

DERIVATIVES OF BENZOTHIAZINES, PREPARATION THEREOF AND
APPLICATION THEREOF AS DRUGS

The object of the present invention is derivatives
of benzothiazine, the method for making them, the
5 pharmaceutical compositions which contain them and
their use as drugs intended for treating and/or
preventing diabetes of type 2, obesity, dyslipidemias,
arterial hypertension and atherosclerosis. These
compounds may also find use in treating and/or
10 preventing hyperglycemias, intolerance to glucose,
insulin resistance, hypertriglyceridemias,
hypercholesterolemias, restenoses, pancreatitis,
retinopathies, nephropathies, neuropathies (Reichard et
al., N. Engl. J. Med. 1993, 329:304-309), certain types
15 of cancer (Strickler et al., Diabetes Technology &
Therapeutics 2001, 3(2): 263-274) or glaucomas (Pascale
et al., Ophthalmology 2006, 113(7): 1081-86).

The present invention also relates to the
combinations between the described compounds and other
20 agents used in the treatment of these pathologies.
Indeed, the treatment of pathologies such as diabetes
of type 2 often requires the combined use of several
classes of compounds in order to attain the recommended

values of glycemia and to keep it balanced (Nathan et al., Diabetes Care 2009 32:193-203). These associations may also relate to combined treatments of obesity and diabetes of type 2 (Grundy et al., Circulation 2005, 112: 2735-2752).

The metabolic syndrome is an early stage of several serious cardiovascular pathologies. It develops as a consequence of insulin-resistance and is characterized by visceral obesity (Després et al., Nature 2006 444(14): 881-87), associated with certain risk factors such as intolerance to glucose and certain dyslipidemias which may be associated with arterial hypertension (Grundy, Nat. Rev. Drug Discov. 2006, 5:295-309).

Diabetes of type 2 is a well-documented pathology since the glycemic disorders are explained by three main mechanisms: a deficiency of the function of the Langerhans β islets at the pancreas, a decrease in the use of glucose at the peripheral tissues and excess production of glucose by the liver (Monnier et al., Diabetes & Metabolism 2008, 34: 207-216). However, in spite of existing treatments, many patients affected with diabetes of type 2 do not reach the recommended glycemia target values (notably HbA_{1c}). Therefore, there is always a strong demand for treatments of this pathology based on new mechanisms.

Obesity is an ailment affecting an increasing number of persons worldwide. It is often associated with an increased risk of diabetes of type 2, of cardiovascular diseases, of cerebro-vascular strokes and of certain types of cancer. Obesity therefore

represents a major risk factor for pathologies associated with a high level of morbidity or mortality.

Glucocorticoids (cortisol in humans, corticosterone in rodents) are ubiquitous hormones which play a predominant role in the regulation of energy metabolism. They promote gluconeogenesis and inhibit insulin secretion by beta pancreatic cells as well as peripheral recapture of glucose (Dallman *et al.*, Front Neuroendocrinol. 1993, 14: 303-347).

It was recently demonstrated that 11β -hydroxysteroid dehydrogenases (11β -HSDs) regulated the glucocorticoid levels in certain target tissues (liver, adipous tissue, kidney, brain ...). In humans, this mechanism may cause a local increase in cortisol. At the adipous tissue, this may lead to an increase in the visceral fatty mass due to the effect of glucocorticoids on the differentiation of pre-adipocytes into adipocytes and lipogenesis; in certain situations, glucocorticoids promote lipolysis and deleterious impacts of free plasma fatty acids at the liver, pancreas, skeletal muscle for example (lipotoxicity). At the liver, this generation of cortisol may cause an increase in glycemia which may develop into diabetes of type 2.

Two isoforms of 11β -HSD are known: type 1 and type 2. 11β -HSD2 is mainly localized in the kidneys. It catalyses the transformation of active glucocorticoids into inactive glucocorticoids (cortisol into cortisone in humans) and consequently it is essentially involved in the protection of the mineralocorticoid receptors (MR) towards activation by cortisol (Edwards *et al.*,

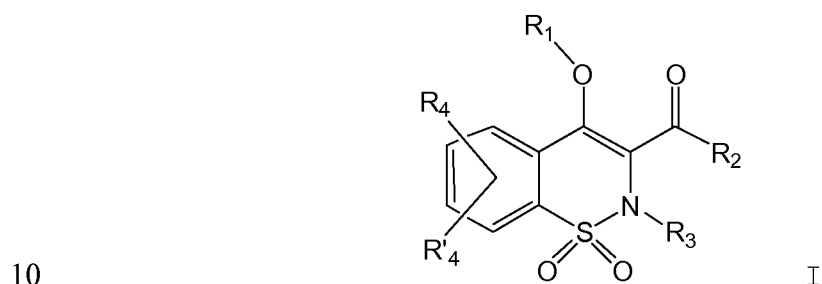
Lancet, 1988, 2: 986-989). Conversely, 11 β -HSD1 predominantly acts like an 11-keto-reductase and transforms inactive glucocorticoids into active glucocorticoids in the tissues where it is strongly expressed (liver and adipous tissue). The inhibition of this enzyme at a hepatic and adipocyte level should therefore be expressed by a reduction of the effects mentioned earlier. Several studies conducted in animals have confirmed the implication of 11 β -HSD1 in models of obesity and/or diabetes. Thus, the expression of 11 β -HSD1 is increased in diabetic Zucker rats and this increase was correlated with the progression of the pathology (Duplomb et al., Biochem. Biophys. Res. Commun., 2004, 313: 594-599). Mice without any gene coding for 11 β -HSD1 (KO mice) have proved to be resistant to hyperglycemia caused by obesity or stress (Kotelevtsev Y. et al. PNAS 1997, 94: 14924-14929). Conversely, transgenic mice selectively over-expressing 11 β -HSD1 at the adipous tissue developed visceral obesity, insulin-resistant diabetes and hyperlipidemia (Masuzika et al., Science, 2001, 294: 2166-2170). These experimental data emphasize the inhibition advantage of 11 β -HSD1 as a therapeutic target (Wamil et al., Drug Discovery Today, 2007, 12: 504-520)

The compounds of the present invention have the capability of selectively inhibiting 11 β -HSD1 relatively to 11 β -HSD2 which should be expressed in human by beneficial action on diabetes of type 2, obesity, hyperlipidemias, arterial hypertension, atherosclerosis and the whole of the pathologies which are associated therewith such as coronary strokes, cerebro-vascular strokes or arteritis of the lower limbs (Wilcox et al., Stroke, 2007, 38: 865-873; Wilcox et al., Am. Heart J. 2008, 155:712-7).

These compounds are distinguished from the prior art by their different chemical structure and their remarkable biological property.

The object of the present invention is
 5 benzothiazine derivatives having the capability of inhibiting 11 β -HSD1 not only at an enzyme level but also at a cell level.

The compounds of the present invention are of the general formula (I):



wherein:

R₁ represents:

Hydrogen; C₁-C₆ alkyl; COR₅; SO₂R₅; CO(CH₂)_mR₆;
 CO(CH₂)_mOR₆; (CH₂)_mR₆; (CH₂)_mCONR₇R₈; (CH₂)_nNR₇R₈;
 15 (CH₂)_nOR₆; CHR₇OR₉; (CH₂)_mR₁₀

m represents:

1 to 6

n represents:

2 to 6

R₂ represents:

A phenyl substituted with one or more groups selected from a halogen, C₁-C₆ alkyl, CN, OH, CF₃, OCF₃, SMe, COMe, CMe(OH)CF₃, CH(OH)CF₃, COOR₇, CONR₇R₁₁; a naphthyl, 1,2,3,4-tetrahydro-naphthalene, biphenyl, phenyl, pyridine or a heterocycle different from indole in the case where R₁, R₄ and R'₄ represent a hydrogen, either non-substituted or substituted with one or more groups selected from a halogen or C₁-C₆ alkyl, CN, OH, CF₃, OCF₃, OMe, SMe; a cycloalkyl either non-substituted or substituted with OH, CONH₂, SO₂Me, SO₂NH₂; a C₁-C₆ alkyl aryl or cycloalkyl aryl,

Proviso: - the R₂ group is always bound to the carbonyl through a carbon atom.

- When R₂ is a phenyl, the COOR₇ substituent is never in the position 4 relatively to the carbonyl.

R₃ represents:

Methyl or ethyl

R₄ and R'₄, either identical or different, represent:

Hydrogen; halogen; C₁-C₆ alkyl; CN; CF₃; OCF₃; SMe; OMe; NR₇R₈; SO₂Me

R₅ represents:

C₁-C₆ alkyl; phenyl either non-substituted or substituted with one or more groups selected from a halogen, C₁-C₆ alkyl, CN, OH, CF₃, OCF₃, SMe; a naphthyl either non-substituted or substituted with one or more
5 groups selected from halogen or C₁-C₆ alkyl, CN, OH, CF₃, OCF₃, SMe; a cycloalkyl either non-substituted or substituted with a CONH₂, SO₂Me, SO₂NH₂, heteroaryl either non-substituted or substituted with one or more groups selected from halogen, C₁-C₆ alkyl, CN, OH, CF₃,
10 OCF₃, SMe

R₆ represents:

Hydrogen; C₁-C₆ alkyl; phenyl either non-substituted or substituted with one or more groups selected from halogen, C₁-C₆ alkyl, CN, OH, CF₃, OCF₃,
15 SMe; a naphthyl or heterocycle, either non-substituted or substituted with one or more groups selected from halogen or C₁-C₆ alkyl, CN, OH, CF₃, OCF₃, SMe; a cycloalkyl either non-substituted or substituted with CONH₂, SO₂Me, SO₂NH₂

20 R₇ represents:

Hydrogen, C₁-C₆ alkyl

R₈ represents:

Hydrogen, C₁-C₆ alkyl, phenyl either non-substituted or substituted with one or more groups
25 selected from halogen, C₁-C₆ alkyl, CN, OH, CF₃, OCF₃, SMe; a naphthyl or heterocycle, either non-substituted or substituted with one or more groups selected from

halogen, C₁-C₆ alkyl, CN, OH, CF₃, OCF₃, SMe; a cycloalkyl either non-substituted or substituted with CONH₂, SO₂Me, SO₂NH₂

- 5 R₇ and R₈ taken together may form a cycle of 4-6 members with the nitrogen atom to which they are bound and which may contain one or more heteroatoms selected from N, S or O and may be either non-substituted or substituted with one or more groups selected from C₁-C₆ alkyl, C₁-C₆ alkyl aryl or aryl.

- 10 R₉ represents:

COOMe, COOEt

R₁₀ represents:

Halogen, COOH, COOR₇

R₁₁ represents:

- 15 Hydrogen, C₁-C₆ alkyl, C₁-C₆ alkyl cycloalkyl, cycloalkyl, aryl, C₁-C₆ alkyl aryl

as well as their stereoisomers, salts and solvates acceptable for therapeutic use.

In the foregoing definitions:

- 20 All the combinations of substituents or of variables are possible insofar that they lead to stable compounds.

The term « halogen » represents fluorine, chlorine, bromine or iodine.

The term « alkyl » represents saturated or unsaturated linear or branched, aliphatic hydrocarbon
5 chains and comprising the specified number of carbon atoms.

The term « cycloalkyl » represents cyclic or polycyclic hydrocarbon chains comprising from 3-12 carbon atoms. As an example, mention may be made of
10 adamantyl, cyclohexyl.

The term « aryl » represents any monocyclic or bicyclic carbon ring which may contain up to 7 atoms per ring and in which at least one of the rings is an aromatic ring. As an example, mention may be made of
15 phenyl, biphenyl, naphthyl.

The term « heteroaryl » either represents a stable monocycle containing 5-7 atoms or a stable bicycle containing 8-11 atoms, unsaturated and consisting of carbon atoms and of one to four heteroatoms selected
20 from N, O or S. As an example mention may be made of a furane, thiophene, pyridine, benzothiophene.

The term « heterocycle » either represents a stable monocycle containing from 5-7 atoms or a stable bicycle containing 8-11 atoms which may be either
25 saturated or unsaturated, and consisting of carbon atoms and of one to four heteroatoms selected from N, O or S. Are also included in the bicycle definition, monocyclic heterocycles condensed with a benzene ring except for indole when in formula I, the radicals R₁,

R_4 and R'_4 represent hydrogen. As an example, mention may be made of furane, pyrrole, thiophene, thiazole, isothiazole, oxadiazole, imidazole, oxazole, isoxazole, pyridine, pyrimidine, quinazoline, quinoline,
 5 quinoxaline, benzofurane, benzothiophene, indoline, indolizine, benzothiazole, benzothienyl, benzopyrane, benzoxazole, benzo[1,3]dioxole, benzoisoxazole, benzimidazole, chromane, chromene, dihydrobenzofurane, dihydrobenzothienyl, dihydroisoxazole, isoquinoline,
 10 dihydrobenzo[1,4]dioxin, imidazo[1,2-a] pyridine, furo[2,3-c] pyridine, 2,3-dihydro-1*H*-indene, [1,3]dioxolo [4,5-c]pyridine, pyrrolo[1,2-c]pyrimidine, pyrrolo [1,2-a] pyrimidine, tetrahydronaphthalene, benzo [b][1,4]oxazine.

15 By OR_1 , being an ester or an ether, is meant in the sense of the present invention taht R_1 represents: C_1-C_6 alkyl or COR_5 or $CO(CH_2)_mR_6$ or $CO(CH_2)_mOR_6$ or $(CH_2)_mR_6$ or $(CH_2)_mCONR_7R_8$ or $(CH_2)_nNR_7R_8$ or $(CH_2)_nOR_6$ or CHR_7OR_9 or $(CH_2)_mR_{10}$, as defined earlier.

20 The salts acceptable for therapeutic use of the compounds of the present invention comprise the conventional non-toxic salts of the compounds of the invention such as those formed from organic or inorganic acids or from organic or inorganic bases. As
 25 an example, mention may be made of the salts derived from inorganic acids such as hydrochloric, hydrobromic, phosphoric, sulfuric acids, and those derived from organic acids such as acetic, trifluoroacetic, propionic, succinic, fumaric, malic, tartaric, citric,
 30 ascorbic, maleic, glutamic, benzoic, salicylic, toluenesulfonic, methanesulfonic, stearic, lactic acids. As an example, mention may be made of the salts derived from inorganic bases such as soda, potash or

calcium hydroxide and the salts derived from organic bases such as lysine or arginine.

These salts may be synthesized from the compounds of the invention containing a basic or acid portion and
5 the corresponding acids or bases according to conventional chemical methods.

The solvates acceptable for therapeutic use of the compounds of the present invention comprise conventional solvates such as those formed during the
10 last step of preparation of the compounds of the invention because of the presence of solvents. As an example, mention may be made of the solvates due to the presence of water or ethanol.

All the stereoisomers including all the optical
15 isomers of the compounds of general formula (I) are also part of the present invention as well as their mixture in a racemic form.

According to a particular feature of the invention, the compounds of general formula (I) are
20 those for which:

- R_2 represents: A phenyl substituted with one or more groups selected from halogen, C_1 - C_6 alkyl, CN, OH, CF_3 , OCF_3 , SMe; a naphthyl, 1,2,3,4-tetrahydronaphthalene, biphenyl, or heterocycle different from
25 indole in the case when R_1 , R_4 and R'_4 represent a hydrogen atom, either non-substituted or substituted with one or more groups selected from a halogen or C_1 - C_6 alkyl, CN, OH, CF_3 , OCF_3 , OMe, SMe; a cycloalkyl

either non-substituted or substituted with CONH₂, SO₂Me, SO₂NH₂;

With the proviso: the group R₂ is always bound to the carbonyl through a carbon atom.

- 5 -R₄ and R'₄, either identical or different, represent: hydrogen; halogen; C₁-C₆ alkyl; CN; CF₃; OCF₃; SMe; OMe; NR₇R₈;

- R₈ represents:

- 10 A hydrogen, C₁-C₆ alkyl, a phenyl either non-substituted or substituted with one or more groups selected from a halogen, C₁-C₆ alkyl, CN, OH, CF₃, OCF₃, SMe; a naphthyl, or a heterocycle, either non-substituted or substituted with one or more groups selected from a halogen, C₁-C₆ alkyl, CN, OH, CF₃, OCF₃,
15 SMe; a cycloalkyl either non-substituted or substituted with CONH₂, SO₂Me, SO₂NH₂

- R₇ and R₈ taken together may form a ring with 4-6 members with the nitrogen atom to which they are bound and which may contain one or more heteroatoms selected
20 from N, S or O and may either be non-substituted or substituted with one or more groups selected from a C₁-C₆ alkyl or aryl,

with R₁ as defined earlier or as defined hereafter.

- 25 According to an embodiment of the invention, the compounds of general formula (I) are those for which R₁ represents a hydrogen.

According to another embodiment of the invention, the compounds of general formula (I) are those for which OR_1 represents an ester or an ether, with R_1 representing a C_1 - C_6 alkyl or COR_5 or $CO(CH_2)_mR_6$ or
5 $CO(CH_2)_mOR_6$ or $(CH_2)_mR_6$ or $(CH_2)_mCONR_7R_8$ or $(CH_2)_nNR_7R_8$ or $(CH_2)_nOR_6$ or CHR_7OR_9 or $(CH_2)_mR_{10}$.

According to a particular embodiment of the invention OR_1 represents an ester, with R_1 representing COR_5 or $CO(CH_2)_mR_6$ or $CO(CH_2)_mOR_6$.

10 The object of the present invention also relates to the compounds of general formula (I) for which R_2 represents a naphthyl or a 1,2,3,4-tetrahydro-naphthalene or biphenyl or a phenyl pyridine either non-substituted or substituted with one or more groups
15 selected from a halogen, C_1 - C_6 alkyl, CN, OH, CF_3 , OCF_3 , OMe, SMe; or a phenyl substituted with one or more halogens, CN, CF_3 or C_1 - C_6 alkyl.

According to an embodiment of the invention, the compounds of general formula (I) are those for which R_4
20 and R'_4 represent a hydrogen.

Among the compounds of general formula (I) belonging to the present invention, an appreciated class of compounds corresponds to the compounds of general formula (I) wherein R_1 is a hydrogen and R_2 is a
25 naphthyl or else a 1,2,3,4-tetrahydro-naphthalene.

Also, the present invention relates to the compounds of general formula (I) wherein OR_1 represents an ester or an ether and R_2 is a naphthyl or else a 1,2,3,4-tetrahydro-naphthalene.

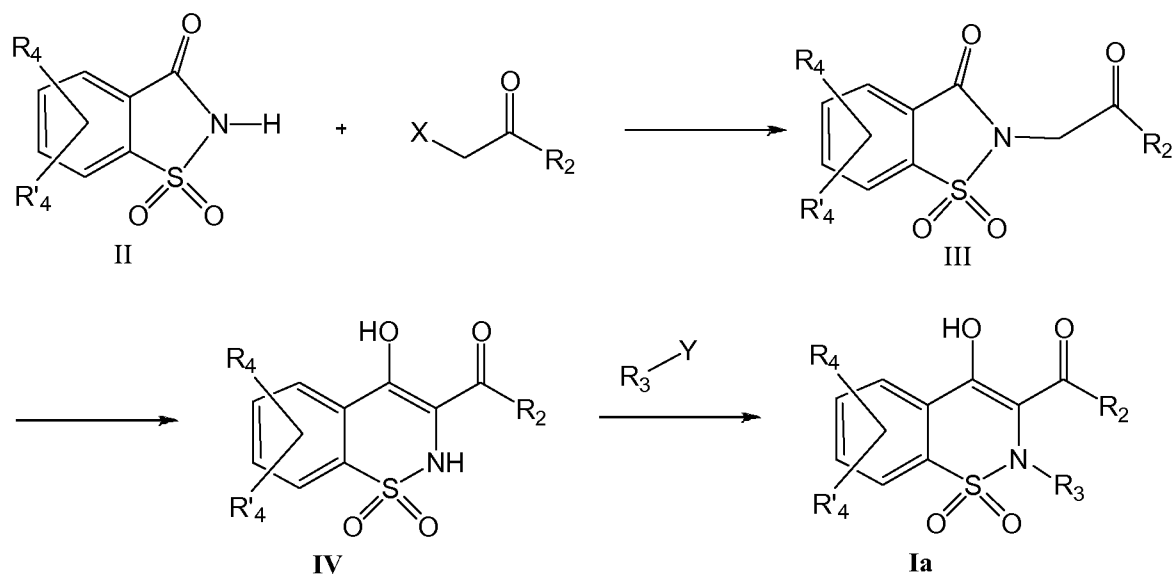
Another appreciated class of compounds corresponds to the compounds of general formula (I) wherein R₁ is a hydrogen and R₂ is a phenyl substituted with one or more halogens, CN, CF₃ or C₁-C₆ alkyl.

5 Another appreciated class of compounds corresponds to the compounds of general formula (I) wherein R₁ is a hydrogen and R₂ is a biphenyl or a phenyl pyridine, either non-substituted or substituted as defined in the description of general formula (I).

10 Also, the present invention relates to the compounds of general formula (I) wherein OR₁ represents an ester or an ether and R₂ is a phenyl substituted with one or more halogen, CN, CF₃ or C₁-C₆ alkyl.

15 Another appreciated class of compounds corresponds to the compounds of general formula (I) wherein OR₁ represents an ester or an ether and R₂ is a biphenyl or a phenyl pyridine non-substituted or substituted as defined in the description of the general formula (I).

20 The present invention also relates to the preparation of the compounds of general formula (I) by general methods described in the following synthesis schemes if necessary completed with all the standard manipulations described in the literature or well-known to one skilled in the art or else still exemplified in
25 the experimental part.

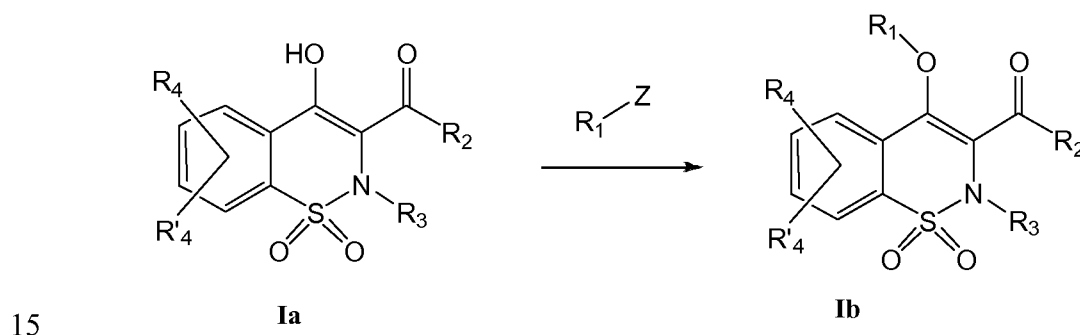


Scheme 1

Scheme 1 illustrates the first general method which may
5 be used for preparing the compounds of general formula
(Ia). In the general formulae above R₂, R₃, R₄ and R'₄,
are defined as in the previous description of the
general formula (I) and R₁ is equal to hydrogen. X may
represent a leaving group such as for example Cl, Br,
10 I, OSO₂CH₃, OSO₂CF₃ or O-tosyl. In this case, the
reaction with the compound of general formula (II) will
be conducted in the presence of an inorganic base such
as for example NaH in a polar anhydrous solvent such as
THF or DMF at a temperature comprised between - 20° and
15 100°C. The intermediate of general formula (III) is
transformed into an intermediate of general formula
(IV) by a rearrangement reaction in the presence of a
base such as for example MeONa, EtONa in a polar
anhydrous solvent such as MeOH or EtOH (possibly mixed
20 with an apolar solven such as toluene) at a temperature
comprised between 25° and 100°C. The intermediate of
general formula (IV) is transformed into a product of

general formula (Ia) by reaction with R_3Y wherein Y may represent a leaving group such as for example Cl, Br, I, OSO_2CH_3 , OSO_2CF_3 or O-tosyl and R_3 is defined as earlier. In this case, the reaction with the compound of general formula (IV) will be conducted in the presence of an inorganic base such as for example NaH in a polar anhydrous solvent such as THF or DMF at a temperature comprised between -20° and $100^\circ C$.

Scheme 2 illustrates the general method which may be used for preparing the compounds of general formula (Ib). In the general formulae below, R_1 , R_2 , R_3 , R_4 and R'_4 , are defined as in the previous description of the general formula (I) except that R_1 is different from a hydrogen.



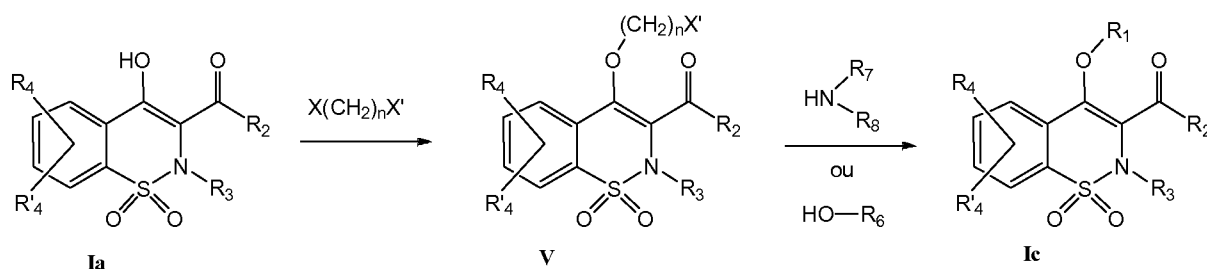
Scheme 2

The intermediate of general formula (Ia) is transformed into a compound of general formula (Ib) by reaction with R_1-Z . When R_1 represents a C_1-C_6 alkyl, $(CH_2)_mR_6$, $(CH_2)_mCONR_7R_8$, $(CH_2)_nNR_7R_8$, $(CH_2)_nOR_6$, CHR_7OR_9 or $(CH_2)_mR_{10}$ with R_6 , R_7 , R_8 , R_9 , R_{10} , m and n defined as in the previous description of the general formula (I), except that R_{10} does not represent an acid, and Z is a leaving group such as for example Cl, Br, I, OSO_2CH_3 , OSO_2CF_3 or

O-tosyl, the reaction with the enol of general formula (Ia) may be conducted in the presence of an organic or inorganic base such as for example Et_3N , iPr_2NEt , NaH , pyridine, Cs_2CO_3 , K_2CO_3 in a polar anhydrous solvent such as THF, DMF, DMSO, acetone at a temperature comprised between -20° and 140°C , either in the presence or not of a salt as a catalyst and which may be KI , Bu_4NI , LiI , AgBF_4 , AgClO_4 , Ag_2CO_3 , KF , Bu_4NF or CsF . The reaction may also be conducted in a « sealed or threaded tube » heated by heat energy or microwave energy, at temperatures comprised between 80 and 180°C . Z may also represent an alcohol. In this case, the reaction with the intermediate (Ia) will be of the « Mitsunobu » type and may be conducted in the presence of diethylazodicarboxylate (DEAD) and of triphenylphosphine in a polar anhydrous solvent such as THF at a temperature comprised between 0 and 60°C . When R_1 represents COR_5 , SO_2R_5 or $\text{CO}(\text{CH}_2)_m\text{R}_6$ with R_5 , R_6 and m defined as in the previous description of the general formula (I) then Z may represent a chlorine. In this case, the reaction with the enol of general formula (Ia) boils down to the reaction between an acid chloride and a sulfonyl chloride and an alcohol. This reaction may be conducted in the presence of an organic or inorganic base such as for example Et_3N , iPr_2NEt , NaH , pyridine, Cs_2CO_3 , K_2CO_3 in a polar anhydrous solvent such as THF, DMF, DMSO, dichloromethane at a temperature comprised between -20° and 140°C . When R_1 represents COR_5 , $\text{CO}(\text{CH}_2)_m\text{R}_6$ or $\text{CO}(\text{CH}_2)_m\text{OR}_6$ with R_5 , R_6 and m defined as in the previous description of the general formula (I) then Z may also represent a hydroxyl. In this case, the reaction with the enol of general formula (Ia) boils down to the reaction between an acid and an alcohol. This reaction may be conducted by methods and techniques well-known to one skilled in the

art. A particularly appreciated method consists of producing this condensation in the presence of 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide (EDC), of 3-hydroxy-1,2,3-benzotriazin-4(3H)-one, of a tertiary amine such as diisopropylethylamine, in a polar aprotic solvent such as dichloromethane, at a temperature comprised between -15°C and 40°C.

Scheme 3 illustrates the general method which may be used for preparing the compounds of general formula (Ic) wherein R_1 represents $(CH_2)_nNR_7R_8$ or $(CH_2)_nOR_6$ with R_6 , R_7 , R_8 , n and R_2 , R_3 , R_4 and R'_4 defined as in the previous description of general formula (I). The intermediate of general formula (Ia) is transformed into an intermediate of general formula (V) by reaction with a reagent of general formula $X(CH_2)_nX'$ wherein X and X' represent a leaving group either identical or different such as for example Cl, Br, I, OSO_2CH_3 , OSO_2CF_3 or O-tosyl and n is defined as earlier.



Scheme 3

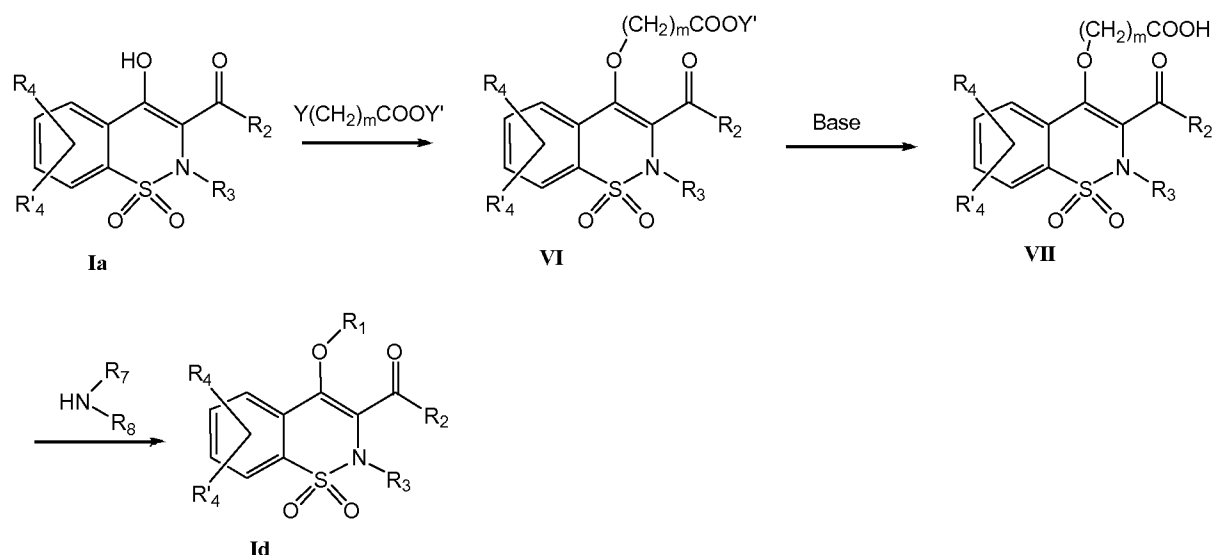
The reaction between this reagent and the enol of general formula (Ia) for leading to the intermediate of general formula (V) may be conducted in the presence of an organic or inorganic base such as for example Et_3N , iPr_2NEt , NaH , pyridine, Cs_2CO_3 , K_2CO_3 in a polar anhydrous solvent such as THF, DMF, DMSO, acetone at a temperature comprised between -20° and 140°C, either in

the presence or not of a salt as a catalyst and which may be KI, Bu₄NI, LiI, AgBF₄, AgClO₄, Ag₂CO₃, KF, Bu₄NF or CsF. This reaction may also be conducted without any solvent, with a large excess of reagent X(CH₂)_nX'. The
5 reaction may also be conducted in a « sealed or threaded tube » heated by heat energy or microwave energy, at temperatures comprised between 80 and 180 °C. X or X' may also represent an alcohol. In this case, the reaction with the intermediate (V) will be of the
10 « Mitsunobu » type and may be conducted in the presence of diethylazodicarboxylate (DEAD) and of triphenylphosphine in a polar anhydrous solvent such as THF at a temperature comprised between 0 and 60 °C.

The intermediate of general formula (V) is transformed
15 into a product of general formula (Ic) by reaction with HNR₇R₈ or HOR₆ wherein R₆, R₇ and R₈ are defined as in the previous description of the general formula (I). This reaction may be conducted in the presence of an organic or inorganic base such as for example Et₃N,
20 iPr₂NEt, NaH, pyridine, Cs₂CO₃, K₂CO₃ in a polar anhydrous solvent such as THF, DMF, DMSO, acetone at a temperature comprised between -20° and 140 °C, either in the presence or not of a solvent as a catalyst and which may be KI, Bu₄NI, LiI, AgBF₄, AgClO₄, Ag₂CO₃, KF,
25 Bu₄NF or CsF. The selection of the experimental conditions and of the reagents for conducting this reaction of course depends on the nature of the substituents R₆, R₇ and R₈ and will be performed according to the methods and techniques well-known to
30 one skilled in the art.

Scheme 4 illustrates the general method which may be used for preparing the compounds of general formula (Id) wherein R₁ represents (CH₂)_mCONR₇R₈ with R₇, R₈, m

and R_2 , R_3 , R_4 and R'_4 , defined as in the previous description of general formula (I).



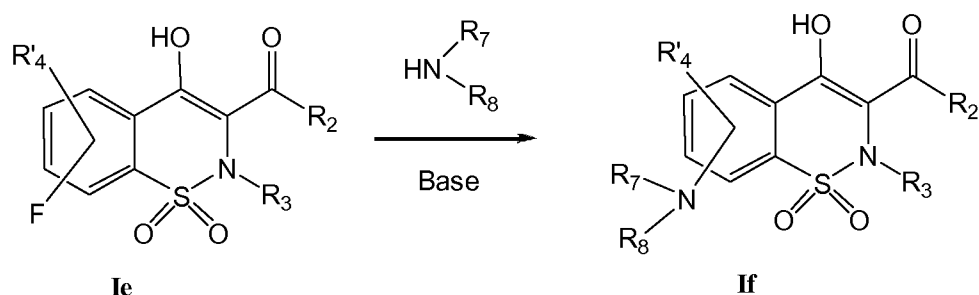
Scheme 4

- 5 The intermediate of general formula (Ia) is transformed into an intermediate of general formula (VI) by reaction with a reagent of general formula $\text{Y}(\text{CH}_2)_m\text{COOY}'$ wherein Y represents a leaving group such as for example Cl, Br, I, OSO_2CH_3 , OSO_2CF_3 or O-tosyl, m is defined as earlier and Y' represents a $\text{C}_1\text{-C}_4$ alkyl radical. This reaction may be conducted in the presence of an organic or inorganic base such as for example Et_3N , iPr_2NEt , NaH, pyridine, Cs_2CO_3 , K_2CO_3 in a polar anhydrous solvent such as THF, DMF, DMSO, acetone at a temperature comprised between -20° and 140°C , either in the presence or not of a salt as a catalyst and which may be KI, Bu_4NI , LiI, AgBF_4 , AgClO_4 , Ag_2CO_3 , KF, Bu_4NF or CsF. The reaction may also be conducted in a « sealed or threaded tube » heated by heat energy or microwave energy, to temperatures comprised between 80 and 180°C . The intermediate of general formula (VI) is

transformed into an intermediate of general formula (VII) by reaction with an inorganic base such as for example NaOH, KOH, LiOH in a polar solvent such as methanol, ethanol, THF and water, at a temperature
5 comprised between 20° and 80°C. The obtained carboxylic acid (VII) may react with an amine in order to lead to the compounds of general formula (Id). This reaction may be conducted by the methods and techniques well-known to one skilled in the art. A particularly
10 appreciated method consists of condensing these 2 entities in the presence of 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide (EDC), of 3-hydroxy-1,2,3-benzotriazin-4(3H)-one, of a tertiary amine such as diisopropylethylamine, in a polar aprotic solvent such
15 as dichloromethane or DMF, at a temperature comprised between -15°C and 50°C. Or further, as an example, by using benzotriazol-1-yloxy-tris(dimethylamino) phosphonium hexafluorophosphate (BOP) in the presence of 1-hydroxybenzotriazole, of a tertiary amine such as
20 diisopropylethylamine, in a polar solvent such as DMF, CH₂Cl₂ or DMSO at a temperature comprised between 10° and 50°C. Another particularly appreciated method consists of transforming the carboxylic acid into an acid chloride by reaction with oxalyl chloride or
25 thionyl chloride in the absence or in the presence of a base such as pyridine or triethylamine with or without a solvent such as toluene or dichloromethane at a temperature comprised between 20 and 100°C. This acid chloride may then react with the amine HNR₇R₈ in the
30 presence of a base such as pyridine or triethylamine in a solvent such as dichloromethane at a temperature comprised between 0 and 100°C.

Scheme 5 illustrates the general method which may be used for transforming the compounds of general formula

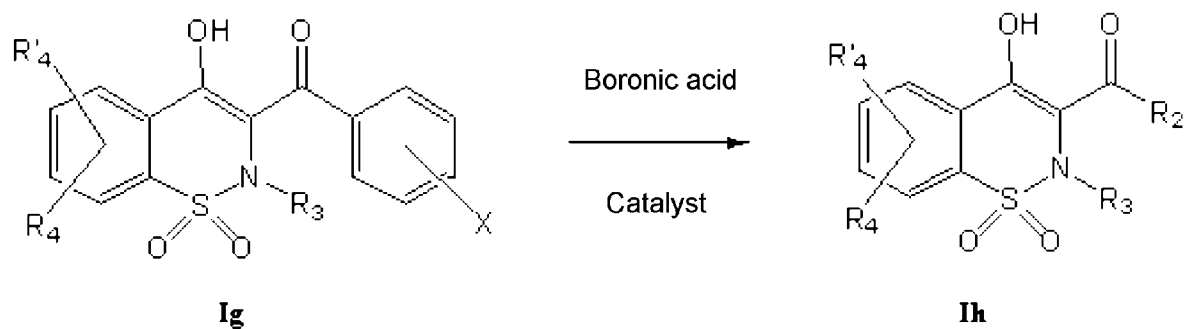
(Ie) wherein R_4 represents a fluorine and R_2 , R_3 and R'_4 are defined as in the previous description of the general formula (I) into compounds of general formula (If) wherein R_4 represents NR_7R_8 with R_7 , R_8 and R_2 , R_3 and R'_4 defined as in the previous description of the general formula (I).



Scheme 5

The compounds of general formula (Ie) may be transformed into compounds of general formula (If) by reaction with an amine of general formula HNR_7R_8 in the presence of an organic or inorganic base such as for example Et_3N , iPr_2NEt , NaH , Cs_2CO_3 , K_2CO_3 in a polar anhydrous solvent such as a DMF, DMSO at a temperature comprised between 20° and $140^\circ C$.

Scheme 6 illustrates the general method which may be used for transforming the compounds of general formula (Ig) wherein R_3 , R_4 and R'_4 are defined as in the previous description of the general formula (I) and wherein R_2 represents a phenyl substituted with a group X representing a bromine, chlorine or an OTf, into compounds of general formula (Ih) where R_2 represents a biphenyl or a phenyl pyridine either substituted or not and wherein R_3 , R_4 and R'_4 are defined as in the previous description of the general formula (I).

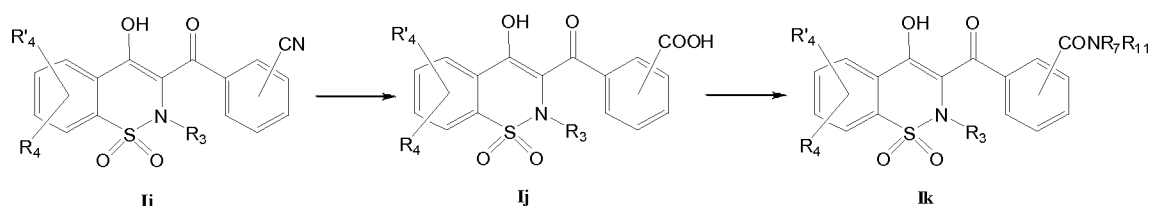


Scheme 6

The compounds of general formula (Ig) may be transformed into compounds of general formula (Ih) by a Suzuki type reaction with a boronic acid in the presence of an organic or inorganic base such as for example Et₃N, NMP, iPr₂NEt, NaH, Cs₂CO₃, K₂CO₃, K₃PO₄ with a catalyst such as for example palladium acetate, palladium tetrakis triphenylphosphine, tris(dibenzilideneacetone) dipalladium in a polar solvent such as for example acetone, methyl ethyl ketone, ethanol, DME, water, dioxane, and optionally in the presence of a phosphine such as triphenylphosphine or tricyclohexylphosphine at a temperature comprised between 20° and 140°C.

Scheme 7 illustrates the general method which may be used for transforming the compounds of general formula (Ii) wherein R₃, R₄ and R'₄ are defined as in the previous description of general formula (I) and wherein R₂ represents a phenyl substituted with a CN group in the ortho or meta position into compounds of general formula (Ij) wherein R₂ represents a phenyl substituted

with a carboxylic acid in the ortho or meta position and then into compounds of general formula (Ik) wherein R_2 represents a phenyl substituted with an amide of formula $\text{CONR}_7\text{R}_{11}$ and wherein R_3 , R_4 , R_7 , R_{11} and R'_4 are defined as in the previous description of the general formula (I).



Scheme 7

The compounds of general formula (Ii) may be transformed into compounds of general formula (Ij) by treatment with an inorganic base such as for example NaOH, KOH, LiOH in a polar solvent such as ethanol, methanol, THF, water at a temperature comprised between 20° and 140°C followed by acidification by treatment with an acid such as HCl, H₂SO₄, HCOOH. The compounds of general formula (Ij) may be transformed into compounds of general formula (Ik) by reaction with an amine of formula HNR₇R₁₁. This reaction may be conducted with methods and techniques well-known to one skilled in the art. A particularly appreciated method consists of condensing these 2 entities in the presence of 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide (EDC), of 3-hydroxy-1,2,3-benzotriazin-4(3H)-one, of a tertiary amine such as diisopropylethylamine, in a polar aprotic solvent such as dichloromethane or DMF, at a temperature comprised between -15°C and 50°C. Or further, as an example, by using benzotriazol-1-yloxy-tris(dimethylamino) phosphonium hexafluorophosphate (BOP) in the presence of 1-hydroxybenzotriazole, of a

tertiary amine such as diisopropylethylamine, in a polar solvent such as DMF, CH₂Cl₂ or DMSO at a temperature comprised between 10° and 50°C. Another particularly appreciated method consists of transforming the carboxylic acid into an acid chloride by reaction with oxalyl chloride or thionyl chloride in the absence or in the presence of a base such as pyridine or triethylamine with or without a solvent such as toluene or dichloromethane at a temperature comprised between 20 and 100°C. This acid chloride may then react with the amine HNR₇R₁₁ in the presence of a base such as pyridine or triethylamine in a solvent such as dichloromethane at a temperature comprised between 0 and 100°C.

When it is desired to isolate a compound of general formula (I) containing at least one acid or basic function in the salt state by addition with a base or an acid, this may be achieved by treating the free base or acid of general formula (I) (wherein at least one acid or basic function exists) with a suitable base or acid, preferably in an equivalent amount.

The examples which follow illustrate the invention without however limiting the scope thereof.

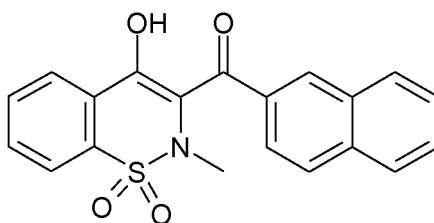
Note: for the whole of the following compounds (except if mention otherwise) the HPLC purities were determined under the following conditions:

Column Waters XTerra MS C₁₈, 4.6 x 50 mm, 5µm, λ = 220 nm, Gradient 100 % H₂O (+ 0.05 % TFA) at 100 % CH₃CN (+ 0.05 % TFA) in 6 minutes, and then 1 minute at 100%

CH₃CN (+ 0.05 % TFA). Pump Waters 600E, flow rate of 3 ml/min.

Example 1

5 (4-Hydroxy-2-methyl-1,1-dioxo -2*H*-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl)methanone



Example 1A - 2-(2-(naphthalen-2-yl)-2-oxoethyl)benzo[d]isothiazol-3(2*H*)-one-1,1-dioxide.

10 The saccharin (25 g, 136 mmol) and DMF (350 mL) are introduced into a three-neck flask equipped with a thermometer and a condenser. The medium is inertized by a vacuum/nitrogen succession (3x). Sodium hydride (6 g, 150 mmol) is slowly added, followed by 2-bromo-1-(naphthalen-2-yl)ethanone (37.4 g, 150 mmol). The
15 reaction medium is heated to 65°C for 4 hours, and then cooled to room temperature. The formed precipitate is filtered, rinsed with water and dried until constant weight for obtained 37 g of the product 1A as a pale being solid (HPLC: RT = 4.97 min, 100%). A second
20 product batch is obtained by adding water into the filtrate. The formed precipitate is filtered, rinsed with water and then with a minimum of ethyl in order to obtain after drying, 10 g of product (HPLC: RT = 4.97 min, 93%). The global yield of this reaction is 96%.

^1H NMR, $\text{dms}\text{-d}_6$, δ (ppm): 5.62 (s, 2H); 7.68 (t, 1H); 7.73 (t, 1H); 8.00-8.25 (m, 7H); 8.39 (d, 1H); 8.92 (s, 1H).

Mass spectrum (ESI+): m/z 352 (MH^+ , 100%); 369 (MNH_4^+ , 24%).

Example 1B - (4-hydroxy-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl)(naphthalen-2-yl) methanone.

In a two-neck flash equipped with a condenser and under an inert atmosphere, ethanol (165 mL) is introduced followed by slow addition of sodium cut into thin slices and rinsed with heptane (8 g, 347 mmol). At the end of the addition, the reaction medium is heated to 70°C until complete reaction of the sodium. The reaction is then cooled to room temperature, and the compound **1A** (47 g, 131 mmol) is added rapidly. An intense vermilion red and then blood red coloration appears as well as a thick precipitate. The reaction medium is heated briefly to 60°C where it solidifies. It is then cooled to room temperature and diluted in 500 mL of ethyl acetate. A 1N HCl aqueous solution is then added until a canary yellow suspension is obtained. The precipitate is filtered, rinsed with water and a minimum of a 50/50 water/EtOH mixture. It is then dried *in vacuo* until it has constant weight in order to obtain the product **1B** as a canary yellow solid (40.9 g; 88%). HPLC: RT = 5.15 min, 100%.

^1H NMR, $\text{dms}\text{-d}_6$, δ (ppm): 7.66 (t, 1H); 7.72 (t, 1H); 7.95 (broad s, 3H); 8.05 (d, 2H); 8.11 (broad s, 2H); 8.22 (broad s, 1H); 8.64 (s, 1H); 9.99 (s, 1H); 15.59 (s, 1H).

Mass spectrum (ESI+): m/z 352 (MH^+ , 100%); 369 (MNH_4^+ , 31%).

Example 1 -(1,1-dioxo-4-hydroxy-2-methyl-2H-benzo[e][1,2]thiazin-3-yl)(naphthalen-2-yl)methanone

5 In a two-neck flask under an inert atmosphere, the compound **1B** (40.9 g, 116 mmol) is dissolved in DMF (409 mL). NaH (6.05g, 151 mmol) is added. This reaction is slightly exothermic and the reaction medium assumes an intense blood red coloration. Methane iodide (10.8 mL,
10 174 mmol) is added and the reaction medium is stirred at room temperature for 2 hours. Water (10 mL) is added and the reaction medium is concentrated. The residue is taken up in ethyl acetate and the precipitate is filtered, washed with water and with a minimum of ethyl
15 acetate (solid 1). The filtrate is washed twice with an aqueous solution half-saturated with NaCl, and then concentrated until half of the volume is obtained and filtered. The precipitate (solid 2) is rinsed with a minimum of 50/50 EtOAc/Et₂O. The filtrate is
20 concentrated. The residue is filtered on silica (eluent: 50/50 heptane/CH₂Cl₂, and then 25/75 heptane/CH₂Cl₂), in order to obtain after evaporation of the solvents, a yellow powder (solid 3). The 3 solids are collected in order to obtain the product **1**
25 as a canary yellow solid (40.1 g; 89%) HPLC: RT = 5.65 min, 99%

¹H NMR, dmso-d₆, δ (ppm): 2.65 (s, 3H); 7.66 (t, 1H); 7.72 (t, 1H); 8.00 (broad s, 3H); 8.02 (d, 1H); 8.12 (broad s, 3H); 8.22 (broad s, 1H); 8.67 (s, 1H).

30 Mass spectrum (ESI+): m/z 366 (MH^+ , 100%).

Preparation of the sodium salt of 4-hydroxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]-thiazin-3-yl)(naphthalen-2-yl)methanone

A fraction of the compound **1** is dissolved and methanol
5 and treated at room temperature with 1.05 equivalents
of an aqueous 1N soda solution. The reaction medium is
concentrated and the solid residue rinsed with a
mixture of dichloromethane and ethyl ether. The thereby
obtained canary yellow solid is dried *in vacuo* for
10 several days.

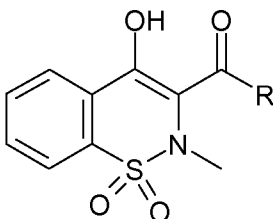
HPLC: RT = 11.73 min, 99.71% (column: XBridge C8, 5 μ M,
4.6x250mm (Waters); eluent: CH₃CN/H₂O/KH₂PO₄
600/400/6.8g, pH4, 25°C; 1 mL/min; 220nm)

¹H NMR, dmsO-d₆, δ (ppm): 2.61 (s, 3H); 7.50 (broad s,
15 2H); 7.62 (broad s, 2H); 7.65-7.72 (m, 2H); 7.80 (d,
1H); 7.89 (broad s, 2H); 7.93-7.98 (m, 2H).

Mass spectrum (ESI+): m/z 366 (MH⁺, 100%).

Examples 2 to 12

The compounds **2** to **12** were synthesized according to the
20 procedure used for preparing the derivative **1**, from
saccharin and various 2-bromo-1-(alkyl or
aryl)ethanones in the first step and from methyl iodide
or ethyl iodide in the third step. The rearrangement
protocol in the second step is unchanged.

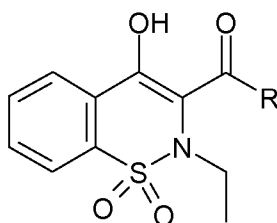


Ex. *	R	Name of the compounds	HPLC	Yld. (3 steps)	Mass MH ⁺
2	adamantan-1-yl	(4-hydroxy-2-methyl-2H-1,1-dioxo-benzo[e][1,2]thiazin-3-yl) (adamantan-1-yl) methanone	6.11' 98.9%	30%	374
3	4-methylphenyl	(4-hydroxy-2-methyl-2H-1,1-dioxo-benzo[e][1,2]thiazin-3-yl) (4-methylphenyl) methanone	5.33' 99%	49%	330
4	4-chlorophenyl	(4-hydroxy-2-methyl-2H-1,1-dioxo-benzo[e][1,2]thiazin-3-yl) (4-chlorophenyl) methanone	5.43' 99%	38%	350
5	4-cyanophenyl	(4-hydroxy-2-methyl-2H-1,1-dioxo-benzo[e][1,2]thiazin-3-yl) (4-cyanophenyl) methanone	4.97' 99%	82%	339*
6	biphenyl-4-yl	biphenyl-4-yl- (4-hydroxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) methanone	5.86' 98%	57%	392
7	2,4-dichlorophenyl	(4-hydroxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (2,4-dichlorophenyl) methanone	5.52' 98%	14%	384

* negative ESI (M-H).

** ¹H NMR, dmso-d₆, Ex. **2**: 1.72 (broad s, 6H); 2.05 (broad s, 3H); 2.10 (broad s, 6H); 2.83 (s, 3H); 7.91 (broad s, 3H); 8.10 (t, 1H); 16.1 (s, 1H). Ex. **5**: 2.63 (s, 3H); 7.99 (s, 3H); 8.11 (s, 4H); 8.19 (broad s, 1H); 14.5-15.5 (m, 1H, exch). Ex. **6**: 2.70 (s, 3H); 7.46 (t, 1H); 7.54 (t, 2H); 7.82 (d, 2H); 7.95-8.00 (m, 5H); 8.18-8.23 (m, 3H); 15.65 (broad s, 1H, exch). Ex. **7**: 2.67 (s, 3H); 7.54-7.64 (m, 2H); 7.83

(s, 1H); 7.93 (broad s, 3H); 8.11 (broad s, 1H); 13.5-14.5 (broad s, 1H).

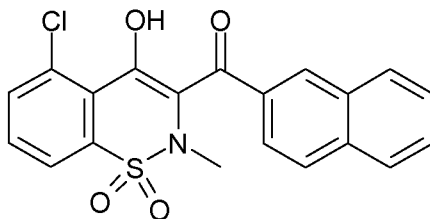


Ex. *	R	Name of the compounds	HPLC	Yld. (3 steps)	Mass (M+H) ⁺
8	adamantan-1-yl	(4-hydroxy-2-ethyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (adamantan-1-yl) methanone	6.24' 99%	32%	388
9	naphthalen-2-yl	(4-hydroxy-2-ethyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl) methanone	5.72' 99%	55%	380
10	4-methylphenyl	(4-hydroxy-2-ethyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (4-methylphenyl) methanone	5.49' 99%	40%	344
11	4-chlorophenyl	(4-hydroxy-2-ethyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (4-chlorophenyl) methanone	5.58' 99%	35%	364
12	biphenyl-4-yl	biphenyl-4-yl-(4-hydroxy-2-ethyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl)methanone	6.06' 99%	61%	406

* ¹H NMR, dmsO-d₆, Ex. **8**: 0.68 (t, 3H); 1.71 (broad s, 6H); 2.05 (broad s, 3H); 2.09 (broad s, 6H); 3.44 (q, 2H); 7.89 (broad s, 3H); 8.05 (broad s, 1H); 15.00 (s, 1H, exch.). Ex. **9**: 0.51 (t, 3H); 3.13 (q, 2H); 7.66 (t, 1H); 7.72 (t, 1H); 7.99 (broad s, 3H); 8.05 (d, 1H); 8.12 (broad s, 3H); 8.22 (broad s, 1H); 8.64 (s, 1H); 15.39 (s, 1H, exch.). Ex. **11**: 0.53 (t, 3H); 3.13 (q, 2H); 7.71 (d, 2H); 7.98 (broad s, 3H); 8.03 (d, 1H); 8.19 (broad s, 1H). Ex. **12**: 0.56 (t, 3H); 3.18 (q, 2H); 7.45 (t, 1H); 7.53 (t, 2H); 7.82 (d, 2H); 7.94-7.98 (m, 5H); 8.16 (d, 2H); 8.20-8.21 (m, 1H); 15.46 (s, 1H, exch.)

Example 13

(5-Chloro-4-hydroxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl)methanone



5 **Example 13A** - 2-Chloro-6-sulfamoylbenzoic acid.

In a three-neck flask provided with a condenser, 3-chloro-2-methylbenzenesulfonamide (13.27 g, 64.5 mmol) is introduced in the presence of 5% soda in water (385 mL). Potassium permanganate (25.5 g, 161 mmol) is
10 slowly added and then the reaction mixture is heated to 100°C for 4 hours. The reaction is returned to room temperature, filtered, acidified up to a pH of 1 and extracted 3 times with ethyl acetate. The organic phases are combined, washed once with an aqueous NaCl
15 saturated solution, and then dried on magnesium sulfate, filtered and concentrated in order to obtain the product **13A** as a white solid (12.87 g; 83%)

HPLC: RT = 1.55 min, 98%

¹H NMR, dmsO-d₆, δ (ppm): 7.48 (s, 2H, exch.); 7.62 (t, 20 1H); 7.75 (d, 1H); 7.87 (d, 1H); 11-15 (mL, 1H, exch.).

Mass spectrum (ESI⁻): m/z 234 (M-H⁻, 55%).

Example 13B - 4-chlorosaccharin.

The compound **13A** (12.87 g, 54.6 mmol) is introduced into a flask followed by 38.8 mL of concentrated sulfuric acid. The reaction mixture is stirred at room
5 temperature for 1.5 hours and then poured on a mixture of water and ice. The formed precipitate is filtered, rinsed with water and dried until its weight is constant in order to obtain the compound **13B** as a white solid (9.16 g; 77%).

10 HPLC: RT = 2.57 min, 100%

¹H NMR, dms_o-d₆, δ (ppm): 7.91 (broad s, 2H); 8.08 (broad s, 1H).

Example 13C - 4-chloro-2-(2-(naphthalen-2-yl)-2-oxoethyl)benzo[d]isothiazol-3(2H)-one-1,1-dioxide.

15 The compound **13C** was synthesized from the compound **13B** (2.2 g, 10 mmol) according to the procedure used for preparing the derivative **1A** in order to obtain the compound **13C** as a pale beige solid (3.3 g; 84%).

HPLC: RT = 5.11 min, 99%

20 ¹H NMR, dms_o-d₆, δ (ppm): 5.62 (s, 2H); 7.69 (t, 1H), 7.74 (t, 1H); 7.95-8.20 (m, 6H); 8.38 (d, 1H); 8.92 (s, 1H).

Mass spectrum (ESI⁺): m/z 386 (MH⁺, 100%).

Example 13D - (5-chloro-1,1-dioxo-4-hydroxy-2H-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl)methanone.

The compound **13D** was synthesized from the compound **13C** (3.3 g, 8.5 mmol) according to the procedure used for
5 preparing the derivative **1B** in order to obtain the compound **13D** as a golden yellow solid (1.7 g; 51%).

HPLC: RT = 5.3 min, 99%

¹H NMR, dmso-d₆, δ (ppm): 7.68 (t, 1H), 7.72 (t, 1H); 7.85-8.15 (m, 8H); 8.59 (s, 1H); 10.11 (s, 1H).

10 Mass spectrum (ESI+): m/z 386 (MH⁺, 100%).

Example 13 - The compound **13** was synthesized from the compound **13D** (3 g, 7.7 mmol) according to the procedure used for preparing the derivative **1** in order to obtain the compound **13** as a yellow solid (2.3 g; 70%).

15 HPLC: RT = 5.75 min, 95%

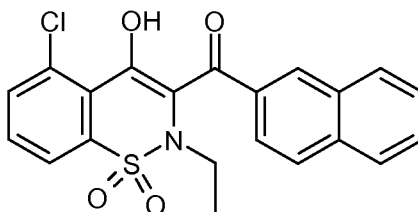
¹H NMR, dmso-d₆, δ (ppm): 2.69 (s, 3H); 7.66 (t, 1H); 7.72 (t, 1H); 7.9-8.2 (m, 7H); 8.60 (broad s, 1H); 16.15 (broad s, 1H, exch.).

Mass spectrum (ESI+): m/z 400 (MH⁺, 100%).

20

Example 14

(5-Chloro-4-hydroxy-2-ethyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl)methanone



The compound **14** was synthesized from the compound **13D** (1 g, 2.6 mmol) and from iodoethane according to the procedure used for preparing the derivative **1** in order to obtain 805 mg (60%) of the desired product.

HPLC: RT = 5.77 min, 81%

A fraction of this product (200 mg) was purified on a column of 12 g of spherical silica (flow rate 12 mL/min, 100% heptane (2 min), EtOAc/heptane gradient from 0 to 50% (30 min), 50% EtOAc/heptane (5 min)), in order to obtain 64 mg of desired product as a yellow solid.

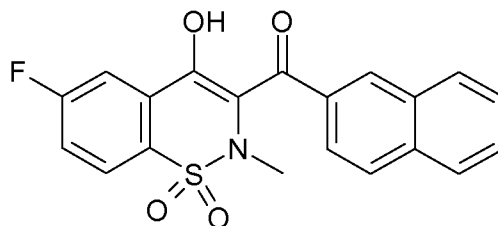
HPLC: RT = 5.77 min, 97%

¹H NMR, dms_o-d₆, δ (ppm): 0.51 (t, 3H); 3.11 (q, 2H); 7.66 (t, 1H); 7.72 (t, 1H); 7.85-8.2 (m, 7H); 8.60 (s, 1H); 15.9 (s, 1H, exch.).

Mass spectrum (ESI⁺): m/z 414 (MH⁺, 100%).

Example 15

(6-Fluoro-4-hydroxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl)methanone



Example 15A - (6-fluoro-4-hydroxy-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl)methanone.

The compound **15A** was synthesized from the compound 4-fluoro-2-methylbenzenesulfonamide according to the same sequence of steps involved in preparing the compound **13D**. The product is obtained as a yellow solid with an overall yield of 79%.

HPLC: RT = 5.26 min, 96%

¹H NMR, dmso-d₆, δ (ppm): 7.66 (t, 1H); 7.72 (t, 1H); 7.80 (t, 1H); 7.94-8.11 (m, 6H); 8.64 (s, 1H); 10.18 (s, 1H, exch.); 15.2 (broad s, 1H, exch.).

Mass spectrum (ESI⁻): m/z 368 (M-H⁻, 100%).

Example 15 - (6-fluoro-4-hydroxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl)methanone

The compound **15** was synthesized from the compound **15A** (1.5 g, 4 mmol) according to the procedure used for preparing the derivative **1** in order to obtain 1.47 g (89%) of the desired product as a yellow solid.

HPLC: RT = 5.6 min, 93%

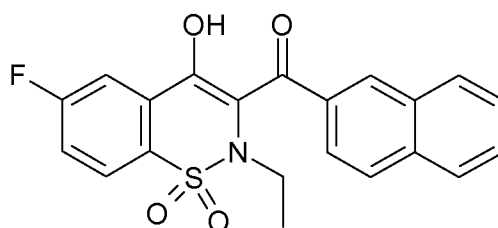
A fraction of this product was recrystallized from ethanol in order to obtain 186 mg of compound **15** with greater purity (HPLC: RT = 5.6 min, 99.4%).

¹H NMR, dmso-d₆, δ (ppm): 2.68 (s, 3H); 7.66 (t, 1H);
5 7.72 (t, 1H); 7.84 (t, 1H); 7.97 (d, 1H); 8.02-8.15 (m, 5H); 8.66 (s, 1H); 15.22 (broad s, 1H, exch.).

Mass spectrum (ESI+): m/z 384 (MH⁺, 100%).

Example 16

10 (6-Fluoro-4-hydroxy-2-ethyl-1,1-dioxo-2H-
benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl)methanone



The compound **16** was synthesized from the compound **15A** (1.5 g, 4 mmol) and from iodoethane according to the procedure used for preparing the derivative **1** in order
15 to obtain 520 mg (29%) of the desired product as a yellow solid.

HPLC: RT = 5.8 min, 91%

A fraction of this product was recrystallized from ethanol in order to obtain 71 mg of compound **16** with
20 greater purity.

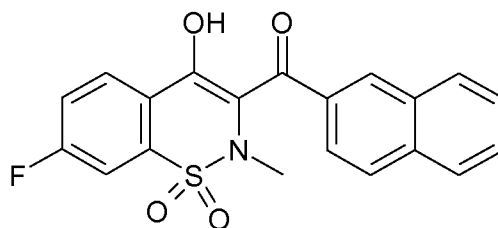
HPLC: RT = 5.8 min, 97%

^1H NMR, $\text{dms}\text{-d}_6$, δ (ppm): 0.56 (t, 3H); 3.15 (q, 2H); 7.66 (t, 1H); 7.72 (t, 1H); 7.82 (t, 1H); 7.97 (d, 1H); 8.00-8.2 (m, 5H); 8.63 (s, 1H); 14.95 (broad s, 1H).

5 Mass spectrum (ESI+): m/z 398 (MH^+ , 100%).

Example 17

(7-Fluoro-4-hydroxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl)methanone



10 Example 17A - 5-fluoro-2-methylbenzenesulfonamide.

5-fluoro-2-methylbenzenesulfonyl chloride (5.00 g, 23.9 mmol) is slowly added at 0°C onto 23 mL of a concentrated ammonia solution. The reaction medium is then heated to 100°C for 1 hour and then cooled to room temperature. The formed precipitate is filtered, rinsed with water and dried until it has constant weight. The compound 17A is obtained as a white powder (4.55g; 100%).

HPLC: RT = 3.10 min, 96%

^1H NMR, dmso-d_6 , δ (ppm): 2.54 (s, 3H); 7.35-7.45 (m, 2H); 7.53 (broad s, 2H, exch.); 7.58 (de, 1H).

Mass spectrum (ESI-): m/z 188 (M-H^- , 100%).

Example 17B - (7-Fluoro-4-hydroxy-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl)methanone.

The compound **17B** was synthesized from the compound **17A** according to the same sequence of steps involved in preparing the compound **13D**. The product is obtained as a yellow solid with an overall yield of 73%.

10 HPLC: RT = 5.18 min, 98%

^1H NMR, dmso-d_6 , δ (ppm): 7.66 (t, 1H); 7.72 (t, 1H); 7.81 (t, 1H); 7.90 (d, 1H); 8.04 (d, 2H); 8.11 (broad s, 2H); 8.30 (dd, 1H); 8.63 (s, 1H); 10.19 (broad s, 1H); 15.63 (broad s, 1H).

15 Mass spectrum (ESI-): m/z 368 (M-H^- , 100%).

Mass spectrum (ESI+): m/z 370 (MH^+ , 100%).

Example 17 - (7-Fluoro-4-hydroxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl)methanone.

20 The compound **17** was synthesized from the compound **17B** (4.00 g, 10.8 mmol) according to the procedure used for preparing the derivative **1** in order to obtain two batches of the desired product with different purities.

First batch: 3.79 g; pale brown solid; HPLC: RT = 5.65 min, 94%.

Second batch: 320 mg; yellow solid; HPLC: RT = 5.65 min, 99%.

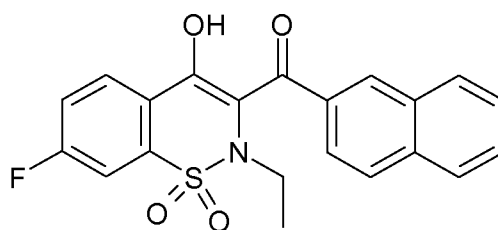
5 The yield of this reaction is 93%.

^1H NMR, $\text{dms}\text{-d}_6$, δ (ppm): 2.68 (s, 3H); 7.66 (t, 1H); 7.72 (t, 1H); 7.83 (t, 1H); 7.92 (d, 1H); 8.02-8.15 (m, 4H); 8.28 (dd, 1H); 8.62 (s, 1H); 15.62 (broad s, 1H, exch.).

10 Mass spectrum (ESI⁺): m/z 384 (MH^+ , 100%).

Example 18

(7-Fluoro-4-hydroxy-2-ethyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl)methanone



15 The compound **18** was synthesized from the compound **17A** (1.0 g, 2.7 mmol) and from iodoethane according to the procedure used for preparing the derivative **1** in order to obtain two batches of the desired product with different purities.

First batch: 716 mg; pale brown solid; HPLC: RT = 5.78 min, 89%.

Second batch: 68 mg; yellow solid; HPLC: RT = 5.78 min, 99%.

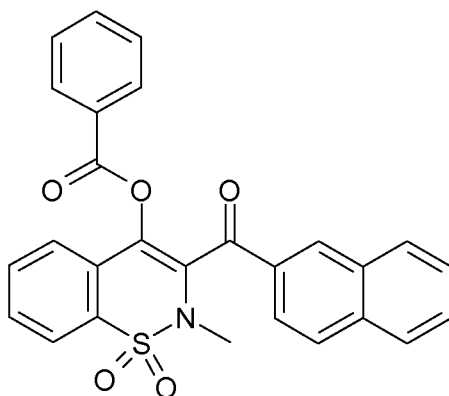
5 The yield of this reaction is 65%.

^1H NMR, $\text{dms}\text{-d}_6$, δ (ppm): 0.54 (t, 3H); 3.14 (q, 2H); 7.66 (t, 1H); 7.71 (t, 1H); 7.82 (t, 1H); 7.92 (d, 1H); 8.00–8.15 (m, 4H); 8.29 (dd, 1H); 8.60 (s, 1H); 15.45 (broad s, 1H, exch.).

10 Mass spectrum (ESI+): m/z 398 (MH^+ , 100%).

Example 19

Benzoic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester



15 The compound **1** (86 mg, 0.18 mmol) is dissolved under an inert atmosphere in 0.5 mL of dichloromethane and 0.5 mL of pyridine. The reaction medium is cooled to 0°C

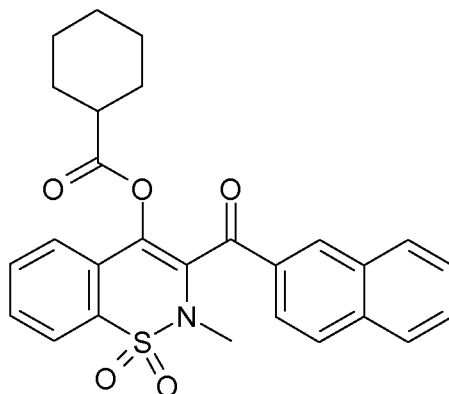
and then benzoyl chloride (33 μ l, 0.27 mmol) is added. The cold bath is removed and the reaction is stirred for 4 hours at room temperature. As the reaction is incomplete, 16 μ l (0.14 mmol) of benzoyl chloride are
5 further added and the reaction medium is stirred at room temperature for a further 20 hours before being concentrated. The residue is taken up in ethyl acetate, washed once with water and once with an aqueous NaCl saturated solution, dried on sodium sulfate, filtered
10 and concentrated. This second residue is co-evaporated three times with toluene in order to remove the remaining pyridine. The thereby obtained yellow syrup is purified on a column of 12 g of spherical silica (flow rate 12 mL/min, CH₂Cl₂/heptane gradient from 20
15 to 100% (30 min)), in order to obtain the compound **19** as a yellow foam (38 mg; 44%).

HPLC: RT = 5.65 min, 96%

¹H NMR, dms^o-d₆, δ (ppm): 3.10 (s, 3H); 7.32 (t, 2H);
7.55-7.30 (m, 6H); 7.86 (dd, 2H); 7.90-8.05 (m, 5H);
20 8.70 (s, 1H).

Example 20

Cyclohexanecarboxylic acid 2-methyl-3-(naphthalene-2-carbonyl)- 1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester



The compound **1** (86 mg, 0.18 mmol) is dissolved under an inert atmosphere in 0.5 mL of pyridine. The reaction medium is cooled to 0°C and then cyclohexanecarbonyl chloride (62 µl, 0.46 mmol) is added. The cold bath is removed and the reaction is stirred for 18 hours at room temperature, and then heated to 60°C for 8 hours. The reaction mixture is concentrated and co-evaporated three times with toluene. The thereby obtained residue is purified on a column of 12 g of spherical silica (flow rate 12 mL/min, CH₂Cl₂/heptane gradient from 20 to 100% (20 min)), in order to obtain the compound **20** as a yellow foam (65 mg; 28%).

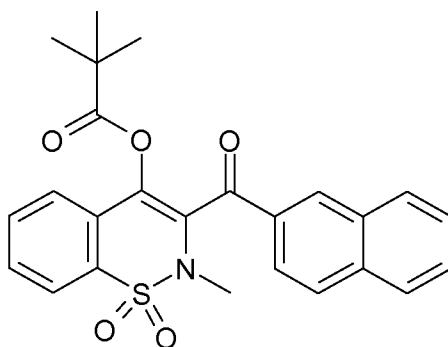
HPLC: RT = 5.99 min, 95%

¹H NMR, dmsd-d₆, δ (ppm): 0.85-1.00 (m, 6H); 1.38 (de, 2H); 1.49 (de, 2H); 2.28 (tt, 1H); 3.06 (s, 3H); 7.66 (t, 2H); 7.75 (t, 1H); 7.83 (t, 1H); 7.88 (t, 1H); 7.95-8.15 (m, 5H); 8.66 (s, 1H).

Mass spectrum (ESI+): m/z 493 (MNH₄⁺, 100%).

Example 21

***tert*Butylcarboxylic acid 2-methyl-3-(naphthalene-2-carbonyl)- 1,1-dioxo-2*H*-benzo[e][1,2]thiazin-4-yl ester**



5

The compound **1** (86 mg, 0.18 mmol) is dissolved under inert atmosphere in 0.5 mL of pyridine. The reaction medium is cooled to 0°C and then *tert*butylcarbonyl chloride (57µl, 0.46 mmol) is added. The cold bath is removed and the reaction is stirred for 18 hours at room temperature. The reaction medium is concentrated and co-evaporated three times with toluene. The thereby obtained residue is purified on a column of 12 g of spherical silica (flow rate 12 mL/min, CH₂Cl₂/heptane gradient from 20 to 100% (20 min)), in order to obtain the compound **21** as a yellow foam (47 mg; 53%).

HPLC: RT = 5.71 min, 98%

¹H NMR, dmso-d₆, δ (ppm): 0.88 (s, 9H); 3.07 (s, 3H); 7.59 (d, 1H); 7.66 (t, 1H); 7.75 (t, 1H); 7.84 (t, 1H); 7.89 (t, 1H); 8.00-8.09 (m, 4H); 8.12 (d, 1H); 8.69 (s, 1H).

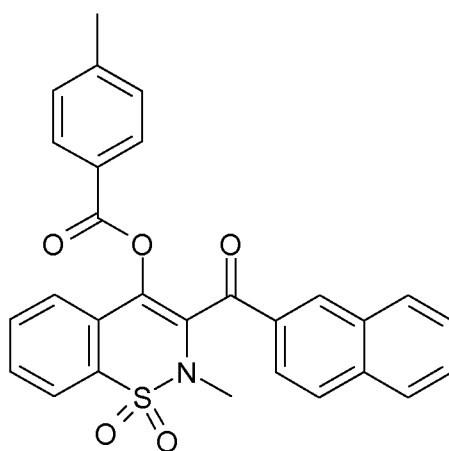
20

Mass spectrum (ESI+): m/z 467 (MNH_4^+ , 100%).

Example 22

4-Methylbenzoic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester

5



The compound **22** was synthesized according to the same procedure as for compound **21** from the compound **1** (86 mg, 0.18 mmol) and from 4-methylbenzoyl chloride (62 μ l, 0.46 mmol). The product is obtained as a yellow foam (27 mg; 31%).

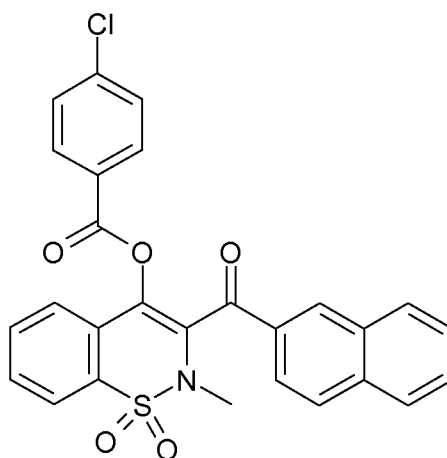
10

HPLC: RT = 5.82 min, 95%

1H NMR, $dmsO-d_6$, δ (ppm): 2.28 (s, 3H); 3.10 (s, 3H); 7.11 (d, 2H); 7.54 (d, 2H); 7.65 (t, 1H); 7.73 (te, 2H); 7.86 (dd, 2H); 7.95 (d, 1H); 7.97-8.05 (m, 4H); 8.69 (s, 1H).

15

Mass spectrum (ESI+): m/z 501 (MNH_4^+ , 100%).

Example 23**4-Chlorobenzoic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester**

5

4-chlorobenzoic acid (87 mg, 0.55 mmol) is dissolved in 2 mL of toluene under an inert atmosphere. Oxalyl chloride (100 μ l, 1.1 mmol) is added at room temperature. The reaction mixture is heated for 2 hours to 80°C, and then concentrated and co-evaporate three times with toluene. The residue is put back under an inert atmosphere and cooled to 0°C. The compound **1** (86 mg, 0.18 mmol) dissolved under an inert atmosphere in 0.5 mL of pyridine and cooled to 0°C is added. The cold bath is removed and the reaction is stirred for 2 hours at room temperature. The reaction medium is concentrated and co-evaporated three times with toluene. The thereby obtained residue is purified on a column of 12 g of spherical silica (flow rate 12 mL/min, CH₂Cl₂/heptane gradient from 20 to 100% (20 min)), in order to obtain the compound **23** as a yellow foam (51 mg; 42%).

20

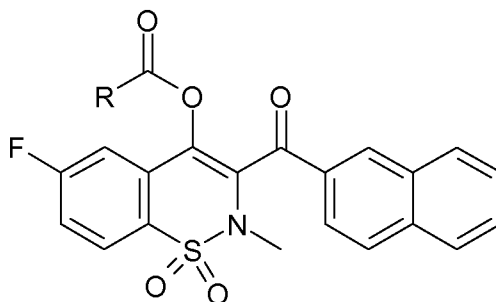
HPLC: RT = 5.92 min, 97%

^1H NMR, $\text{dms}\text{-d}_6$, δ (ppm): 3.10 (s, 3H); 7.37 (d, 2H);
 7.63-7.67 (m, 3H); 7.72 (t, 1H); 7.79 (broad s, 1H);
 7.86 (broad s, 2H); 7.94 (d, 1H); 7.95-8.07 (m, 4H);
 5 8.66 (s, 1H).

Mass spectrum (ESI+): m/z 521 (MNH_4^+ , 100%); 523 (MNH_4^+ , 37%).

Examples 24 to 27

The compounds 24 to 27 were synthesized according to
 10 the procedure described for preparing the compound 21,
 from the compound 15 and from various acid chlorides.



Ex. ★	R	Name of the compounds	HPLC	Yld.	Mass MNH_4^+
24	<i>tert</i> Butyl	<i>tert</i> Butylcarboxylic acid 6-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	5.82' 98%	61%	485
25	Cyclohexane	Cyclohexanecarboxylic acid 6-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	6.09' 90%	36%	511

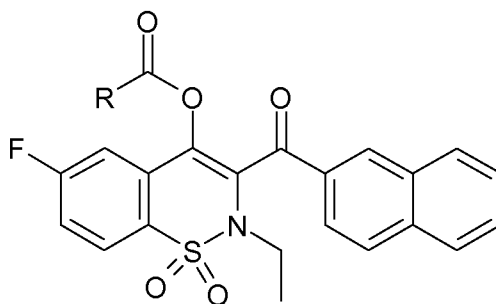
26	Phenyl	Benzoic acid 6-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	5.73' 96%	64%	505
27	4-methylphenyl	4-methylbenzoic acid 6-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	5.91' 95%	56%	519

* ^1H NMR, dms $\text{O}-d_6$, Ex. **24**: 0.87 (s, 9H); 3.08 (s, 3H); 7.32 (d, 1H); 7.63-7.80 (m, 3H); 7.95-8.15 (m, 5H); 8.69 (s, 1H).
 Ex. **25**: 0.80-1.10 (m, 5H); 1.15-1.55 (m, 5H); 2.39 (te, 1H); 3.08 (s, 3H); 7.56 (d, 1H); 7.65-7.70 (m, 2H); 7.76 (t, 1H);
 5 7.95-8.15 (m, 5H); 8.67 (s, 1H). Ex. **26**: 3.12 (s, 3H); 7.29 (t, 2H); 7.55-7.75 (m, 7H); 7.94 (d, 1H); 7.98-8.15 (m, 3H); 8.15 (dd, 1H); 8.69 (s, 1H). Ex. **27**: 2.28 (s, 3H); 3.11 (s, 3H); 7.09 (d, 2H); 7.51 (d, 2H); 7.60-7.76 (m, 4H); 7.94 (d, 1H); 7.99-8.08 (m, 3H); 8.13 (dd, 1H); 8.69 (s, 1H).

10

Examples 28 to 31

The compounds **28** to **31** were synthesized according to the procedure described for preparing compound **21**, from the compound **16** and various acid chlorides.



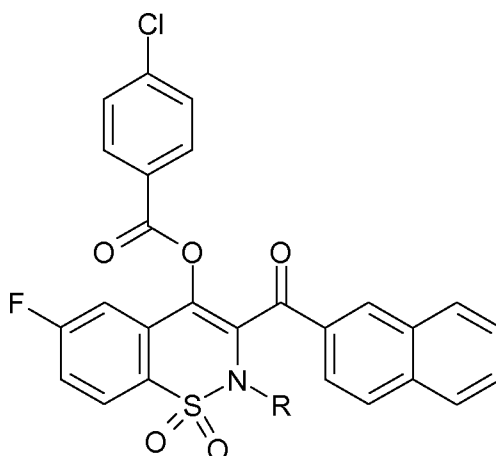
15

Ex. *	R	Name of the compounds	HPLC	Yld	Mass MNH ₄ ⁺
28	<i>tert</i> Butyl	<i>tert</i> Butylcarboxylic acid 6-fluoro-2-ethyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2 <i>H</i> -benzo[e][1,2]thiazin-4-yl ester	6.00 ' 98%	53%	499
29	Cyclohexane	Cyclohexanecarboxylic acid 6-fluoro-2-ethyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2 <i>H</i> -benzo[e][1,2]thiazin-4-yl ester	6.26 ' 95%	42%	525
30	Phenyl	Benzoic acid 6-fluoro-2-ethyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2 <i>H</i> -benzo[e][1,2] thiazin-4-yl ester	5.90 ' 99%	40%	519
31	4-methylphenyl	4-methylbenzoic acid 6-fluoro-2-ethyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2 <i>H</i> -benzo[e][1,2]thiazin-4-yl ester	6.08 ' 95%	59%	533

* ¹H NMR, dms_o-d₆, Ex. **28**: 0.92 (broad s, 12H); 3.56 (q, 2H); 7.34 (d, 1H); 7.63-7.80 (m, 3H); 8.00-8.15 (m, 5H); 8.68 (s, 1H). Ex. **29**: 0.80-1.10 (m, 8H); 1.38 (broad s, 3H); 1.53 (de, 2H); 2.45 (te, 1H); 3.55 (q, 2H); 7.56 (d, 1H); 7.65-7.70 (m, 2H); 7.76 (t, 1H); 7.95-8.15 (m, 5H); 8.67 (s, 1H). Ex. **30**: 0.95 (t, 3H); 3.58 (q, 2H); 7.35 (t, 2H); 7.55-7.75 (m, 7H); 7.96 (d, 1H); 7.98-8.10 (m, 3H); 8.14 (dd, 1H); 8.69 (s, 1H). Ex. **31**: 0.95 (t, 3H); 2.30 (s, 3H); 3.57 (q, 2H); 7.15 (d, 2H); 7.60-7.76 (m, 6H); 7.95 (d, 1H); 7.99-8.08 (m, 3H); 8.14 (dd, 1H); 8.68 (s, 1H).

Examples 32 and 33

The compounds **32** and **33** were synthesized according to the procedure described for preparing the compound **23**, from 4-chlorobenzoic acid and from the compounds **15** and **16**, respectively.

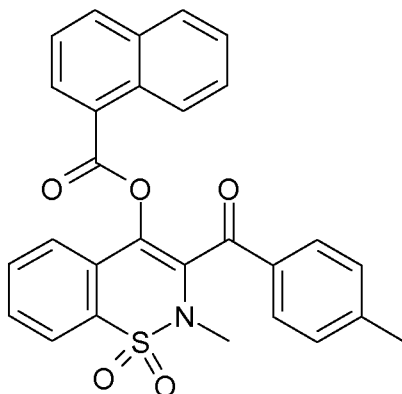


Ex. *	R	Name of the compounds	HPLC	Yld	Mass MNH ₄ ⁺
32	Methyl	4-Chlorobenzoic acid 6-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	6.00' 95%	18%	539
33	Ethyl	4-Chlorobenzoic acid 6-fluoro-2-ethyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	6.16' 95%	19%	553

* ¹H NMR, dmsO-d₆, Ex. **32**: 3.12 (s, 3H); 7.34 (d, 2H); 7.55-7.76 (m, 6H); 7.92 (d, 1H); 7.95-8.05 (m, 3H); 8.14 (dd, 1H); 8.65 (s, 1H). Ex. **33**: 0.95 (t, 3H); 3.58 (q, 2H); 7.40 (d, 2H); 7.60-7.80 (m, 6H); 7.94 (d, 1H); 7.00-8.05 (m, 3H); 8.14 (dd, 1H); 8.65 (s, 1H).

Example 34

Naphthalen-1-ylcarboxylic acid 2-methyl-3-(4-methylbenzoyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester



The compound **3** (150 mg, 0.455 mmol) is dissolved under an inert atmosphere in 3 mL of tetrahydrofurane. Sodium hydride (27 mg, 0.68 mmol) is added, followed by
5 naphthalen-2-ylcarbonyl chloride (105 μ l, 0.68 mmol) 30 minutes later. The reaction is stirred for 4 hours at room temperature. The reaction medium is neutralized with water and the aqueous phase is extracted twice with ethyl acetate. The organic phases are combined,
10 dried on magnesium sulfate, filtered and concentrated. The thereby obtain residue is purified on a column of 12 g of spherical silica (flow rate 12 mL/min, gradient of 0 to 45% EtOAc in heptane (20 min)). The product is obtained as a yellow solid (134 mg; 61%).

15 HPLC: RT = 6.59 min, 98%

^1H NMR, $\text{dms}\text{-d}_6$, δ (ppm): 2.35 (s, 3H); 3.08 (s, 3H); 7.36 (d, 2H); 7.54 (t, 1H); 7.58–7.63 (m, 2H); 7.79–7.87 (m, 3H); 7.92 (d, 2H); 8.00 (d, 1H); 8.04–8.07 (m, 2H); 8.27 (d, 1H); 8.50–8.55 (m, 1H).

20 Mass spectrum (ESI⁺): m/z 501 (MNH_4^+ , 100%).

Examples 35 to 45

The compounds **35** to **45** were synthesized according to the procedure described for preparing the compound **34**, from the compound **3** or from the compound **5** and from various acid chlorides.

In the examples **40** to **45**, the acid chlorides required for the reaction are prepared in two steps from the corresponding aromatic alcohol. The preparation of (naphthalen-2-yloxy)acetyl chloride is given as an example:

In a two-neck flash provided with a condenser and placed under an inert atmosphere, 2-naphthol (3.0 g, 20 mmol) is dissolved in 95 mL of methylethylketone (MEK) in the presence of soda (40 g, 93 mmol), and then heated to 50°C for 30 minutes. 2-bromoethanoic acid (5.76 g, 41 mmol) dissolved in 23 mL of MEK is added dropwise under hot conditions. The heating is maintained for a further 4 hours. The reaction medium is cooled to room temperature and then filtered. The solid collected by filtration is taken up in a mixture of ethyl acetate and of 1N HCl in water. Both phases are separated and the aqueous phase is extracted once with ethyl acetate. The organic phases are collected, dried on magnesium sulfate, filtered and concentrated until the first crystals appear. Heptane is added (about 20% of the remaining volume), and the formed precipitate is recovered, rinsed with heptane and dried until it has constant weight in order to obtain 3.04 g (72%) of (naphthalen-2-yloxy)acetic acid as a white solid.

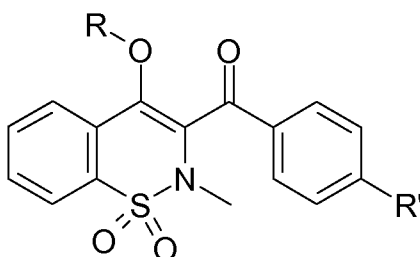
HPLC: RT = 4.10' min, 99%

^1H NMR, $\text{dmsO}-d_6$, δ (ppm): 4.80 (s, 2H); 7.20 (dd, 1H); 7.26 (d, 1H); 7.35 (td, 1H); 7.45 (td, 1H); 7.79 (d, 1H); 7.80-7.86 (m, 2H); 13.07 (broad s, 1H, exch.).

5 Mass spectrum (ESI+): m/z 203 (MH^+ , 100%).

Mass spectrum (ESI-): m/z 201 ($\text{M}-\text{H}$, 100%).

The acid formed earlier (3.04 g, 15 mmol) is partly dissolved under an inert atmosphere and at room temperature in 34 mL of dichloromethane. Oxalyl chloride (1.35 mL, 15.7 mmol) is added followed by 100 μl of DMF. Caution, a violent reaction occurs upon adding DMF. The reaction mixture is stirred for 1 hour and then concentrated, co-evaporated twice with toluene and dried until it has constant weight in order to obtain 3.4 g (100%) of (naphthalen-2-yloxy)acetyl chloride as an orangey solid. The thereby formed acid chloride was used as such in preparing the compounds **40** and **41**.



Ex .	R	R'	Name of the compounds	HPLC	Yld	Mass MNH_4^+
35	Naphthalen-2-carbonyl	CH_3	Naphthalen-2-ylcarboxylic acid 2-methyl-3-(4-methylbenzoyl)- 1,1-dioxo-	5.89' 99%	81%	501

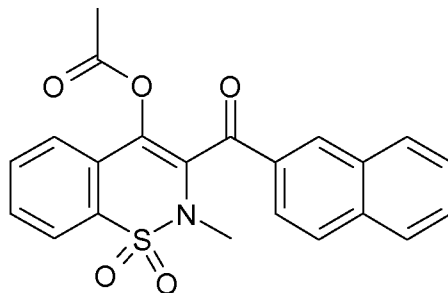
			2 <i>H</i> -benzo[e][1,2] thiazin-4-yl ester			
36	Naphthalen-1-carbonyl	CN	Naphthalen-1-ylcarboxylic acid 2-methyl-3-(4-cyanobenzoyl)- 1,1-dioxo-2 <i>H</i> -benzo[e][1,2] thiazin-4-yl ester	5.59' 98%	85%	512
37	Naphthalen-2-carbonyl	CN	Naphthalen-2-ylcarboxylic acid 2-methyl-3-(4-cyanobenzoyl)- 1,1-dioxo-2 <i>H</i> -benzo[e][1,2] thiazin-4-yl ester	5.58' 93%	30%	512
38	4-chloro benzoyl	CH ₃	4-Chlorobenzoic acid 2-methyl-3-(4-methylbenzoyl)- 1,1-dioxo-2 <i>H</i> -benzo[e][1,2]thiazin-4-yl ester	5.82' 96%	24%	485
39	4-chloro benzoyl	CN	4-Chlorobenzoic acid 2-methyl-3-(4-cyanobenzoyl)- 1,1-dioxo-2 <i>H</i> -benzo[e][1,2]thiazin-4-yl ester	5.48' 91%	19%	496
40	(Naphthalen-2-yloxy) acetyl	CH ₃	(Naphthalene-2-yloxy)acetic acid 2-methyl-3-(4-methylbenzoyl)- 1,1-dioxo-2 <i>H</i> -benzo[e][1,2] thiazin-4-yl ester	5.87' 98%	85%	531
41	(Naphthalen-2-yloxy) acetyl	CN	(Naphthalene-2-yloxy)acetic acid 2-methyl-3-(4-cyanobenzoyl)- 1,1-dioxo-2 <i>H</i> -benzo[e][1,2] thiazin-4-yl ester	5.59' 98%	21%	542
42	(Naphthalen-1-yloxy) acetyl	CH ₃	(Naphthalene-1-yloxy)acetic acid 2-methyl-3-(4-methylbenzoyl)- 1,1-dioxo-2 <i>H</i> -benzo[e][1,2] thiazin-4-yl ester	5.89' 98%	60%	531
43	(Naphthalen-1-yloxy) acetyl	CN	(Naphthalene-1-yloxy)acetic acid 2-methyl-3-(4-cyanobenzoyl)- 1,1-dioxo-2 <i>H</i> -benzo[e][1,2] thiazin-4-yl ester	5.64' 97%	29%	542
44	(4-chloro phenoxy) acetyl	CH ₃	(4-Chlorophenoxy)acetic acid 2-methyl-3-(4-methylbenzoyl)- 1,1-dioxo-2 <i>H</i> -benzo[e][1,2] thiazin-4-yl ester	5.76' 99%	64%	515
45	(4-chloro phenoxy)	CN	(4-Chlorophenoxy)acetic acid 2-methyl-3-(4-	5.50' 90%	31%	526

	acetyl		cyanobenzoyl)- 1,1-dioxo- 2H-benzo[e][1,2] thiazin- 4-yl ester			
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* ¹H NMR, dmsO-d₆, Ex. **35**: 2.34 (s, 3H); 3.07 (s, 3H); 7.35 (d, 2H); 7.65 (t, 1H); 7.72 (t, 1H); 7.75-7.92 (m, 6H); 7.95-8.06 (m, 4H); 8.39 (s, 1H). Ex. **36**: 3.07 (s, 3H); 7.58 (t, 1H); 7.61-7.68 (m, 2H); 7.89 (broad s, 3H); 7.98 (d, 2H); 8.00-8.10 (m, 5H); 8.31 (d, 1H); 8.60 (dd, 1H). Ex. **37**: 3.08 (s, 3H); 7.67 (t, 1H); 7.71-7.79 (m, 2H); 7.90 (broad s, 3H); 7.99-8.11 (m, 8H); 8.40 (s, 1H). Ex. **38**: 2.38 (s, 3H); 3.04 (s, 3H); 7.35 (d, 2H); 7.58 (d, 2H); 7.70-7.80 (m, 3H); 7.83-8.88 (m, 4H); 8.02 (broad s, 1H). Ex. **39**: 3.04 (s, 3H); 7.59 (d, 2H); 7.79 (d, 2H); 7.83-7.90 (m, 3H); 7.99-8.07 (m, 5H). Ex. **40**: 2.38 (s, 3H); 2.97 (s, 3H); 5.10 (s, 2H); 7.13 (dd, 1H); 7.20 (d, 1H); 7.36-7.41 (m, 3H); 7.48 (t, 1H); 7.67 (d, 1H); 7.80-7.99 (m, 7H); 8.00 (broad s, 1H). Ex. **41**: 2.94 (s, 3H); 5.14 (s, 2H); 7.15 (dd, 1H); 7.25 (d, 1H); 7.38 (t, 1H); 7.47 (t, 1H); 7.69 (d, 1H); 7.81-7.94 (m, 5H); 7.99-8.10 (m, 5H). Ex. **42**: 2.38 (s, 3H); 2.99 (s, 3H); 5.14 (s, 2H); 6.70 (d, 1H); 7.28 (t, 1H); 7.40 (d, 2H); 7.47-7.55 (m, 3H); 7.81-7.88 (m, 4H); 7.92 (d, 2H); 8.00 (d, 1H); 8.08 (d, 1H).). Ex. **43**: 2.96 (s, 3H); 5.20 (s, 2H); 6.82 (d, 1H); 7.34 (t, 1H); 7.49-7.56 (m, 3H); 7.88-7.56 (m, 4H); 8.00-8.02 (m, 1H); 8.05-8.11 (m, 5H). Ex. **44**: 2.42 (s, 3H); 2.97 (s, 3H); 4.98 (s, 2H); 6.81 (d, 2H); 7.23 (d, 2H); 7.42 (d, 2H); 7.81-7.92 (m, 5H); 7.99 (d, 1H). Ex. **45**: 2.95 (s, 3H); 5.01 (s, 2H); 6.90 (d, 2H); 7.28 (d, 2H); 7.85-8.15 (m, 8H).

Example 46

Acetic acid 2-methyl-3-(naphthalene-2-carbonyl)- 1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester



The compound **1** (100 mg, 0.274 mmol) is dissolved under an inert atmosphere in 2 mL of dichloromethane. Triethylamine (230 μ l, 1.64 mmol) is added at 0°C, followed by acetyl chloride (78 μ l, 1.09 mmol). The reaction medium is stirred at room temperature for 18 hours and then concentrated. The thereby obtained residue is purified on a column of 12 g of spherical silica in order to obtain the compound **46** (21 mg; 30%).

HPLC: RT = 5.34 min, 97%.

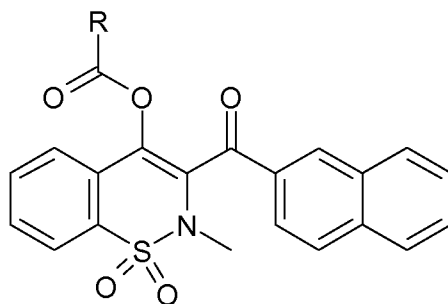
^1H NMR, $\text{dms}\text{-d}_6$, δ (ppm): 1.96 (s, 3H); 3.03 (s, 3H); 7.66 (t, 1H); 7.75 (t, 1H); 7.80-7.91 (m, 3H); 7.99-8.08 (m, 4H); 8.12 (d, 1H); 8.67 (s, 1H).

Mass spectrum (ESI+): m/z 425 (MNH_4^+ , 100%).

15

Examples 47 to 54

The compounds **47** to **54** were synthesized according to the procedure described for preparing the compound **46**, from the compound **1** and from various acid chlorides.



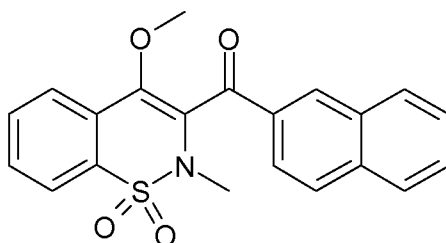
Ex .	R	Name of the compounds	HPLC	Yld.	Mass MNH ₄ ⁺
47	2,4-dichlorophenyl	2,4-Dichlorobenzoic acid 2-methyl-3-(naphthalene-2-carbonyl)- 1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	6.05' 98%	47%	555
48	4-fluorophenyl	4-Fluorobenzoic acid 2-methyl-3-(naphthalene-2-carbonyl)- 1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	5.86' 98%	69%	505
49	Cyclopentyl	Cyclopentanoic acid 2-methyl-3-(naphthalene-2-carbonyl)- 1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	5.99' 91%	48%	479
50	Furan-2-yl	2-Furanoic acid 2-methyl-3-(naphthalene-2-carbonyl)- 1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	5.33' 97%	68%	477
51	Thiophen-2-yl	Thiophen-2-carboxylic acid 2-methyl-3-(naphthalene-2-carbonyl)- 1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	5.68' 99%	61%	493
52	3-chlorophenyl	3-Chlorobenzoic acid 2-methyl-3-(naphthalene-2-carbonyl)- 1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	5.87' 98%	45%	521
53	2-chlorophenyl	2-Chlorobenzoic acid 2-methyl-3-(naphthalene-2-carbonyl)- 1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	5.74' 96%	63%	521
54	Phenoxy-methyl	Phenoxyacetic acid 2-methyl-3-(naphthalene-2-ylcarbonyl)-	5.63' 97%	71%	517

		1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester			
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* ¹H NMR, dmsO-d₆, Ex. **47**: 3.11 (s, 3H); 7.29 (d, 1H); 7.58 (d, 1H); 7.62-7.68 (m, 2H); 7.72 (t, 1H); 7.82-7.92 (m, 3H); 7.95-8.09 (m, 5H); 8.66 (s, 1H). Ex. **48**: 3.10 (s, 3H); 7.15 (t, 2H); 7.63-8.08 (m, 12H); 8.67 (s, 1H). Ex. **49**: 1.20-1.31 (m, 6H); 1.50-1.58 (m, 2H); 2.75 (quintet, 1H); 3.07 (s, 3H); 7.64-7.70 (m, 2H); 7.74 (t, 1H); 7.84 (t, 1H); 7.89 (t, 1H); 7.99-8.08 (m, 4H); 8.12 (d, 1H); 8.67 (s, 1H). Ex. **50**: 3.08 (s, 3H); 6.60 (d, 1H); 7.19 (d, 1H); 7.65 (t, 1H); 7.72-7.77 (m, 2H); 7.88 (broad s, 2H); 7.95-8.08 (m, 6H); 8.69 (s, 1H). Ex. **51**: 3.09 (s, 3H); 7.09 (dd, 1H); 7.62-8.04 (m, 12H); 8.20 (s, 1H). Ex. **52**: 3.12 (s, 3H); 7.6 (t, 1H); 7.41 (s, 1H); 7.60-7.67 (m, 3H); 7.72 (t, 1H); 7.82-8.08 (m, 8H); 8.69 (s, 1H). Ex. **53**: 3.11 (s, 3H); 7.20 (t, 1H); 7.49-7.57 (m, 3H); 7.65 (t, 1H); 7.73 (t, 1H); 7.80 (d, 1H); 7.85-7.93 (m, 2H); 7.98-8.09 (m, 5H); 8.71 (s, 1H). Ex. **51**: 3.04 (s, 3H); 4.89 (s, 2H); 6.66 (d, 2H); 6.86 (t, 1H); 7.09 (t, 2H); 7.65 (t, 1H); 7.76 (t, 1H); 7.83-7.92 (m, 3H); 8.03-8.09 (m, 4H); 8.14 (d, 1H); 8.71 (s, 1H).

Example 55

20 **(4-Methoxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl)methanone**



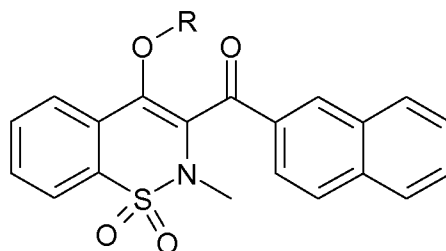
The compound 1 (159 mg, 0.435 mmol) is dissolved under an inert atmosphere in 2 mL of DMF. Sodium hydride (26 mg, 0.65 mmol) is added, followed by methane iodide (30 μ l, 0.48 mmol) 30 minutes later. The reaction is stirred for 2 hours at room temperature, and then for 26 hours at 60°C. At this stage, the reaction is still incomplete. Cesium carbonate (213 mg, 0.65 mmol) and methane iodide (150 μ l, 2.1 mmol) are added. The reaction medium is stirred for 24 hours at room temperature and then neutralized with water, and the aqueous phase is extracted twice with ethyl acetate. The organic phases are combined, dried on magnesium sulfate, filtered and concentrated. The thereby obtained residue is purified on a column of 12 g of spherical silica (flow rate 12 mL/min, gradient of 20 to 60% dichloromethane in heptane), in order to obtain the compound 55 as a yellow foam (70 mg; 38%).

HPLC: RT = 5.27 min, 90%

Mass spectrum (ESI+): m/z 380 (MH^+ , 100%).

20

Examples 56 to 58



The compounds 56 to 58 were prepared according to the following procedure:

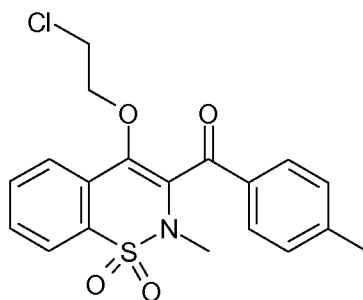
The compound **1** (150 mg, 0.42 mmol) is dissolved under an inert atmosphere in 0.3 mL of DMF. Cesium carbonate (201 mg, 0.61 mmol) and the require alkyl iodide (4 mmol) are added. The reaction medium is stirred for 18 hours at room temperature, for 4 hours at 50°C and then neutralized with water, and the aqueous phase is extracted twice with ethyl acetate. The organic phases are combined, dried on magnesium sulfate, filtered and concentrated. The thereby obtained residues are purified on columns of 12 g of spherical silica (flow rate 12 mL/min, gradient of 20 to 60% dichloromethane in heptane), in order to obtain the desired products.

Ex .	R	Name of the compounds	HPLC	Yld.	Mass MH ⁺
56	Ethyl	(4-ethoxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2] thiazin-3-yl) (naphthalen-2-yl)methanone	5.43 ' 99%	66%	394
57	<i>n</i> -Propyl	(4-propyloxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2] thiazin-3-yl) (naphthalen-2-yl)methanone	5.61 ' 99%	65%	408
58	<i>n</i> -Butyl	(4-butyloxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2] thiazin-3-yl) (naphthalen-2-yl)methanone	5.81 ' 97%	24%	422

* ¹H NMR, dmso-d₆, Ex. **56**: 0.87 (t, 3H); 2.98 (s, 3H); 3.74 (q, 2H); 7.64 (t, 1H); 7.72 (t, 1H); 7.80-7.93 (m, 3H); 7.95-8.15 (m, 5H); 8.67 (s, 1H). Ex. **57**: 0.49 (t, 3H); 1.28 (sextet, 2H); 2.97 (s, 3H); 3.63 (t, 2H); 7.64 (t, 1H); 7.72 (t, 1H); 7.80-7.93 (m, 3H); 7.95-8.15 (m, 5H); 8.68 (s, 1H). Ex. **58**: 0.50 (t, 3H); 0.89 (sextet, 2H); 1.23 (quintet, 2H); 2.97 (s, 3H); 3.66 (t, 2H); 7.64 (t, 1H); 7.72 (t, 1H); 7.80-7.93 (m, 3H); 7.95-8.15 (m, 5H); 8.67 (s, 1H).

Example 59

(4-(2-Chloroethoxy)-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (p-tolyl)methanone



The compound **3** (100 mg, 0.3 mmol) is dissolved in 3 mL of THF, under an inert atmosphere and in the presence of 2-chloroethanol (100 μ l, 1.5 mmol). The reaction mixture is cooled to 0°C, and then triphenylphosphine (318 mg, 1.2 mmol) and diethyldiazene-1,2-dicarboxylate (DEAD, 211 mg, 1.2 mmol) are successively added dropwise. Stirring is continued for 20 hours at room temperature, and then the reaction is neutralized with an aqueous solution saturated with ammonium chloride. This aqueous phase is extracted twice with ethyl acetate. The organic phases are combined, dried on magnesium sulfate, filtered and concentrated. The thereby obtained residue is purified on a column of 35 g of silica (flow rate 20 mL/min, gradient of 0 to 100% ethyl acetate in heptane), in order to obtain the compound **59** (70 mg; 58%).

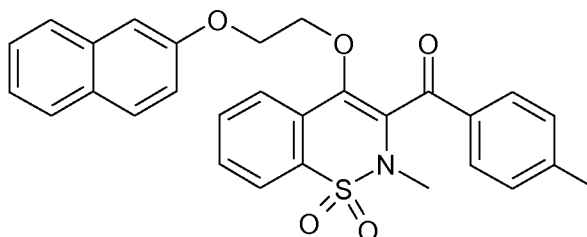
HPLC: RT = 5.28 min, 99%

¹H NMR, dmso-d₆, δ (ppm): 2.41 (s, 3H); 2.91 (s, 3H); 3.57 (t, 2H); 3.92 (t, 2H); 7.40 (d, 2H); 7.75–7.98 (m, 6H).

Mass spectrum (ESI+): m/z 392 (MH⁺, 100%); 394 (MH⁺, 42%).

Example 60

(4-[2-(Naphthalen-2-yloxy)ethoxy]-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (p-tolyl)methanone



5 The compound **59** (70 mg, 0.17 mmol) is dissolved in 2 mL of DMF, under an inert atmosphere and in the presence of potassium carbonate (64 mg, 0.53 mmol), potassium iodide (31 mg, 0.19 mmol) and 2-naphthol (38 mg, 0.27 mmol). The reaction medium is heated to 65°C, for 22
10 hours, and then neutralized with water and extracted twice with ethyl acetate. The organic phases are combined, dried on magnesium sulfate, filtered and concentrated. The thereby obtained residue is purified by semi-preparative HPLC on a Waters Sunfire column
15 (19x100 mm, 5µm), with a flow of 20 mL/min and a 15 minute gradient of 10 to 100% acetonitrile in water (0.1% TFA buffer), in order to obtain the compound **60** (30 mg; 29%).

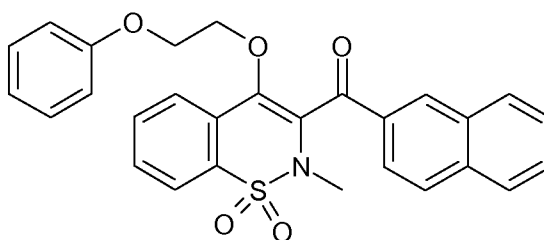
HPLC: RT = 5.95 min, 99%

20 ¹H NMR, dms_o-d₆, δ (ppm) 2.26 (s, 3H); 2.90 (s, 3H); 4.03 (d, 2H); 4.10 (d, 2H); 6.92 (dd, 1H); 7.06 (d, 1H); 7.24 (d, 2H); 7.33 (t, 1H); 7.44 (t, 1H); 7.70-7.90 (m, 7H); 7.94-7.98 (m, 2H).

Mass spectrum (ESI+): m/z 500 (MH^+ , 100%).

Example 61

(4-(2-Phenoxy-ethoxy)-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl)methanone



5

The compound **1** (100 mg, 0.274 mmol) is dissolved in 0.5 mL of DMF in presence of potassium carbonate (90 mg, 0.55 mmol) and 2-phenoxyethyl bromide (110 mg, 0.55 mmol). The reaction medium is heated in a sealed tube, to 80°C for 16 hours. The medium is taken up in ethyl acetate and then washed with water and with a saturated NaCl solution. The organic phases are combined, dried on sodium sulfate, filtered and concentrated. The thereby obtained residue is purified on a column of 12 g of silica (flow rate 20 mL/min, gradient of 0 to 10% dichloromethane in heptane), in order to obtain the compound **61** as a yellow syrup (45 mg; 34%).

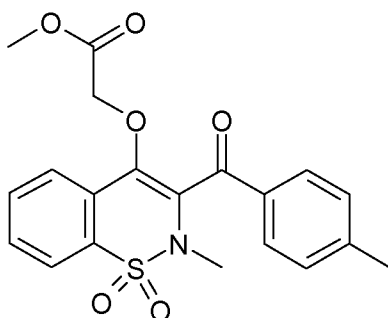
HPLC: RT = 5.88 min, 98%

20 1H NMR, $dms\text{-}d_6$, δ (ppm) 2.97 (s, 3H); 3.85-3.87 (m, 2H); 4.01-4.05 (m, 2H); 6.59 (d, 2H); 6.82 (t, 1H); 7.11 (t, 2H); 7.62 (t, 1H); 7.71 (t, 1H); 7.83 (t, 1H); 7.88 (t, 1H); 7.91-8.04 (m, 6H); 8.62 (s, 1H).

Mass spectrum (ESI+): m/z 486 (MH^+ , 100%).

Example 62

Methyl 2-(2-methyl-3-(4-methylbenzoyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy) acetate



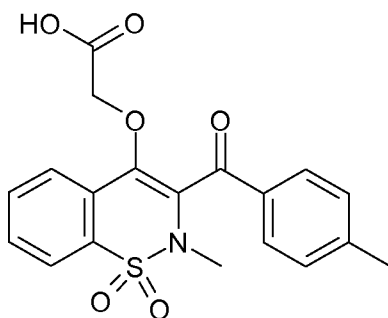
5

The compound **62** was synthesized according to the same procedure as the compound **59** from the compound **3** (300 mg, 0.91 mmol) and from methyl glycolate (350 μ l, 4.5 mmol) in order to obtain 300 mg (79%) of the
10 desired product as a yellow syrup.

HPLC: RT = 4.97 min, 97%

1H NMR, $dmso-d_6$, δ (ppm): 2.42 (s, 3H); 2.88 (s, 3H); 3.47 (s, 3H); 4.42 (s, 2H); 7.40 (d, 2H,); 7.75-7.98 (m, 6H).

15 Mass spectrum (ESI+): m/z 402 (MH^+ , 100%); 419 (MNH_4^+ , 42%).

Example 63**(2-Methyl-3-(4-methylbenzoyl)- 1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy)acetic acid**

- 5 The compound **62** (75 mg, 0.18 mmol) is dissolved in 1 mL of THF, and lithium hydroxide (1M/H₂O, 0.37 mmol) is added. The reaction medium is stirred at room temperature for 2 hours, and then diluted in water and extracted twice with dichloromethane. The organic
- 10 phases are combined, dried on magnesium sulfate, filtered and concentrated in order to obtain 22 mg of the desired product (HPLC: RT = 4.55 min, 97%). The yield of this operation is 30%.

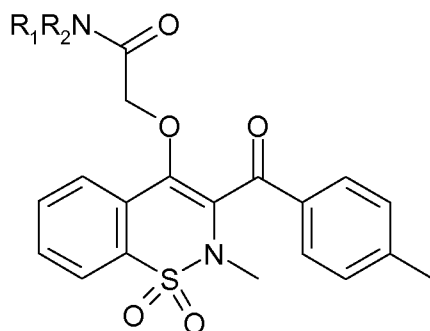
¹H NMR, dmso-d₆, δ (ppm) 2.41 (s, 3H); 2.88 (s, 3H); 4.28 (s, 2H); 7.39 (d, 2H); 7.81 (t, 1H); 7.85-7.95 (m, 5H); 12.96 (se, 1H, exch.).

15

Mass spectrum (ESI+): m/z 388 (MH⁺, 100%); 405 (MNH₄⁺, 54%)

Examples 64 to 66

The compound **63** (110 mg, 0.28 mmol) is dissolved in 3 mL of DMF. Different amines (0.23 mmol), DIEA (82 μ l, 0.472 mmol), HOOBT (35 mg, 0.26 mmol) EDCI (50 mg, 0.26 mmol) are added. The reaction medium is stirred for 18 hours at room temperature. The medium is taken up in dichloromethane and then washed with 1N soda, water, and a saturated NaCl solution. The organic phases are combined, dried on magnesium sulfate, filtered and concentrated. The thereby obtained residues are purified on columns of 12 g of spherical silica (flow rate 12 mL/min, 0 to 50% AcOEt in heptane), in order to obtain the desired products.



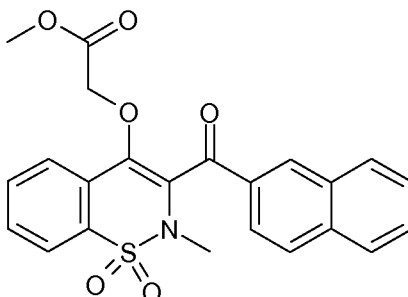
Ex.	R1R2N	Name of the compounds	HPLC	Yld	Mass MNH ₄ ⁺
64	Naphthalen-1-yl	2-(2-methyl-3-(4-methylbenzoyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy)-N-(naphthalen-1-yl)acetamide	5.45 ' 95%	40%	530
65	Adamantan-1-yl	2-(2-methyl-3-(4-methylbenzoyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy)-N-(adamantan-1-yl)acetamide	5.90 ' 99%	72%	538
66	Adamantan-2-yl	2-(2-methyl-3-(4-methylbenzoyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy)-N-(adamantan-2-yl)acetamide	5.83 ' 99%	85%	538

* ^1H NMR, dmsO-d_6 , Ex. **64**: 2.33 (s, 3H); 2.93 (s, 3H); 4.55 (s, 2H); 7.35 (d, 2H); 7.43-7.55 (m, 4H); 7.76 (d, 1H); 7.82-7.85 (m, 2H); 7.91-7.99 (m, 5H); 8.12 (d, 1H); 7.76 (s, 1H, exch). **65**: 1.51-1.59 (m, 6H); 1.71 (s, 6H); 1.94 (s, 3H); 2.41 (s, 3H); 2.88 (s, 3H); 4.05 (s, 2H); 6.78 (s, 1H); 7.42 (d, 2H); 7.81 (t, 1H); 7.87-7.95 (m, 4H); 7.99 (d, 1H). **66**: 1.39-1.41 (m, 2H); 1.64-1.77 (m, 12H); 2.41 (s, 3H); 2.88 (s, 3H); 3.65-3.75 (m, 1H); 4.21 (s, 2H); 7.39 (d, 3H); 7.81 (t, 1H); 7.87-7.95 (m, 4H); 8.0 (d, 1H).

10

Example 67

Methyl 2-(2-methyl-3-(4-methylbenzoyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy) acetate



The compound **1** (1.0 g, 2.74 mmol) is dissolved in 2 mL of DMF in the presence of potassium carbonate (682 mg, 4.1 mmol) and methyl bromoacetate (1.26 mL, 13.68 mmol). The reaction medium is stirred at room temperature for 5 hours and then the same amount of methyl bromoacetate is added again. After one night at room temperature, the mixture is taken up in ethyl acetate and then washed with water and with a saturated NaCl solution. The organic phases are combined, dried on sodium sulfate, filtered and concentrated. The thereby obtained residue is purified on a column of

90 g of silica (flow rate 32 mL/min, gradient of 40 to 100% dichloromethane in heptane), in order to obtain the compound **67** as a yellow syrup (486 mg; 41%).

HPLC: RT = 5.23 min, 86%

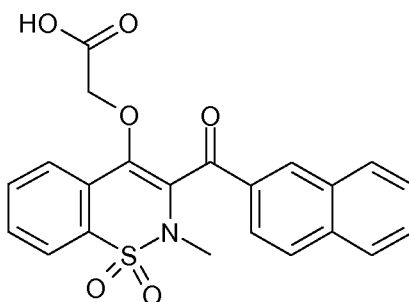
5 ^1H NMR, $\text{dms}\text{-}d_6$, δ (ppm) 2.95 (s, 3H); 3.39 (s, 3H); 4.45 (s, 2H); 7.64 (t, 1H); 7.72 (t, 1H); 7.81-7.89 (m, 1H); 7.93 (d, 2H); 7.97 (d, 1H); 7.99-8.11 (m, 4H); 8.66 (s, 1H).

Mass spectrum (ESI+): m/z 438 (MH^+ , 100%).

10

Example 68

2-(2-methyl-3-(4-methylbenzoyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy)acetic acid



The compound **67** (480 mg, 1.1 mmol) is dissolved in
15 THF/water 5:1 mixture (6 mL) and then treated with LiOH
(103 mg, 4.39 mmol) at room temperature for 15 minutes.
The medium is taken up in ethyl acetate and then washed
with 1N HCl, water and with a saturated NaCl solution.
The organic phases are combined, dried on sodium
20 sulfate, filtered and concentrated. The thereby

obtained residue is purified on a column of 30 g of silica (dichloromethane/methanol/acetic acid 95/4.5/0 eluent), in order to obtain the compound **68** as a yellow foam (321 mg; 69%).

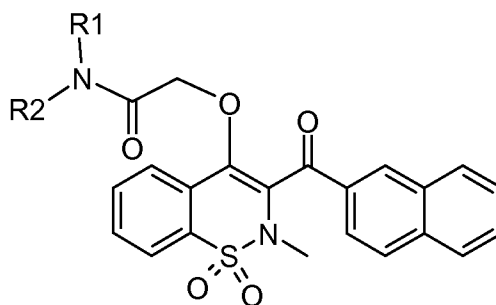
5 HPLC: RT = 4.86 min, 99%

^1H NMR, $\text{dms}\text{-d}_6$, δ (ppm) 2.93 (s, 3H); 4.29 (s, 2H); 7.64 (t, 1H); 7.72 (t, 1H); 7.83 (t, 1H); 7.89-8.09 (m, 7H); 8.66 (s, 1H).

Mass spectrum (ESI+): m/z 424 (MH^+ , 100%).

10

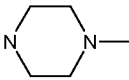
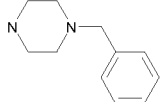
Examples 69 to 71



The compounds **69** to **71** were prepared according to the following procedure:

15 The compound **1** (100 mg, 0.23 mmol) is dissolved in 1.5 mL of dichloromethane. Different amines (0.23 mmol), DIEA (82 μl , 0.472 mmol), HOBT (35 mg, 0.26 mmol) and EDCI (50 mg, 0.26 mmol) are added. The reaction mixture is stirred for 24 hours at room temperature and then amine in excess is added (0.07 mmol) and the medium is
20 stirred for a further 5 hours. The medium is taken up

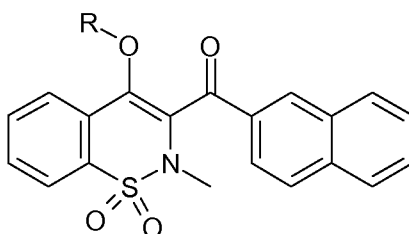
in dichloromethane and washed with 1N soda, water and with a saturated NaCl solution. The organic phases are combined, dried on sodium sulfate, filtered and concentrated. The thereby obtained residues are
 5 purified on columns of 12 g of spherical silica (flow rate 12 mL/min, 1% of a methanol/ammonia 9:1 mixture in dichloromethane), in order to obtain the desired products.

Ex .	NR ₁ R ₂	Name of the compounds	HPLC	Yld	Mass MH ⁺
69		2-[2-Methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy]-1-piperidin-1-yl-ethanone	5.26' 98%	49%	491
70		2-[2-Methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy]-1-(4-methyl-piperazin-1-yl)-ethanone	3.93' 98%	47%	506
71		1-(4-Benzyl-piperazin-1-yl)-2-[2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy]-ethanone	4.28' 98%	20%	582

* ¹H NMR, dmso-d₆, Ex. **69**: 1.08-1.31 (m, 6H); 2.87 (t, 2H);
 10 2.95 (s, 3H); 3.04 (t, 2H); 4.41 (s, 2H); 7.64 (t, 1H); 7.72 (t, 1H); 7.84 (m, 1H); 7.92 (d, 2H); 7.97-8.10 (m, 5H); 8.65 (s, 1H). Ex. **70**: 1.85 (t, 2H); 1.92 (t, 2H); 1.95 (s, 3H); 2.94 (broad s, 5H); 3.04 (broad s, 2H); 4.44 (s, 2H); 7.64 (t, 1H); 7.72 (t, 1H); 7.84 (m, 1H); 7.92 (m, 2H); 7.97-8.10 (m, 5H); 8.65 (s, 1H). Ex. **71**: 1.88 (broad s, 2H); 1.96 (broad s, 2H); 2.92 (m, 5H); 3.08 (broad s, 2H); 3.22 (s, 2H); 4.42 (s, 2H); 7.16 (d, 2H); 7.21-7.31 (m, 3H); 7.63 (t, 1H); 7.72 (t, 1H); 7.82 (m, 1H); 7.78 (m, 2H); 7.97-8.09 (m, 5H); 8.65 (s, 1H).

Examples 72 to 74

The compounds **72** to **74** were synthesized according to the procedure described for preparing the compound **46**, from the compound **1** and from various acid chlorides.



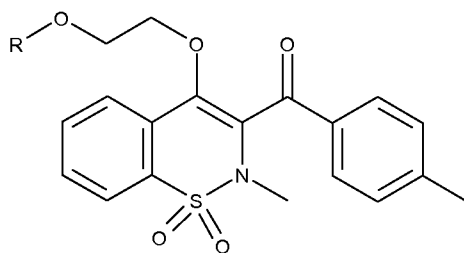
5

Ex .	R	Name of the compounds	HPLC	Yld .	Mass MNH ₄ ⁺
72	4-chlorophenyl- loxy - acetyl	(4-Chloro-phenoxy)-acetic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	6.02' 94%	77%	551
73	Naphthalen-1-yloxy- acetyl	(Naphthalen-1-yloxy)-acetic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	6.16' 98%	84%	567
74	Naphthalen-2-yloxy- acetyl	(Naphthalen-2-yloxy)-acetic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	6.11' 96%	83%	567

* ¹H NMR, dmsO-d₆, Ex. **72**: 3.04 (s, 3H); 4.94 (s, 2H); 6.67 (d, 2H); 7.07 (d, 2H); 7.64 (t, 1H); 7.72 (t, 1H); 7.84-7.93 (m, 3H); 8.02 (m, 3H); 8.08 (d, 1H); 8.14 (d, 1H); 8.69 (s, 1H). Ex. **73**: 3.05 (s, 3H); 5.10 (s, 2H); 6.59 (d, 1H); 7.12 (t, 1H); 7.38-7.41 (m, 2H); 7.49 (t, 1H); 7.66 (t, 1H); 7.75 (t, 1H); 7.81-7.90 (m, 4H); 7.98 (d, 1H); 8.02-8.08 (m, 4H); 8.13 (d, 1H); 8.72 (s, 1H). Ex. **74**: 3.02 (s, 3H); 5.07 (s, 2H); 7.01 (dd, 1H); 7.12 (d, 1H); 7.32-7.41 (m, 2H); 7.57 (d, 1H); 7.63 (t, 1H); 7.70-7.79 (m, 3H); 7.85-7.94 (m, 3H); 8.02-8.12 (m, 5H); 8.71 (s, 1H).

Examples 75 and 76

The compounds **75** and **76** were synthesized according to the procedure described for preparing the compound **60**, from the compound **59** and various alcohols.



5

Ex .	R	Name of the compounds	HPLC	Yld.	Mass MH ⁺
75	Naphthalen-1-yl	(4-[2-(naphthalen-1-yloxy)ethoxy]-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (p-tolyl)methanone	6.00' 97%	38%	500
76	4-Chlorophenyl	(4-[2-(4-chlorophenyl)ethoxy]-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (p-tolyl)methanone	5.87' 98%	48%	484

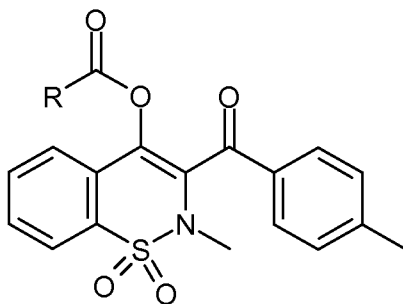
* ¹H NMR, dmsO-d₆, Ex. **75**: 2.31 (s, 3H); 2.90 (s, 3H); 4.10-4.20 (m, 4H); 6.75 (d, 1H); 7.21 (d, 2H); 7.33 (t, 1H); 7.40-7.44 (m, 2H); 7.51 (t, 1H); 7.78-7.85 (m, 6H); 7.97 (t, 2H). Ex. **76**: 2.37 (s, 3H); 2.89 (s, 3H); 3.85-3.95 (m, 2H); 4.00-4.05 (m, 2H); 6.69 (d, 2H); 7.23 (d, 2H); 7.29 (d, 2H); 7.78-7.96 (m, 6H).

10

Examples 77 and 78

The compounds **77** and **78** were synthesized according to the procedure described for preparing the compound **34**, from the compound **3** and from acetyl chloride and propanoyl chloride respectively.

15

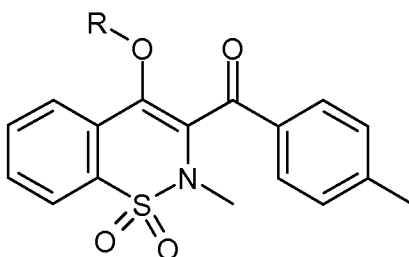


Ex .	R	Name of the compounds	HPLC	Yld .	Mass MNH ₄ ⁺
77	Me-thyl	Acetic acid 2-methyl-3-(4-methylbenzoyl)- 1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	5.05' 99%	81%	389
78	Ethyl	Propanoic acid 2-methyl-3-(4-methylbenzoyl)- 1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	5.25' 99%	88%	403

* ¹H NMR, dmsO-d₆, Ex. **77**: 2.04 (s, 3H); 2.42 (s, 3H); 2.98 (s, 3H); 7.42 (d, 2H); 7.76-7.90 (m, 5H); 7.98 (d, 1H). Ex. **78**: 0.86 (t, 3H); 2.33 (q, 2H); 2.42 (s, 3H); 2.99 (s, 3H); 7.41 (d, 2H); 7.73 (d, 1H); 7.79-7.89 (m, 4H); 7.98 (d, 1H).

Examples 79 and 80

The compounds **79** et **80** were synthesized according to the procedure described for preparing the compound **59**, from the compound **3** and from methanol and ethanol respectively.

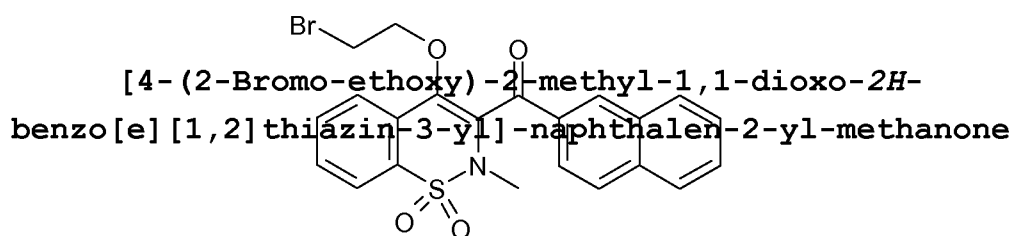


Ex .	R	Name of the compounds	HPLC	Yld .	Mass MH ⁺
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79	Methyl	(4-methyloxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (p-tolyl)methanone	5.13' 98%	58%	344
80	Ethyl	(4-ethyloxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2] thiazin-3-yl) (p-tolyl)methanone	5.29' 99%	63%	358

* ^1H NMR, $\text{dmsO}-d_6$, Ex. **79**: 2.42 (s, 3H); 2.91 (s, 3H); 3.50 (s, 3H); 7.41 (d, 2H); 7.78-7.95 (m, 6H). Ex. **80**: 0.93 (t, 3H); 2.41 (s, 3H); 2.90 (s, 3H); 3.73 (q, 2H); 7.40 (d, 2H); 7.78-7.94 (m, 6H).

5

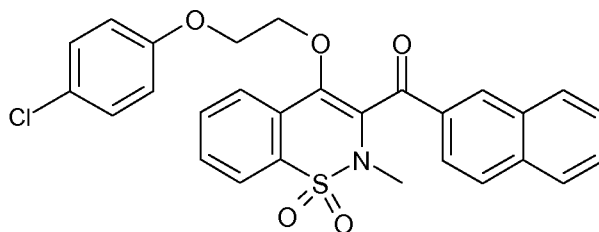
Example 81

The compound **1** (150 mg, 0.41 mmol) is dissolved in methylethylketone (3 mL) and then treated with dibromoethane (71 μl , 0.82 mmol) in the presence of K_2CO_3 (170 mg, 1.02 mmol). The reaction is heated with microwave energy in a sealed tube at 130 °C for 4h 30min. The medium is taken up in ethyl acetate and then washed with water and with a saturated NaCl solution. The organic phases are combined, dried on sodium sulfate, filtered and concentrated. The thereby obtained residue (brown syrup, 197 mg) is directly engaged into the next reaction.

20

Example 82

{4-[2-(4-Chloro-phenoxy)-ethoxy]-2-methyl-1,1-dioxo-2H-benzo[e][1,2] thiazin-3-yl}-naphthalen-2-yl-methanone



The compound **81** (197 mg, 0.41 mmol) is dissolved in methylethylketone (1.5 mL) and then treated with 4-chlorophenol (107 μ l, 0.82 mmol) in the presence of
5 K_2CO_3 (173 mg, 1.04 mmol). The reaction is heated with microwave energy in a sealed tube at 130°C for 2 hours. The medium is taken up in ethyl acetate and then washed with water and with a saturated NaCl solution. The organic phases are combined, dried on sodium sulfate,
10 filtered and concentrated. The thereby obtained residue is purified on a column of 12 g of silica (flow rate 12 mL/min, gradient of 10 to 100% dichloromethane in heptane), in order to obtain the compound **82** as a yellow syrup (21 mg; 14%).

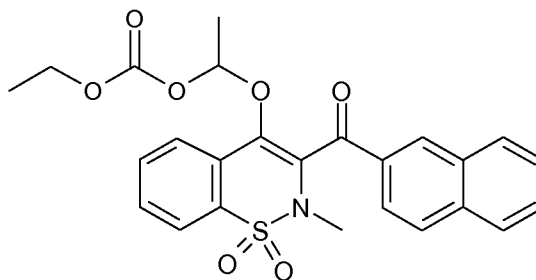
15 HPLC: RT = 6.10 min, 89%

1H NMR, $dmsO-d_6$, δ (ppm) 2.96 (s, 3H); 3.85 (m, 2H); 3.97 (m, 2H); 6.57 (d, 2H); 7.08 (d, 2H); 7.61 (t, 1H); 7.70 (t, 1H); 7.83 (t, 1H); 7.89-8.02 (m, 7H); 8.60 (s, 1H).

20 Mass spectrum (ESI+): m/z 520 (MH^+ , 66%).

Example 83

Carbonic acid ethyl ester 1-[2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy]-ethyl ester



5 The compound **1** (100 mg, 0.27 mmol) is dissolved in DMF (1 mL) and then treated with ethyl 2-chloropropanoate (110 μ L, 0.82 mmol) in the presence of K_2CO_3 (91 mg, 0.55 mmol). The reaction is heated in a sealed to 60°C overnight and then the same amount of ethyl 2-chloropropanoate is added and the reaction is stirred for a further 24 hours. The medium is taken up into ethyl acetate and then washed with water and with a saturated NaCl solution. The organic phases are combined, dried on sodium sulfate, filtered and concentrated. The thereby obtained residue is purified on a column of 12 g of silica (flow rate 12 mL/min, gradient of 25 to 80% dichloromethane in heptane), in order to obtain the compound **83** as a yellow syrup (100 mg; 76%).

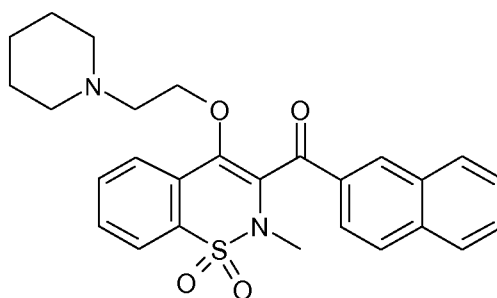
20 HPLC: RT = 5.55 min, 97%

1H NMR, $dmsO-d_6$, δ (ppm) 0.94 (t, 3H); 1.25 (d, 3H); 2.94 (s, 3H); 3.80-3.93 (m, 2H); 5.99 (q, 1H); 7.65 (t, 1H); 7.73 (t, 1H); 7.85 (m, 1H); 7.90 (d, 2H); 7.97 (d, 1H); 8.01-8.11 (m, 4H); 8.69 (s, 1H).

25 Mass spectrum (ESI+): m/z 504 (MNa^+ , 100%).

Example 84

[2-Methyl-1,1-dioxo-4-(2-piperidin-1-yl-ethoxy)-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl]-naphthalen-2-yl-methanone



5

The compound **1** (100 mg, 0.27 mmol) is dissolved in methylethylketone (0.5 mL) and then treated with 1-(2-chloroethyl)piperidine (252 mg, 1.37 mmol) in the presence of K₂CO₃ (159 mg, 0.96 mmol). The reaction is
10 heated to 80°C overnight. The medium is further taken up with ethyl acetate and then washed with water and with a saturated NaCl solution. The organic phases are combined, dried on sodium sulfate, filtered and concentrated. The thereby obtained residue is purified
15 on a 12 g silica column (flow rate 12 mL/min, dichloromethane/MeOH/NH₄OH 99/09/01), in order to obtain the compound **84** as a yellow syrup (50 mg; 43%).

HPLC: RT = 4.17 min, 92%

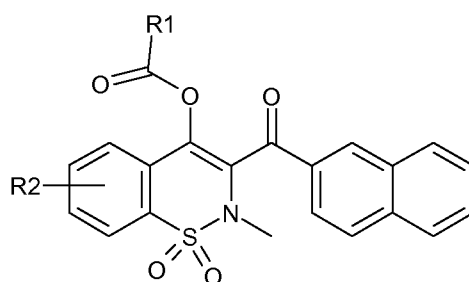
¹H NMR, dmso-d₆, δ (ppm): 1.21 (broad s, 6H); 1.99
20 (broad s, 4H); 2.19 (t, 2H); 2.98 (s, 3H); 3.72 (t, 2H); 7.64 (t, 1H); 7.72 (t, 1H); 7.83 (t, 1H); 7.90 (t, 1H); 7.97 (d, 1H); 8.01-8.11 (m, 5H); 8.66 (s, 1H).

Mass spectrum (ESI+): m/z 477 (MH⁺, 100%).

Examples 85 to 96

The compounds **85** to **96** were synthesized according to the following procedure:

- 5 The compounds **13**, **15**, or **17** (100 mg) are dissolved under an inert atmosphere in 2 mL of dichloromethane in the presence of triethylamine (6 eq.) and then treated with various acid chlorides (4 eq.) at 0°C. The reaction mixtures are stirred for 2 hours at 0°C and
- 10 then at room temperature for 20 hours. The media are taken up in ethyl acetate and then washed with water and with a saturated NaCl solution. The organic phases are combined, dried on sodium sulfate, filtered and concentrated. The thereby obtained residues are
- 15 purified on a column of 12 g of silica (flow rate 12 mL/min, gradient of 0 to 20% ethyl acetate in heptane), in order to obtain the expected compounds.

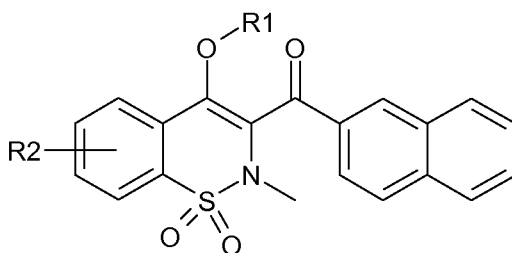


Ex	R1	R2	Name of the compounds	HPLC	Yld	Mass MH ⁺ /M Na ⁺
85	4-chlorophenyl	5-Cl	4-Chloro-benzoic acid 5-chloro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	6.43' 96%	29%	555
86	Cyclohexyl		Cyclohexanecarboxylic acid 5-	6.50'	26%	527

		5-Cl	chloro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	98%		
87	Phenyl	5-Cl	Benzoic acid 5-chloro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	6.11' 92%	65%	521
88	4-chlorophenyl	6-F	4-Chloro-benzoic acid 6-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	6.30' 99%	40%	539
89	Cyclohexyl	6-F	Cyclohexanecarboxylic acid 6-fluoro -2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	6.30' 97%	55%	511
90	Phenyl	6-F	Benzoic acid 6-fluoro -2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	5.90' 94%	50%	505
91	4-chlorophenyl	7-F	4-Chloro-benzoic acid 7-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	6.20' 98%	60%	539
92	Cyclohexyl	7-F	Cyclohexanecarboxylic acid 7-fluoro -2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	6.37' 98%	19%	511
93	Phenyl	7-F	Benzoic acid 7-fluoro -2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	5.91' 93%	69%	505
94	Methyl	7-F	Acetic acid 7-fluoro -2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	5.46' 97%	62%	448
95	Phenoxymethyl	7-F	Phenoxy-acetic acid 7-fluoro -2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	5.89' 92%	50%	540
96	4-Cl-phenoxymethyl	7-F	(4-Chloro-phenoxy)-acetic acid 7-fluoro -2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	6.10' 93%	18%	574

Examples 97 to 104

The compounds **97** to **104** were synthesized according to the procedure used for preparing examples **56** to **58** from the compound **13**, **15**, or **17** and from corresponding alkyl iodides or sulfates.



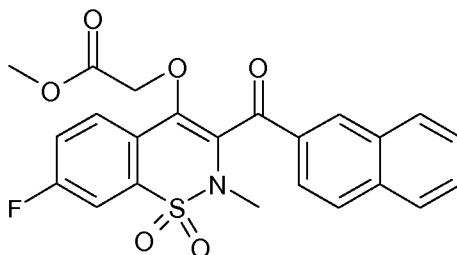
Ex.	R1	R2	Name of the compounds	HPLC	Yld .	Mass MH ⁺ /MNH ₄ ⁺
97	Ethyl	5-Cl	(5-Chloro-4-ethoxy-2-methyl-1,1-di oxo-2 <i>H</i> -benzo[e][1,2]thiazin -3-yl)-naphthalen-2-yl- methanone	5.61' 97%	11%	428
98	Propyl	5-Cl	(5-Chloro-4-propoxy-2- methyl-1,1-di oxo-2 <i>H</i> -benzo[e][1,2]thiazin -3-yl)-naphthalen-2-yl- methanone	6.02' 96%	44%	442
99	Methyl	6-F	(6-Fluoro-4-methoxy-2- methyl-1,1-di oxo-2 <i>H</i> -benzo[e][1,2]thiazin -3-yl)-naphthalen-2-yl- methanone	5.65' 93%	34%	398
100	Ethyl	6-F	(6-Fluoro-4-ethoxy-2-methyl- 1,1-di oxo-2 <i>H</i> -benzo[e][1,2]thiazin -3-yl)-naphthalen-2-yl- methanone	5.72' 97%	52%	429
101	Propyl	6-F	(6-Fluoro-4-propoxy-2- methyl-1,1-di oxo-2 <i>H</i> -benzo[e][1,2]thiazin -3-yl)-naphthalen-2-yl- methanone	5.92' 97%	56%	426
102	Methyl	7-F	(7-Fluoro-4-methoxy-2- methyl-1,1-di oxo-2 <i>H</i> -benzo[e][1,2]thiazin	5.56' 97%	20%	398

			-3-yl)-naphthalen-2-yl-methanone			
103	Ethyl	7-F	(7-Fluoro-4-ethoxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl)-naphthalen-2-yl-methanone	5.77' 95%	47%	412
104	Propyl	7-F	(7-Fluoro-4-propoxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl)-naphthalen-2-yl-methanone	5.90' 98%	52%	426

Example 105

[7-Fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy]-acetic acid methyl ester

5



The compound **105** was synthesized according to the procedure used for preparing example **67** from the compound **17** (1 g, 2.61 mmol). The product is obtained as a yellow syrup (810 mg; 68%).

10

HPLC: RT = 5.37 min, 95%

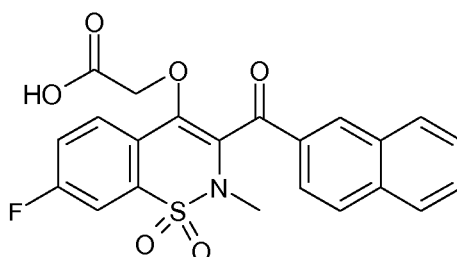
¹H NMR, dmso-d₆, δ (ppm): 2.95 (s, 3H); 3.40 (s, 3H); 4.45 (s, 2H); 7.64 (t, 1H); 7.70 (t, 1H); 7.80 (dt, 1H); 7.91 (dd, 1H); 7.99-8.10 (m, 5H); 8.65 (s, 1H).

15

Mass spectrum (ESI+): m/z 456 (MH⁺, 100%).

Example 106

[7-Fluoro-2-methyl-3- (naphthalene-2-carbonyl) -1,1-dioxo-2H-benzo[e] [1,2]thiazin-4-yloxy]-acetic acid
methyl ester



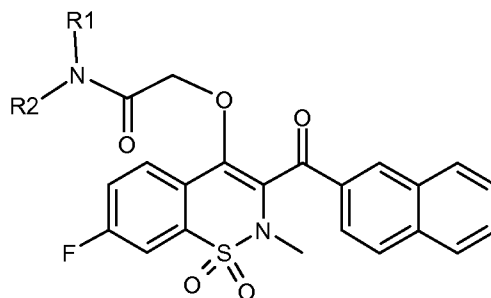
The compound **106** was synthesized according to the procedure used for preparing example **68** from the compound **105** (598 mg, 1.31 mmol). The product is obtained as a beige powder (262 mg; 45%).

HPLC: RT = 4.92 min, 97%

Mass spectrum (ESI+): m/z 442 (MH⁺, 100%).

Examples 107 to 109

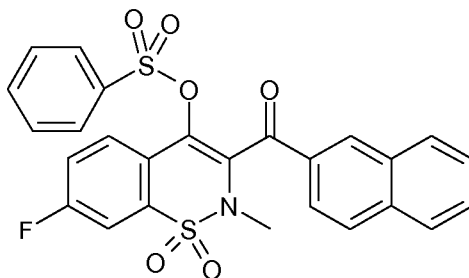
The compounds **107** to **109** were synthesized according to the procedure used for preparing examples **69** to **71** from the compound **106** and the corresponding amines.



Ex.	NR ₁ R ₂	Name of the compounds	HPLC	Yld.	Mass MH ⁺
107		2-[7-Fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy]-1-piperidin-1-yl-ethanone	5.40', 91%	64%	509
108		2-[7-Fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy]-1-(4-methyl-piperazin-1-yl)-ethanone	3.99', 99%	67%	524
109		1-(4-Benzyl-piperazin-1-yl)-2-[7-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy]-ethanone	4.35', 98%	69%	600

- * ¹H NMR, dmsO-d₆, Ex. **107**: 1.09-1.14 (m, 4H); 1.31 (m, 2H); 2.87 (t, 2H); 2.95 (s, 3H); 3.05 (t, 2H); 4.41 (s, 2H); 7.64 (t, 1H); 7.72 (t, 1H); 7.79 (dt, 1H); 7.89 (dd, 1H); 7.99-8.10 (m, 5H); 8.64 (s, 1H). Ex. **108**: 1.86 (t, 2H); 1.92 (t, 2H); 1.96 (s, 3H); 2.92-2.95 (m, 5H); 3.05 (t, 2H); 4.44 (s, 2H); 7.64 (t, 1H); 7.72 (t, 1H); 7.79 (dt, 1H); 7.90 (dd, 1H); 7.98-8.10 (m, 5H); 8.64 (s, 1H). Ex. **109**: 1.90 (broad s, 2H); 1.97 (broad s, 2H); 2.92 (broad s, 2H); 2.95 (s, 3H); 3.09 (broad s, 2H); 3.22 (s, 2H); 4.43 (s, 2H); 7.16 (d, 2H); 7.21-7.31 (m, 3H); 7.64 (t, 1H); 7.72 (t, 1H); 7.80 (dt, 1H); 7.90 (dd, 1H); 7.98-8.09 (m, 5H); 8.64 (s, 1H).

Benzenesulfonic acid 7-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester



- 5 The compound **17** (200 mg, 0.52 mmol) is dissolved in dichloromethane (2 mL) and then treated at 0°C with benzene sulfonyl chloride (67 µl, 0.52 mmol) in the presence of Et₃N (145 µl, 1.04 mmol). The reaction is stirred from 0°C to room temperature for 4 hours and
- 10 then the medium is taken up in dichloromethane and washed with water and with a saturated NaCl solution. The organic phases are combined, dried on magnesium sulfate, filtered and concentrated. The thereby obtained residue is purified on a column of 12 g of
- 15 silica (flow rate 12 mL/min, gradient of 20 to 50% dichloromethane in heptane), in order to obtain the compound **110** as a cream-colored powder (177 mg; 65%).

HPLC: RT = 5.72 min, 94%

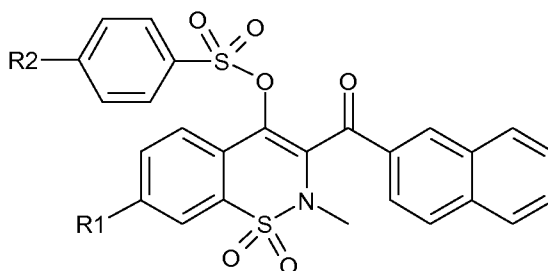
¹H NMR, dmso-d₆, δ (ppm): 2.98 (s, 3H); 7.40 (t, 2H);

20 7.54-7.61 (m, 4H); 7.66 (t, 1H); 7.75 (m, 2H); 7.84-7.90 (m, 2H); 8.04-8.09 (m, 3H); 8.57 (s, 1H).

Mass spectrum (ESI+): m/z 541 (MNH₄⁺, 100%).

Examples 111 to 117

The compounds **111** to **117** were synthesized according to the procedure used for preparing example **110** from the compound **1** or **17** and the corresponding sulfonyl chlorides.

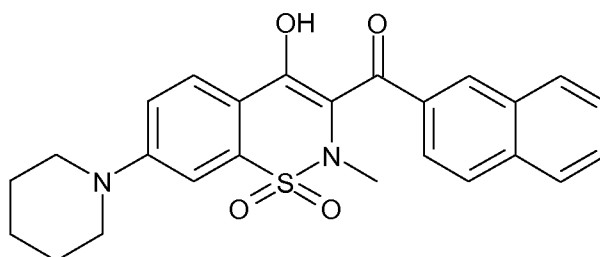


Ex.	R1	R2	Name of the compounds	HPLC	Yld .	Mass MH ⁺ /MNa ⁺
111	H	H	Benzenesulfonic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	5.59' 99%	71%	506
112	H	Cl	4-Chloro-benzenesulfonic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	5.84' 99%	94%	540
113	H	Me	4-Methyl-benzenesulfonic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	5.74' 99%	93%	520
114	H	CN	4-Cyano-benzenesulfonic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	5.50' 99%	89%	531
115	F	Cl	4-Chloro-benzenesulfonic acid 7-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester	5.96' 96%	55%	558 580

116	F	Me	4-Methyl-benzenesulfonic acid 7-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2 <i>H</i> -benzo[e][1,2]thiazin-4-yl ester	5.88' 97%	59%	538 560
117	F	CN	4-Cyano-benzenesulfonic acid 7-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2 <i>H</i> -benzo[e][1,2]thiazin-4-yl ester	5.59' 97%	56%	549 571

Example 118

(4-Hydroxy-2-methyl-7-piperidin-1-yl-1,1-dioxo-2*H* - benzo[e][1,2]thiazin-3-yl) -naphthalen-2-yl-methanone



5

The compound **17** (200 mg, 0.52 mmol) is dissolved in DMSO (2 mL) in the presence of K₂CO₃ (144 mg, 1.04 mmol) and then treated at room temperature with piperidine (154 µl, 1.56 mmol). The reaction is stirred at 100°C for 20 hours and then the medium is taken up in ethyl acetate and washed with water and with a saturated NaCl solution. The organic phases are combined, dried on magnesium sulfate, filtered and concentrated. The thereby obtained residue is purified on a column of 12 g of silica (flow rate 12 mL/min, gradient of 0 to 50% ethyl acetate in heptane) in order to obtain the compound **118** as a yellow powder (22 mg; 9.5%).

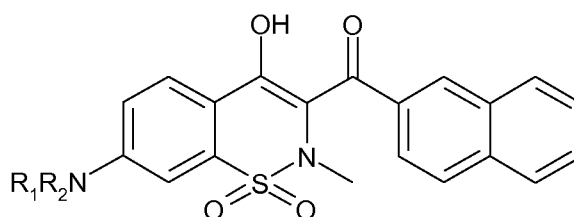
HPLC: RT = 6.39 min, 96%

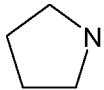
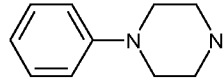
^1H NMR, $\text{dms}\text{-d}_6$, δ (ppm): 1.64 (broad s, 6H); 2.63 (s, 3H); 3.57 (broad s, 4H); 7.22 (d, 1H); 7.34 (dd, 1H); 7.65-7.70 (m, 2H); 7.96 (d, 1H); 8.03 (d, 1H); 8.09-8.11 (m, 3H); 8.62 (s, 1H).

Mass spectrum (ESI+): m/z 449 (MH^+ , 100%).

Examples 119 to 121

The compounds **119** to **121** were synthesized according to the procedure used for preparing example **118** from the compound **17** and the corresponding amines.

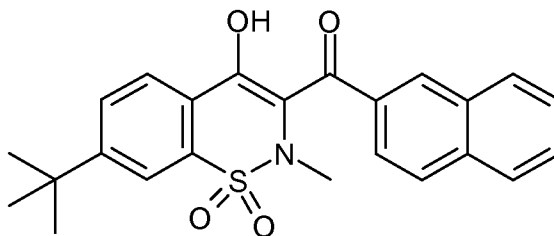


Ex.	NR_1R_2	Name of the compounds	HPLC	Yld.	Mass $\text{MH}^+/\text{M}-\text{H}^-$
119	NMe_2	(7-Dimethylamino-4-hydroxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl)-naphthalen-2-yl-methanone	5.86', 100%	35%	409
120		(4-Hydroxy-2-methyl-7-pyrrolidin-1-yl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl)-naphthalen-2-yl-methanone	6.18', 100%	13%	435
121		[4-Hydroxy-2-methyl-7-(4-phenyl-piperazin-1-yl)-1,1-dioxo-2H-	6.18', 94%	93%	524

		benzo[e][1,2]thiazin-3-yl]-naphthalen-2-yl-methanone			
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Example 122

(7-*tert*Butyl-4-hydroxy-2-methyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl)methanone



5

The compound **122** was synthesized from 2-methyl-5-*tert*butylbenzenesulfonyl chloride according to the same sequence of steps involved in preparing the compound **17**. The compound is obtained as a yellow solid with an overall yield of 10%.

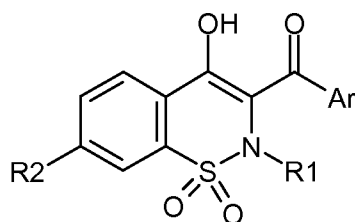
10

HPLC: RT = 6.33 min, 95%

¹H NMR, dmso-d₆, δ (ppm): 1.38 (s, 9H); 2.65 (s, 3H); 7.66 (t, 1H); 7.72 (t, 1H); 7.88 (s, 1H); 8.05 (d, 2H); 8.12-8.17 (m, 4H); 8.65 (s, 1H); 15.69 (s, 1H, exch).

15 Mass spectrum (ESI⁺): m/z 422 (MH⁺, 100%).

Examples 123 to 130



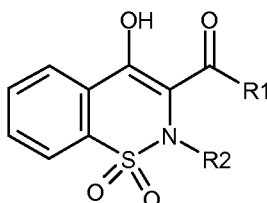
The compounds **123** to **130** were synthesized from saccharine and from corresponding 2-bromo-1-arylethanones according to the same sequence of steps 5 described for preparing the compound **1** (for **123**, **125**, **127** and **128**) from the compound **8** (for **124** and **126**) and from the compound **17** (for **129** and **130**)

Ex.	R1	R2	Ar	Name of the compounds	HPLC	Yld. ¹	Mass MH ⁺ /M- H
123	Me	H	3,4-dichlorophenyl	(4-hydroxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (3,4-dichlorophenyl)methanone	5.88' 99%	60%	382 & 384
124	Et	H	3,4-dichlorophenyl	(4-hydroxy-2-ethyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (3,4-dichlorophenyl)methanone	6.07' 99%	64%	396 & 398
125	Me	H	benzofuran-2-yl	(4-hydroxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (benzofuran-2-yl)methanone	5.31' 99%	68%	356
126	Et	H	benzofuran-2-yl	(4-hydroxy-2-ethyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (benzofuran-2-yl)methanone	5.54' 99%	63%	370
127	Me	H	5,6,7,8-tetrahydronaphthalen-2-yl	(4-Hydroxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) - (5,6,7,8-tetrahydronaphthalen-2-yl) - methanone	6.04' 100%	60%	370

128	Me	H	5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl	(4-Hydroxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl)-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-methanone	6.66' 100%	70%	426
129	Me	F	5,6,7,8-tetrahydro-naphthalen-2-yl	(7-Fluoro-4-hydroxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl)-(5,6,7,8-tetrahydro-naphthalen-2-yl)-methanone	6.14' 95%	68%	386
130	Me	F	5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl	(7-Fluoro-4-hydroxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl)-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-methanone	6.75' 93%	80%	442

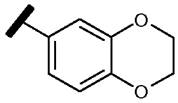
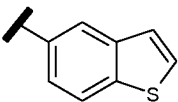
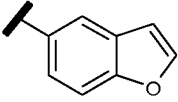
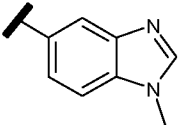
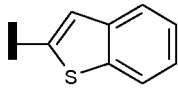
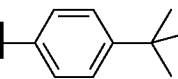
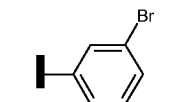
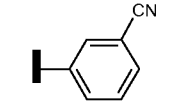
¹ Overall yield for the 3 steps.

* ¹H NMR, dms_o-d₆, Ex. **123**: 2.68 (s, 3H); 7.95 (d, 1H); 7.98-8.00 (m, 4H); 8.16 (d, 1H); 8.19-8.21 (m, 1H); 14.93 (s, 1H, exch). Ex. **124**: 0.55 (t, 3H); 3.16 (q, 2H); 7.92 (d, 1H); 7.97-7.98 (m, 4H); 8.16 (d, 1H); 8.19-8.20 (m, 1H); 14.77 (s, 1H, exch). Ex. **125**: 2.98 (s, 3H); 7.43 (t, 1H); 7.62 (dt, 1H); 7.80 (d, 1H); 7.99-8.04 (m, 4H); 8.20 (se, 1H); 8.34 (s, 1H); 15.56 (se, exch., 1H). Ex. **126**: 0.67 (t, 3H); 3.57 (q, 2H); 7.43 (t, 1H); 7.63 (dt, 1H); 7.80 (d, 1H); 7.96-8.18 (m, 4H); 8.20 (se, 1H); 8.31 (s, 1H); 15.33 (se, exch., 1H). Ex. **127**: 1.78 (s, 4H); 2.64 (s, 3H); 2.81 (s, 4H); 7.30 (d, 1H); 7.45 (s, 1H); 7.86 (d, 1H); 7.98 (m, 3H); 8.18-8.21 (m, 1H); 15.75 (s, 1H). Ex. **128**: 1.30 (d, 12H); 1.70 (s, 4H); 2.64 (s, 3H); 7.58 (d, 1H); 7.78 (d, 1H); 7.98 (m, 3H); 8.18-8.21 (m, 1H); 8.25 (d, 1H); 15.62 (s, 1H). Ex. **129**: 1.77 (broad s, 4H); 2.67 (s, 3H); 2.80 (broad s, 4H); 7.23 (broad s, 1H); 7.60-7.85 (m, 4H); 8.21 (m, 1H); 15.85 (s, 1H). Ex. **130**: 1.28 (d, 12H); 1.69 (s, 4H); 2.65 (s, 3H); 7.51 (d, 1H); 7.66 (d, 1H); 7.88 (m, 2H); 8.08 (broad s, 1H); 8.21 (q, 1H); 15.65 (s, 1H).

Examples 131 to 143

The compounds **131** to **143** were synthesized from saccharine and from the
 5 corresponding 2-bromo-1-arylethanones according to the same sequence of steps
 described for preparing the compound **1** (R2 = Me) or the compound **8** (R2 = Et).

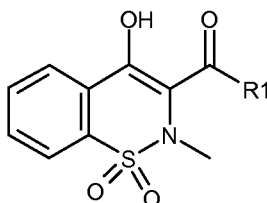
Ex. *	R1	R2	Name of the compounds	HPLC	Yld. ¹	MH ⁺
131		Me	(2,3-Dihydro-benzofuran-5-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	5.59' 98%	24%	358
132		Et	(2,3-Dihydro-benzofuran-5-yl)-(4-hydroxy-2-ethyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	5.75' 98%	23%	372
133		Me	Benzo[1,3]dioxol-5-yl-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	5.50' 99%	34%	360
134		Et	Benzo[1,3]dioxol-5-yl-(4-hydroxy-2-ethyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	5.66' 97%	34%	374
135		Me	(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	5.53' 96%	45%	374

136		Et	(2,3-Dihydro-benzo[1,4]dioxin-6-yl) - (4-hydroxy-2-ethyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	5.68', 99%	42%	388
137		Me	Benzo[b]thiophen-5-yl- (4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	5.56', 99%	31%	372
138		Me	Benzofuran-5-yl- (4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	5.34', 99%	36%	356
139		Me	(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl) - (1-methyl-1H-benzimidazol-5-yl) - methanone	3.72', 99%	5%	370
140		Me	Benzo[b]thiophen-2-yl- (4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	5.89', 99%	48%	372
141		Me	(4-tert-Butyl-phenyl) - (4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	6.97', 99%**	32%	372
142		Me	(3-Bromo-phenyl) - (4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	6.47', 99%**	57%	394/396
143		Me	3- (4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazine -3-carbonyl)-benzonitrile	5.84', 93%**	37%	358

¹ Overall yield for the 3 steps.

* ^1H NMR, $\text{dms}\text{-d}_6$, Ex. **131**: 2.68 (s, 3H); 3.33 (m, 2H); 4.69 (t, 2H); 7.02 (d, 1H); 7.97-7.98 (m, 3H); 8.03 (s, 1H); 8.08 (dd, 1H), 8.18-8.20 (m, 1H); 16.03 (s, 1H, exch). Ex. **132**: 0.55 (t, 3H); 3.18 (q, 2H); 3.28-3.34 (m, 2H); 4.69 (t, 2H);
5 7.00 (d, 1H); 7.94-7.98 (m, 4H); 8.03 (d, 1H); 8.17-8.19 (m, 1H); 15.77 (s, 1H, exch). Ex. **133**: 2.69 (s, 3H); 6.21 (s, 2H); 7.19 (d, 1H); 7.56 (d, 1H); 7.82 (dd, 1H); 7.96-7.99 (m, 3H); 8.18-8.20 (m, 1H); 15.66 (s, 1H, exch). Ex. **134**: 0.56 (t, 3H); 3.18 (q, 2H); 6.20 (s, 2H); 7.18 (d, 1H); 7.53
10 (d, 1H); 7.77 (dd, 1H); 7.94-7.96 (m, 3H); 8.17-8.19 (m, 1H); 15.39 (s, 1H, exch). Ex. **135**: 0.55 (t, 3H); 3.18 (q, 2H); 4.33 (t, 2H); 4.37 (t, 2H); 7.09 (d, 1H); 7.64 (d, 1H); 7.67 (dd, 1H); 7.94-7.96 (m, 3H); 8.17-8.19 (m, 1H); 15.55 (s, 1H, exch). Ex. **136**: 0.55 (t, 3H); 3.18 (q, 2H); 4.33 (t, 2H); 4.37 (t, 2H); 7.09 (d, 1H); 7.64 (d, 1H); 7.67 (dd, 1H); 7.94-7.96 (m, 3H); 8.17-8.19 (m, 1H); 15.55 (s, 1H, exch). Ex. **137**: 2.65 (s, 3H); 7.69 (d, 1H); 7.96 (d, 1H); 7.98-8.00 (m, 3H); 8.07 (d, 1H); 8.21-8.23 (m, 1H); 8.28 (d, 1H); 8.60 (s, 1H); 15.69 (s, 1H, exch). Ex. **138**: 2.64 (s, 3H); 7.22 (d, 1H); 7.86 (d, 1H); 7.98-8.00 (m, 3H); 8.09 (dd, 1H); 8.19 (d, 1H); 8.21-8.45 (m, 1H); 8.45 (s, 1H); 15.71 (s, 1H, exch). Ex. **139**: 2.63 (s, 3H); 3.92 (s, 3H); 7.81 (d, 1H); 7.98-8.05 (m, 4H); 8.20-8.23 (m, 1H); 8.52 (s, 1H); 8.52 (s, 1H); 15.87 (s, 1H, exch). Ex. **140**: 2.97 (s, 3H); 7.53 (t, 1H); 7.61 (t, 1H); 8.00-8.02 (m, 3H); 8.17-8.22 (m, 3H); 8.67 (s, 1H); 15.70 (s, 1H, exch). Ex. **141**: 1.34 (s, 9H), 2.66 (s, 3H); 7.66 (d, 2H); 7.98-8.00 (m, 3H); 8.06 (d, 2H); 8.18-8.21 (m, 1H); 15.71 (s, 1H, exch). Ex. **142**: 2.65 (s, 3H); 7.60 (t, 1H); 7.90 (d, 1H); 7.95-8.05 (m, 4H); 8.11 (s, 1H); 8.19 (broad s, 1H); 15.06 (s, 1H, exch). Ex. **143**: 2.65 (s, 3H); 7.84 (t, 1H); 7.95-8.00 (m, 3H); 8.15-8.21 (m, 2H); 8.28-8.31 (m, 2H); 14.86 (broad s, 1H, exch).

** XBridge column

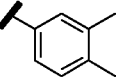
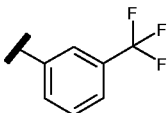
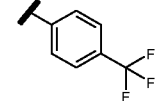
Examples 144 to 146

The compounds **144** to **146** were synthesized from saccharine and from the corresponding 2-bromo-1-arylethanones according to the same sequence of steps described for the preparation of the compound **1**.

The 2-bromo-1-arylethanones were prepared by bromination of the corresponding arylethanones, according to the procedure described for preparing the compound **144A**: 1-(3,4-dimethylphenyl)ethanone (2.5 g, 16.9 mmol) is dissolved under a nitrogen atmosphere in 42 mL of THF at room temperature. Trifluoroacetic acid (1.5 mL, 16.9 mmol) is added followed by pyridinium tribromide (6.5 g, 20.2 mmol). The solution turns vermilion red and a white precipitate gradually appears. After three hours of stirring at room temperature, the reaction is neutralized by adding 50 mL of water, and then extracted with 100 mL of ethyl acetate. The organic phase is washed with 40 mL of a saturated CuSO₄ solution, 40 mL of a saturated NaCl solution, and then dried on magnesium sulfate, filtered and concentrated under reduced pressure. The residue is purified on a column of 130 of silica with a gradient of 0% to 5% ethyl acetate in heptane in order to obtain two batches of 2-bromo-1-(3,4-dimethyl-phenyl)-ethanone (**144A**, 57%).

Batch 1: 1.25 g; HPLC: RT = 4.90 min, 90%.

Batch 2: 1.90 g; HPLC: RT = 4.90 min, 70%.

Ex. *	R1	Name of the compounds	HPLC	Yld. ¹	MH+
144		(3,4-Dimethyl-phenyl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	5.62' 99%	27%	344
145		(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-(3-trifluoromethyl-phenyl)-methanone	6.56' 99%**	23%	384
146		(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-(4-trifluoromethyl-phenyl)-methanone	6.64' 99%**	17%	384

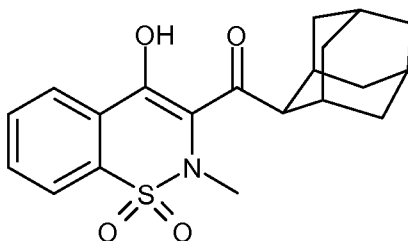
¹ Overall yield for the 4 steps.

* ¹H NMR, dms_o-d₆, Ex. **144**: 2.33 (s, 3H); 2.34 (s, 3H); 2.63 (s, 3H); 7.40 (d, 1H); 7.82 (s, 1H); 7.90 (d, 1H); 7.98-8.00 (m, 3H); 8.18-8.21 (m, 1H); 15.73 (s, 1H, exch). Ex. **145**: 2.65 (s, 3H); 7.89 (t, 1H); 8.00-8.01 (m, 3H); 8.08 (d, 1H); 8.20-8.22 (m, 1H); 8.30 (broad s, 2H), 15.00 (broad s, 1H, exch). Ex. **146**: 2.64 (s, 3H); 8.00-8.03 (m, 5H); 8.17-8.21 (m, 3H); 15.06 (broad s, 1H, exch).

10 ** XBridge column.

Example 147

Adamantan-2-yl-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone



Example 147A - Adamantan-2-carbonitrile.

Adamantanone (2.5 g, 16.6 mmol) is dissolved under an
5 nitrogen atmosphere under 58 mL of 1,2-dimethoxyethane
(DME) in the presence of ethanol (1.7 mL) and of TosMIC
(4.22 g, 21.6 mmol). The reaction medium is cooled with
an ice bath. Potassium *tert*-butylate (5.72 g, 51 mmol)
10 is slowly added, while maintaining the temperature of
the reaction medium between 2°C and 11°C. The reaction
is stirred for 30 minutes between 5°C and 12°C before
being brought back to room temperature and stirring is
continued for 2 hours. The reaction medium is filtered
and the white precipitate is rinsed with DME. The
15 filtrate is concentrated. The thereby obtained residue
is purified on silica (5% ethyl acetate in heptane), in
order to obtain the compound **147A** as a white solid
(2.38 g, 88%).

¹H NMR, dms_o-d₆, δ (ppm): 1.65-1.95 (m, 12 H); 2.07
20 (broad s, 2H); 3.14 (broad s, 1H).

Mass spectrum (ESI⁺): m/z 162 (MH⁺, 20%); 194
(MH⁺.MeOH, 100%).

Example 147B - 1-Adamantan-2-yl-ethanone.

The compound **147A** (4.63 g, 28.7 mmol) is dissolved under a nitrogen atmosphere in 61 mL of ether, and then cooled with an ice bath. Methyllithium (27 mL, 1.6 M / Et₂O, 43 mmol) is added dropwise while maintaining the
5 reaction medium between 5°C and 12°C. As soon as the addition is finished, the cold bath is removed and stirring is continues for 30 minutes at room temperature. The reaction medium is then neutralized with 46 ml of water. The organic phase is recovered,
10 dried on magnesium sulfate, dried and concentrated under reduced pressure. The residue is taken up in 28 mL of acetone and 28 mL of 6N HCl, and then refluxed for heating for 80 minutes. The acetone is then evaporated and the residual aqueous phase is extracted
15 twice with ethyl acetate. The organic phases are combined, dried on magnesium sulfate, filtered and concentrated. The thereby obtained residue is purified on a column of 90 g of silica (32 mL / min, 6% ethyl acetate in heptane), in order to obtain the compound
20 **147B** as a yellow solid (3.66 g, 71%).

¹H NMR, dmso-d₆, δ (ppm): 1.45-1.55 (m, 2H); 1.65-1.90 (m, 10H); 2.09 (s, 3H); 2.29 (broad s, 2H); 2.54 (broad s, 1H).

Mass spectrum (ESI+): m/z 179 (MH⁺, 100%).

25 **Example 147C** - 1-Adamantan-2-yl-2-bromo-ethanone.

The compound **147B** (500 mg, 2.8 mmol) is dissolved in 8.6 mL of methanol under a nitrogen atmosphere, and then cooled to 0°C. Bromine (151 µl, 2.94 mmol) is slowly added. The reaction medium is stirred for 1h
30 40min at 0°C and then neutralized with water and

extracted twice with ethyl acetate. The organic phases are combined, dried on magnesium sulfate, filtered and concentrated. The thereby obtained residue is purified on a column of 35 g of silica (20 mL / min, gradient of 0% to 15% ethyl acetate in heptane in 25 minutes), in order to obtain the compound **147C** (1.37 g, 85%).

^1H NMR, dmsO-d_6 , (ppm): 1.5-1.6 (m, 2H); 1.65-1.90 (m, 10H); 2.38 (broad s, 2H); 2.86 (broad s, 1H); 4.45 (s, 2H).

Example 147 - Adamantan-2-yl-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e] [1,2]thiazin-3-yl)-methanone.

The compound **147** was synthesized from saccharin and from the compound **147C** according to the same sequence of steps described for preparing the compound **1** with a yield of 11% for the three steps.

White solid

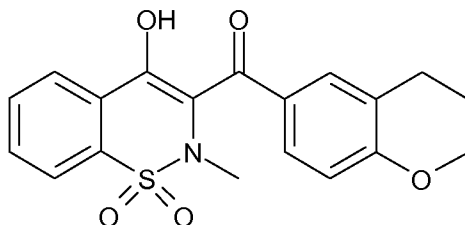
HPLC: RT = 6.28 min, 97%

^1H NMR, dmsO-d_6 , δ (ppm): 1.54-1.61 (m, 2H); 1.68-1.93 (m, 8H); 2.05-2.25 (m, 2H); 2.36 (broad s, 2H); 2.89 (s, 3H); 3.27 (s, 1H); 7.93-7.96 (m, 3H); 8.08-8.11 (m, 1H); 15.22 (s, 1H, exch).

Mass spectrum (ESI-): m/z 372 (M-H^- , 100%).

Example 148

Chroman-6-yl-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone



Example 148A - Chromane

- 5 4-chromanone (5.0 g, 33.7 mmol) is dissolved in 102 mL of THF under a nitrogen atmosphere. $\text{BF}_3 \cdot \text{OEt}_2$ (12.8 mL, 101 mmol) is added at room temperature and sodium cyanoborohydride (4.33 g, 67.4 mmol) is added slowly (violent reaction). The thereby obtained white
- 10 suspension is heated to 65°C of 18 hours, and then neutralized with water. The reaction mixture is extracted twice with ethyl acetate. The organic phases are combined, successively washed with a saturated NaHCO_3 solution and a saturated NaCl solution, and then
- 15 dried on magnesium sulfate, filtered and concentrated under reduced pressure. The thereby obtained residue is purified on silica (gradient of 0% to 50% dichloromethane in heptane, and then 10% ethyl acetate in heptane), in order to obtain the partly purified
- 20 compound **148A** (3.34 g, 61%).

HPLC: RT = 4.56 min, 83%

^1H NMR, $\text{dms}\text{-d}_6$, δ (ppm): 1.91 (q, 2H); 2.72 (t, 2H); 4.11 (t, 2H); 6.70 (d, 1H); 6.80 (t, 1H); 7.0-7.05 (m, 2H).

Example 148B - 1-Chroman-6-yl-ethanone

Chromane (4.64 g, 29.4 mmol) is dissolved in 30 mL of anhydrous dichloromethane (DCM) under a nitrogen atmosphere. The reaction medium is cooled to -30°C, and
5 then a cold solution (-10°C) of ethanoyl chloride (4.75 mL, 67 mmol) in 20 mL of anhydrous DCM is added within 5 minutes. The mixture is stirred for 45 min at -15°C, and then poured over a mixture of 100 g of ice and 50 mL of concentrated HCl and extracted three times with
10 DCM. The organic phases are combined, dried on magnesium sulfate, filtered and concentrated under reduced pressure. The thereby obtained residue is purified on a column of 120 g of silica (gradient of 0% to 20% EtOAc in heptane in 60 minutes), in order to
15 obtain two batches of compound **148B** (70%).

Batch 1: 2.25 g; HPLC: RT = 4.09 min, 96.6%.

¹H NMR, dmso-d₆, δ (ppm): 1.93 (q, 2H); 2.49 (s, 3H); 2.79 (t, 2H); 4.21 (t, 2H); 6.81 (d, 1H); 7.65-7.75 (m, 2H).

20 Mass spectrum (ESI+): m/z 177 (MH⁺, 100%).

Batch 2: 1.79 g; HPLC: RT = 4.09 min, 81%.

Example 148C - 2-Bromo-1-chroman-6-yl-ethanone

The compound **148C** was synthesized from the compound **148B** according to the procedure for preparing the
25 compound **144A**, with a yield of 65%.

HPLC: RT = 4.59 min, 74%.

^1H NMR, $\text{dms}\text{-d}_6$, (ppm): 1.95 (q, 2H); 2.80 (t, 2H); 4.20 (t, 2H); 4.80 (s, 2H); 6.85 (d, 1H); 7.70-7.85 (m, 2H).

- 5 **Example 148** - Chroman-6-yl-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e] [1,2]thiazin-3-yl)-methanone.

The compound **148** was synthesized from saccharin and from the compound **148C** according to the same sequence
10 of steps described for preparing the compound **1**, with an overall yield of 36%.

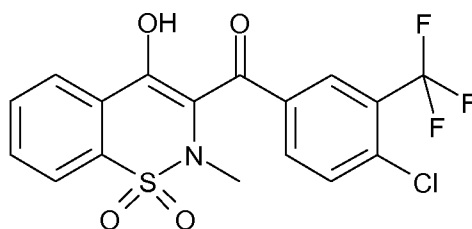
HPLC: RT = 5.45 min, 98%

^1H NMR, $\text{dms}\text{-d}_6$, δ (ppm): 1.98 (t, 2H); 2.69 (s, 3H); 2.84 (t, 2H); 4.27 (t, 2H); 6.96 (d, 1H); 7.89 (s, 1H);
15 7.97-8.02 (m, 4H); 8.17-8.18 (m, 1H); 16.02 (s, 1H, exch).

Mass spectrum (ESI+): m/z 372 (MH^+ , 100%).

Example 149

(4-Chloro-3-trifluoromethyl-phenyl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e] [1,2]thiazin-3-yl)-methanone
20



Example 149A - 1-(4-Chloro-3-trifluoromethyl-phenyl)-ethanol

4-chloro-3-trifluoromethyl-benzaldehyde (6.19 g, 29.7 mmol) is dissolved in 124 mL of THF under a nitrogen atmosphere. The reaction medium is cooled to -78°C before adding dropwise MeMgBr (13 mL, 3M / Et₂O, 38.6 mmol), and then stirred for a further 2 hours at this low temperature, and finally neutralized by adding 60 mL of a saturated NH₄Cl solution. The reaction medium is extracted twice with ethyl acetate. The organic phases are combined, washed with a saturated NaCl solution, and then dried on magnesium sulfate, filtered and concentrated under reduced pressure. The thereby obtained residue is purified on a column of 120 g of silica (92 mL / min; gradient of 0% to 35% ethyl acetate in heptane in 40 min), in order to obtain the compound **149A** (5.71 g, 62%).

HPLC: RT = 5.71 min, 98% (colonne XBridge)

¹H NMR, dmsO-d₆, δ (ppm): 1.33 (d, 3H); 4.81 (quintet, 1H); 5.46 (d, 1H, exch); 7.60-7.69 (m, 2H); 7.81 (s, 1H).

Example 149B - 1-(4-Chloro-3-trifluoromethyl-phenyl)-ethanone

The compound **149A** (2.62 g, 11.7 mmol) is dissolved in 53 mL of DCM in the presence of 3.8 g of celite. PCC (3.77 g, 17.5 mmol) is added at room temperature and the reaction medium is stirred overnight before being
5 filtered. The filtrate is concentrated under reduced pressure. The thereby obtained residue is purified on a column of 80 g of silica (32 mL / min, gradient of 0% to 30% EtOAc in heptane in 26 minutes), in order to obtain the compound **149B** (2.27 g, 87%).

10 HPLC: RT = 5.84 min, 97% (colonne XBridge)

¹H NMR, dmsO-d₆, δ (ppm): 2.65 (s, 3H); 7.92 (d, 1H); 8.22-8.27 (m, 2H).

Example 149C - 2-Bromo-1-(4-chloro-3-trifluoromethyl-phenyl)-ethanone

15 The compound **149C** was synthesized from the compound **149B** according to the procedure for preparing the compound **144A**, with a yield of 66%.

HPLC: RT = 6.18 min, 89% (colonne XBridge)

20 ¹H NMR, dmsO-d₆, δ (ppm): 5.05 (s, 2H); 7.96 (d, 1H); 8.28 (d, 1H); 8.34 (s, 1H).

Example 149 - (4-Chloro-3-trifluoromethyl-phenyl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone.

25 The compound **149** was synthesized from saccharin and from the compound **149C** according to the same sequence

of steps described for preparing the compound **1**, with an overall yield of 20%.

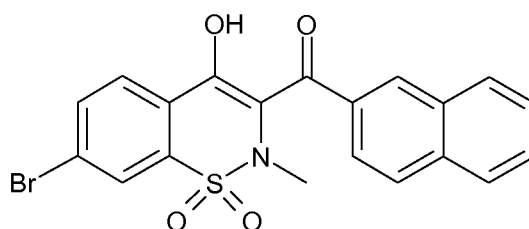
HPLC: RT = 6.71 min, 99% (XBridge column)

¹H NMR, dms_o-d₆, (ppm): 2.68 (s, 3H); 7.98-8.04 (m, 4H); 8.18-8.21 (m, 1H); 8.29 (d, 1H); 8.40 (s, 1H); 14.82 (s, 1H, exch).

Mass spectrum (ESI-): m/z 416 (M-H⁻, 100%); 418 (M-H⁻, 25%).

Example 150

10 **(7-Bromo-4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-naphthalen-2-yl-methanone**



Example 150A - 4-Bromo-2-sulfamoyl-benzoic acid

5-bromo-2-methyl-benzenesulfonamide (2.5 g, 9.99 mmol)
15 is dissolved in 62 mL of soda (5% in water). The reaction is heated to 100°C and KMnO₄ (6.43 g, 25 mmol) is gradually added within 15 minutes. Heating is continued for 140 minutes. The reaction medium is cooled to room temperature and then filtered. The pH of
20 the filtrate is brought back to 1.2 with a concentrated HCl solution, and then filtered. The precipitate is

rinsed with ethyl acetate. The two phases of the filtrate are separated and the aqueous phase is extracted once with ethyl acetate. The organic phases are collected, dried on magnesium sulfate, filtered and concentrated under reduced pressure, in order to obtain the compound **150A** (1.64 g, 58%).

HPLC: RT = 0.29 min, 99.5%

¹H NMR, dms_o-d₆, δ (ppm): 7.35 (s, 2H, exch); 7.67 (d, 1H); 7.91 (d, 1H); 8.08 (s, 1H); 13.83 (broad s, 1H, exch).

Mass spectrum (ESI⁻): m/z 278 (M-H⁻, 100%); 280 (M-H⁻, 87%).

Example 150B - 6-Bromo-1,1-dioxo-1,2-dihydro-2H-benzo[d]isothiazol-3-one

The compound **150A** (1.59 g, 5.56 mmol) is dissolved in 6 mL of concentrated sulfuric acid at room temperature and the reaction medium is stirred for 3 hours before being poured over ice. The suspension is filtered. The precipitate is rinsed three times with water, and then dried for 24 hours at 50°C and *in vacuo*. The compound **150B** (1.33 g, 89%) is obtained as a white solid.

HPLC: RT = 3.16 min, 96%

¹H NMR, dms_o-d₆, δ (ppm): 7.85 (d, 1H); 8.08 (d, 1H); 8.48 (s, 1H).

Mass spectrum (ESI-): m/z 260 ($M-H^-$, 100%); 262 ($M-H^-$, 94%).

Example 150 - (7-Bromo-4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2] thiazin-3-yl)-naphthalen-2-yl-methanone.

The compound **150** was synthesized from the compound **150B** and from 2-bromo-1-(naphthalen-2-yl)ethanone according to the same sequence of steps described for preparing the compound **1**, with an overall yield of 55%.

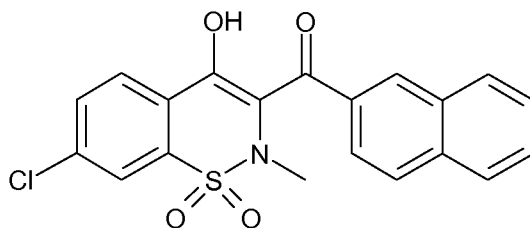
10 HPLC: RT = 6.14 min, 97%

1H NMR, $dmsO-d_6$, δ (ppm): 2.68 (s, 3H); 7.66 (t, 1H); 7.73 (t, 1H); 8.04-8.15 (m, 5H); 8.19-8.22 (m, 2H); 8.65 (s, 1H); 15.38 (s, 1H, exch).

Mass spectrum (ESI+): m/z 444 (MH^+ , 100%); 446 (MH^+ , 99%).

Example 151

(7-Chloro-4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-naphthalen-2-yl-methanone



Example 151A - 6-Chloro-1,1-dioxo-1,2-dihydro-2H-benzo[d]isothiazol-3-one

Methyl 2-amino-4-chlorobenzoate (5 g, 26.9 mmol) is heated in 18 mL of HCl (20% in water) until complete
5 dissolution, and then cooled to 0°C. A solution of NaNO₂ (1.85 g, 26.9 mmol) in 4.5 mL of water is added dropwise while maintaining the temperature between 2°C and 6°C. The reaction medium is then stirred for 1 hour at room temperature. In a second flask, about 15 g of
10 SO₂ gas is bubbled in 22 mL of acetic acid and 2.3 mL of water at 0°C. CuCl (666 mg, 6.7 mmol) is then added. The first reaction medium is then added to this blue-green solution between 1°C and 3°C. Gas evolution is observed; Stirring at low temperature is continued for
15 45 minutes before removing the cold bath, and then the reaction medium is poured over 100 g of ice and extracted three times with ethyl acetate. The organic phases are collected, washed with a saturated NaHCO₃ solution, dried on magnesium sulfate, filtered and
20 concentrated under reduced pressure. The residue is taken up into 5 mL of THF at 0°C and 2.8 mL of a concentrated ammonia solution are added slowly. The cold bath is removed and stirring is continued for 1 hour. The reaction medium is concentrated, taken up
25 with a saturated NaHCO₃ solution, washed once with ether, and then brought back to pH=1 with a concentrated HCl solution. The formed precipitate is filtered, rinsed with water and dried under reduced pressure at 50°C in order to obtain the compound **151A**
30 (896 mg, 15%).

HPLC: RT = 3.07 min, 99%

^1H NMR, $\text{dms}\text{-d}_6$, δ (ppm): 7.94 (broad d, 2H); 8.38 (s, 1H).

Mass spectrum (ESI⁻): m/z 216 (M-H^- , 100%); 218 (M-H^- , 32%).

- 5 **Example 151** - (7-Chloro-4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2] thiazin-3-yl)-naphthalen-2-yl-methanone

The compound **151** was synthesized from the compound **151A** and from 2-bromo-1-(naphthalen-2-yl)ethanone according to the same sequence of steps described for preparing the compound **1**, with an overall yield of 39%.

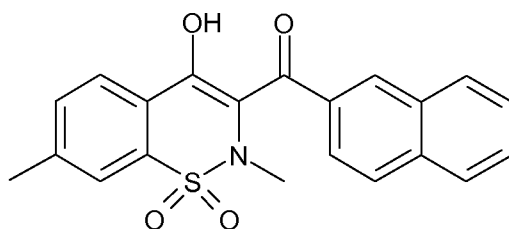
HPLC: RT = 6.13 min, 95%

^1H NMR, $\text{dms}\text{-d}_6$, δ (ppm): 2.68 (s, 3H); 7.66 (t, 1H); 7.74 (t, 1H); 8.03-8.16 (m, 6H); 8.21 (d, 1H); 8.65 (s, 1H); 15.41 (se, 1H, exch).

Mass spectrum (ESI⁻): m/z 398 (M-H^- , 100%); 400 (M-H^- , 32%).

Example 152

(4-Hydroxy-2,7-dimethyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-naphthalen-2-yl-methanone



Example 152A - 2-Cyano-5-methyl-benzenesulfonamide

2-amino-4-methyl-benzonitrile (2.5 g, 18.9 mmol) is heated in 12 mL of HCl (20% in water) until complete dissolution), and then cooled to 0°C. A solution of NaNO₂ (1.3 g, 18.9 mmol) in 3.2 mL of water is added dropwise while maintaining the temperature between 2°C and 6°C. The reaction medium is then stirred for 1 hour at room temperature. In a second flask, about 15.7 g of SO₂ gas is bubbled in 15 mL of acetic acid and 1.6 mL of water at 0°C. CuCl (468 mg, 4.7 mmol) is then added. The first reaction medium is then added to this blue-green solution between 1°C and 3 °C. Gas evolution is observed. Stirring at low temperature is continued for 45 minutes before removing the cold bath, and then the reaction mixture is poured over 70 g of ice and extracted three times with a mixture of 20% methanol in DCM. The organic phases are collected, washed with a saturated NaHCO₃ solution, dried on magnesium sulfate, filtered and concentrated under reduced pressure. The residue is taken up into 5 mL of THF at 0°C and 2.8 mL of a concentrated ammonia solution are added slowly. The cold bath is removed and stirring is continued for 1 hour. The reaction medium is concentrated, taken up with a saturated NaHCO₃ solution, washed once with ether, and then brought back to pH=1 with a concentrated HCl solution. The formed precipitate is filtered, rinsed with water and dried under reduced

pressure at 50°C in order to obtain the compound **152A** (800 mg, 21%).

HPLC: RT = 3.67 min, 99% (colonne XBridge)

¹H NMR, dmso-d₆, δ (ppm): 7.61 (d, 1H); 7.77 (s, 1H);
5 7.99 (d, 1H); 8.77 (broad s, 2H).

Mass spectrum (ESI+): m/z 197 (MH⁺, 100%).

Example 152B - 4-Methyl-2-sulfamoyl-benzoic acid

The compound **152A** (620 mg, 3.15 mmol) is dissolved in
7.5 mL of KOH (30% in water) and 530 µl of hydrogen
10 peroxide (30% in water). The reaction medium is
refluxed with heating for 4 hours, and then cooled to
room temperature, brought back to pH=1 with a
concentrated HCl solution and extracted three times
with a mixture of 20% methanol in DCM. The organic
15 phases are collected, dried on magnesium sulfate,
filtered and concentrated under reduced pressure, in
order to obtain the compound **152B** (428 g, 60%).

HPLC: RT = 4.11 min, 95% (colonne XBridge)

¹H NMR, dmso-d₆, δ (ppm): 2.41 (s, 3H); 7.19 (broad s,
20 2H, exch); 7.48 (d, 1H); 7.65 (d, 1H); 7.77 (s, 1H);
12.5-14.5 (broad s, 1H, exch).

Mass spectrum (ESI-): m/z 214 (M-H⁻, 100%).

Example 152C - 6-Methyl-1,1-dioxo-1,2-dihydro-2H-benzo[d]isothiazol-3-one

The compound **152B** (428 mg, 1.94 mmol) is dissolved in 3 mL of concentrated sulfuric acid at room temperature.

- 5 The reaction mixture is stirred for 2 hours and then poured over ice and filtered. The precipitate is abundantly rinsed with water and then dried in order to obtain the compound **152C** (359 mg, 93%) as a pink solid.

HPLC: RT = 4.00 min, 96% (XBridge column)

- 10 ^1H NMR, $\text{dms}\text{-d}_6$, δ (ppm): 7.74 (d, 1H); 7.89 (d, 1H); 8.00 (s, 1H).

Mass spectrum (ESI⁻): m/z 196 (M-H⁻, 100%).

- Example 152** - (4-Hydroxy-2,7-dimethyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-naphthalen-2-yl-methanone
- 15

The compound **152** was synthesized from the compound **152C** and from 2-bromo-1-(naphthalen-2-yl)ethanone according to the same sequence of steps described for preparing the compound **1**, with an overall yield of 21%.

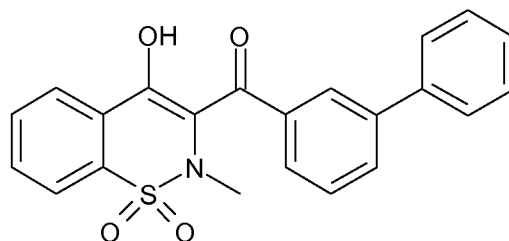
- 20 HPLC: RT = 6.87 min, 98% (XBridge column)

^1H NMR, $\text{dms}\text{-d}_6$, δ (ppm): 2.55 (s, 3H); 2.64 (s, 3H); 7.66 (t, 1H); 7.72 (t, 1H); 7.80 (d, 1H); 7.84 (s, 1H); 8.05 (d, 1H); 8.11-8.11 (m, 4H); 8.67 (s, 1H); 15.75 (s, 1H, exch).

Mass spectrum (APCI+): m/z 380 (MH^+ , 24%).

Example 153

Biphenyl-3-yl-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone



5

Example 153 - Biphenyl-3-yl-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone

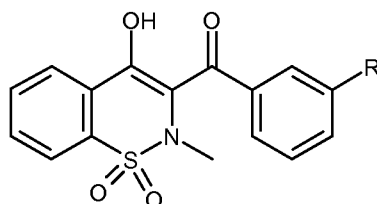
The compound **142** (200 mg, 0.5 mmol) is dissolved under an inert atmosphere in 1.1 mL of acetone and 1.2 mL of water in the presence of benzene boronic acid (68 mg, 0.55 mmol), of potassium carbonate (175 mg, 1.27 mmol) and palladium acetate (5 mg, 0.02 mmol). The reaction mixture is heated to 85°C for 1 hour and 30 minutes and then brought back to room temperature, diluted with water and extracted three times with DCM. The organic phases are combined, dried on magnesium sulfate, filtered and concentrated under reduced pressure. The thereby obtained residue is purified on a column of 12 g of silica with DCM, in order to obtain the compound **153** (141 mg, 68%).

HPLC: RT = 7.07 min, 96% (colonne XBridge)

^1H NMR, dmso-d_6 , δ (ppm): 2.68 (s, 3H); 7.44 (t, 1H); 7.53 (t, 2H); 7.69-7.76 (m, 3H); 7.97-8.04 (m, 5H); 8.21 (broad s, 1H); 8.31 (s, 1H); 15.36 (broad s, 1H, exch).

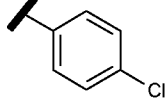
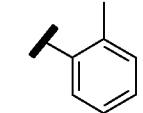
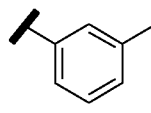
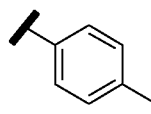
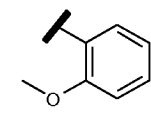
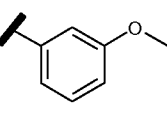
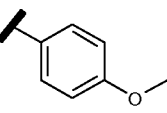
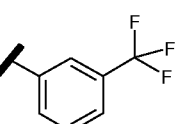
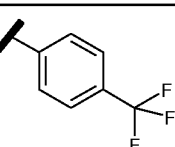
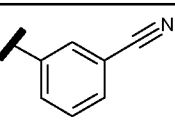
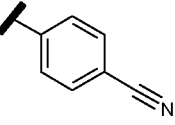
5 Mass spectrum (ESI $^-$): m/z 390 (M-H^- , 100%).

Examples 154 to 169



The compounds **154** to **169** were synthesized from the compound **142** and from various boronic acids according to the same method described for preparing the compound **153**.

Ex. *	R	Name of the compounds	HPLC**	Yld .	M-H $^-$ (MH $^+$)
154		(2'-Fluoro-biphenyl-3-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	6.80' 95.9%	27%	404
155		(3'-Fluoro-biphenyl-3-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	6.93' 98.2%	66%	408
156		(4'-Fluoro-biphenyl-3-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	6.92' 98.7%	64%	408
157		(2'-Choro-biphenyl-3-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	6.99' 94.8%	11%	(426)
158		(3'-Choro-biphenyl-3-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	7.19' 98%	58%	(426)

159		(4'-Chloro-biphenyl-3-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	7.22' 97.9%	67%	(426)
160		(2'-Methyl-biphenyl-3-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	7.08' 98.4%	61%	404
161		(3'-Methyl-biphenyl-3-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	7.15' 99.6%	60%	404
162		(4'-Methyl-biphenyl-3-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	7.16' 99.5%	70%	404
163		(2'-Methoxy-biphenyl-3-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	6.85' 100%	69%	420
164		(3'-Methoxy-biphenyl-3-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	6.86' 98.5%	53%	420
165		(4'-Methoxy-biphenyl-3-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	6.83' 99.5%	72%	420
166		(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-(3'-trifluoromethyl-biphenyl-3-yl)-methanone	7.17' 97.5%	45%	458
167		(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-(4'-trifluoromethyl-biphenyl-3-yl)-methanone	7.22' 98.3%	44%	458
168		3'-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazine-3-carbonyl)-biphenyl-3-carbonitrile	6.57' 99.5%	50%	415
169		3'-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazine-3-carbonyl)-biphenyl-4-carbonitrile	6.57' 97.1%	61%	415

* ¹H NMR, dms_o-d₆, Ex. **154**: 2.68 (s, 3H); 7.35-7.41 (m, 2H); 7.47-7.52 (m, 1H); 7.62 (t, 1H); 7.75 (t, 1H); 7.89 (d, 1H); 7.99-8.01 (m, 3H); 8.08 (d, 1H); 8.21-8.22 (m, 1H); 8.26 (s,

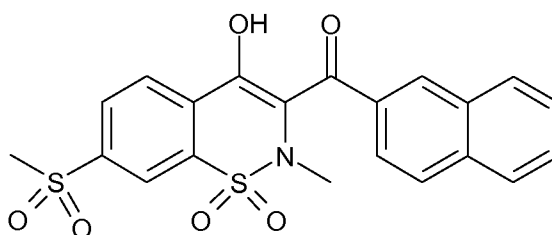
1H); 15.41 (broad s, exch, 1H). Ex. **155**: 2.67 (s, 3H); 7.28 (t, 1H); 7.55-7.61 (m, 3H); 7.74 (t, 1H); 8.00-8.06 (m, 5H); 8.21-8.23 (m, 1H); 8.32 (s, 1H); 15.26 (broad s, exch, 1H). Ex. **156**: 2.67 (s, 3H); 7.37 (t, 2H); 7.72 (t, 1H); 7.77-7.80 (m, 2H); 7.99-8.05 (m, 5H); 8.20-8.23 (m, 1H); 8.27 (s, 1H); 15.32 (broad s, exch, 1H). Ex. **157**: 2.68 (s, 3H); 7.45-7.50 (m, 3H); 7.63-7.65 (m, 1H); 7.71-7.74 (m, 2H); 7.97-7.99 (m, 3H); 8.03 (d, 1H); 8.15 (s, 1H); 8.19-8.20 (m, 1H); 15.41 (broad s, exch, 1H). Ex. **158**: 2.67 (s, 3H); 7.51 (d, 1H); 7.57 (t, 1H); 7.72-7.76 (m, 2H); 7.81 (d, 1H); 7.98-8.07 (m, 5H); 8.21-8.23 (m, 1H); 8.31 (s, 1H); 15.26 (broad s, exch, 1H). Ex. **159**: 2.67 (s, 3H); 7.59 (d, 2H); 7.72-7.78 (m, 3H); 7.99-8.02 (m, 4H); 8.06 (d, 1H); 8.20-8.23 (m, 1H); 8.28 (s, 1H); 15.30 (broad s, exch, 1H). Ex. **160**: 2.32 (s, 3H); 2.68 (s, 3H); 7.27-7.38 (m, 4H); 7.67-7.73 (m, 2H); 7.98-8.04 (m, 5H); 8.20-8.22 (m, 1H); 15.45 (broad s, exch, 1H). Ex. **161**: 2.41 (s, 3H); 2.67 (s, 3H); 7.25 (d, 1H); 7.41 (t, 1H); 7.53 (d, 1H); 7.56 (s, 1H); 7.71 (t, 1H); 7.98-8.03 (m, 5H); 8.21-8.23 (m, 1H); 8.32 (s, 1H); 15.35 (broad s, 1H, exch). Ex. **162**: 2.37 (s, 3H); 2.67 (s, 3H); 7.34 (d, 2H); 7.63 (d, 2H); 7.70 (t, 1H); 7.97-8.01 (m, 5H); 8.20-8.21 (m, 1H); 8.30 (s, 1H); 15.37 (broad s, 1H, exch). Ex. **163**: 2.70 (s, 3H); 3.83 (s, 3H); 7.09 (t, 1H); 7.18 (d, 1H); 7.35-7.44 (m, 2H); 7.67 (t, 1H); 7.79 (d, 1H); 7.97-8.01 (m, 4H); 8.19-8.23 (m, 1H); 8.29 (s, 1H); 15.58 (broad s, 1H, exch). Ex. **164**: 2.68 (s, 3H); 3.86 (s, 3H); 7.00 (dd, 1H); 7.27 (s, 1H); 7.31 (d, 1H); 7.44 (t, 1H); 7.72 (t, 1H); 7.98-8.03 (m, 5H); 8.19-8.24 (m, 1H); 8.37 (s, 1H); 15.32 (broad s, 1H, exch). Ex. **165**: 2.67 (s, 3H); 3.82 (s, 3H); 7.09 (d, 2H); 7.66-7.71 (m, 3H); 7.94-8.02 (m, 5H); 8.19-8.23 (m, 1H); 8.28 (s, 1H); 15.38 (broad s, 1H, exch). Ex. **166**: 2.66 (s, 3H); 7.74-7.83 (m, 3H); 7.97-8.12 (m, 7H); 8.19-8.24 (m, 1H); 8.37 (s, 1H); 15.22 (broad s, 1H, exch). Ex. **167**: 2.68 (s, 3H); 7.78 (t, 1H); 7.89 (d, 2H); 7.95-8.02 (m, 5H); 8.08-8.13 (m, 2H); 8.19-8.24 (m, 1H); 8.34 (s, 1H);

15.27 (broad s, 1H, exch). Ex. **168**: 2.67 (s, 3H); 7.73 (d, 1H); 7.78 (d, 1H); 7.91 (d, 1H); 8.00 (broad s, 3H); 8.07-8.10 (m, 3H); 8.19-8.25 (m, 2H); 8.32 (s, 1H); 15.23 (broad s, 1H, exch). Ex. **169**: 2.67 (s, 3H); 7.78 (t, 1H); 7.94-8.03 (m, 7H); 8.08-8.12 (m, 2H); 8.19-8.23 (m, 1H); 8.33 (s, 1H); 15.23 (broad s, 1H, exch).

** XBridge column.

Example 170

(4-Hydroxy-7-methanesulfonyl-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-naphthalen-2-yl-methanone



Example 170 - (4-Hydroxy-7-methanesulfonyl-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-naphthalen-2-yl-methanone

The compound **170** was synthesized from 5-methanesulfonyl-2-methyl-benzenesulfonyl chloride according to the same sequence of steps described for preparing the compound **17**, with an overall yield of 7%.

HPLC: RT = 5.43 min, 97%

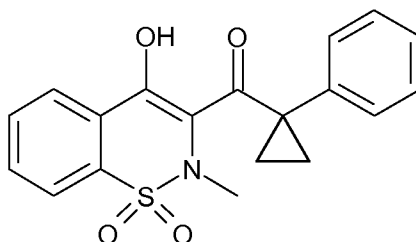
^1H NMR, $\text{dms}\text{-d}_6$, δ (ppm): 2.71 (s, 3H); 3.47 (s, 3H); 7.67 (t, 1H); 7.73 (t, 1H); 8.05-8.15 (m, 4H); 7.42-8.49 (m, 3H); 8.67 (s, 1H); 14.76 (se, 1H, exch).

Mass spectrum (ESI+): m/z 444 (MH^+ , 100%).

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Example 171

(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-(1-phenyl-cyclopropyl)-methanone

10 **Example 171A** - 1-(1-Phenyl-cyclopropyl)-ethanone

The compound **171A** was synthesized from 1-phenyl-cyclopropanecarbonitrile according to the same procedure described for preparing the compound **147B**, with a yield of 40%.

15 HPLC: RT = 4.30 min, 96% (XBridge column)

^1H NMR, $\text{dms}\text{-d}_6$, δ (ppm): 1.15 (dd, 2H); 1.47 (dd, 1H); 1.92 (s, 3H); 7.23-7.40 (m, 5H).

Mass spectrum (ESI+): m/z 161 (MH^+ , 100%).

Example 171 - (4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-(1-phenyl-cyclopropyl)-methanone

The compound **171** was synthesized from the compound **171A** according to the same sequence of steps described for preparing the compound **144**, with an overall yield of 6%.

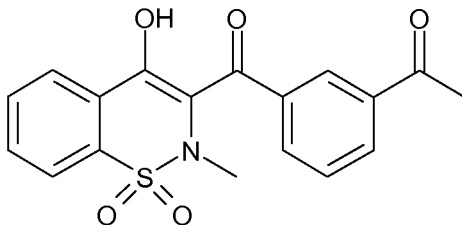
HPLC: RT = 6.40 min, 96% (XBridge column)

¹H NMR, dms_o-d₆, δ (ppm): 1.38-1.41 (m, 2H); 1.65-1.68 (m, 2H); 2.46 (s, 3H); 7.25-7.37 (m, 5H); 7.78-7.83 (m, 1H); 7.86-7.91 (m, 2H); 8.06-8.08 (m, 1H), 15.31 (s, 1H, exch).

Mass spectrum (ESI+): m/z 356 (MH⁺, 100%).

Example 172

1-[3-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazine-3-carbonyl)-phenyl]-ethanone



Example 172 - 1-[3-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazine-3-carbonyl)-phenyl]-ethanone

The compound **172** was synthesized from 1-(3-acetyl-phenyl)-ethanone according to the same sequence of steps described for preparing the compound **144**, with an overall yield of 21%.

5 HPLC: RT = 6.25 min, 97% (XBridge column)

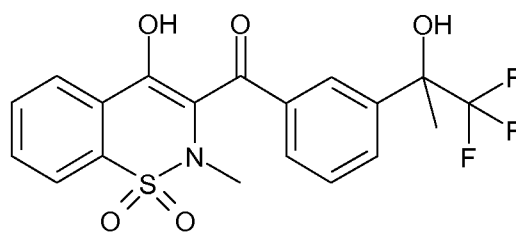
^1H NMR, $\text{dms}\text{-d}_6$, δ (ppm): 2.64 (s, 3H); 2.66 (s, 3H); 7.79 (t, 1H); 8.00 (broad s, 3H); 8.15-8.35 (m, 3H); 8.58 (s, 1H); 15.21 (broad s, 1H, exch).

Mass spectrum (ESI⁻): m/z 356 (M-H^- , 100%).

10

Example 173

(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-[3-(2,2,2-trifluoro-1-hydroxy-1-methyl-ethyl)-phenyl]-methanone



15 **Example 173A** - 1-[3-(2,2,2-Trifluoro-1-hydroxy-1-methyl-ethyl)-phenyl]-ethanone

1-(3-acetyl-phenyl)-ethanone (2.5 g, 15.4 mmol) is dissolved in 120 mL of THF under a nitrogen atmosphere and at 0°C in the presence of TMS-CF₃ (2.7 mL, 18.4 mmol). TBAF (1M / THF, 18.4 mL, 18.4 mmol) is added within 20 minutes by means of a syringe pump. The cold

20

bath is removed and the reaction medium is stirred for a further 18 hours and then neutralized by adding a saturated NaHCO₃ solution, and finally extracted 3 times with ethyl acetate. The organic phases are
5 combined, washed with water and then dried on magnesium sulfate, filtered and concentrated under reduced pressure. The thereby obtained residue is purified on silica (gradient of 0% to 50% ethyl acetate in heptane in 20 min), in order to obtain the partly purified
10 compound **173A** (2.87 g). It is used as such in the next step.

Example 173B - 2-Bromo-1-[3-(2,2,2-trifluoro-1-hydroxy-1-methyl-ethyl)-phenyl]-ethanone

The compound **173B** was synthesized from the compound
15 **173A** according to the procedure for preparing the compound **144A**, with a yield of 57%.

HPLC: RT = 5.50 min, 74% (XBridge column)

¹H NMR, dmsO-d₆, δ (ppm): 1.73 (s, 3H); 4.96 (s, 2H);
6.81 (broad s, 1H, exch); 7.60 (t, 1H); 7.89 (d, 1H);
20 8.03 (d, 1H); 8.17 (s, 1H).

Example 173 - (4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-[3-(2,2,2-trifluoro-1-hydroxy-1-methyl-ethyl)-phenyl]-methanone.

The compound **173** was synthesized from saccharin and
25 from the compound **173B** according to the same sequence of steps described for preparing the compound **1**, with an overall yield of 52%.

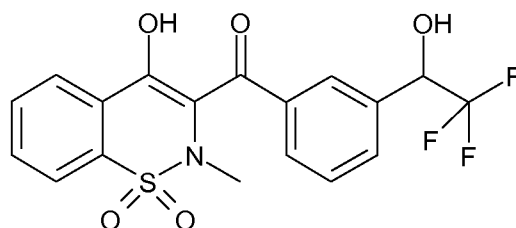
HPLC: RT = 6.05 min, 95% (XBridge column)

¹H NMR, dms_o-d₆, (ppm): 1.76 (s, 3H); 2.61 (s, 3H);
 6.84 (s, 1H, exch); 7.67 (t, 1H); 7.90-8.05 (m, 5H);
 8.17-8.23 (m, 1H); 8.36 (s, 1H); 15.47 (broad s, 1H,
 5 exch).

Mass spectrum (ESI⁺): m/z 445 (MNH₄⁺, 100%).

Example 174

(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-
 benzo[e][1,2]thiazin-3-yl)-[3-(2,2,2-trifluoro-1-
 10 hydroxy-ethyl)-phenyl]-methanone



Example 174A - 1-[3-(2,2,2-Trifluoro-1-
 trimethylsilanyloxy-ethyl)-phenyl]-ethanone

3-acetylbenzaldehyde (1.27 g, 8.57 mmol) is dissolved
 15 in 30 mL of DMF under a nitrogen atmosphere in the
 presence of potassium carbonate (59 mg, 0.42 mmol) and
 of TMS-CF₃ (1.52 mL, 10.3 mmol). The reaction mixture
 is stirred for 30 minutes at room temperature and then
 neutralized with 1 mL of a saturated NH₄Cl solution and
 20 concentrated under reduced pressure. The residue is
 taken up in ethyl acetate and then washed once with HCl
 (1N in water), dried on magnesium sulfate, filtered and

concentrated under reduced pressure in order to obtain the partly purified compound **174A** (2.55 g). It is used as such in the next step.

HPLC: RT = 5.15 min, 42% (OH) et 6.91 min, 40% (OTMS)
5 (XBridge column, partial deprotection on the column).

¹H NMR, dms_o-d₆, δ (ppm): 0.09 (s, 9H); 2.60 (s, 3H); 5.60 (q, 1H); 7.60 (t, 1H); 7.76 (d, 1H); 8.02 (d, 1H); 8.08 (s, 1H).

Mass spectrum (ESI⁺): m/z 291 (MH⁺, 100%).

10 **Example 174B** - 2-Bromo-1-[3-(2,2,2-trifluoro-1-hydroxy-ethyl)-phenyl]-ethanone

The compound **174B** was synthesized from the compound **174A** according to the procedure for preparing the compound **144A**, with a yield of 60%.

15 HPLC: RT = 5.23 min, 83% (XBridge column)

¹H NMR, dms_o-d₆, δ (ppm): 4.93 (s, 2H); 5.32 (q, 1H); 7.03 (broad s, 1H, exch); 7.61 (t, 1H); 7.81 (d, 1H); 8.05 (d, 1H); 8.11 (s, 1H).

20 **Example 174** - (4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-[3-(2,2,2-trifluoro-1-hydroxy-ethyl)-phenyl]-methanone.

The compound **174** was synthesized from saccharin and from the compound **174B** according to the same sequence

of steps described for preparing the compound **1**, with an overall yield of 33%.

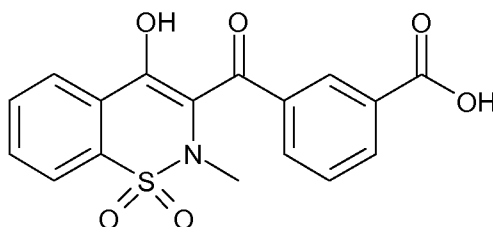
HPLC: RT = 5.92 min, 92% (XBridge column)

¹H NMR, dms_o-d₆, δ (ppm): 2.60 (s, 3H); 5.32 (broad s, 1H); 7.05 (d, 1H, exch); 7.67 (t, 1H); 7.80 (d, 1H); 7.98 (broad s, 3H); 8.08 (d, 1H); 8.20 (broad s, 2H); 15.45 (broad s, 1H, exch).

Mass spectrum (ESI⁺): m/z 431 (MNH₄⁺, 100%).

Example 175

10 **3-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazine-3-carbonyl)-benzoic acid**



Example 175 - 3-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazine-3-carbonyl)-benzoic acid

The compound **143** (100 mg, 0.29 mmol) is dissolved in 1 mL of KOH (30% in water) in the presence of 330 µl of ethanol, and then heated to 70°C for 18 hours. The reaction medium is diluted with 10 mL of water, washed twice with ether, brought back to pH = 2 with an HCl (6N in water) and finally extracted three times with a

solution of 20% methanol in DCM. The organic phases are combined, dried on magnesium sulfate, filtered and concentrated in order to obtain the compound **175** as a yellow solid (99 mg, 93%).

5 HPLC: RT = 5.49 min, 98% (XBridge column)

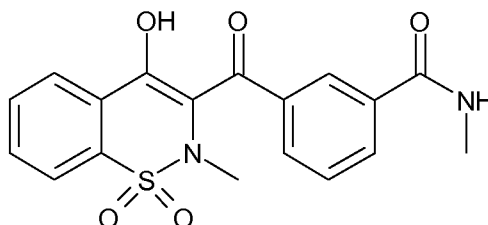
^1H NMR, $\text{dms}\text{-d}_6$, δ (ppm): 2.64 (s, 3H); 7.77 (t, 1H); 7.99-8.00 (m, 3H); 8.20-8.24 (m, 2H); 8.28 (d, 1H); 8.61 (s, 1H); 13.33 (s,exch, 1H); 15.32 (s, exch, 1H).

Mass spectrum (ESI-): m/z 358 (M-H^- , 100%).

10

Example 176

3-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazine-3-carbonyl)-N-methyl-benzamide



Example 176 - 3-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazine-3-carbonyl)-N-methyl-benzamide

15

The compound **175** (150 mg, 0.41 mmol) is dissolved in 3 mL of DMF under an inert atmosphere in the presence of (3-dimethylamino-propyl)-ethyl-carbodiimide

20 hydrochloride (120 mg, 0.62mmol), of 3-hydroxy-3H-benzo[d][1,2,3]triazin-4-one (102 mg, 0.62 mmol) and

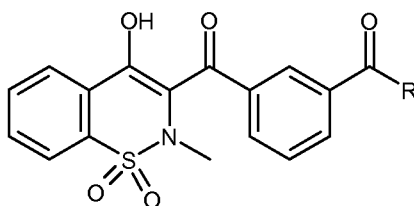
iPr₂NEt (162 mg, 1.25 mmol), and then stirred at room temperature for 72 hours. The reaction mixture is concentrated under reduced pressure, diluted with 20 mL of DCM and washed twice with HCl (1N in water). The aqueous phases are collected and extracted DCM. The organic phases are combined, dried on magnesium sulfate, filtered and concentrated. The thereby obtained residue is purified on a column of 12 g of silica (12 mL / min, gradient of 0% to 25% acetone in DCM in 20 minutes), in order to obtain the compound **176** as a yellow solid (101 mg, 64%).

HPLC: RT = 5.21 min, 97% (XBridge column)

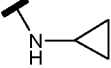
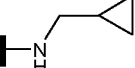
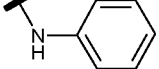
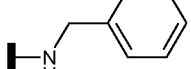
¹H NMR, dmsO-d₆, δ (ppm): 2.63 (s, 3H); 2.82 (d, 3H); 7.72 (t, 1H), 7.99 (d, 3H); 8.10 (d, 1H); 8.20-8.22 (m, 2H); 8.42 (s, 1H); 8.66 (d, 1H); 15.35 (broad s, 1H, exch).

Mass spectrum (ESI+): m/z 373 (MH⁺, 100%).

Examples 177 to 183



The compounds **177** to **183** were synthesized from the compound **175** and from various amines according to the same procedure described for preparing the compound **176**.

Ex. *	R	Name of the compounds	HPLC**	Yld.	MH ⁺
177		3-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazine-3-carbonyl)-N,N-dimethyl-benzamide	5.33' 95.8%	44%	387
178		N-Ethyl-3-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazine-3-carbonyl)-benzamide	5.41' 96.9%	39%	387
179		3-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazine-3-carbonyl)-N,N-diethyl-benzamide	5.71' 96.9%	34%	415
180		N-Cyclopropyl-3-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazine-3-carbonyl)-benzamide	5.43' 96.6%	33%	399
181		N-Cyclopropylmethyl-3-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazine-3-carbonyl)-benzamide	5.71' 98.7%	33%	413
182		3-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazine-3-carbonyl)-N-phenyl-benzamide	6.09' 99.5%	67%	435
183		N-Benzyl-3-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazine-3-carbonyl)-benzamide	5.96' 93.8%	6%	449

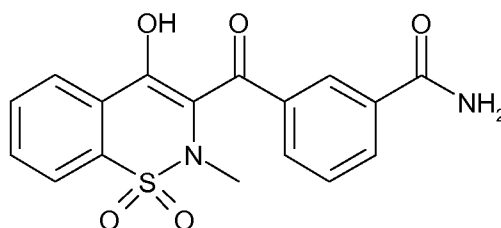
* ¹H NMR, dms_o-d₆, Ex. **177**: 2.65 (s, 3H); 2.98 (s, 3H); 3.03 (s, 3H); 7.68-7.75 (m, 2H); 7.99-8.07 (m, 4H); 8.08 (d, 1H); 8.20-8.21 (d, 1H); 15.28 (broad s, exch, 1H). Ex. **178**: 1.15 (t, 3H); 2.63 (s, 3H); 3.29-3.36 (m, 2H + H₂O); 7.71 (t, 1H); 7.99-8.00 (m, 3H); 8.12 (d, 1H); 8.21-8.22 (m, 2H); 8.42 (s, 1H); 8.68 (t, 1H); 15.36 (broad s, exch, 1H). Ex. **179**: 1.09-1.23 (m, 6H); 2.64 (s, 3H); 3.24-3.47 (m, 4H + H₂O); 7.66-7.72 (m, 2H); 7.95-8.08 (m, 5H); 8.20-8.21 (m, 1H); 15.28 (broad s, exch, 1H). Ex. **180**: 0.71-0.75 (m, 2H); 0.8 (m, 2H); 2.63 (s, 3H); 2.86-2.91 (m, 1H); 7.70 (t, 1H); 7.99-8.00 (m, 3H); 8.09 (d, 1H); 8.20-5.21 (m, 2H); 8.40 s(1H); 8.66 (d, 1H); 15.34 (broad s, exch, 1H). Ex. **181**: 0.45-0.47 (m, 2H); 0.6 (m, 2H); 1.06 (m, 1H); 2.64 (s, 3H); 3.18 (t, 2H); 7.72 (t, 1H); 7.99-8.00 (m, 3H); 8.13 (d, 1H);

8.21 (m, 2H); 8.43 (s, 1H); 8.78 (t, 1H); 15.35 (broad s, exch, 1H). Ex. **182**: 2.66 (s, 3H); 7.13 (t, 1H); 7.38 (t, 2H); 7.78-7.81 (m, 3H), 8.00 (d, 3H); 8.21-8.28 (m, 3H); 8.52 (s, 1H); 10.47 (s, 1H); 15.33 (broad s, exch, 1H). Ex.
5 **183**: 2.63 (s, 3H); 4.52 (d, 2H); 7.25-7.28 (m, 1H); 7.32-7.36 (m, 4H); 7.73 (t, 1H); 8.00 (d, 3H); 8.17-8.25 (m, 3H); 8.49 (s, 1H); 9.26-9.27 (m, 1H); 15.34 (broad s, exch, 1H).

** XBridge column.

Example 184

10 **3-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazine-3-carbonyl)-benzamide**



Example 184 - 3-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazine-3-carbonyl)-benzamide

15 The compound **175** (150 mg, 0.42 mmol) is dissolved in 3 mL of THF in the presence of PyBOP (239 mg, 0.46 mmol), of ammonia (152 µl, 1.25 mmol) and of DIEA (80 µl, 0.46 mmol) and stirred at room temperature for 4 hours. The reaction medium is diluted with 20 mL of DCM and washed
20 with HCl (1N in water). The aqueous phase is extracted four times with DCM. The organic phases are combined, dried on magnesium sulfate, filtered and concentrated

in order to obtain the compound **184** as a yellow solid (71 mg, 46%).

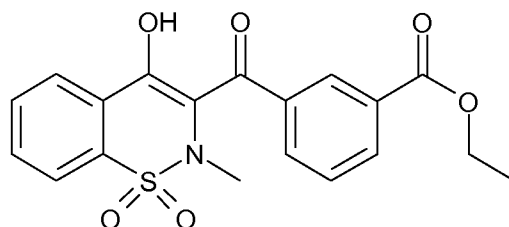
HPLC: RT = 5.06 min, 97.4% (XBridge column)

¹H NMR, dms_o-d₆, δ (ppm): 2.63 (s, 3H); 7.57 (s, 1H);
5 7.71 (t, 1H); 7.99 (d, 3H); 8.14-8.23 (m, 4H); 8.46 (s, 1H); 15.36 (broad s, exch, 1H).

Mass spectrum (ESI+): m/z 359 (MH⁺, 100%).

Example 185

10 **3-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-
benzo[e][1,2]thiazine-3-carbonyl)-benzoic acid ethyl
 ester**



Example 185 - 3-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-
15 dihydro-2H-benzo[e][1,2]thiazine-3-carbonyl)-benzoic
acid ethyl ester.

The compound **175** (150 mg, 0.42 mmol) is dissolved in 6 mL ethanol in the presence of pTsOH (8 mg, 0.04 mmol), and refluxed with stirring for 18 hours. The reaction medium is concentrated under reduced pressure. The
20 thereby obtained residue is purified on a column of 12

g of silica (12 mL/min, DCM), in order to obtain the compound **185** as a yellow solid (138 mg, 84%).

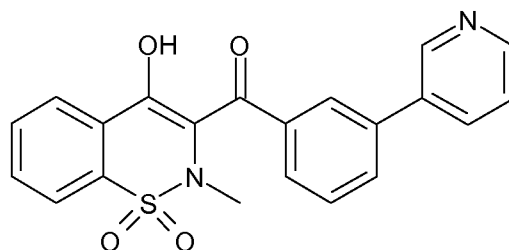
HPLC: RT = 6.28 min, 95.8% (XBridge column)

¹H NMR, dms_o-d₆, δ (ppm): 1.36 (t, 3H); 2.64 (s, 3H);
5 4.37 (q, 2H); 7.79 (t, 1H); 8.00 (d, 3H); 8.20-8.30 (m, 3H); 8.65 (s, 1H), 15.23 (broad s, exch, 1H).

Mass spectrum (ESI+): m/z 405 (MH⁺, 100%).

Example 186

10 (4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-(3-pyridin-3-yl-phenyl)-methanone



Example 186 - (4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-(3-pyridin-3-yl-phenyl)-methanone.
15

The compound **142** (200 mg, 0.5 mmol) is dissolved under an inert atmosphere in 1.5 mL of 1,4-dioxane in the presence of pyridin-3-ylboronic acid (104 mg, 0.76 mmol), of tripotassium orthophosphate (1.27 mol/l, 679
20 μl, 0.86 mmol), of

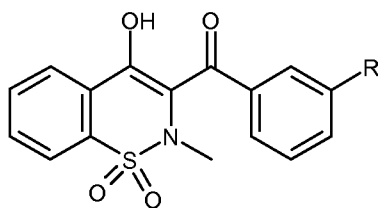
tris(dibenzylideneacetone)dipalladium (23 mg, 0.025 mmol) and of tricyclo-hexylphosphine (21 mg, 0.076 mmol). The reaction medium is heated to 100°C for 18 hours and then brought back to room temperature,
5 diluted with DCM and washed with a saturated NH₄Cl solution. The organic phase is dried on magnesium sulfate, filtered and concentrated under reduced pressure. The thereby obtained residue is purified on a column of 12 g of silica (16 mL/min, gradient of 0% to
10 5% methanol in 7 min), in order to obtain the compound **186** (128 mg, 62%).

HPLC: RT = 5.07 min, 97.5% (XBridge column)

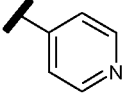
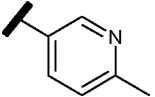
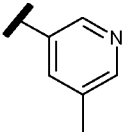
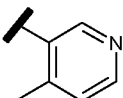
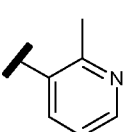
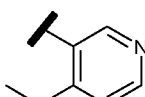
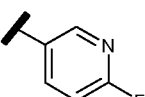
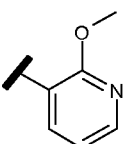
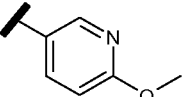
¹H NMR, dmso-d₆, (ppm): 2.67 (s, 3H); 7.77-7.82 (m, 3H); 7.98-8.01 (m, 3H); 8.11-8.15 (m, 2H); 8.22 (dd, 1H); 8.39 (s, 1H); 8.71 (d, 2H); 15.20 (broad s, 1H, exch).

Mass spectrum (ESI+): m/z 393 (MH⁺, 100%).

Examples 187 to 195



20 The compounds **187** to **195** were synthesized from the compound **144** and from various boronic acids according to the same method as described for preparing the compound **186**.

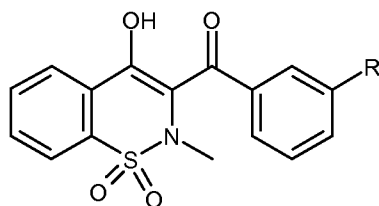
Ex. *	R	Name of the compounds	HPLC**	Yld .	M-H ⁻ (MH ⁺)
187		(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-(3-pyridin-4-yl-phenyl)-methanone	5.02' 97.5%	62%	393
188		(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-[3-(6-methyl-pyridin-3-yl)-phenyl]-methanone	5.04' 93%	49%	407
189		(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-[3-(5-methyl-pyridin-3-yl)-phenyl]-methanone	5.09' 97.9%	53%	407
190		(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-[3-(4-methyl-pyridin-3-yl)-phenyl]-methanone	5.05' 98.1%	60%	407
191		(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-[3-(2-methyl-pyridin-3-yl)-phenyl]-methanone	5.02' 100%	70%	407
192		(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-[3-(4-methoxy-pyridin-3-yl)-phenyl]-methanone	5.07' 100%	21%	423
193		(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-[3-(6-fluoro-pyridin-3-yl)-phenyl]-methanone	6.28' 97.3%	37%	411
194		(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-[3-(2-methoxy-pyridin-3-yl)-phenyl]-methanone	6.41' 96.9%	63%	423
195		(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-[3-(6-methoxy-pyridin-3-yl)-phenyl]-methanone	6.35' 97.5%	27%	423

* ¹H NMR, dmsO-d₆, Ex. **187**: 2.67 (s, 3H); 7.77-7.82 (m, 3H); 7.98-8.01 (m, 3H); 8.11-8.15 (m, 2H); 8.22 (dd, 1H); 8.39 (s, 1H); 8.71 (d, 2H); 15.20 (broad s, 1H, exch). Ex. **188**:

2.54 (s, 3H); 2.67 (s, 3H); 7.41 (d, 1H); 7.75 (t, 1H);
7.98-8.07 (m, 6H); 8.19-8.23 (m, 1H); 8.31 (s, 1H); 8.82 (s,
1H); 15.28 (broad s, 1H, exch). Ex. **189**: 2.40 (s, 3H); 2.97
(s, 3H); 7.76 (t, 1H); 7.98-8.09 (m, 6H); 8.19-8.24 (m, 1H);
5 8.32 (s, 1H); 8.48 (s, 1H); 8.76 (s, 1H); 15.25 (broad s,
1H, exch). Ex. **190**: 2.35 (s, 3H); 2.68 (s, 3H); 7.42 (d,
1H); 7.76 (d, 2H); 7.97-8.07 (m, 5H); 8.19-8.23 (m, 1H);
8.46 (s, 1H); 8.49 (d, 1H); 15.35 (broad s, 1H, exch). Ex.
191: (CDCl₃) 2.58 (s, 3H); 2.74 (s, 3H); 7.24 (dd, 1H);
10 7.51-7.64 (m, 3H); 7.78-7.84 (m, 2H); 7.91-7.96 (m, 1H);
8.10 (s, 1H); 8.19-8.23 (m, 2H); 8.56 (dd, 1H); 15.75 (s,
1H, exch). Ex. **192**: 2.70 (s, 3H); 3.93 (s, 3H); 7.24 (d,
1H); 7.69 (t, 1H); 7.82 (d, 1H); 7.96-8.00 (m, 4H); 8.17-
8.21 (m, 1H); 8.27 (s, 1H); 8.45 (s, 1H); 8.51 (d, 1H);
15 15.48 (broad s, 1H, exch). Ex. **193**: 2.67 (s, 3H); 7.37 (dd,
1H); 7.77 (t, 1H); 8.00 (broad s, 3H); 8.04-8.11 (m, 2H);
8.19-8.23 (m, 1H); 8.29 (s, 1H); 8.32-8.39 (td, 1H); 8.32
(s, 1H); 15.24 (broad s, 1H, exch). Ex. **194**: 2.70 (s, 3H);
3.95 (s, 3H); 7.16 (dd, 1H); 7.70 (t, 1H); 7.82-7.89 (m,
20 2H); 7.98-8.03 (m, 4H); 8.17-8.24 (m, 2H); 8.37 (s, 1H);
15.53 (broad s, 1H, exch). Ex. **195**: 2.67 (s, 3H); 3.92 (s,
3H); 6.98 (d, 1H); 7.73 (t, 1H); 7.99-8.05 (m, 5H); 8.09
(dd, 1H); 8.21 (broad s, 1H); 8.28 (s, 1H); 8.55 (s, 1H);
15.30 (broad s, 1H, exch).

25 ** XBridge column.

Examples 196 and 197



The compounds **196** and **197** were synthesized from saccharin and from 2-bromo-1-(3-chlorophenyl)ethanone and 2-bromo-1-(3-fluorophenyl)ethanone respectively according to the same method described for preparing the compound **1**.

Ex. *	R	Name of the compounds	HPLC**	Yld. ¹	M-H ⁻
196	Cl	(3-Chloro-phenyl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	6.43' 98.7%	37%	348/350
197	F	(3-Fluoro-phenyl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2H-benzo[e][1,2]thiazin-3-yl)-methanone	6.14' 96.5%	19%	332

¹ Overall yield for the 3 steps.

* ¹H NMR, dms_o-d₆, Ex. **196**: 2.66 (s, 3H); 7.67 (t, 1H); 7.78 (d, 1H); 7.99 (s, 5H); 8.15 (broad s, 1H); 15.07 (broad s, 1H, exch.). Ex. **197**: 2.65 (s, 3H); 7.58 (t, 1H); 7.70 (dd, 1H); 7.76 (d, 1H); 7.90 (d, 1H); 7.99 (broad s, 3H); 8.20 (broad s, 1H); 15.15 (broad s, 1H, exch.).

** XBridge column.

The derivatives of the present invention are selective inhibitors of 11 -HSD1 relatively to 11 -HSD2 as shown by the results of the models described below:

1) Human enzymatic activity of 11 β -HSD1 from liver microsomes after treatment with inhibitor compounds (inhibition %).

The enzymatic test is based on the conversion of
5 cortisone into cortisol by 11 β -HSD1. The enzymatic
reaction is started by adding 1 μ g of human hepatic
microsome (Xenotech) to wells (half volume 96-well
plates, reaction volume of 50 μ L) containing 160 nM of
cortisone in a Tris 20 mM buffer (pH 7.4) with 5 mM
10 EDTA, 200 μ M NADPH and the inhibitor compound or the
carrier (1% DMSO). A calibration curve of known
cortisol concentrations is produced simultaneously
under the same experimental conditions. The plates are
incubated for 2 hours at 37°C (enzymatic phase). By
15 adding 25 μ L of conjugate cortisol-d2 and of 25 μ L of
anti-cortisol antibody labeled with Eu³⁺ cryptate per
well, the enzymatic reaction may be stopped and after
incubation of 2 hours at room temperature the formed
cortisol (detection phase) may be quantified by HTRF®
20 (CIS bio international, reference 62CO2PEC). The
fluorescence measurements are conducted with a Fusion™
 α (Perkin Elmer) reader. For each well, fluorescence is
measured at 620 nm and at 665 nm. A ratio ($\lambda_{665 \text{ nm}}/\lambda_{620 \text{ nm}}$)
and a specific FRET signal are calculated, with which
25 an inhibition percentage may be determined for each
concentration of evaluated inhibitor compound.

References (posters):

IC₅₀ determination of Carbenoxolone and Glycyrrhetic acid on 11-beta hydroxysteroid dehydrogenase type 1 activity by HTRF®: C. Tokuda et al., Screentech, March 5 2004, San Diego (USA).

New Cortisol assay for 11-beta hydroxysteroid dehydrogenase type 1 activity using a new HTRF® acceptor, d2: M. Amoravain et al., SBS, 12th Annual Conference, September 2006, Seattle (USA).

10 2) *Human enzymatic activity of 11β-HSD1 from liver microsomes after treatment with inhibitor compounds (inhibition % or EC₅₀).*

The enzymatic test is based on the conversion of [³H] cortisone into [³H] cortisol by 11β-HSD1. The enzymatic
15 reaction is stated by adding 1 µg (standardization of this amount in order to obtain 80% of the substrate conversion maximum under the experimental conditions) of human hepatic microsomes (Xenotech) to wells (Optiplat™ 96-well plates, reaction volume of 50 µL)
20 containing 20 nM of [1,2-³H] cortisone (specific activity of 40-50 Ci/mmol, Amersham-GE Healthcare) in a 50 mM HEPES buffer at (pH 7.4) with 100 mM KCl, 5 mM NaCl, 2 mM MgCl₂, 1 mM NADPH and the inhibitor compound or the carrier (1% DMSO). The sealed plates are
25 centrifuged at low speed for mixing the components and then incubated for 2 hours at 37°C (enzymatic phase). The enzymatic reaction is stopped by adding 70 µl/well of complex [10 mg/mL of yttrium silicate SPA beads associated with the protein A (GE Healthcare) and pre-
30 incubated with an anti-cortisol monoclonal antibody

(East Coast Biologics, ME)] containing 10 μ M of 18 β -glycerrhitinic acid. The plates are sealed and then incubated under slow orbital stirring for 2 hours at room temperature (detection phase). After
5 centrifugation, measurements are conducted with a scintillation counter (TopCount NXT (Perkin Elmer). A percentage of inhibition for each evaluated compound concentration is calculated relatively to the standard enzymatic activity (carrier 1% DMSO) with which the
10 potential of each compound may then be determined (EC₅₀ obtained by the software SigmaPlot v.11, a logistic equation with 4 parameters).

References:

Development and application of a scintillation
15 proximity assay (SPA) for identification of selective inhibitors of 11 β -hydroxysteroid dehydrogenase type 1: S. Mundt et al., ASSAY and Drug Development Technologies, volume 3, number 4, 367-375, 2005.

High-throughput screening of 11 β -hydroxysteroid
20 dehydrogenase type 1 in scintillation proximity assay format: K. Solly et al., ASSAY and Drug Development Technologies, volume 3, number 4, 377-384, 2005.

3) *Human enzymatic activity of 11 β -HSD2 from kidney microsomes after treatment with the inhibitor*
25 *compounds (inhibition %).*

The enzymatic test is based on the conversion of [³H] cortisol into [³H] cortisone by 11 β -HSD2. The enzymatic reaction is started by adding 0.75 μ g (standardization of this amount in order to obtain 80% of the conversion

maximum of the substrate under the experimental conditions) of human kidney microsomes (Xenotech) to wells (Optiplate™ 96-well plates, a reaction volume of 50 µL) containing 8 nM [1,2,6,7-³H] cortisol (specific activity of 70-75 Ci/mmol, Amersham-GE Healthcare) in a 50 mM HEPES buffer (pH 7.4) with 100 mM KCl, 5 mM NaCl, 2 mM MgCl₂, 1 mM NAD⁺ and the inhibitor compound or the carrier (1% DMSO). The sealed plates are centrifuged at low speed in order to mix the components and then incubated for 2 hours at 37°C (enzymatic phase). The enzymatic reaction is stopped by adding 70 µl/well of complex [10 mg/mL of yttrium silicate SPA beads associated with protein A (GE Healthcare) and pre-incubated with an anti-cortisol monoclonal antibody (East Coast Biologics, ME)] containing 10 µM of 18β-glycerrhitinic acid. The plates are sealed and then incubated under slow orbital stirring for 2 hours at room temperature (detection phase). After centrifugation, the measurements are conducted with a scintillation counter TopCount NXT (Perkin Elmer). An inhibition percentage for each evaluated compound concentration is calculated relatively to the standard enzymatic activity (carrier 1% DMSO).

References:

- 25 Development and application of a scintillation proximity assay (SPA) for identification of selective inhibitors of 11β-hydroxysteroid dehydrogenase type 1: S. Mundt et al., ASSAY and Drug Development Technologies, volume 3, number 4, 367-375, 2005.
- 30 High-throughput screening of 11β-hydroxysteroid dehydrogenase type 1 in scintillation proximity assay

format: K. Solly *et al.*, ASSAY and Drug Development Technologies, volume 3, number 4, 377-384, 2005.

Results:

5 The few examples which follow, selected from compounds of the present invention, illustrate the quite unexpected capability of these compounds of selectively inhibiting 11 β -HSD1 relatively to 11 β -HSD2:

10

Exemples	11 β -HSD1/HTRF	11 β -HSD1/SPA		11 β -HSD2/SPA
	% inhib. (10 ⁻⁶ M)	% inhib. (10 ⁻⁶ M)	EC ₅₀ (nM)	% inhib. (10 ⁻⁵ M)
1	99	97	16	42
3	99	93	64	33
9	98	88	60	5
17	100	99	11	61
18	100	91	69	25
46	100	91	72	63
54	100	97	27	71
123	100	93	43	31
142	100	87	21	-
192	100	98	17	-

15 The object of the present invention is the compounds of general formula (I) or one of their stereoisomers or one of their salts acceptable for pharmaceutical use, for their use as a drug.

The object of the present invention is also the pharmaceutical compositions containing as an active ingredient a compound of general formula (I) or one of its stereoisomers, or one of its salts acceptable for pharmaceutical use in association with a pharmaceutically acceptable carrier, as drugs. These compositions may for example assume the form of solid, liquid compositions, emulsions, lotions or creams.

These pharmaceutical compositions containing as an active ingredient a compound of general formula (I) or one of their stereoisomers or one of their salts acceptable for pharmaceutical use may be used for inhibiting 11β -hydroxysteroid dehydrogenase type 1 (11β HSD1).

These pharmaceutical compositions containing as an active ingredient a compound of general formula (I) or one of its stereoisomers or one of its salts acceptable for pharmaceutical use for both curative and preventive treatment of diabetes of type 2.

These pharmaceutical compositions containing as an active ingredient a compound of general formula (I) or one of its stereoisomers or one of its salts acceptable for pharmaceutical use for both curative and preventive treatment of disorders related to the type 1 11β -hydroxysteroid dehydrogenase (11β HSD1); or obesity; or dyslipidemias; or arterial hypertension; or atherosclerosis and clinical pathologies which result therefrom such as coronary strokes, or cerebro-vascular strokes, or arteritis of the lower limbs; or hyperglycemias; of intolerance to glucose; or insulin-resistance; or hypertriglyceridemias; or

hypercholesterolemias; or restenoses, or
pancreatitises; or retinopathies; or nephropathies; or
neuropathies; or certain types of cancer or glaucomas.

These compositions may be administered in
5 association with an anti-diabetic such as biguanides
(for example metformine), various forms of insulin,
sulfonylureas (for example carbutamide, glibornuride,
glipizide, gliclazide, glibenclamide, glimepiride),
meglitinides (for example nateglinide, repaglinide,
10 mitiglinide), PPAR modulators (for example
pioglitazone), inhibitors of alpha-glucosidase (for
example acarbose, miglitol, voglibose), GLP-1 analogs
(for example exenatide, liraglutide), DPP-4 inhibitors
(for example sitagliptin, vildagliptin), analogs of
15 amyline (for example pramlintide).

These compositions may also be administered in
association with an anti-obesity agent such as for
example orlistat or sibutramine.

As solid compositions for oral administration,
20 tablets, pills, powders (gelatin capsules, tablets) or
granules may be used. In these compositions, the
active ingredient according to the invention is mixed
with one or more inert diluents such as starch,
cellulose, saccharose, lactose or silica, under an
25 argon stream. These compositions may also comprise
substances other than diluents, for example one or
more lubricants such as magnesium stearate or talc, a
coloring agent, a coating (dragees) or a varnish.

As liquid compositions for oral administration,
30 pharmaceutically acceptable solutions, suspensions,

emulsions, syrups and elixirs containing inert diluents such as water, ethanol, glycerol, vegetable oils or paraffin oil may be used. These compositions may comprise substances other than diluents, for example
5 wetting products, sweeteners, thickeners, flavoring agents or stabilizers.

The sterile compositions for parenteral administration may preferably aqueous or non-aqueous solutions, suspensions or emulsions. As a solvent or
10 carrier, water, propyleneglycol, polyethyleneglycol, vegetable oils, in particular olive oil, injectable organic esters for example ethyl oleate or other suitable organic solvents may be used. These compositions may also contain adjuvants, in particular
15 wetting, isotonizing, emulsifying, dispersing and stabilizing agents. Sterilization may be accomplished in several ways, for example by aseptizing filtration, by incorporating to the composition sterilizing agents, by irradiation or by heating. They may also be prepared
20 as sterile solid compositions which may be dissolved at the moment of use in sterile water or any other injectable sterile medium.

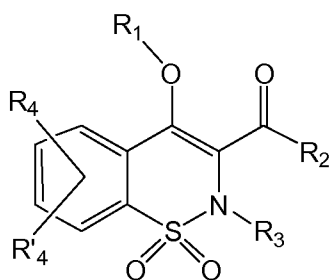
The compositions for rectal administration are suppositories or rectal capsules which contain in
25 addition to the active product, excipients such as cocoa butter, semi-synthetic glycerides or polyethyleneglycols.

The compositions for topical administration may for example be creams, lotions, collyria, collutories,
30 nasal drops or aerosols.

The doses depend on the sought effect, on the duration of the treatment and on the administration route used; they are generally comprised between 0.001 g and 1 g (preferably comprised between 0.005 g and 0.75 g) per day preferably orally for an adult with unit doses ranging from 0.1 mg to 500 mg of active substance. Generally, the physician will determine the suitable dosage depending on the age, the weight and all the other factors specific to the subject to be treated.

CLAIMS

1. Compounds fitting general formula (I):



I

5 wherein:

R_1 represents:

Hydrogen; C_1 - C_6 alkyl; COR_5 ; SO_2R_5 ; $CO(CH_2)_mR_6$;
 $CO(CH_2)_mOR_6$; $(CH_2)_mR_6$; $(CH_2)_mCONR_7R_8$; $(CH_2)_nNR_7R_8$;
 $(CH_2)_nOR_6$; CHR_7OR_9 ; $(CH_2)_mR_{10}$

10 m represents:

1 to 6

n represents:

2 to 6

R_2 represents:

A phenyl substituted with one or more groups selected from a halogen, C₁-C₆ alkyl, CN, OH, CF₃, OCF₃, SMe, COMe, CMe(OH)CF₃, CH(OH)CF₃, COOR₇, CONR₇R₁₁; a
5 phenyl, pyridine or a heterocycle different from indole in the case where R₁, R₄ and R'₄ represent a hydrogen, either non-substituted or substituted with one or more groups selected from a halogen or C₁-C₆ alkyl, CN, OH, CF₃, OCF₃, OMe, SMe; a cycloalkyl either non-
10 substituted or substituted with OH, CONH₂, SO₂Me, SO₂NH₂; C₁-C₆ alkyl aryl or cycloalkyl aryl,

Proviso: - the R₂ group is always bound to the carbonyl through a carbon atom.

- When R₂ is a phenyl, the COOR₇ substituent is never
15 in the position 4 relatively to the carbonyl.

R₃ represents:

Methyl or ethyl

R₄ and R'₄, either identical or different, represent:

Hydrogen; halogen; C₁-C₆ alkyl; CN; CF₃; OCF₃; SMe;
20 OMe; NR₇R₈; SO₂Me

R₅ represents:

C₁-C₆ alkyl; phenyl either non-substituted or substituted with one or more groups selected from halogen, C₁-C₆ alkyl, CN, OH, CF₃, OCF₃, SMe; a
25 naphthyl, either non-substituted or substituted with

one or more groups selected from halogen or C₁-C₆ alkyl, CN, OH, CF₃, OCF₃, SMe; a cycloalkyl either non-substituted or substituted with a CONH₂, SO₂Me, SO₂NH₂, heteroaryl either non-substituted or substituted with
5 one or more groups selected from halogen, C₁-C₆ alkyl, CN, OH, CF₃, OCF₃, SMe

R₆ represents:

Hydrogen; C₁-C₆ alkyl; phenyl either non-substituted or substituted with one or more groups
10 selected from halogen, C₁-C₆ alkyl, CN, OH, CF₃, OCF₃, SMe; a naphthyl or heterocycle, either non-substituted or substituted with one or more groups selected from halogen or C₁-C₆ alkyl, CN, OH, CF₃, OCF₃, SMe; a
15 cycloalkyl either non-substituted or substituted with CONH₂, SO₂Me, SO₂NH₂

R₇ represents:

Hydrogen, C₁-C₆ alkyl

R₈ represents:

Hydrogen, C₁-C₆ alkyl, phenyl either non-substituted or substituted with one or more groups
20 selected from halogen, C₁-C₆ alkyl, CN, OH, CF₃, OCF₃, SMe; a naphthyl or heterocycle, either non-substituted or substituted with one or more groups selected from halogen, C₁-C₆ alkyl, CN, OH, CF₃, OCF₃, SMe; a
25 cycloalkyl either non-substituted or substituted with CONH₂, SO₂Me, SO₂NH₂

R₇ and R₈ taken together may form a cycle of 4 to 6 members with the nitrogen atom to which they are bound and which may contain one or more heteroatoms selected from N, S or O and may either be non-substituted or
5 substituted with one or more groups selected from C₁-C₆ alkyl, C₁-C₆ alkyl aryl or aryl.

R₉ represents:

COOMe, COOEt

R₁₀ represents:

10 Halogen, COOH, COOR₇

R₁₁ represents:

Hydrogen, C₁-C₆ alkyl, C₁-C₆ alkyl cycloalkyl, cycloalkyl, aryl, C₁-C₆ alkyl aryl

as well as their stereoisomers, salts and solvates
15 acceptable for therapeutic use.

2. The compounds according to claim 1 characterized in that R₁ is a hydrogen.

3. The compounds according to claim 1 characterized in that OR₁ represents an ester or an
20 ether.

4. The compounds according to any of claims 1 to 3 characterized in that R₂ represents a naphthyl or a

1,2,3,4-tetrahydro-naphthalene or a biphenyl or a phenyl pyridine either non-substituted or substituted with one or more groups selected from a halogen, C₁-C₆ alkyl, CN, OH, CF₃, OCF₃, OMe, SMe; or a phenyl
5 substituted with one or more halogens, CN, CF₃ or C₁-C₆ alkyl.

5. The compounds according to any of claims 1 to 3 characterized in that R₄ and R'₄ represent a hydrogen.

6. A compound according to claim 1, selected from:

10 (4-Hydroxy-2-methyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl)(naphthalen-2-yl)methanone

(4-Hydroxy-2-methyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl)(adamantan-1-yl) methanone

15 (4-Hydroxy-2-methyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl)(4-methylphenyl) methanone

(4-Hydroxy-2-methyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl)(4-chlorophenyl) methanone

(4-Hydroxy-2-methyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl)(4-cyanophenyl) methanone

20 Biphenyl-4-yl-(4-hydroxy-2-methyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl) methanone

(4-Hydroxy-2-methyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl)(2,4-dichlorophenyl) methanone

(4-Hydroxy-2-ethyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl) (adamantan-1-yl) methanone

(4-Hydroxy-2-ethyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl) methanone

- 5 (4-Hydroxy-2-ethyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl) (4-methylphenyl) methanone

(4-Hydroxy-2-ethyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl) (4-chlorophenyl) methanone

- 10 Biphenyl-4-yl-(4-hydroxy-2-ethyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl)methanone

(5-Chloro-4-hydroxy-2-methyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl) methanone

(5-Chloro-4-hydroxy-2-ethyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl) methanone

- 15 (6-Fluoro-4-hydroxy-2-methyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl) methanone

(6-Fluoro-4-hydroxy-2-ethyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl) methanone

- 20 (7-Fluoro-4-hydroxy-2-methyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl) methanone

(7-Fluoro-4-hydroxy-2-ethyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl) methanone

Benzoic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-4-yl ester

Cyclohexanecarboxylic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-4-yl ester

- 5 *tert*Butylcarboxylic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-4-yl ester

4-Methylbenzoic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-4-yl ester

- 10 4-Chlorobenzoic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-4-yl ester

*tert*Butylcarboxylic acid 16-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-4-yl ester

- 15 Cyclohexanecarboxylic acid 6-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-4-yl ester

Benzoic acid 6-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-4-yl ester

- 20 4-Methylbenzoic acid 6-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-

benzo[e][1,2]thiazin-4-yl ester

*tert*Butylcarboxylic acid 6-fluoro-2-ethyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-

benzo[e][1,2]thiazin-4-yl ester

5 Cyclohexanecarboxylic acid 6-fluoro-2-ethyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-
benzo[e][1,2]thiazin-4-yl ester

Benzoic acid 6-fluoro-2-ethyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-benzo[e][1,2] thiazin-4-yl ester

10 4-Methylbenzoic acid 6-fluoro-2-ethyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-benzo [e][1,2]thiazin-4-yl ester

4-Chlorobenzoic acid 6-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-

benzo[e][1,2]thiazin-4-yl ester

15 4-Chlorobenzoic acid 6-fluoro-2-ethyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-

benzo[e][1,2]thiazin-4-yl ester

Naphthalen-1-ylcarboxylic acid 2-methyl-3-(4-methylbenzoyl)-1,1-dioxo-2*H*-

benzo[e][1,2]thiazin-4-yl ester

- Naphthalen-2-ylcarboxylic acid 2-methyl-3-(4-methylbenzoyl)-1,1-dioxo-2*H*-benzo[e] [1,2]thiazin-4-yl ester
- 5 Naphthalen-1-ylcarboxylic acid 2-methyl-3-(4-cyanobenzoyl)-1,1-dioxo-2*H*-benzo[e] [1,2]thiazin-4-yl ester
- Naphthalen-2-ylcarboxylic acid 2-methyl-3-(4-cyanobenzoyl)-1,1-dioxo-2*H*-benzo[e] [1,2] thiazin-4-yl ester
- 10 4-Chlorobenzoic acid 2-methyl-3-(4-methylbenzoyl)-1,1-dioxo-2*H*-benzo[e] [1,2] thiazin-4-yl ester
- 4-Chlorobenzoic acid 2-methyl-3-(4-cyanobenzoyl)-1,1-dioxo-2*H*-benzo[e] [1,2]thiazin-4-yl ester
- 15 (Naphthalene-2-yloxy)acetic acid 2-methyl-3-(4-methylbenzoyl)-1,1-dioxo-2*H*-benzo [e] [1,2]thiazin-4-yl ester
- (Naphthalene-2-yloxy)acetic acid 2-methyl-3-(4-cyanobenzoyl)-1,1-dioxo-2*H*-benzo[e] [1,2]thiazin-4-yl ester
- 20 (Naphthalene-1-yloxy)acetic acid 2-methyl-3-(4-methylbenzoyl)-1,1-dioxo-2*H*-benzo [e] [1,2]thiazin-4-yl ester
- 25 (Naphthalene-1-yloxy)acetic acid 2-methyl-3-(4-cyanobenzoyl)-1,1-dioxo-2*H*-benzo [e] [1,2] thiazin-4-yl ester

(4-Chlorophenoxy)acetic acid 2-methyl-3-(4-methylbenzoyl)-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-4-yl ester

5 (4-Chlorophenoxy)acetic acid 2-methyl-3-(4-cyanobenzoyl)-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-4-yl ester

Acetic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-4-yl ester

10 2,4-Dichlorobenzoic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-4-yl ester

4-Fluorobenzoic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-4-yl ester

15 Cyclopentanoic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-4-yl ester

2-Furanoic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-4-yl ester

20 Thiophen-2-carboxylic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-4-yl ester

3-Chlorobenzoic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-4-yl ester

2-Chlorobenzoic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-benzo[e][1,2] thiazin-4-yl ester

Phenoxyacetic acid 2-methyl-3-(naphthalene-2-ylcarbonyl)-1,1-dioxo-2*H*-benzo[e][1,2] thiazin-4-yl
5 ester

(4-Methoxy-2-methyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl) methanone

(4-Ethoxy-2-methyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl) methanone

10 (4-Propyloxy-2-methyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl) methanone

(4-Butyloxy-2-methyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl) methanone

(4-(2-Chloroethoxy)-2-methyl-1,1-dioxo-2*H*-
15 benzo[e][1,2]thiazin-3-yl) (p-tolyl) methanone

(4-[2-(Naphthalen-2-yloxy)ethoxy]-2-methyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl) (p-tolyl) methanone

(4-(2-Phenoxy-ethoxy)-2-methyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl) (naphthalen-2-yl) methanone

20 Methyl 2-(2-methyl-3-(4-methylbenzoyl)-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-4-yloxy) acetate

2-(2-methyl-3-(4-methylbenzoyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy)acetic acid

2-(2-Methyl-3-(4-methylbenzoyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy)-N-(naphthalen-1-yl)acetamide
5

2-(2-Methyl-3-(4-methylbenzoyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy)-N-(adamantan-1-yl)acetamide

2-(2-Methyl-3-(4-methylbenzoyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy)-N-(adamantan-2-yl)acetamide
10

Methyl 2-(1,1-dioxo-2-methyl-3-(4-methylbenzoyl)-2H-benzo[e][1,2]thiazin-4-yloxy) acetate

(1,1-dioxo-2-methyl-3-(4-methylbenzoyl)-2H-benzo[e][1,2]thiazin-4-yloxy)acetic acid
15

2-[2-Methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy]-1-piperidin-1-yl-ethanone

2-[2-Methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy]-1-(4-methyl-piperazin-1-yl)-ethanone
20

1-(4-Benzyl-piperazin-1-yl)-2-[2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy]-ethanone

(4-Chloro-phenoxy)-acetic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester

5 (Naphthalen-1-yloxy)-acetic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester

(Naphthalen-2-yloxy)-acetic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester

10 (4-[2-(naphthalen-1-yloxy)ethoxy]-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (p-tolyl)methanone

(4-[2-(4-chlorophenyloxy)ethoxy]-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (p-tolyl)methanone

15 Acetic acid 2-methyl-3-(4-methylbenzoyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester

Propanoic acid 2-methyl-3-(4-methylbenzoyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester

(4-methyloxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (p-tolyl)methanone

20 (4-ethyloxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl) (p-tolyl)methanone

[4-(2-Bromo-ethoxy)-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl]-naphthalen-2-yl-methanone

{4-[2-(4-Chloro-phenoxy)-ethoxy]-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl}-naphthalen-2-yl-methanone

Carbonic acid ethyl ester 1-[2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy]-ethyl ester

[2-Methyl-4-(2-piperidin-1-yl-ethoxy)-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl]-naphthalen-2-yl-methanone

4-Chloro-benzoic acid 5-chloro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester

Cyclohexanecarboxylic acid 5-chloro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester

Benzoic acid 5-chloro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester

4-Chloro-benzoic acid 6-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester

Cyclohexanecarboxylic acid 6-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester

Benzoic acid 6-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester

4-Chloro-benzoic acid 7-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-benzo[e] [1,2]thiazin-4-yl ester

5 Cyclohexanecarboxylic acid 7-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-benzo[e] [1,2]thiazin-4-yl ester

Benzoic acid 7-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-benzo[e] [1,2]thiazin-4-yl ester

10 Acetic acid 7-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-benzo[e] [1,2] thiazin-4-yl ester

Phenoxy-acetic acid 7-fluoro -2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-benzo[e] [1,2]thiazin-4-yl ester

15 (4-Chloro-phenoxy)-acetic acid 7-fluoro -2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2*H*-benzo[e] [1,2]thiazin-4-yl ester

(5-Chloro-4-ethoxy-2-methyl-1,1-dioxo-2*H*-benzo[e] [1,2]thiazin-3-yl)-naphthalen-2-yl-methanone

20 (5-Chloro-4-propoxy-2-methyl-1,1-dioxo-2*H*-benzo[e] [1,2]thiazin-3-yl)-naphthalen-2-yl-methanone

(6-Fluoro-4-methoxy-2-methyl-1,1-dioxo-2*H*-benzo[e] [1,2]thiazin-3-yl)-naphthalen-2-yl-methanone

(6-Fluoro-4-ethoxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl)-naphthalen-2-yl-methanone

(6-Fluoro-4-propoxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl)-naphthalen-2-yl-methanone

5 (7-Fluoro-4-methoxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl)-naphthalen-2-yl-methanone

(7-Fluoro-4-ethoxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl)-naphthalen-2-yl-methanone

10 (7-Fluoro-4-propoxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl)-naphthalen-2-yl-methanone

[7-Fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy]-acetic acid methyl ester

15 [7-Fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy]-acetic acid methyl ester

2-[7-Fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy]-1-piperidin-1-yl-ethanone

20 2-[7-Fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy]-1-(4-methylpiperazin-1-yl)-ethanone

1-(4-Benzyl-piperazin-1-yl)-2-[7-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yloxy]-ethanone

Benzenesulfonic acid 7-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester

Benzenesulfonic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester

4-Chloro-benzenesulfonic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester

4-Methyl-benzenesulfonic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester

4-Cyano-benzenesulfonic acid 2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester

4-Chloro-benzenesulfonic acid 7-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester

4-Methyl-benzenesulfonic acid 7-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester

4-Cyano-benzenesulfonic acid 7-fluoro-2-methyl-3-(naphthalene-2-carbonyl)-1,1-dioxo-2H-benzo[e][1,2]thiazin-4-yl ester

(4-Hydroxy-2-methyl-1,1-dioxo-7-piperidin-1-yl-2H-benzo[e][1,2]thiazin-3-yl)-naphthalen-2-yl-methanone

(7-Dimethylamino-4-hydroxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl)-naphthalen-2-yl-methanone

- 5 (4-Hydroxy-2-methyl-1,1-dioxo-7-pyrrolidin-1-yl-2H-benzo[e][1,2]thiazin-3-yl)-naphthalen-2-yl-methanone

[4-Hydroxy-2-methyl-1,1-dioxo-7-(4-phenyl-piperazin-1-yl)-2H-benzo[e][1,2]thiazin-3-yl]-naphthalen-2-yl-methanone

- 10 (7-*tert*butyl-4-hydroxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl)(naphthalen-2-yl) methanone

(4-hydroxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl)(3,4-dichlorophenyl) methanone

- 15 (4-Hydroxy-2-ethyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl)(3,4-dichlorophenyl) methanone

(4-Hydroxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl)(benzofuran-2-yl) methanone

(4-Hydroxy-2-ethyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl)(benzofuran-2-yl) methanone

- 20 (4-Hydroxy-2-methyl-1,1-dioxo-2H-benzo[e][1,2]thiazin-3-yl)-(5,6,7,8-tetrahydro-naphthalen-2-yl)-methanone

(4-Hydroxy-2-methyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl)-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-methanone

(7-Fluoro-4-hydroxy-2-methyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl)-(5,6,7,8-tetrahydro-naphthalen-2-yl)-methanone

(7-Fluoro-4-hydroxy-2-methyl-1,1-dioxo-2*H*-benzo[e][1,2]thiazin-3-yl)-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-methanone

10 (2,3-Dihydro-benzofuran-5-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-methanone

(2,3-Dihydro-benzofuran-5-yl)-(4-hydroxy-2-ethyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-methanone

Benzo[1,3]dioxol-5-yl-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-methanone

Benzo[1,3]dioxol-5-yl-(4-hydroxy-2-ethyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-methanone

20 (2,3-Dihydro-benzo[1,4]dioxin-6-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-methanone

(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-(4-hydroxy-2-ethyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-methanone

Benzo[b]thiophen-5-yl-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e] [1,2]thiazin-3-yl)-methanone

Benzofuran-5-yl-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e] [1,2]thiazin-3-yl)-methanone

- 5 (4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e] [1,2]thiazin-3-yl)-(1-methyl-1*H*-benzoimidazol-5-yl)-methanone

Benzo[b]thiophen-2-yl-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e] [1,2]thiazin-3-yl)-methanone

- 10 (4-tert-Butyl-phenyl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e] [1,2]thiazin-3-yl)-methanone

(3-Bromo-phenyl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e] [1,2]thiazin-3-yl)-methanone

- 15 3-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e] [1,2]thiazine-3-carbonyl)-benzonitrile

(3,4-Dimethyl-phenyl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e] [1,2]thiazin-3-yl)-methanone

- 20 (4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e] [1,2]thiazin-3-yl)-(3-trifluoromethyl-phenyl)-methanone

(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e] [1,2]thiazin-3-yl)-(4-trifluoromethyl-phenyl)-methanone

Adamantan-2-yl-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-methanone

Chroman-6-yl-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-methanone

- 5 (4-Chloro-3-trifluoromethyl-phenyl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-methanone

(7-Bromo-4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-naphthalen-2-yl-methanone

- 10 (7-Chloro-4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-naphthalen-2-yl-methanone

(4-Hydroxy-2,7-dimethyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-naphthalen-2-yl-methanone

- 15 Biphenyl-3-yl-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-methanone

(2'-Fluoro-biphenyl-3-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-methanone

- 20 (3'-Fluoro-biphenyl-3-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-methanone

(4'-Fluoro-biphenyl-3-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e] [1,2]thiazin-3-yl)-methanone

5 (2'-Choro-biphenyl-3-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e] [1,2]thiazin-3-yl)-methanone

(3'-Choro-biphenyl-3-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e] [1,2]thiazin-3-yl)-methanone

(4'-Choro-biphenyl-3-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e] [1,2]thiazin-3-yl)-methanone

10 (2'-Methyl-biphenyl-3-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e] [1,2]thiazin-3-yl)-methanone

15 (3'-Methyl-biphenyl-3-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e] [1,2]thiazin-3-yl)-methanone

(4'-Methyl-biphenyl-3-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e] [1,2]thiazin-3-yl)-methanone

20 (2'-Methoxy-biphenyl-3-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e] [1,2]thiazin-3-yl)-methanone

(3'-Methoxy-biphenyl-3-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e] [1,2]thiazin-3-yl)-methanone

(4'-Methoxy-biphenyl-3-yl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-methanone

5 (4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-(3'-trifluoromethyl-biphenyl-3-yl)-methanone

(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-(4'-trifluoromethyl-biphenyl-3-yl)-methanone

10 3'-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazine-3-carbonyl)-biphenyl-3-carbonitrile

15 3'-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazine-3-carbonyl)-biphenyl-4-carbonitrile

(4-Hydroxy-7-methanesulfonyl-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-naphthalen-2-yl-methanone

20 (4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-(1-phenyl-cyclopropyl)-methanone

1-[3-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazine-3-carbonyl)-phenyl]-ethanone

(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-
benzo[e][1,2]thiazin-3-yl)-[3-(2,2,2-trifluoro-1-
hydroxy-1-methyl-ethyl)-phenyl]-methanone

(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-
5 benzo[e][1,2]thiazin-3-yl)-[3-(2,2,2-trifluoro-1-
hydroxy-ethyl)-phenyl]-methanone

3-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-
benzo[e][1,2]thiazine-3-carbonyl)-benzoic acid

3-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-
10 benzo[e][1,2]thiazine-3-carbonyl)-*N*-methyl-benzamide

3-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-
benzo[e][1,2]thiazine-3-carbonyl)-*N,N*-dimethyl-
benzamide

N-Ethyl-3-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-
15 benzo[e][1,2]thiazine-3-carbonyl)-benzamide

3-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-
benzo[e][1,2]thiazine-3-carbonyl)-*N,N*-diethyl-benzamide

N-Cyclopropyl-3-(4-hydroxy-2-methyl-1,1-dioxo-1,2-
dihydro-2*H*-benzo[e][1,2] thiazine-3-carbonyl)-benzamide

20 *N*-Cyclopropylmethyl-3-(4-hydroxy-2-methyl-1,1-dioxo-
1,2-dihydro-2*H*-benzo[e][1,2]thiazine-3-carbonyl)-
benzamide

3-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazine-3-carbonyl)-*N*-phenyl-benzamide

N-Benzyl-3-(4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazine-3-carbonyl)-benzamide

- 5 3-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazine-3-carbonyl)-benzamide

3-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazine-3-carbonyl)-benzoic acid ethyl ester

- 10 (4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-(3-pyridin-3-yl-phenyl)-methanone

- (4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-(3-pyridin-4-yl-phenyl)-methanone
15

(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-[3-(6-methyl-pyridin-3-yl)-phenyl]-methanone

- (4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-[3-(5-methyl-pyridin-3-yl)-phenyl]-methanone
20

(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-[3-(4-methyl-pyridin-3-yl)-phenyl]-methanone

(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-
benzo[e][1,2]thiazin-3-yl)-[3-(2-methyl-pyridin-3-yl)-
phenyl]-methanone

(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-
5 benzo[e][1,2]thiazin-3-yl)-[3-(4-methoxy-pyridin-3-yl)-
phenyl]-methanone

(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-
benzo[e][1,2]thiazin-3-yl)-[3-(6-fluoro-pyridin-3-yl)-
phenyl]-methanone

10 (4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-
benzo[e][1,2]thiazin-3-yl)-[3-(2-methoxy-pyridin-3-yl)-
phenyl]-methanone

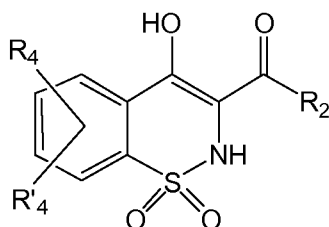
(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-2*H*-
benzo[e][1,2]thiazin-3-yl)-[3-(6-methoxy-pyridin-3-yl)-
15 phenyl]-methanone

(3-Chloro-phenyl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-
dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-methanone

(3-Fluoro-phenyl)-(4-hydroxy-2-methyl-1,1-dioxo-1,2-
dihydro-2*H*-benzo[e][1,2]thiazin-3-yl)-methanone

20

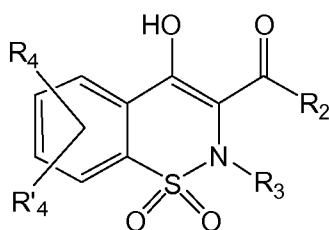
7. A method for preparing the compounds of
general formula (Ia) which corresponds to formula I
according to any of claims 1 to 6 wherein R₁ represents
a hydrogen atom characterized in that an intermediate
25 of general formula (IV) is condensed



IV

wherein R_2 , R_4 , et R'_4 are defined according to claim 1,
 with an intermediate of general formula R_3 -Y wherein R_3
 5 is defined according to claim I and Y represents a
 leaving group.

8. A method for preparing the compounds of
 general formula (Ib) which corresponds to formula I
 according to any of claims 1 to 6, wherein R_1 is
 10 different from a hydrogen atom characterized in that an
 intermediate of general formula (Ia) is condensed

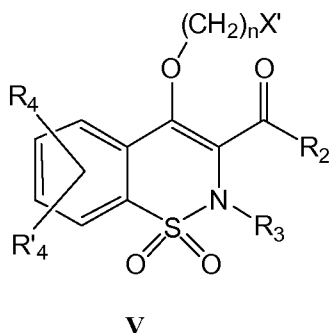


Ia

wherein R_2 , R_3 , R_4 , and R'_4 are defined according to
 claim 1, with an intermediate of general formula R_1 -Z
 15 wherein R_1 is defined as earlier and Z represents a
 leaving group.

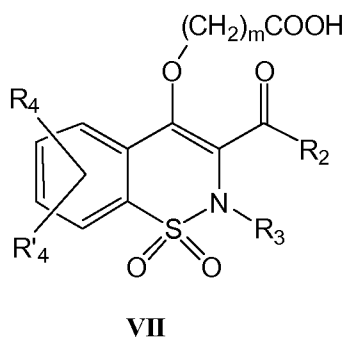
9. A method for preparing the compounds of
 general formula (Ic) which corresponds to formula I

according to any of claims 1 to 6 wherein R_1 represents $(CH_2)_nNR_7R_8$ or $(CH_2)_nOR_6$ characterized in that an intermediate of general formula (V) is condensed



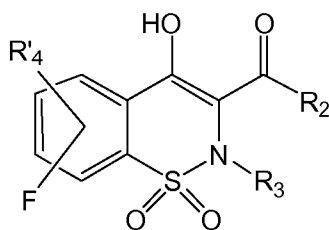
- 5 wherein R_2 , R_3 , R_4 , R'_4 , n are defined according to claim 1 and X' represents a leaving group, with an intermediate of general formula R_7R_8NH or R_6OH wherein R_7 , R_8 and R_6 are defined according to claim 1.

10. A method for preparing the compounds of general formula (Id) which corresponds to formula I according to any of claims 1 to 6 wherein R_1 represents $(CH_2)_nCONR_7R_8$ characterized in that an intermediate of general formula (VII) is condensed



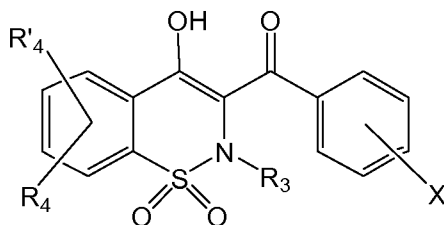
- 15 wherein R_2 , R_3 , R_4 , R'_4 and m are defined according to claim 1, with an intermediate of general formula R_7R_8NH wherein R_7 and R_8 are defined according to claim 1.

11. A method for preparing the compounds of general formula (If) which corresponds to formula I according to any of claims 1 to 6 wherein R_4 represents NR_7R_8 characterized in that an intermediate of general
5 formula (Ie) is condensed

**Ie**

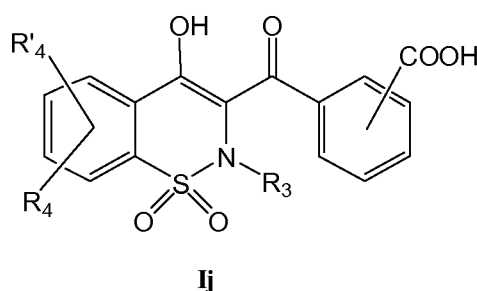
wherein R_2 , R_3 , and R'_4 are defined according to claim 1, with an intermediate of general formula R_7R_8NH wherein R_7 and R_8 are defined according to claim 1.

- 10 12. A method for preparing the compounds of general formula (Ih) which corresponds to formula I according to any of claims 1 to 6 wherein R_2 represents a biphenyl or phenyl pyridine either substituted or not, characterized in that an intermediate of general
15 formula (Ig) is condensed

**Ig**

wherein R_3 , R_4 , R'_4 are defined according to claim 1 and X represents a leaving group, with a boronic acid.

13. A method for preparing the compounds of general formula (Ik) which corresponds to formula I according to any of claims 1 to 6 wherein R_2 represents a phenyl substituted with an amide in the ortho or meta position characterized in that an intermediate of general formula (Ij) is condensed



- wherein R_3 , R_4 , R'_4 are defined according to claim 1, with an amine of general formula $R_7R_{11}NH$ wherein R_7 and R_{11} are defined according to claim 1.

14. The compounds according to any of claims 1 to 6 for their use as drugs.

15. Pharmaceutical compositions containing as an active ingredient at least one compound according to any of claims 1 to 6, in combination with a pharmaceutically acceptable carrier, as drugs.

16. The pharmaceutical compositions according to claim 15 as an inhibitor of type 1 11β -hydroxysteroid dehydrogenase (11β HSD1).

17. The pharmaceutical compositions according to claim 15 for both curative and preventive treatment of diabetes of type 2.

18. The pharmaceutical compositions according to claim 15, for the both curative and preventive treatment of disorders related to type 1 11β -hydroxysteroid dehydrogenase (11β HSD1); or of obesity;
5 or dyslipidemias; or arterial hypertension; or atherosclerosis and clinical pathologies which result therefrom such as coronary strokes, or cerebro-vascular strokes or arteritis of the lower limbs; or hyperglycemias; or intolerance to glucose; or insulin-
10 resistance; or hypertriglyceridemias; or hypercholesterolemias; or restenoses; or pancreatitises; or retinopathies; or nephropathies; or neuropathies; or certain types of cancer or glaucomas.

19. The pharmaceutical compositions according to
15 claim 15 in combination with a pharmaceutically acceptable carrier and administered in association with an anti-diabetic agent such as biguanides, various forms of insulin, sulfonylureas, meglitinides, PPAR modulators, alpha-glucosidase inhibitors, GLP-1
20 analogs, DPP-4 inhibitors, amyline analogs.

20. The pharmaceutical compositions according to claim 15 in combination with a pharmaceutically acceptable carrier and administered in association with an anti-obesity agent such as for example orlistat or
25 sibutramine.