-1-(3-fluoro-4-methyl-phenyl)-ethyl]-amine of formula (I)

1c



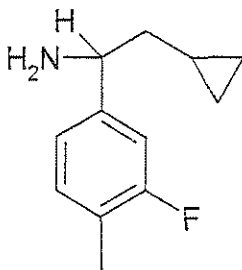
I

characterized by that the 2-thiocyanato-1-(2-chloro-4-methoxy-5-methylphenyl)-propan-1-one of formula (III)



III

is reacted with the 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)-ethyl-amine of formula (IV)

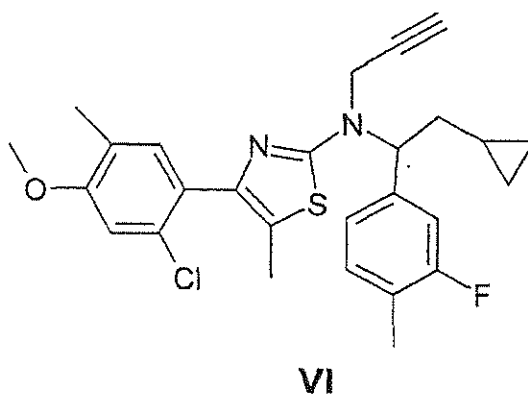


IV

in a way that the ketone of formula (III) is added to the amine of formula (IV).

DETAILED DESCRIPTION

The compound of formula (I) is the key intermediate to the preparation of the [4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-propynyl-5-methyl-thiazolo-2-yl]-[2-cyclopropyl-1-(3-fluoro-4-methylphenyl)-ethyl]-amine of formula (VI)

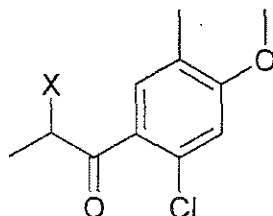


- which is a known CRF1 (corticotropin releasing factor 1) receptor antagonist with potential antidepressant and / or anxiolytic effect.

2

The thiazolamine of formula (I) is presently prepared in several steps, utilizing the Hantzsch synthesis (WO2001005776 Sanofi-Aventis).

The preparation process used so far (WO2001005776 Sanofi-Aventis) starts from the compound of the general formula (II)

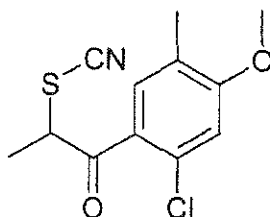


II

5

– where X means halogen atom. This compound, however, easily decomposes, it is irritative, its quality is hard to reproduce, its isolation and treatment involves difficulties.

- 10 Our aim was to find a starting material for the preparation of the compound of formula (I) which is well characterized, easy to treat, which is well crystallizable, and can be prepared conveniently, in high yield. To our surprise, we found that the 2-thiocyanato-1-(2-chloro-4-methoxy-5-methylphenyl)-propan-1-one of formula (III)



III

15

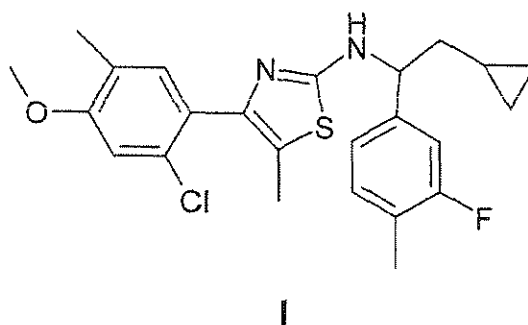
- is a starting material which fulfills all our needs. A further advantage of applying the compound of formula (III) is that under specific conditions, *i.e.* in the presence of a phase transfer catalyst, it can be prepared easily in aqueous medium, from the previously used compound of general formula (II). This new process according to
20 our invention is environment friendly, since only aqueous effluent is formed, the amount of the used organic solvents is small and the solvents can be re-used, the

process can be performed in industrial scale and it results high purity product in high yield.

The preparation of the ketone derivative (III) in aqueous conditions is surprising, since the thiocyanate group is sensitive to water, it can easily transform into isothiocyanate, or it can suffer hydrolysis. Therefore, in the state of art, it is prepared either in ionic liquid (Tetrahedron Letters 46 (2005) 1489-1491) or in alcoholic medium (J. Indian Chem. Soc., 81 (2004) 786-788), but in any case in the absence of water.

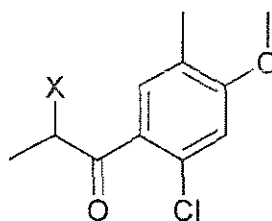
10

The subject of the invention is novel process for the preparation of [4-(2-chloro-4-methoxy-5-methylphenyl)-5-methyl-thiazolo-2-yl]-[2-cyclopropyl-1-(3-fluoro-4-methylphenyl)-ethyl]-amine of formula (I)



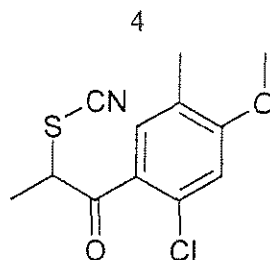
15 wherein

a.) the 2-halogeno-1-(2-chloro-4-methoxy-5-methylphenyl)-propan-1-one of the general formula (II)



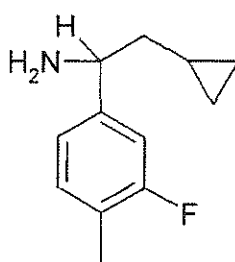
where X means halogen, is reacted with an alkali metal-thiocyanate, in the presence of a phase-transfer catalyst, and

b.) the thus obtained 2-thiocyanato-1-(2-chloro-4-methoxy-5-methylphenyl)-propan-1-one of formula (III)



III

or a tautomeric form of it is reacted with the 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)-ethyl-amine



IV

5

of formula (IV).

To prepare the appropriate optically active isomer of the compound of formula (I) we have to start from the respective optically active amine of formula (IV).

10

In one embodiment of the process according to the invention, in step a.) the reaction is performed in the binary system consisting of an aprotic solvent and water.

In one alternative of the process according to the invention, the compound of the general formula (II) – where X favourably means chloro or bromo group, preferably bromo group, – is dissolved in an aprotic organic solvent and reacted with the aqueous solution of an alkali metal-thiocyanate – preferably potassium-thiocyanate – in the presence of a phase transfer catalyst – preferably TBAB (tetrabutyl-ammonium bromide). The reaction mixture is worked-up by separation of the organic phase after dilution of the mixture with water. In a given case after

20

5

solvent exchange, the compound of the formula (III) can be well crystallized, in high yield.

In one variant of step b.) the compound of formula (III) is added to the compound of formula (IV), to obtain the desired product with a favourable impurity profile and in high yield.

To achieve the best yield the addition period lasts for at least one hour.

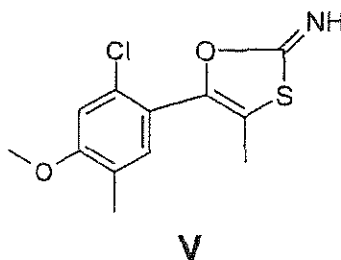
In step b.) favourably an apolar aprotic solvent is applied, preferably methylcyclohexane or toluene. Step b.) is preferably performed at a temperature range between 25°C and reflux temperature, most preferably at reflux temperature.

The compounds of the general formula (II) and the amine of formula (IV), as well as their preparation are known from the patent application of publication number WO2001005776 .

A further subject of the invention is the new compound of formula (III) and its tautomers, as well as their preparation.

Of the tautomers of compound (III), the 5-(2-chloro-4-methoxy-5-methylphenyl)-4-methyl-[1.3]-oxathiol-2-ylideneamine of formula (V)

20



is also the subject of the invention.

Further details of our process are demonstrated in the following examples without limiting the claims to the examples.

25

EXAMPLES**Example 1. Preparation of compound (III) from compound (II) in dichloromethane (DCM)**

- 5 291.5g 2-bromo-1-(2-chloro-4-methoxy-5-methylphenyl)-propan-1-one (II) is dissolved in
291g DCM,
5.3g TBAB (tetrabutyl-ammonium-bromide) catalyst is added to it.
167g KSCN is dissolved in
10 83.6g water. The aqueous solution is added to the DCM solution.
The resulting binary system is heated to 40°C (reflux) and is stirred for 3-4 hours.
The reaction is accompanied by salt precipitation. Water is added to the mixture until the salt dissolves. The lower, aqueous phase is
15 separated, the upper, organic phase is evaporated, while
870ml methanol (MeOH) is added to it.
From the methanol solution compound (III) crystallizes on cooling. The crystals are filtered off, washed several times with MeOH.
Yield: 90-95%
- 20 Melting point: 75°C (MeOH)
IR-spectrum: 2158 cm⁻¹ (CN), 1664 cm⁻¹ (C=O)
¹H-spectrum (DMSO-d₆, TMS): 7.73 (1H, s), 7.14 (1H, s), 5.28 (1H, q, *J* = 7,2Hz), 3.89 (3H, s), 2.16 (3H, s), 1.60 (3H, d, *J* = 7.2Hz)
25 ¹³C-NMR-spectrum: 194.7, 160.9, 132.6, 131.5, 126.3, 125.5, 113.5, 111.4, 56.7, 49.4, 18.8, 15.8

Example 2. Preparation of compound (III) from compound (II) in methyl-cyclohexane (MCH)

The preparation procedure is as described in Example 1, but MCH is used as solvent, instead of DCM. The product is crystallized from MCH on cooling.

Yield: 60%

5

Example 3. Preparation of compound (V) from compound (III) in an apolar solvent in the presence of an amine

26.4g compound (III) (prepared as described in example 1. or 2.) is suspended in

10 52 ml MCH.

In stoichiometric amount an amine (preferably benzylamine) is added to the mixture.

The mixture is stirred for 0.5-1 hour (the structure of the amine influences the reaction time). Thick precipitate is obtained, it is filtered off and washed several times with methyl-cyclohexane.

15

Yield: 85%.

Example 4. Preparation of compound (V) from compound (III) in a tertiary amine as solvent

20 The preparation procedure is as described in Example 3, with the difference that compound (III) is suspended in triethyl-amine as solvent, instead of MCH, and no other amine is added to the mixture.

Yield: 85%.

Melting point: 106°C (EtOH)

25 IR-spectrum: 3253 cm⁻¹ (NH), 1679 cm⁻¹ (C=N)

¹H-spectrum (DMSO-d₆, TMS): 7.30 (1H, s), 7.14 (1H, s), 3.86 (3H, s), 2.14 (3H, s), 1.88 (3H, s)

¹³C-NMR-spectrum: 163.1 (s), 158.9 (s), 138.9 (d), 133.0 (s), 131.4 (s), 125.3 (s), 118.3 (s), 111.8 (d), 111.5 (s), 56.0 (t), 15.3 (t), 11.6 (t)

30

Example 5. Preparation of compound (I) from compound (III) in methyl-cyclohexane (MCH)

26.3g isolated product (III) is dissolved in
52 ml MCH.

5 The reaction mixture is heated to 85-90 °C and is added to the 85-90 °C solution of

19.2 g amine (IV) in MCH (20%). The addition period is 2-4 hours. After the addition, the reaction mixture is stirred at 85-90 °C for one hour. The MCH solution of the crude product (I) is cooled and the precipitated
10 crystals are filtered off. The crystalline product is covered with a small amount of MCH.

Yield: 80%.

Example 6. Preparation of compound (I) from compound (III) in MCH and MeOH

15 The preparation procedure is as described in Example 5, but product (I) is crystallized from MeOH, instead of MCH, after solvent exchange.

Yield: 90%

20

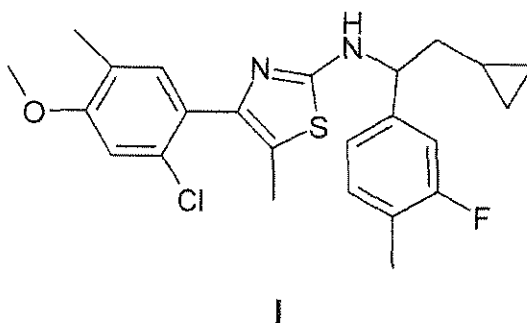
Example 7. Preparation of compound (I) from compound (V)

The preparation procedure is as described in Examples 5 and 6, but instead of compound (III), compound (V) is used, in the same amount.

Yield: 85%

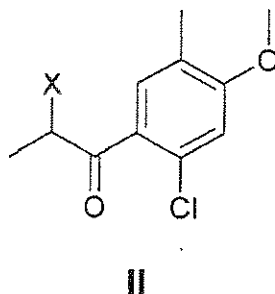
Claims

1. Process for the preparation of the [4-(2-chloro-4-methoxy-5-methylphenyl)-
 5 5-methyl-thiazolo-2-yl]-[2-cyclopropyl-1-(3-fluoro-4-methylphenyl)-ethyl]-amine
 of formula (I)

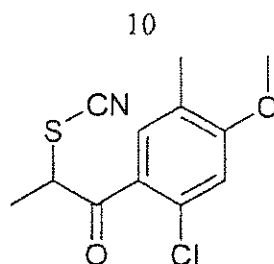


10 **characterized in that**

- a.) the compound of the general formula (II)

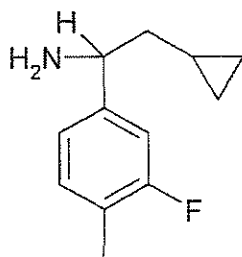


- where X means halogen – is reacted with an alkali metal-thiocyanate, in the
 presence of a phase transfer catalyst,
 15 and
 b.) the thus obtained 2-thiocyanato-1-(2-chloro-4-methoxy-5-methylphenyl)-propan-
 1-one of formula (III)



III

or a tautomeric form of it is reacted with the 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)-ethyl-amine



IV

5

of formula (IV).

2. The process as defined in claim 1., **characterized in that**, in step b.) the ketone of formula (III) is added to the amine of formula (IV).

10

3. The process as defined in claim 2., **characterized in that**, the addition of the ketone of formula (III) to the amine of formula (IV) takes at least 1 hour.

15

4. The process as defined in any of claims 1-3., **characterized in that**, in step a.) the reaction is performed in a binary system consisting of an aprotic solvent and water.

20

5. The process as defined in any of claims 1-4., **characterized in that** step b.) is carried out in an apolar aprotic solvent.

11

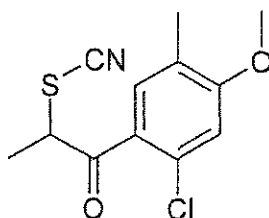
6. The process as defined in claim 5., **c h a r a c t e r i z e d i n**
t h a t the apolar aprotic solvent applied in step b.) is methyl-cyclohexane or
 toluene.

5 7. The process as defined in any of claims 1-6., **c h a r a c t e r i z e d i n**
t h a t step b.) is carried out at a temperature between 25 °C and reflux
 temperature.

8. The process as defined in claim 7., **c h a r a c t e r i z e d i n**
 10 **t h a t** step b.) is carried out at reflux temperature.

9. The process as defined in any of claims 1-8., **c h a r a c t e r i z e d b y**
 that in the general formula (II) X means bromo group.

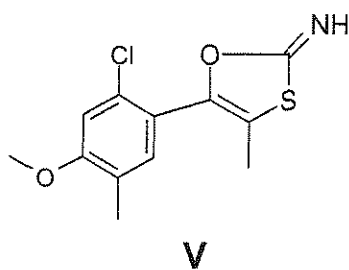
15 10. The 2-thiocyanato-1-(2-chloro-4-methoxy-5-methylphenyl)-propan-1-one



III

of formula (III) and its tautomers.

20 11. Of the tautomers of the compound of formula (III) according to claim 10.,
 the 5-(2-chloro-4-methoxy-5-methylphenyl)-4-methyl-[1.3]-oxathiol-2-ylidene-
 amine of formula (V).

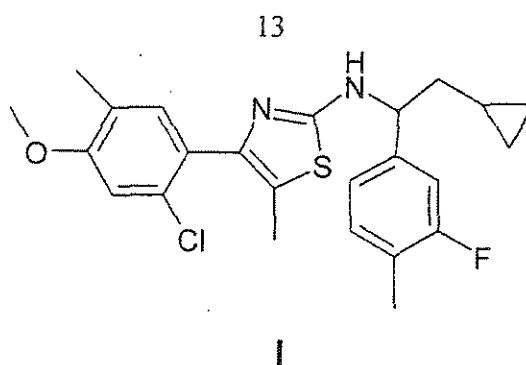


12. Process for the preparation of the [4-(2-chloro-4-methoxy-5-methylphenyl)-
5-methyl-thiazol-2-yl]-[2-cyclopropyl-1-(3-fluoro-4-methyl-phenyl)-ethyl]-amine
5 of formula **(I)**

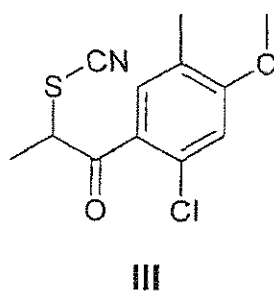
10

15

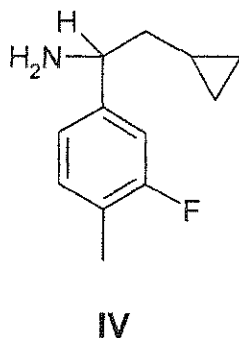
20



characterized by that the 2-thiocyanato-1-(2-chloro-4-methoxy-5-methyl-phenyl)-propan-1-one of formula (III)



5 is reacted with the 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)-ethyl-amine of formula (IV)



10 in a way that the ketone of formula (III) is added to the amine of formula (IV).