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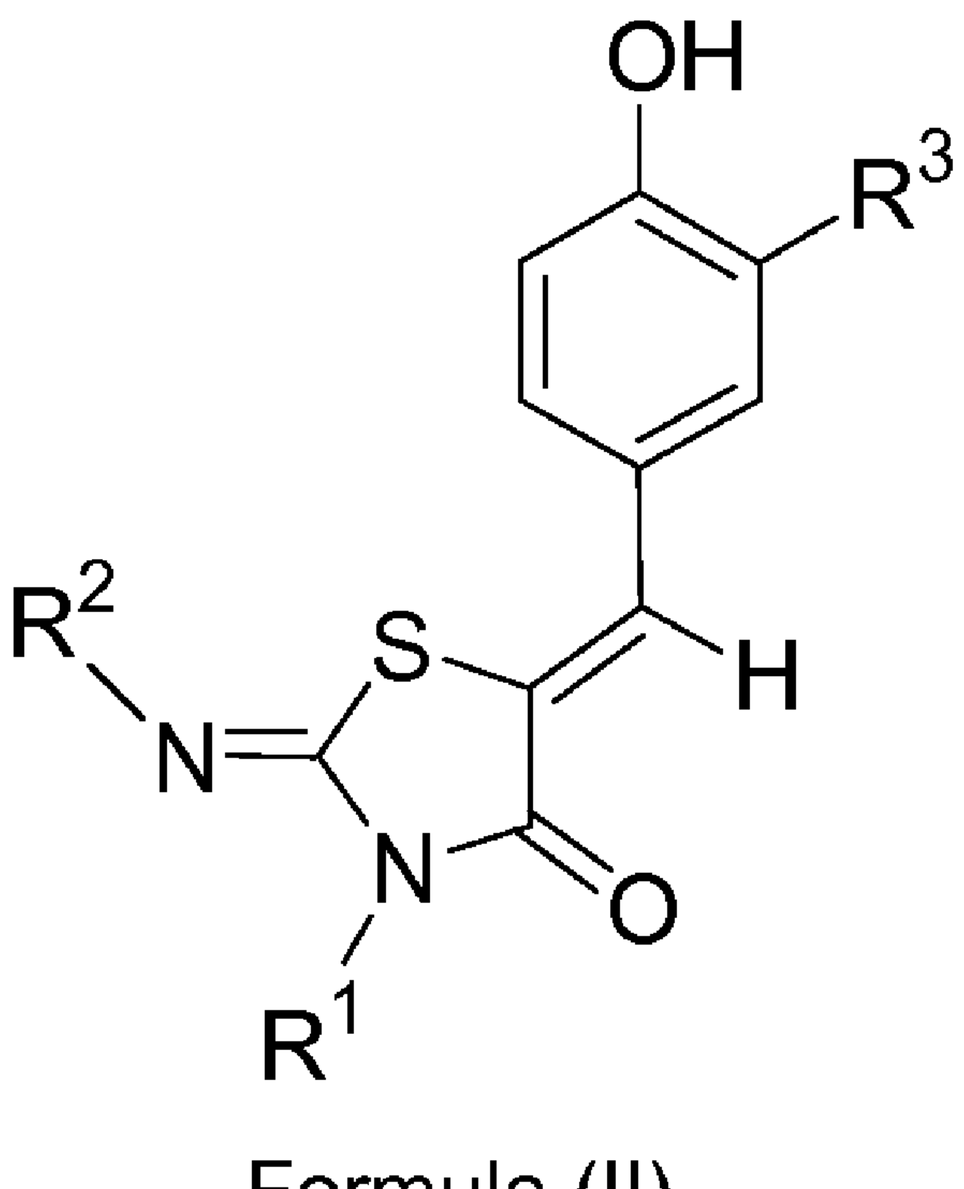
(54) Titre : PROCEDE DE PREPARATION DE DERIVES DE 2-IMINO-THIAZOLIDINO-4-ONE
(54) Title: PROCESS FOR THE PREPARATION OF 2-IMINO-THIAZOLIDIN-4-ONE DERIVATIVES



Formula (II)

(57) Abrégé/Abstract:
The present invention relates to a new process for the preparation of 2-imino- thiazolidin-4-one compounds of the Formula (I) and (II) and to compounds of Formula (II) as such. The present compounds of Formula (II) can be used as intermediates in the preparation of thiazolidin-4-one derivatives of the General Formula (II), said derivatives being described in WO 2005/054215. These compounds of General Formula (II) are described in WO 2005/054215 to act as immunosuppressive agents.

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(54) Title: NEW PROCESS FOR THE PREPARATION OF 2-IMINO-THIAZOLIDIN-4-ONE DERIVATIVES

(57) Abstract: The present invention relates to a new process for the preparation of 2-imino- thiazolidin-4-one compounds of the Formula (I) and (II) and to compounds of Formula (II) as such. The present compounds of Formula (II) can be used as intermediates in the preparation of thiazolidin-4-one derivatives of the General Formula (II), said derivatives being described in WO 2005/054215. These compounds of General Formula (II) are described in WO 2005/054215 to act as immunosuppressive agents.

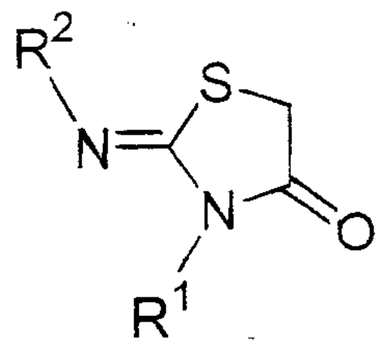
Process for the Preparation of 2-Imino-thiazolidin-4-one Derivatives

Field of the invention

The present invention relates to a new process for the preparation of 2-imino-thiazolidin-4-one compounds of the Formula (I) and (II) and to compounds of Formula (II) as such. The present compounds of Formula (II) can be used as intermediates in the preparation of thiazolidin-4-one derivatives of the General Formula (II), said derivatives being described in the PCT Patent Application with the publication number WO 2005/054215. These compounds of General Formula (II) are described in WO 2005/054215 to act as immunosuppressive agents.

Description of the invention

In a first aspect the present invention relates to a new process for the preparation of a compound of the Formula (I):



Formula (I)

wherein

R^1 represents phenyl which is optionally mono-, di- or tri-substituted wherein the substituents are independently selected from C_{1-7}-alkyl and halogen; and

R^2 represents C_{1-7}-alkyl;

which process comprises reacting a compound of the formula R^1-N=C=S, wherein R^1 is as defined for Formula (I), with a compound of the formula R^2-NH_2, wherein R^2 is as defined for Formula (I), followed by reaction with bromo-acetyl bromide and a pyridine base.

Preferably the above process is performed without the isolation and/or purification of intermediates such as the thiourea intermediate that occurs after reacting a compound of Structure 1 with a compound of Structure 2.

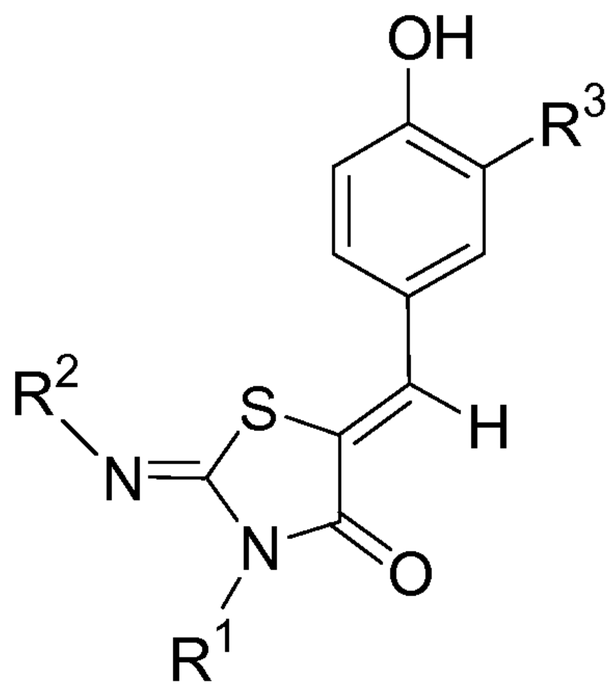
Preferably the pyridine base that is used in the preparation processes described herein is pyridine, lutidine or a cholidine, preferably pyridine.

Preferably the above process is used to prepare compounds of Formula (I), wherein R^1 represents phenyl which is optionally mono-substituted with C_{1-7}-alkyl (such as especially methyl) or halogen, and R^2 represents C_{1-7}-alkyl (such as especially propyl, isopropyl or butyl).

More preferably the above process is used to prepare compounds of Formula (I), wherein R^1 represents phenyl which is optionally mono-substituted with methyl or chloro, and R^2 represents propyl, isopropyl or butyl.

Especially preferred, the above process is used to prepare compounds of Formula (I) selected from the group consisting of:
2-[(Z)-isopropylimino]-3-phenyl-thiazolidin-4-one,
3-phenyl-2-[(Z)-propylimino]-thiazolidin-4-one,
2-[(Z)-n-butylimino]-3-phenyl-thiazolidin-4-one,
2-[(Z)-isopropylimino]-3-o-tolyl-thiazolidin-4-one,
2-[(Z)-isopropylimino]-3-(3-chlorophenyl)-thiazolidin-4-one, and
2-[(Z)-propylimino]-3-o-tolyl-thiazolidin-4-one.

In a further aspect the present invention relates to a process for the preparation of a compound of Formula (II):



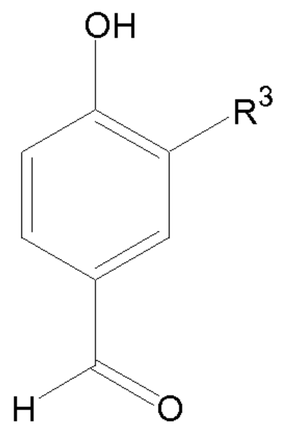
Formula (II)

wherein

R^1 and R^2 are as defined for Formula (I) above; and

R^3 represents hydrogen, hydroxy, C_{1-7}-alkoxy, or halogen;

which process comprises preparing a compound of Formula (I) according to the procedure described above and reacting such compound of Formula (I) with a compound of Structure 3:



Structure 3

wherein R^3 is as defined for Formula (II) above.

In a preferred embodiment the present invention relates to a process for the preparation of a compound of Formula (II) as described above, wherein the compound of Formula (I) is reacted with the compound of Structure 3 in the presence of acetic acid and a base (especially sodium acetate), preferably at elevated temperatures, especially at temperatures between 40 and 80 °C,

preferably at 55 °C. The reaction can also be carried out in a non-polar solvent such as toluene or benzene in the presence of an amine such as pyrrolidine or piperidine.

In another aspect the present invention relates to a process for the preparation of a compound of the Formula (II), wherein R^1, R^2 and R^3 are as defined above, which process comprises reacting a compound of the formula R^1-N=C=S, wherein R^1 is as defined for Formula (I), with a compound of the formula R^2-NH_2, wherein R^2 is as defined for Formula (I), followed by reaction with bromo-acetyl bromide and a pyridine base, such as especially pyridine, to obtain a compound of Formula (I) (especially wherein the preparation of the compound of Formula (I) occurs without the isolation and/or purification of intermediates), followed by reaction with a compound of Structure 3, wherein R^3 is as defined above, characterized in that the compound of Formula (I) is not isolated and/or purified, i.e. for example without any extractive aqueous work-up and concentration to dryness.

In a preferred embodiment the present invention relates to a process for the preparation of a compound of Formula (II) as described in the preceding paragraph, wherein the preparation of the compound of Formula (I) occurs in the presence of dichloromethane, followed by a solvent change in order that the reaction with a compound of Structure 3 occurs in the solvent acetic acid and in the presence of a base (especially sodium acetate), preferably at elevated temperatures, especially at temperatures between 40 and 80 °C, preferably at 55 °C. The reaction with a compound of Structure 3 can also be carried out in a non-polar solvent such as toluene or benzene in the presence of an amine such as pyrrolidine or piperidine.

Preferably the above processes are used to prepare compounds of Formula (II), wherein R^1 represents phenyl which is optionally mono-substituted with C_{1-7}-alkyl (such as especially methyl) or halogen, R^2 represents C_{1-7}-alkyl (such as especially propyl, isopropyl or butyl), and R^3 represents hydrogen, C_{1-7}-alkoxy (such as especially methoxy), or halogen.

More preferably the above processes are used to prepare compounds of Formula (II), wherein R^1 represents phenyl which is optionally mono-substituted with methyl or chloro, R^2 represents propyl, isopropyl or butyl, and R^3 represents hydrogen, methoxy, or chloro.

Especially preferred, the above processes are used to prepare compounds of Formula (II) selected from the group consisting of:
5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-phenyl-thiazolidin-4-one,
5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-phenyl-thiazolidin-4-one,
5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-butylimino]-3-phenyl-thiazolidin-4-one,
5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-(o-tolyl)-thiazolidin-4-one,
5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-(3-chloro-phenyl)-thiazolidin-4-one,
5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-(o-tolyl)-thiazolidin-4-one,
5-(4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-phenyl-thiazolidin-4-one,
5-(4-hydroxy-3-methoxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-phenyl-thiazolidin-4-one,
5-(4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-butylimino]-3-phenyl-thiazolidin-4-one,
5-(4-hydroxy-3-methoxy-benz-(Z)-ylidene)-2-[(Z)-butylimino]-3-phenyl-thiazolidin-4-one,
5-(4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-(o-tolyl)-thiazolidin-4-one, and
5-(4-hydroxy-3-methoxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-(3-chlorophenyl)-thiazolidin-4-one.

Also especially preferred, the above processes are used to prepare compounds of Formula (II) selected from the group consisting of:
5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-phenyl-thiazolidin-4-one,

5-(4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-phenyl-thiazolidin-4-one,
5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-phenyl-thiazolidin-4-one,
5-(4-hydroxy-3-methoxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-phenyl-thiazolidin-4-one,
5-(4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-butylimino]-3-phenyl-thiazolidin-4-one,
5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-butylimino]-3-phenyl-thiazolidin-4-one,
5-(4-hydroxy-3-methoxy-benz-(Z)-ylidene)-2-[(Z)-butylimino]-3-phenyl-thiazolidin-4-one,
5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-(o-tolyl)-thiazolidin-4-one,
5-(4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-(o-tolyl)-thiazolidin-4-one,
5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-(o-tolyl)-thiazolidin-4-one, and
5-(4-hydroxy-3-methoxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-(3-chlorophenyl)-thiazolidin-4-one.

In a further aspect the present invention relates to a compound of the Formula (II), wherein

R^1 represents phenyl which is optionally mono-, di- or tri-substituted wherein the substituents are independently selected from C_{1-7}-alkyl and halogen;

R^2 represents C_{1-7}-alkyl; and

R^3 represents hydrogen, hydroxy, C_{1-7}-alkoxy, or halogen.

In a preferred embodiment, the present invention relates to a compound of the Formula (II), wherein

R^1 represents phenyl which is optionally mono-substituted with C_{1-7}-alkyl (such as especially methyl) or halogen;

R^2 represents C_{1-7}-alkyl (such as especially propyl, isopropyl or butyl); and

R^3 represents hydrogen, C_{1-7}-alkoxy (such as especially methoxy), or halogen.

In an especially preferred embodiment, the present invention relates to a compound of the Formula (II), wherein R^1 represents phenyl which is optionally mono-substituted with methyl or chloro, R^2 represents propyl, isopropyl or butyl, and R^3 represents hydrogen, methoxy, or chloro.

In a more specific embodiment, the present invention relates to a compound of Formula (II) selected from the group consisting of:
5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-phenyl-thiazolidin-4-one,
5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-phenyl-thiazolidin-4-one,
5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-butylimino]-3-phenyl-thiazolidin-4-one,
5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-(o-tolyl)-thiazolidin-4-one,
5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-(3-chloro-phenyl)-thiazolidin-4-one,
5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-(o-tolyl)-thiazolidin-4-one,
5-(4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-phenyl-thiazolidin-4-one,
5-(4-hydroxy-3-methoxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-phenyl-thiazolidin-4-one,
5-(4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-butylimino]-3-phenyl-thiazolidin-4-one,
5-(4-hydroxy-3-methoxy-benz-(Z)-ylidene)-2-[(Z)-butylimino]-3-phenyl-thiazolidin-4-one,
5-(4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-(o-tolyl)-thiazolidin-4-one, and
5-(4-hydroxy-3-methoxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-(3-chlorophenyl)-thiazolidin-4-one.

Compounds of Formula (II) described herein can be transformed into the compounds of General Formula (II) described in the patent application WO 2005/054215 using standard methods for the alkylation of phenols, like reaction in a solvent such as ethanol in the presence of a base such as sodium hydride, cesium

carbonate, potassium carbonate or potassium tert-butoxide, with an appropriate alkyl halide, alkyl tosylate or alkyl triflate.

Any reference hereinbefore or hereinafter to a compound of Formula (I), Formula (II) or Structure 3 is to be understood as referring also to salts of such a compound, as appropriate and expedient.

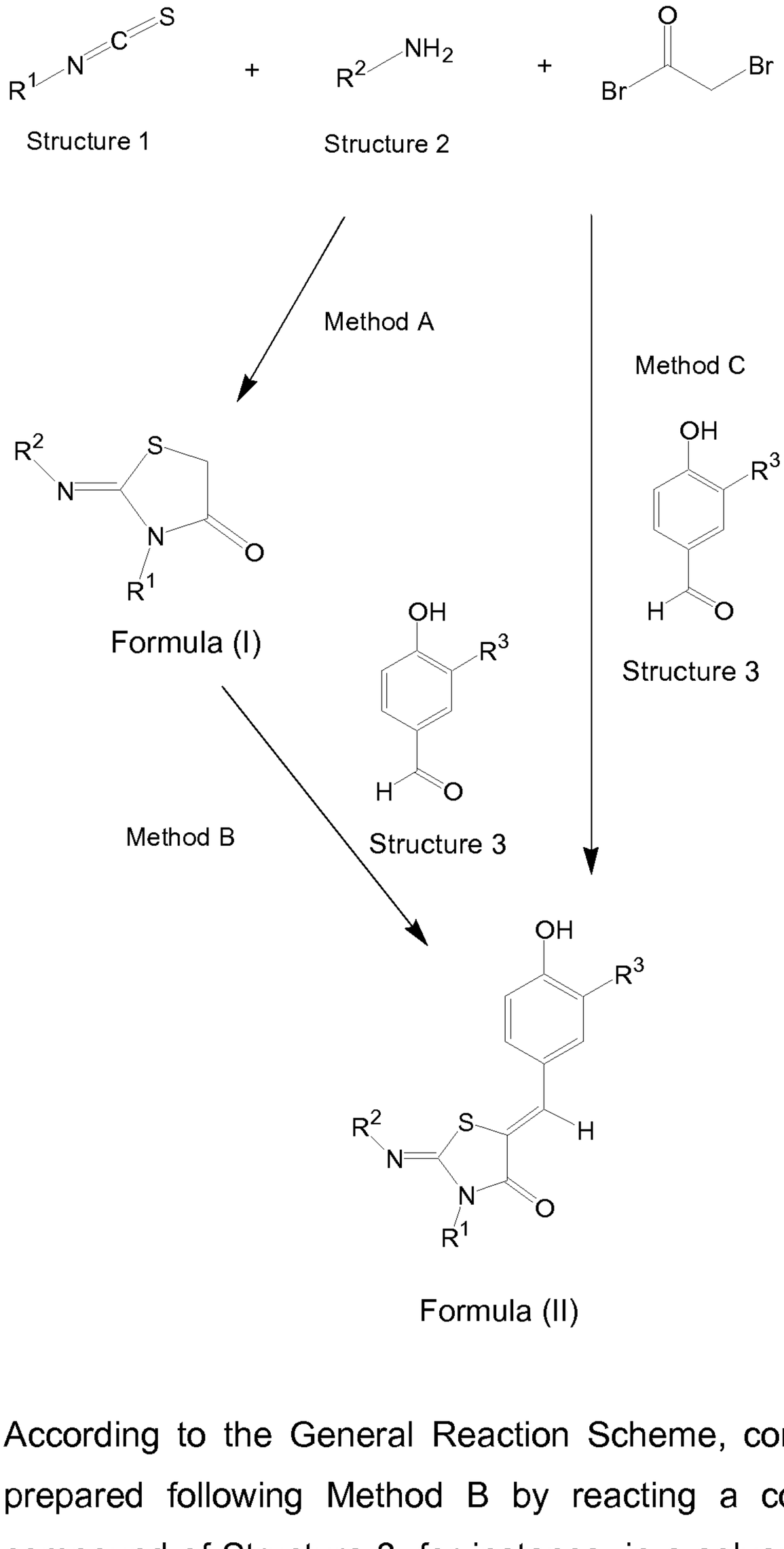
The term **C_{1-7}-alkyl** as used herein means saturated, straight or branched chain groups with one to seven carbon atoms. **C_{1-7}-alkyl** as used for R^2 is preferably n-propyl, isopropyl or n-butyl.

The term **C_{1-7}-alkoxy** as used herein means an R-O- group, wherein R is C_{1-7}-alkyl.

The term **halogen** as used herein means fluoro, chloro, bromo or iodo, preferably chloro.

According to the invention, the compounds of Formulae (I) and (II) are manufactured by the methods given below. In general, they are prepared according to the general sequence of reactions outlined below in the General Reaction Scheme.

General Reaction Scheme:



According to the General Reaction Scheme, compounds of the Formula (II) are prepared following Method B by reacting a compound of Formula (I) with a compound of Structure 3, for instance, in a solvent such as acetic acid at elevated temperatures and in the presence of a base such as sodium acetate. The required compounds of Formula (I) are prepared following Method A by reacting an isothiocyanate of Structure 1 successively with an amine of Structure 2, bromo-acetyl bromide and a pyridine base in a solvent such as dichloromethane. Alternatively, compounds of Formula (II) can be prepared following Method C

without isolating and/or purifying the compounds of Formula (I), such that an isothiocyanate of Structure 1 is reacted successively with an amine of Structure 2, bromo-acetyl bromide and a pyridine base in a solvent such as dichloromethane, followed by the addition of an aldehyde of Structure 3, for instance, in a solvent such as acetic acid at elevated temperatures and in the presence of a base such as sodium acetate. The compounds of Structure 1, 2 and 3 are either commercially available or can be prepared according to procedures known to a person skilled in the art.

Examples

The following examples illustrate the invention.

All temperatures given are external temperatures and are stated in °C. Compounds are characterized by ^{1}H-NMR (400MHz) or ^{13}C-NMR (100MHz) (Bruker; chemical shifts are given in ppm relative to the solvent used; multiplicities: s = singlet, d = doublet, t = triplet, p = pentuplet, hex = hexet, hept = heptet, m = multiplet, br = broad, coupling constants are given in Hz); by LC-MS (Finnigan Navigator with HP 1100 Binary Pump and DAD, column: 4.6x50 mm, Zorbax SB-AQ, 5 μm, 120 Å, gradient: 5-95% acetonitrile in water, 1 min, with 0.04% trifluoroacetic acid, flow: 4.5 mL/min), t_R is given in minutes. Melting point is measured on Büchi melting point apparatus B540 and is not corrected.

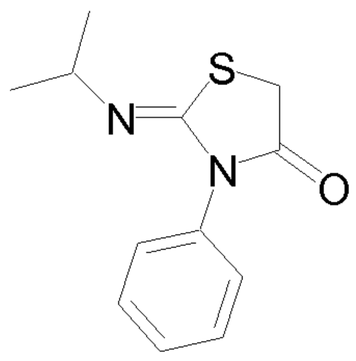
Abbreviations:

DMSO	dimethylsulfoxide
h	hour(s)
LC-MS	liquid chromatography – mass spectrometry
min	minute(s)
m.p.	melting point
t_R	retention time

Typical procedure for the preparation of the 2-imino-thiazolidin-4-ones of Formula (I) (Method A)

To a solution of an arylisothiocyanate of Structure 1 (14.8 mmol) in dichloromethane (20 mL) is added portionwise an alkyl amine of Structure 2 (14.8 mmol) at 20°C. The solution is stirred at 20°C for 15 min. The solution is cooled to 0°C. Bromo-acetyl bromide (1.287 mL, 14.8 mmol) is added carefully such that the temperature does not rise above 5°C. The reaction mixture is stirred at 0°C for 15 min. To the reaction mixture is added pyridine (2.453 mL, 30.3 mmol) at 0°C. The mixture is stirred for another 15 min. The mixture is warmed to 20°C. The reaction mixture is washed with water (10 mL). The aqueous layer is extracted with dichloromethane (10 mL). The organic layers are combined and evaporated under reduced pressure to afford a 2-imino-thiazolidin-4-one of Formula (I).

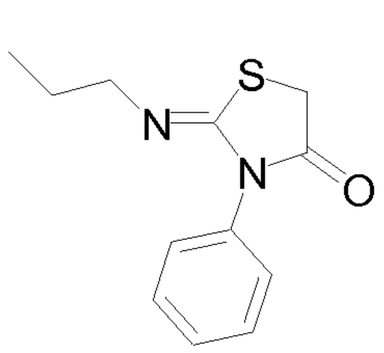
Scaffold 1:



(I)a

2-[(Z)-Isopropylimino]-3-phenyl-thiazolidin-4-one is prepared as described in Method A. LC-MS: t_R = 0.58 min, $[M+1]^+$ = 235; ^{1}H-NMR ($CDCl_3$): δ 7.51-7.47 (m, 2H), 7.43-7.35 (m, 1H), 7.31-7.29 (m, 2H), 3.99 (s, 2H), 3.53 (hept, J = 6.2 Hz, 1H), 1.15 (d, J = 6.2 Hz, 6H); ^{13}C-NMR ($CDCl_3$): δ 171.3, 135.2, 129.0, 128.5, 128.0, 125.8, 53.8, 32.6, 23.2.

Scaffold 2:

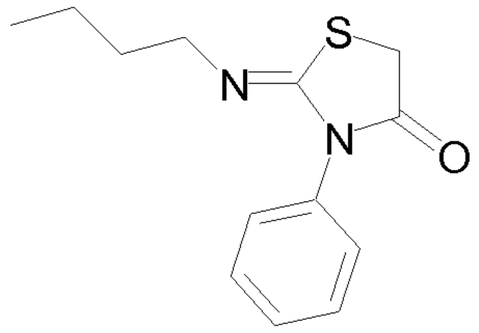


(I)b

3-Phenyl-2-[(Z)-propylimino]-thiazolidin-4-one is prepared as described in Method A. LC-MS: t_R = 0.60 min, $[M+1]^+$ = 235; ^{1}H-NMR ($CDCl_3$): δ 7.51-7.36 (m, 3H), 7.28-

7.24 (m, 2H), 3.99 (s, 2H), 3.27 (t, J = 7.0 Hz, 2H), 1.60 (hex, J = 7.0 Hz, 2H), 0.91 (t, J = 7.6 Hz, 3H); ^{13}C-NMR ($CDCl_3$): δ 171.3, 135.1, 129.2, 128.7, 128.0, 121.0, 54.2, 32.7, 23.5, 11.8.

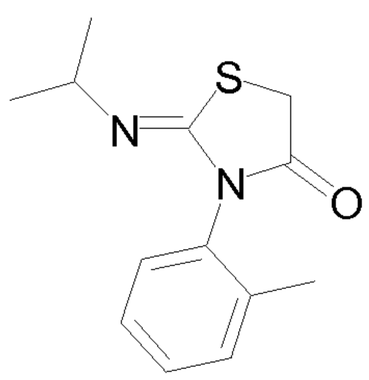
Scaffold 3:



(I)c

2-[(Z)-n-Butylimino]-3-phenyl-thiazolidin-4-one is prepared as described in Method A. LC-MS: t_R = 0.69 min, $[M+1]^+$ = 249; ^{1}H-NMR ($CDCl_3$): δ 7.52-7.48 (m, 2H), 7.44-7.40 (m, 1H), 7.30-7.28 (m, 2H), 4.00 (s, 2H), 3.32 (t, J = 7.0 Hz, 2H), 1.58 (p, 2H), 1.35 (sex, J_1 = 7.2, 2H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C-NMR ($CDCl_3$): δ 171.3, 135.1, 129.2, 128.7, 128.0, 121.0, 52.2, 32.7, 32.3, 20.5, 13.9.

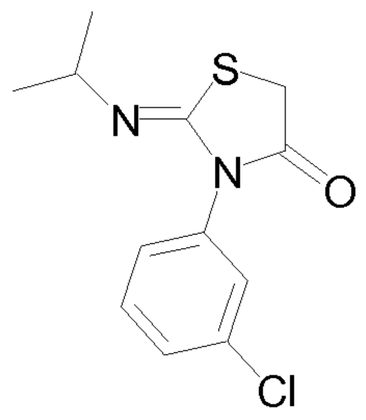
Scaffold 4:



(I)d

2-[(Z)-Isopropylimino]-3-o-tolyl-thiazolidin-4-one is obtained following Method A. LC-MS: t_R = 0.67 min, $[M+1]^+$ = 249; ^{1}H-NMR ($CDCl_3$): δ 7.35-7.28 (m, 3H), 7.15-7.13 (m, 1H), 4.00 (s, 2H), 3.51 (hept, J = 6.4 Hz, 1H), 2.18 (s, 3H), 1.12 (d, 3 H), 1.11 (d, 3H); ^{13}C-NMR ($CDCl_3$): δ 171.1, 136.1, 134.6, 131.1, 129.2, 128.6, 126.9, 53.9, 32.6, 23.4, 23.3, 17.6.

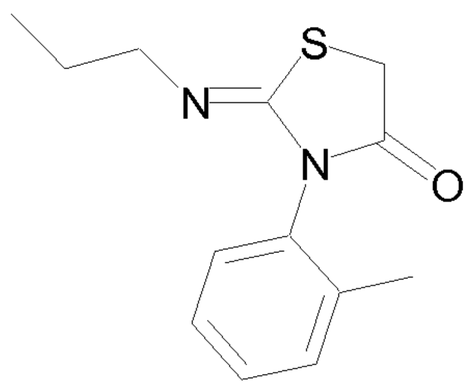
Scaffold 5:



(I)e

2-[(Z)-Isopropylimino]-3-(3-chlorophenyl)-thiazolidin-4-one is prepared as described in Method A. LC-MS: t_R = 0.76 min, $[M+1]^+$ = 269; ^{1}H-NMR ($CDCl_3$): δ 7.43-7.20 (m, 4H), 3.98 (s, 2H), 3.51 (hept, J = 6.2 Hz, 1H), 1.15 (d, 6H); ^{13}C-NMR ($CDCl_3$): δ 171.0, 136.2, 134.4, 129.9, 128.7, 128.5, 126.4, 53.9, 32.5, 23.3.

Scaffold 6:



(I)f

2-[(Z)-Propylimino]-3-o-tolyl-thiazolidin-4-one is obtained following Method A. LC-MS: t_R = 0.67 min, $[M+1]^+$ = 249; ^{1}H-NMR ($CDCl_3$): δ 7.34-7.26 (m, 3H), 7.14-7.09 (m, 1H), 4.02 (s, 2H), 3.34-3.22 (m, 2H), 2.20 (s, 3H), 1.63-1.54 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H); ^{13}C-NMR ($CDCl_3$): δ 171.1, 136.1, 134.5, 131.1, 129.4, 128.6, 127.1, 54.4, 32.6, 23.6, 17.6, 11.8.

Table 1: Summary of the results of the synthesis of the 2-imino-thiazolidin-4-ones of Formula (I)

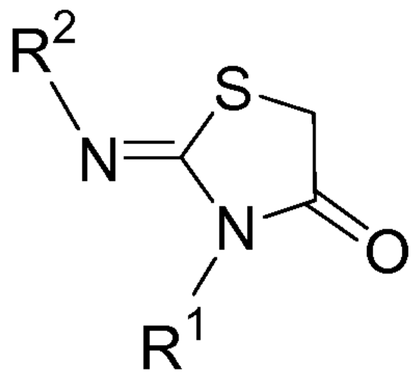
Scaffold	**Compound**	**Yield [%]**	**Ratio of isomers** [a)]	**Purity of compound of Formula (I) by LC-MS [area%]** [b)]
1	(I)a	79	95.0 : 5.0	78.5

2	(I)b	53	91.5 : 8.5	85.4
3	(I)c	74	93.0 : 7.0	89.0
4	(I)d	73	97.0 : 3.0	93.6
5	(I)e	77	96.6 : 3.4	90.1
6	(I)f	72	95.5 : 4.5	85.4

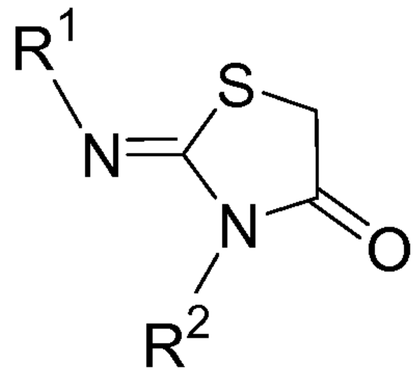
a) Determined by ^{1}H-NMR

b) at 230 nm

The ratio of isomers as given in the above Table 1 refers to the ratio of the major regioisomer of Formula (I) to the minor regioisomer of Formula (III) as determined by ^{1}H-NMR.



Formula (I)

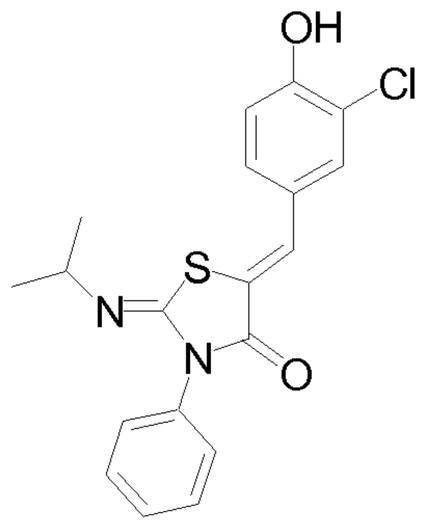


Formula (III)

Typical procedure for the Knoevenagel condensation of compounds of Formula (I) with compounds of Structure 3 to give compounds of Formula (II) (Method B)

A solution of a 2-imino-thiazolidin-4-one of Formula (I) (4.27 mmol), a 4-hydroxy-benzaldehyde of Structure 3 (4.27 mmol) and sodium acetate (700 mg, 8.54 mmol) in acetic acid (10 mL) is stirred at 60°C for 15 h. The suspension is cooled to 20°C and filtered. The cake on the nutsche is washed with a mixture of water and acetic acid (5 mL, 1/1 [v]/[v]). The product is dried under reduced pressure.

Example 1 :



(II)a

5-(3-Chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-phenyl-thiazolidin-4-one is obtained following Method B.

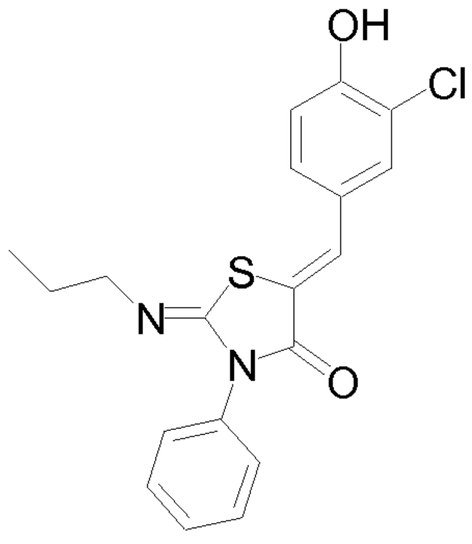
LC-MS : t_R = 1.02 min, $[M+1]^+$ = 373;

^{1}H-NMR (deutero DMSO) : δ 10.9 (s br, 1H), 7.68-7.65 (m, 2H), 7.52-7.49 (m, 3H), 7.45-7.35 (m, 3H), 7.15 (d, J = 8.5 Hz, 1H), 3.55 (hept, J = 6.2 Hz, 1H), 1.10 (d, J = 6.2 Hz, 6H);

^{13}C-NMR (deutero DMSO) : δ 166.0, 155.2, 146.1, 135.9, 132.4, 130.4, 129.3, 128.9, 128.8, 126.3, 121.0, 119.1, 117.7, 54.8, 24.0;

m.p. : 270°C.

Example 2 :



(II)b

5-(3-Chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-phenyl-thiazolidin-4-one is obtained following Method B.

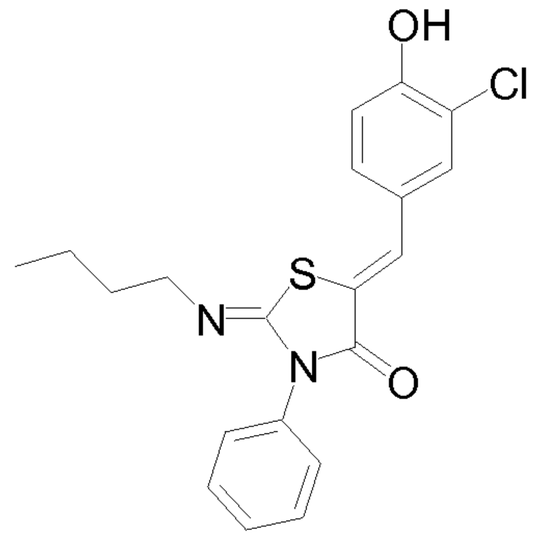
LC-MS : t_R = 1.01 min, $[M+1]^+$ = 373;

^{1}H-NMR (deutero DMSO) : δ 10.2 (s br, 1H), 7.66 (s, 1H), 7.55-7.48 (m, 4H), 7.45-7.41 (m, 1H), 7.37-7.35 (m, 2H), 6.95 (d, J = 8.3 Hz, 2H), 3.29 (t, J = 6.8 Hz, 2H), 1.54 (hex, J= 7.3, 2H), 0.86 (t, J = 7.3 Hz, 3H);

^{13}C-NMR (deutero DMSO): δ 166.1, 155.2, 147.8, 135.9, 132.4, 130.3, 129.3, 128.9, 128.8, 126.3, 121.0, 119.2, 117.7, 54.7, 23.8, 12.2;

m.p.: 200°C.

Example 3 :



(II)c

5-(3-Chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-butylimino]-3-phenyl-thiazolidin-4-one is obtained following Method B.

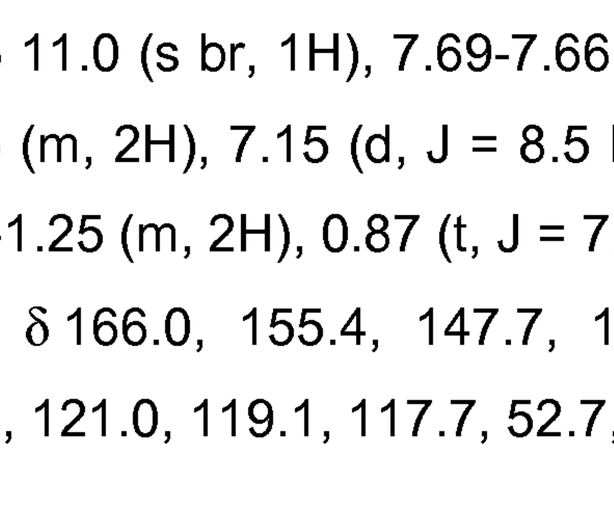
LC-MS : t_R = 1.05 min, $[M+1]^+$ = 387;

^{1}H-NMR (deutero DMSO) : δ 11.0 (s br, 1H), 7.69-7.66 (m, 2H), 7.52-7.48 (m, 3H), 7.45-7.41 (m, 1H), 7.37-7.35 (m, 2H), 7.15 (d, J = 8.5 Hz, 1H), 3.33 (t, J = 6.8 Hz, 2H), 1.54-1.46 (m, 2H), 1.34-1.25 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H);

^{13}C-NMR (deutero DMSO): δ 166.0, 155.4, 147.7, 135.9, 132.5, 130.3, 129.4, 128.95, 128.86, 128.2, 126.2, 121.0, 119.1, 117.7, 52.7, 32.7, 20.4, 14.2;

m.p.: 192°C.

Example 4 :



(II)d

5-(3-Chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-(o-tolyl)-thiazolidin-4-one is obtained following Method B.

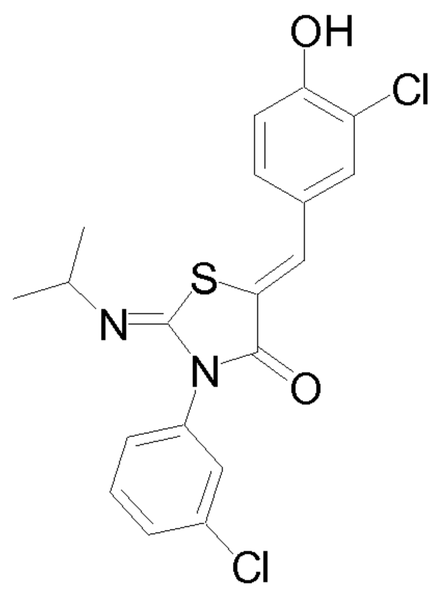
LC-MS : t_R = 1.04 min, $[M+1]^+$ = 387;

^{1}H-NMR (deutero DMSO) : δ 11.0 (s br, 1H), 7.70-7.66 (m, 2H), 7.53-7.51 (m, 1H), 7.38-7.25 (m, 4H), 7.15 (d, J = 8.3 Hz, 1H), 3.55 (hept, J = 6.0 Hz, 1H), 2.08 (s, 3H), 1.10 (d, J = 5.9 Hz, 3H), 1.08 (d, 3H);

^{13}C-NMR (deutero DMSO): δ 165.8, 155.3, 145.3, 136.3, 135.2, 132.5, 131.1, 130.4, 129.50, 129.46, 129.0, 127.3, 126.2, 121.1, 119.0, 117.7, 54.9, 24.1, 24.0, 17.6;

m.p.: 252°C.

Example 5 :



(II)e

5-(3-Chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-(3-chloro-phenyl)-thiazolidin-4-one is obtained following Method B.

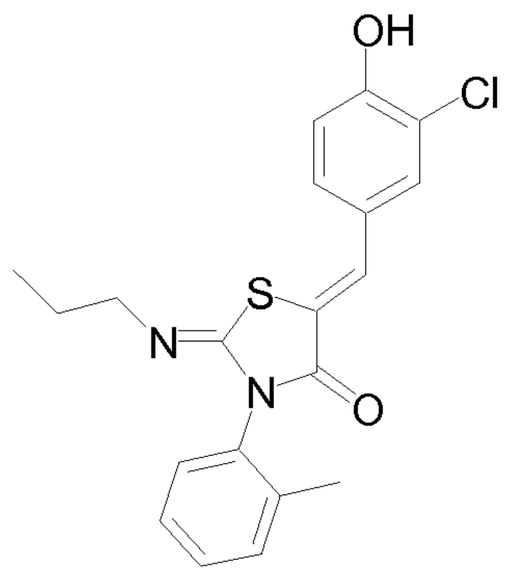
LC-MS : t_R = 1.07 min, $[M+1]^+$ = 407;

^{1}H-NMR (deutero DMSO) : δ 11.0 (s br, 1H), 7.68-7.67 (m, 2H), 7.56-7.49 (m, 4H), 7.39-7.37 (m, 1H), 7.15 (d, J = 8.3 Hz, 1H), 3.55 (hept, J = 6.0 Hz, 1H), 1.10 (d, J = 6.5 Hz, 3H);

^{13}C-NMR (deutero DMSO): δ 165.9, 155.5, 145.9, 137.2, 133.3, 132.5, 130.9, 130.4, 129.05, 129.01, 128.9, 127.9, 126.1, 121.1, 118.8, 117.8, 54.8, 24.0;

m.p.: 272°C.

Example 6 :



(II)f

5-(3-Chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-(o-tolyl)-thiazolidin-4-one is obtained following Method B.

LC-MS : t_R = 1.03 min, $[M+1]^+$ = 387;

^{1}H-NMR (deutero DMSO) : δ 11.0 (s br, 1H), 7.70-7.67 (m, 2H), 7.53-7.51 (m, 1H), 7.38-7.25 (m, 4H), 7.15 (d, J = 8.3 Hz, 1H), 3.36-3.24 (m, 2H), 2.09 (s, 3H), 1.56-1.47 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H);

^{13}C-NMR (deutero DMSO): δ 165.8, 155.3, 147.0, 136.3, 135.2, 132.5, 131.1, 130.3, 129.53, 129.50, 129.0, 127.3, 126.2, 121.1, 119.0, 117.8, 54.8, 23.9, 17.6, 12.2;

m.p.: 199°C.

Table 2: Summary of the results of the Knoevenagel reactions yielding compounds of Formula (II), following Method B

Example	Compound	Yield [%]	Purity of compound of Formula (II) by LC-MS [area%][a)]
1	(II)a	71	100
2	(II)b	77	100
3	(II)c	84	100
4	(II)d	73	100
5	(II)e	60	100
6	(II)f	69	100

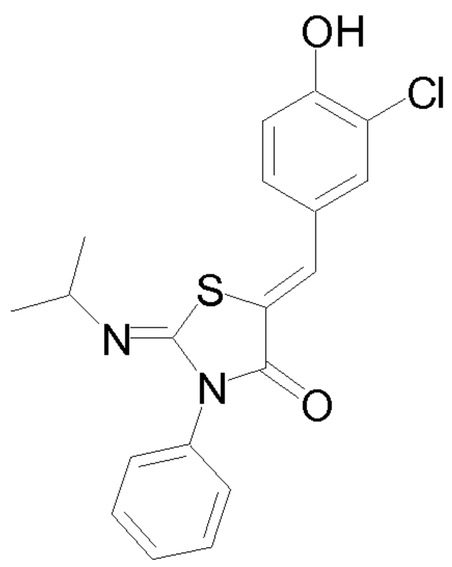
a) at 254 nm

Typical one-pot procedure for the preparation of the Knoevenagel products of Formula (II) (Method C)

To a solution of an arylisothiocyanate of Structure 1 (14.8 mmol) in dichloromethane (20 mL) is added portionwise an alkyl amine of Structure 2 (14.8 mmol) at 20°C. The solution is stirred at 20°C for 15 min. The solution is cooled to 0°C. Bromo-acetyl bromide (1.287 mL, 14.8 mmol) is added carefully such that the temperature does not rise above 5°C. The reaction mixture is stirred at 0°C for 15 min. To the reaction mixture is added pyridine (2.453 mL, 30.3 mmol) at 0°C. The mixture is stirred for another 15 min. The mixture is warmed to 20°C. An in-process control is performed to determine the ratio of the regioisomers of Formula (I) and (III). Dichloromethane is removed under reduced pressure. To the residue is added a 4-hydroxy-benzaldehyde of Structure 3 (14.8 mmol), sodium acetate (2.427 g, 29.6 mmol) and acetic acid (20 mL). The reaction mixture is stirred at 60°C for 15 h. The suspension is cooled to 20°C and water (20 mL) is added. The suspension is filtered. The cake on the nutsche is washed with a mixture of water and acetic acid (10 mL, 1/1 [v]/[v]). The product is dried under reduced pressure.

In an alternative Method C', the same procedure is followed as described for Method C above, except for the following variations: The major part of dichloromethane is removed at ambient pressure at elevated temperatures (55-65°C). Instead of cooling the suspension to 20°C and adding water after the reaction with the benzaldehyde of Structure 3, more solvent is removed under reduced pressure and 75-85 °C, and water (20 mL) is added at 60°C. The suspension is then filtered and the cake on the nutsche is washed with a mixture of water and acetic acid (10 mL), optionally followed by a wash with water (10 mL). The product is then dried under reduced pressure at 20-75 °C.

Example 7:

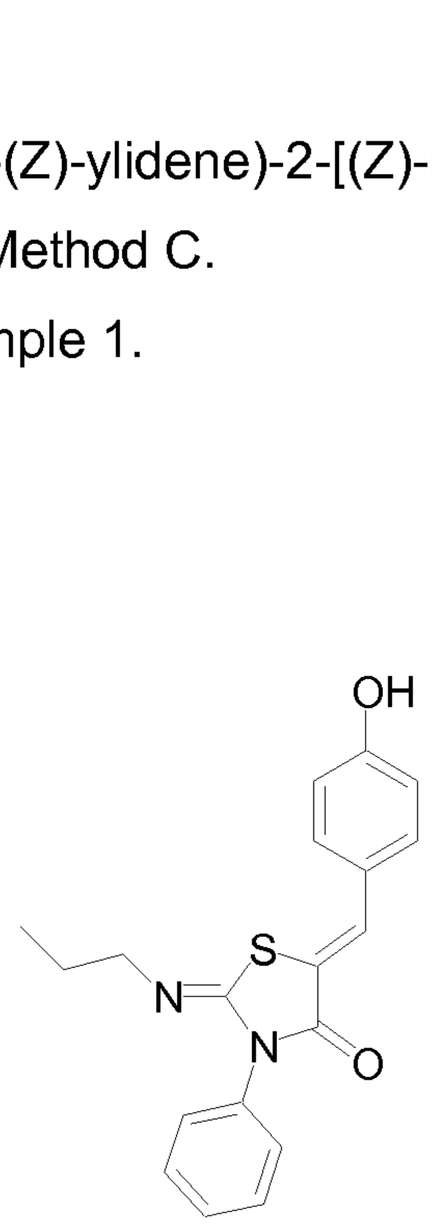


(II)a

5-(3-Chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-phenyl-thiazolidin-4-one is obtained following Method C.

For analytical data see Example 1.

Example 8:



(II)g

5-(4-Hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-phenyl-thiazolidin-4-one is obtained following Method C.

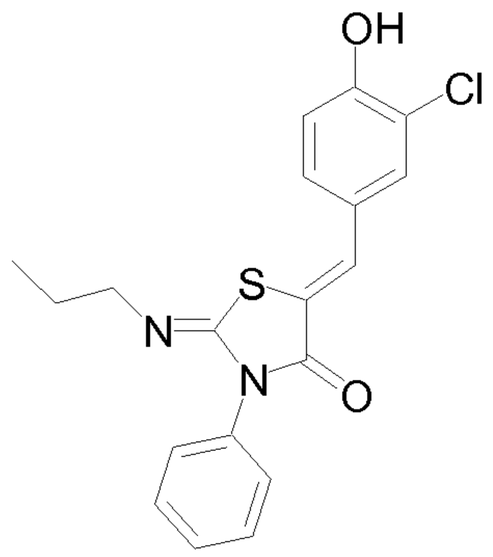
LC-MS: t_R = 0.93 min, $[M+1]^+$ = 339;

^{1}H-NMR (deutero DMSO): δ 10.2 (s br, 1H), 7.66 (s, 1H), 7.55-7.48 (m, 4H), 7.45-7.41 (m, 1H), 7.37-7.35 (m, 2H), 6.95 (d, J = 8.3 Hz, 2H), 3.29 (t, J = 6.8 Hz, 2H), 1.54 (hex, J= 7.3, 2H), 0.86 (t, J = 7.3 Hz, 3H);

^{13}C-NMR (deutero DMSO): δ 166.3, 159.9, 148.2, 136.0, 132.6, 130.3, 129.3, 129.0, 128.8, 125.0, 117.3, 116.8, 54.6, 23.8, 12.2;

m.p.: 232°C.

Example 9:

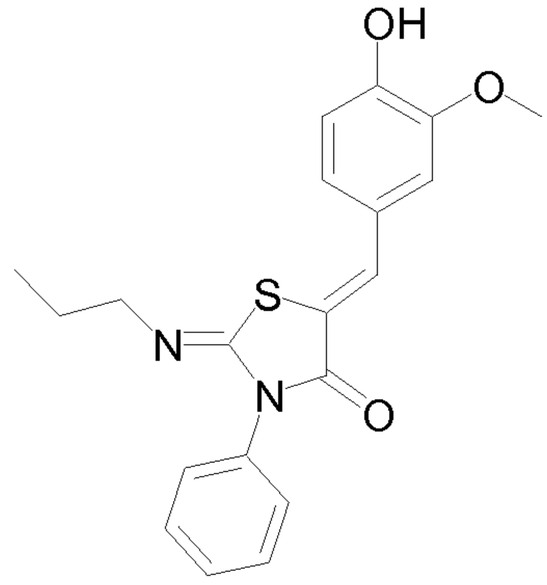


(II)b

5-(3-Chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-phenyl-thiazolidin-4-one is obtained following Method C.

For analytical data see Example 2.

Example 10:



(II)h

5-(4-Hydroxy-3-methoxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-phenyl-thiazolidin-4-one is obtained following Method C.

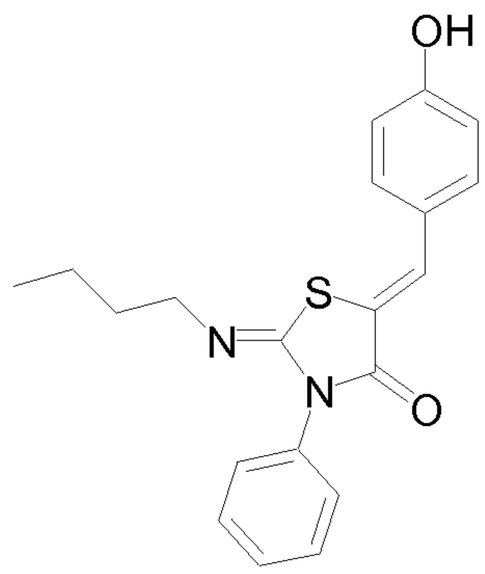
LC-MS: t_R = 0.95 min, $[M+1]^+$ = 369;

^{1}H-NMR (deutero DMSO): δ 9.84 (s br, 1H), 7.69 (s, 1H), 7.53-7.49 (m, 2H), 7.45-7.42 (m, 1H), 7.38-7.36 (m, 2H), 7.26 (s, 1H), 7.16 (d, J = 7.8 Hz, 1H), 6.97 (d, J = 8.3 Hz, 1H), 3.84 (s, 3 H), 3.30 (t, J = 6.8 Hz, 2H), 1.54 (hex, J= 7.3, 2H), 0.86 (t, J = 7.3 Hz, 3H);

^{13}C-NMR (deutero DMSO): δ 166.2, 149.4, 148.4, 135.9, 130.7, 129.4, 129.0, 128.8, 125.4, 123.9, 121.0, 117.5, 116.7, 115.1, 56.2, 54.5, 23.8, 12.2;

m.p.: 173°C.

Example 11:



(II)i

5-(4-Hydroxy-benz-(Z)-ylidene)-2-[(Z)-butylimino]-3-phenyl-thiazolidin-4-one is obtained following Method C.

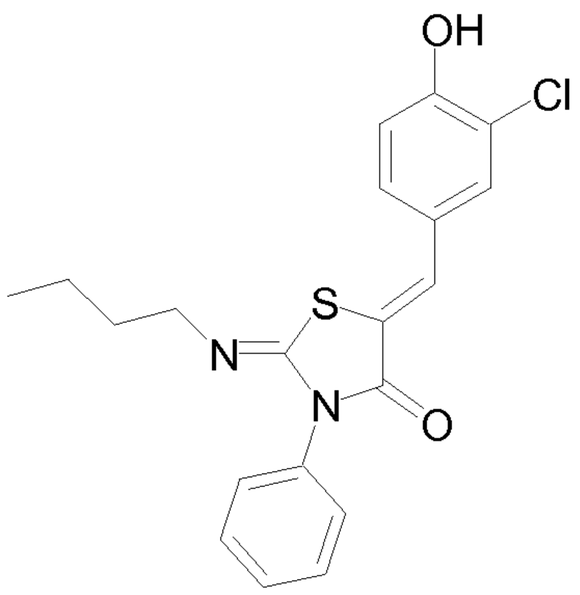
LC-MS: t_R = 0.98 min, $[M+1]^+$ = 353;

^{1}H-NMR (deutero DMSO): δ 10.2 (s br, 1H), 7.67 (s, 1H), 7.55-7.48 (m, 4H), 7.44-7.41 (m, 1H), 7.37-7.35 (m, 2H), 6.95 (d, J = 8.3 Hz, 2H), 3.33 (t, J = 6.8 Hz, 2H), 1.54-1.47 (m, 2H), 1.34-1.25 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H);

^{13}C-NMR (deutero DMSO): δ 166.3, 159.9, 148.1, 136.0, 132.6, 130.3, 129.3, 129.0, 128.8, 125.0, 117.3, 116.7, 52.7, 32.7, 20.4, 14.2;

m.p.: 228°C.

Example 12:

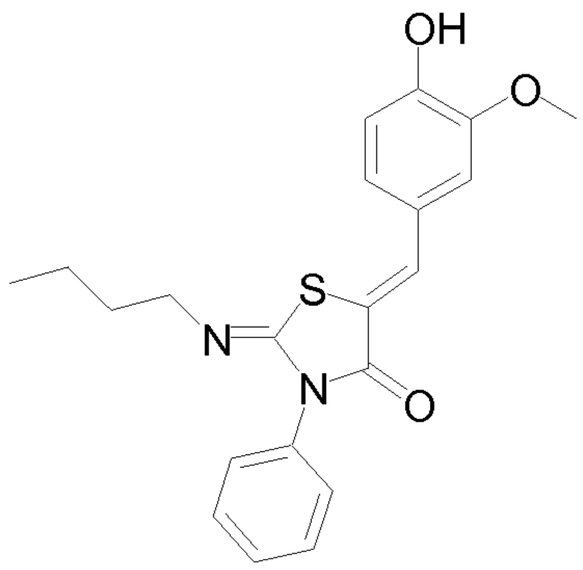


(II)c

5-(3-Chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-butylimino]-3-phenyl-thiazolidin-4-one is obtained following Method C.

For analytical data see Example 3.

Example 13:



(II)j

5-(4-Hydroxy-3-methoxy-benz-(Z)-ylidene)-2-[(Z)-butylimino]-3-phenyl-thiazolidin-4-one is obtained following Method C.

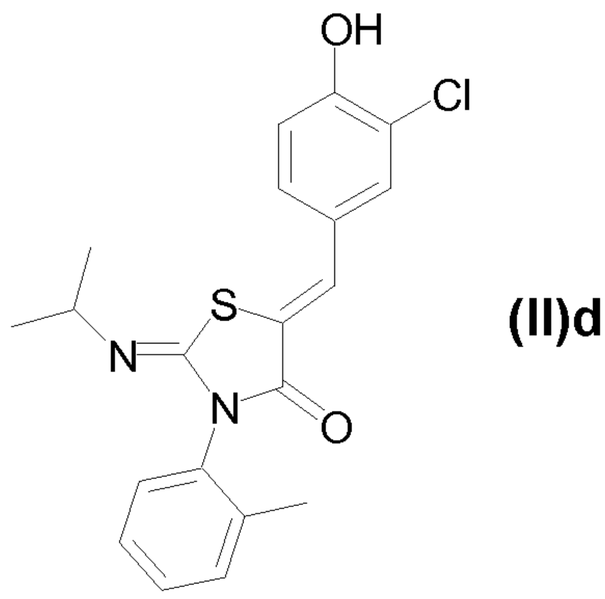
LC-MS: t_R = 0.99 min, $[M+1]^+$ = 383;

^{1}H-NMR (deutero DMSO): δ 9.86 (s br, 1H), 7.68 (s, 1H), 7.52-7.49 (m, 2H), 7.45-7.41 (m, 1H), 7.37-7.35 (m, 2H), 7.26 (s, 1H), 7.15 (d, J = 8.3 Hz, 1H), 6.97 (d, J = 8.3 Hz, 1H), 3.84 (s, 3H), 3.34 (t, J = 6.8 Hz, 2H), 1.54-1.46 (m, 2H), 1.34-1.25 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H);

^{13}C-NMR (deutero DMSO): δ 166.2, 149.4, 148.4, 148.1, 136.0, 130.6, 129.3, 129.0, 128.8, 125.5, 123.9, 117.5, 116.7, 115.1, 56.2, 52.6, 32.6, 20.3, 14.2;

m.p.: 164°C.

Example 14:

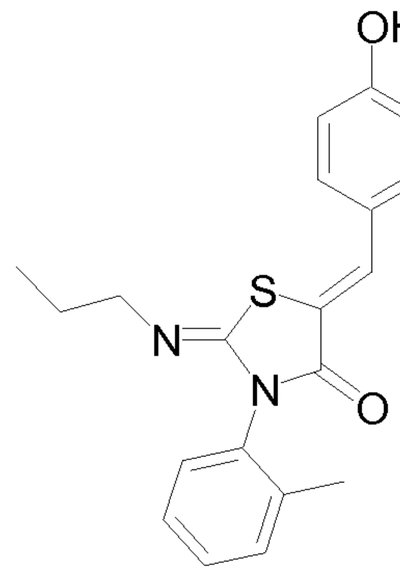


(II)d

5-(3-Chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-(o-tolyl)-thiazolidin-4-one is obtained following Method C.

For analytical data see Example 4.

Example 15:



(II)k

5-(4-Hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-(o-tolyl)-thiazolidin-4-one is obtained following Method C.

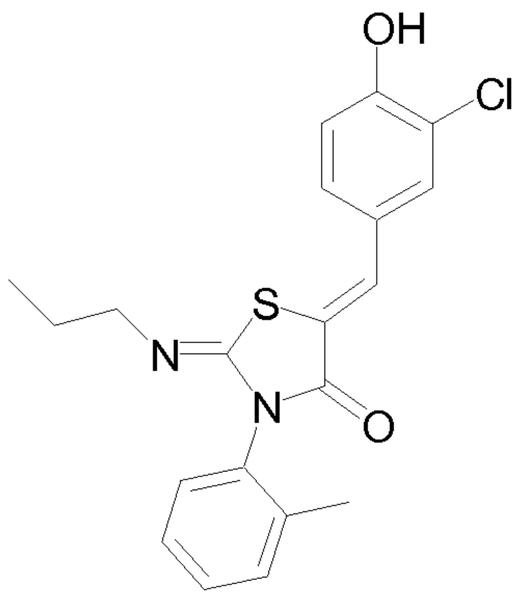
LC-MS: t_R = 0.97 min, $[M+1]^+$ = 353;

^{1}H-NMR (deutero DMSO): δ 11.1 (s br, 1H), 7.67 (s, 1H), 7.55-7.54 (m, 2H), 7.38-7.24 (m, 4H), 6.95 (d, J = 8.3 Hz, 2H), 3.36-3.24 (m, 2H), 2.09 (s, 3H), 1.56-1.47 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H);

^{13}C-NMR (deutero DMSO): δ 166.0, 159.9, 147.5, 136.3, 135.3, 132.7, 131.1, 130.4, 129.6, 129.4, 127.3, 124.9, 117.2, 116.8, 54.7, 23.9, 17.6, 12.2;

m.p.: 198°C.

Example 16:

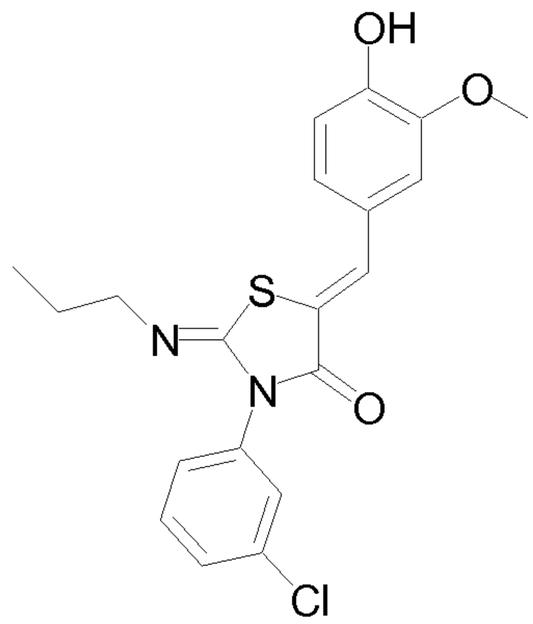


(II)f

5-(3-Chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-(o-tolyl)-thiazolidin-4-one is obtained following Method C.

For analytical data see Example 6.

Example 17:



(II)I

5-(4-Hydroxy-3-methoxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-(3-chlorophenyl)-thiazolidin-4-one is obtained following Method C.

LC-MS: t_R = 1.02 min, $[M+1]^+$ = 403;

^{1}H-NMR (deutero DMSO): δ 9.86 (s br, 1H), 7.69 (s, 1H), 7.56-7.50 (m, 3H), 7.40-7.37 (m, 1H), 7.26 (s, 1H), 7.16 (d, J = 8.5 Hz, 1H), 6.97 (d, J = 7.5 Hz, 1H), 3.85 (s, 3H), 3.30 (t, J = 6.9 Hz, 2H), 1.59-1.50 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H);

^{13}C-NMR (deutero DMSO): δ 166.0, 149.5, 148.4, 148.0, 137.2, 133.3, 130.86, 130.80, 129.1, 128.9, 128.0, 125.4, 123.9, 117.5, 116.7, 115.2, 56.2, 54.5, 23.9, 12.2;

m.p.: 200°C.

Table 3: Results of the one-pot procedure yielding compounds of Formula (II) following Method C

Example	Compound	Yield [%]	Ratio of isomers of intermediates of Formula (I) and (III)[a)]	Purity of compound of Formula (II) by LC-MS [area%][b)]
7	(II)a	88	97:3	100
8	(II)g	80	94:6	100
9	(II)b	80	94:6	89.0

10	(II)h	96	93:7	100
11	(II)i	82	94:6	100
12	(II)c	86	94:6	97
13	(II)j	84	94:6	76
14	(II)d	83	96:4	100
15	(II)k	78	97:3	94
16	(II)f	84	97:3	98
17	(II)l	84	95:5	100

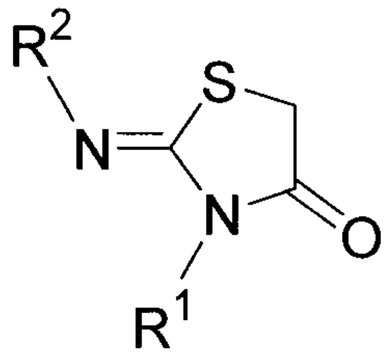
a) Determined by LC-MS at 250 nm after addition of pyridine, prior to the solvent change to acetic acid.

b) at 254 nm

The ratio of isomers as given in the above Table 3 refers to the ratio of the major regioisomer of Formula (I) to the minor regioisomer of Formula (III), said isomers occurring as intermediates in the preparation of compounds of Formula (II). The ratio of the isomers is determined by LC-MS in an in-process control.

Claims

1. A process for the preparation of a compound of the Formula (I):



Formula (I)

wherein

R^1 is phenyl which is optionally mono-, di- or tri-substituted wherein the substituents are independently selected from the group consisting of C_{1-7}-alkyl and halogen; and

R^2 is C_{1-7}-alkyl;

which process comprises reacting a compound of the formula R^1-N=C=S, wherein R^1 is as defined for Formula (I), with a compound of the formula R^2-NH_2, wherein R^2 is as defined for Formula (I), followed by reaction with bromo-acetyl bromide and a pyridine base in the presence of the solvent dichloromethane.

2. The process according to claim 1, wherein no isolation and/or purification of intermediates occurs.

3. The process according to claim 1 or 2, wherein the pyridine base is pyridine.

4. The process according to any one of claims 1 to 3, wherein R^1 is phenyl which is optionally mono-substituted with C_{1-7}-alkyl or halogen, and R^2 is C_{1-7}-alkyl.

5. The process according to claim 4, wherein R^1 is phenyl which is optionally mono-substituted with methyl or chloro, and R^2 is propyl, isopropyl or butyl.

6. The process according to any one of claims 1 to 3 for preparing a compound selected from the group consisting of:

2-[(Z)-isopropylimino]-3-phenyl-thiazolidin-4-one,

3-phenyl-2-[(Z)-propylimino]-thiazolidin-4-one,

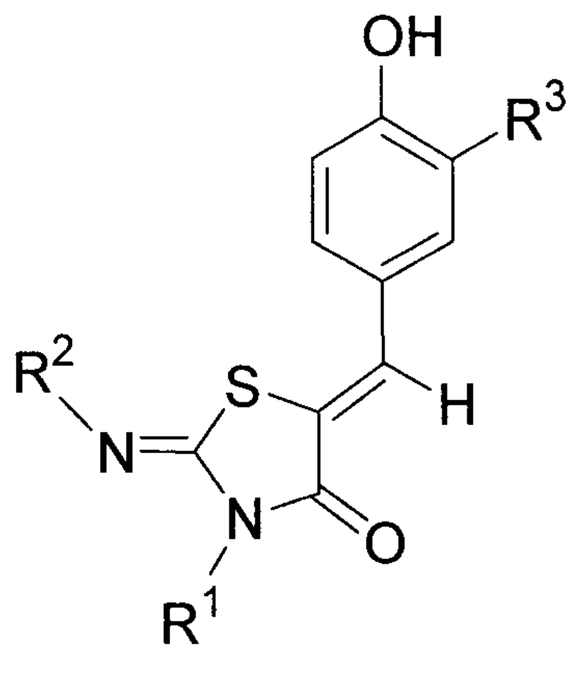
2-[(Z)-n-butylimino]-3-phenyl-thiazolidin-4-one,

2-[(Z)-isopropylimino]-3-o-tolyl-thiazolidin-4-one,

2-[(Z)-isopropylimino]-3-(3-chlorophenyl)-thiazolidin-4-one, and

2-[(Z)-propylimino]-3-o-tolyl-thiazolidin-4-one.

7. A process for the preparation of a compound of Formula (II):



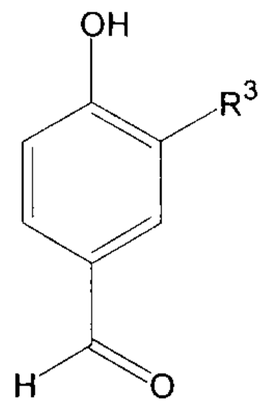
Formula (II)

wherein

R^1 and R^2 are as defined for Formula (I) in claim 1; and

R^3 is hydrogen, hydroxy, C_{1-7}-alkoxy, or halogen;

which process comprises preparing a compound of Formula (I) according to the process of any one of claims 1 to 3 and reacting said compound of Formula (I) with a compound of Structure 3:



Structure 3

wherein R^3 is as defined for Formula (II) above.

8. The process according to claim 7, wherein the compound of Formula (I) is reacted with the compound of Structure 3 in the presence of acetic acid and a base, at elevated temperatures.

9. A process for the preparation of a compound of the Formula (II) according to claim 7, which process comprises reacting a compound of the formula R^1-N=C=S, wherein R^1 is as defined for Formula (I) in claim 1, with a compound of the formula R^2-NH_2, wherein R^2 is as defined for Formula (I) in claim 1, followed by reaction with bromo-acetyl bromide and a pyridine base, to obtain a compound of Formula (I) according to claim 1, followed by reaction with a compound of Structure 3, wherein R^3 is as defined in claim 7, characterized in that the compound of Formula (I) is not isolated and/or purified.

10. The process according to claim 9, wherein the preparation of the compound of Formula (I) occurs in the presence of dichloromethane, followed by a solvent change in order that the reaction with a compound of Structure 3 occurs in the solvent acetic acid and in the presence of a base, at elevated temperatures.

11. The process according to claim 9 or 10, wherein the pyridine base is pyridine.

12. The process according to any one of claims 7 to 11, wherein R^1 is phenyl which is optionally mono-substituted with C_{1-7}-alkyl or halogen, R^2 is C_{1-7}-alkyl, and R^3 is hydrogen, C_{1-7}-alkoxy, or halogen.

13. The process according to claim 12, wherein R^1 is phenyl which is optionally mono-substituted with methyl or chloro, R^2 is propyl, isopropyl or butyl, and R^3 is hydrogen, methoxy, or chloro.

14. The process according to any one of claims 7 to 11 for preparing a compound selected from the group consisting of:

5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-phenyl-thiazolidin-4-one,

5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-phenyl-thiazolidin-4-one,

5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-butylimino]-3-phenyl-thiazolidin-4-one,

5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-(o-tolyl)-thiazolidin-4-one,

5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-(3-chloro-phenyl)-thiazolidin-4-one,

5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-(o-tolyl)-thiazolidin-4-one,

5-(4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-phenyl-thiazolidin-4-one,

5-(4-hydroxy-3-methoxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-phenyl-thiazolidin-4-one,

5-(4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-butylimino]-3-phenyl-thiazolidin-4-one,

5-(4-hydroxy-3-methoxy-benz-(Z)-ylidene)-2-[(Z)-butylimino]-3-phenyl-thiazolidin-4-one,

5-(4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-(o-tolyl)-thiazolidin-4-one, and

5-(4-hydroxy-3-methoxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-(3-chlorophenyl)-thiazolidin-4-one.

15. The process according to any one of claims 7 to 11 for preparing a compound selected from the group consisting of:

5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-phenyl-thiazolidin-4-one,

5-(4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-phenyl-thiazolidin-4-one,

5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-phenyl-thiazolidin-4-one,

5-(4-hydroxy-3-methoxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-phenyl-thiazolidin-4-one,

5-(4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-butylimino]-3-phenyl-thiazolidin-4-one,

5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-butylimino]-3-phenyl-thiazolidin-4-one,

5-(4-hydroxy-3-methoxy-benz-(Z)-ylidene)-2-[(Z)-butylimino]-3-phenyl-thiazolidin-4-one,

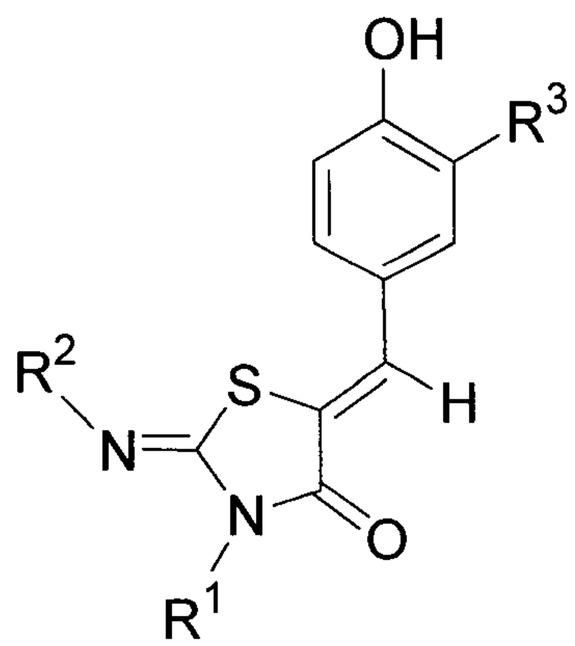
5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-(o-tolyl)-thiazolidin-4-one,

5-(4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-(o-tolyl)-thiazolidin-4-one,

5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-(o-tolyl)-thiazolidin-4-one, and

5-(4-hydroxy-3-methoxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-(3-chlorophenyl)-thiazolidin-4-one.

16. A compound of the Formula (II):



Formula (II)

wherein

R^1 is phenyl which is optionally mono-, di- or tri-substituted wherein the substituents are independently selected from the group consisting of C_{1-7}-alkyl and halogen;

R^2 is C_{1-7}-alkyl; and

R^3 is hydrogen, hydroxy, C_{1-7}-alkoxy, or halogen.

17. A compound according to claim 16, wherein R^1 is phenyl which is optionally mono-substituted with C_{1-7}-alkyl or halogen; R^2 is C_{1-7}-alkyl; and R^3 is hydrogen, C_{1-7}-alkoxy, or halogen.

18. A compound according to claim 17, wherein R^1 is phenyl which is optionally mono-substituted with methyl or chloro, R^2 is propyl, isopropyl or butyl, and R^3 is hydrogen, methoxy, or chloro.

19. A compound according to any one of claims 16 to 18 selected from the group consisting of:

5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-phenyl-thiazolidin-4-one,

5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-phenyl-thiazolidin-4-one,

5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-butylimino]-3-phenyl-thiazolidin-4-one,

5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-(o-tolyl)-thiazolidin-4-one,

5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-(3-chloro-phenyl)-thiazolidin-4-one,

5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-(o-tolyl)-thiazolidin-4-one,

5-(4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-phenyl-thiazolidin-4-one,

5-(4-hydroxy-3-methoxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-phenyl-thiazolidin-4-one,

5-(4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-butylimino]-3-phenyl-thiazolidin-4-one,

5-(4-hydroxy-3-methoxy-benz-(Z)-ylidene)-2-[(Z)-butylimino]-3-phenyl-thiazolidin-4-one,

5-(4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-(o-tolyl)-thiazolidin-4-one, and

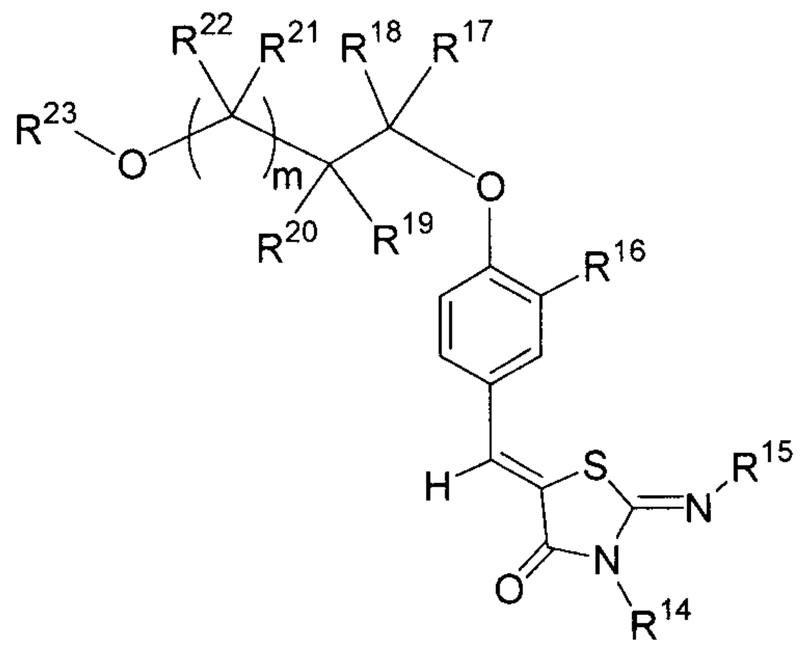
5-(4-hydroxy-3-methoxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-(3-chlorophenyl)-thiazolidin-4-one.

20. The process according to any one of claims 1 to 3 for preparing the compound 2-[(Z)-propylimino]-3-o-tolyl-thiazolidin-4-one.

21. The process according to any one of claims 7 to 11 for preparing the compound 5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-(o-tolyl)-thiazolidin-4-one.

22. A compound according to any one of claims 16 to 18 which is 5-(3-chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)-propylimino]-3-(o-tolyl)-thiazolidin-4-one.

23. Use of a compound according to claim 16 for the preparation of a compound of Formula (III):



Formula (III)

wherein

R^{14} is phenyl which is optionally mono-, di- or tri-substituted wherein the substituents are independently selected from the group consisting of C_{1-7}-alkyl and halogen;

R^{15} is C_{1-7}-alkyl;

R^{16} is hydrogen, hydroxy, C_{1-7}-alkoxy, or halogen;

R^{17} is hydrogen, lower alkyl, or hydroxymethyl;

R^{18}, R^{19}, R^{21} and R^{22} each is independently hydrogen or methyl;

R^{20} is hydrogen or lower alkyl, and in case m is the integer 1, R^{20} in addition is lower alkoxy, hydroxy, $-NH_2$, $-NHR^5$ or $-NR^5R^6$, wherein R^5 and R^6 each is independently lower alkyl;

R^{23} is hydrogen, lower alkyl, hydroxycarbonyl-lower alkyl, 1-glyceryl, or 2-glyceryl; and

m is the integer 0 or 1;

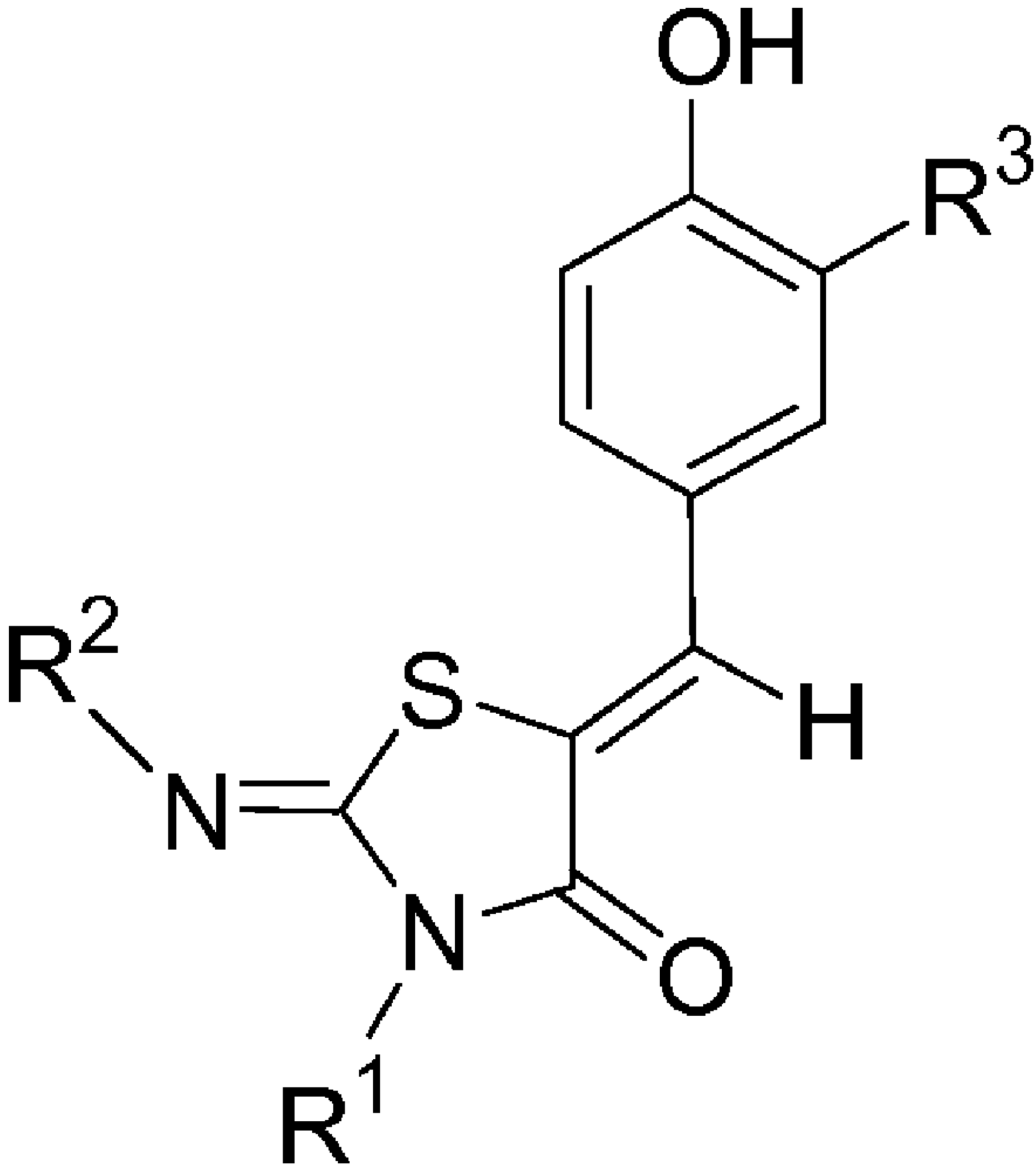
or a pharmaceutically acceptable salt thereof;

and wherein the terms "lower alkyl" and "lower alkoxy" have the following meanings:

"lower alkyl", alone or in combination with other groups, means saturated, straight or branched chain groups with one to seven carbon atoms; and

"lower alkoxy" means an R-O group, wherein R is a lower alkyl.

24. A process for the preparation of a compound of Formula (III) of claim 23 comprising the process according to any one of claims 1 to 3 and 7 to 11.



Formula (II)