The invention relates to compounds acting as selective antagonists of Transient Receptor Potential cation channel subfamily M member 8 (TRPM8), and having formula (I). Said compounds are useful in the treatment of diseases associated with activity of TRPM8 such as pain, inflammation, ischaemia, neurodegeneration, stroke, psychiatric disorders, itch, irritable bowel diseases, cold induced and/or exacerbated respiratory disorders and urological disorders.
2-ARYL-4- HYDROXY-1,3-THIAZOLE DERIVATIVES USEFUL AS TRPM8-INHIBITORS IN TREATMENT OF NEURALGIA, PAIN, COPD AND ASThma

Brief description of the invention

The present invention relates to 2-aryl-4-hydroxy-1,3-thiazole derivatives that are useful for the prevention, reduction of the risk of, amelioration and/or treatment of diseases associated with the activity of the Transient Receptor Potential cation channel subfamily M member 8 (hereinafter TRPM8) also known as Cold Menthol Receptor 1 (CMR-1), and in particular for the prevention, reduction of the risk of, amelioration and/or treatment of itch, irritable bowel diseases, cold induced and/or exacerbated respiratory disorders, ischaemia, pain, neurodegeneration, psychiatric disorders, stroke and urological disorders. The invention further relates to pharmaceutical compositions containing the above compounds.

Background of the invention

Transient Receptor Potential (TRP) channels are one of the largest group of ion channels and, based on their sequence homology, are classified into 6 sub-families (TRPV, TRPM; TRPA, TRPC, TRPP and TRPML). TRP channels are cation-selective channels activated by several physical (such as temperature, osmolarity and mechanical stimuli) and chemical stimuli. TRPM8, which was cloned in 2002, is a non-selective cation channel of the TRP family expressed on a subpopulation of somatic sensory nerves on dorsal root ganglion and trigeminal ganglia that causes sensory nerve excitation. It is activated by mild cold temperatures and synthetic cool-mimetic compounds such as menthol, eucalyptol and icilin [McKemy D.D. et al., Nature (2002) 416, 52-58; Peier A.M. et al. Ca// (2002) 108, 705-715]. Like several other TRP channels, TRPM8 is also gated by voltage [Nilius B. et al., J. Physiol. (2005) 567, 35-44]. The voltage dependence of TRPM8 is characterized by a strong outward rectification at depolarized transmembrane potential and a rapid and potential-dependent closure at negative membrane potentials. Cooling agents and menthol application shifts the activation curve towards more negative potentials, increasing the possibility for the opening of the channel and boosting inward currents at physiological membrane potentials. Other endogenous factors, such as phospholipase A2 products [Vanden Abeele F. et al., J. Biol.Chem. (2006) 281, 401 74-401 82], endocannabinoids [De Petrocellis L. et al., Exp.Cell. Res. (2007) 313, 1911-1920] and PIP2 [Rohacs T. et al., Nat. Neurosci. (2005) 8, 626-634] also participate in channel regulation.

There is a lot of direct and indirect evidence of a pivotal role of TRPM8 channel activity in diseases such as pain, ischemia and itch, irritable bowel diseases, cold induced and/or exacerbated respiratory disorders. Further, it has been demonstrated that TRP channels transduce reflex signals that are involved in the overactive bladder of patients with damaged or abnormal spinal reflex pathways [De Groat W.C. et al., Urology (1997) 50, 36-52]. TRPM8 is activated by temperatures between 8°C and 28°C and expressed on the primary nociceptive neurons, including bladder urothelium, dorsal root ganglia, A-delta and C-fibers. The intravesical ice water or menthol also induce C-fiber mediated spinal micturition reflex in patients with urgency and urinary incontinence [Everaerts W. et al., Neurol. Urodyn. (2008) 27, 264-73].

Furthermore, TRPM8 is known to regulate Ca²⁺ concentration influxes in response to cold temperature or pharmacological stimuli. Finally, in a recent paper, the potential role of TRPM8 in cold-induced asthma and in
asthma exacerbation has been proposed, suggesting TRPM8 also a relevant target for the management of these pathologies [Xing H. et al., Molecular Pain (2008), 4, 22-30]. The expression of the channel in brain, lung, bladder, gastrointestinal tract, blood vessels, prostate and immune cells provide further possibility for therapeutic modulation of the activity of TRPM8 in a wide range of pathologies. In particular, the disorders or diseases that have been proven to be affected by the modulation of TRPM8 are pain such as chronic pain, neuropathic pain including cold allodynia and diabetic neuropathy, postoperative pain, osteoarthritic pain, rheumatoid arthritic pain, cancer pain, neuralgia, neuropathies, algesia, fibromyalgia, nerve injury, migraine, headaches; ischaemia, neurodegeneration, stroke, psychiatric disorders, including anxiety and depression, and itch, irritable bowel diseases, cold induced and/or exahcerbated respiratory disorders such as cold induced and/or exahcerbated pulmonary hypertension, asthma and COPD; urological disorders such as painful bladder syndrome, interstitial cystitis, detrusor overactivity (overactive bladder), urinary incontinence, neurogenic detrusor overactivity (detrusor hyperflexia), idiopathic detrusor overactivity (detrusor instability), benign prostatic hyperplasia, lower urinary tract disorders and lower urinary tract symptoms [Nilius B. et al. Science STKE (2005), 295, re8; Voets T. et al., Nat. Chem. Biol. (2005), 1, 85-92; Mukerji G. et al., Urology (2006), 6, 31-36; Lazzeri M. et al., Ther. Adv. Urol. (2009), 1, 33-42; Nilius B. et al., Biochim. Biophys. Acta (2007), 1772, 805-12; Wissenbach U. et al., Biol. Cell. (2004), 96, 47-54; Nilius B. et al., Physiol. Rev. (2007), 87, 165-217; Proudfoot C.J. et al., Curr. Biol. (2006), 16, 1591-1605].

Along the last few years, several classes of non peptide TRPM8 antagonists have been disclosed. WO 2006/0401 36, WO 2007/01 7092, WO 2007/01 7093, WO 2007/01 7094, and WO 2007/0801 09 describe benzyloxy derivatives as TRPM8 antagonists for the treatment of urological disorders; WO 2007/1 341 07 describes phosphorous-bearing compounds as TRPM8 antagonists for the treatment of TRPM8-related disorders; WO 2009/01 2430 describes sulfonamides for the treatment of diseases associated with TRPM8; WO 201 0/1 03381 describes the use of spirocyclic piperidine derivatives as TRPM8 modulators in prevention or treatment of TRPM8-related disorders or diseases; WO 201 0/1 25831 describes sulfamoyl benzoic acid derivatives as modulators of the TRPM8 receptor and their use in the treatment of inflammatory, pain and urological disorders; and WO 2013/09271 1 describes 2-aryl oxazole and thiazole derivatives as TRPM8 receptor modulators and their use in prevention, reduction of the risk of, amelioration and/or treatment of urological-related disorders.

A therapeutic area in which there is still a particularly high need for the development of antagonists of TRPM8 is that of urological disorders and associated pain. In fact, traditional drugs and medications currently available for the treatment of urinary incontinence and disorders are characterized by several side effects. For example, at the moment, the therapy of overactive bladder syndrome is based on the use of drugs, especially anticholinergic agents that affect peripheral neural control mechanisms or bladder detrusor smooth muscle contraction. These drugs inhibit parasympathetic nerves exerting a direct spasmolytic effect on the muscle of the bladder. The result of this action is the decrease of intravesicular pressure, an increase in capacity and a reduction in the frequency of bladder contraction. However, the use of anticholinergic agents is associated with serious side effects, such as dry mouth, abnormal visions, constipation and CNS disturbances, that impair the
overall patient compliance. The inadequacies of the actual therapies highlight the need for novel, efficacious and safe drugs with fewer side effects.

Summary of the invention

The aim of the present invention is to provide novel antagonists of TRPM8 with high selectivity for this specific receptor and an adequate pharmacokinetic profile for use in therapy.

The present inventors have now found a class of 2-aryl-4-hydroxy-1,3-thiazole compounds acting as selective antagonists of Transient Receptor Potential cation channel subfamily M member 8 (hereinafter referred to as TRPM8), suited with good oral bioavailability and satisfying the above desiderata.

These compounds are useful in the treatment of a disease associated with the activity of TRPM8, preferably a disease deriving from overexpression and/or hyperactivity of TRPM8 receptor.

Detailed description of the Figures

Fig. 1 and 2 show a graph with a typical response obtained in the test described in example 47.

Fig. 1 shows mechanical antiallodynic effect in rats treated with compound 2 (DFL23693os), on day 7 (Fig 1a) and 14 (Fig 1b) following ligation, versus sham rats (Sham) and rats that received vehicle (vehicle).

Fig. 2 shows cold antiallodynic effect in rats treated with compound 2 (DFL23693os) on day 7 (Fig 2a) and 14 (Fig 2b) following ligation, versus sham rats (Sham) and rats that received vehicle (vehicle).

In both Figures the sign * means p<0.05; sign ** means p<0.01 ; sign *** means p<0.001 vs vehicle as measured by two-way ANOVA followed by Dunnett’s test.

Detailed description of the invention

A first object of the present invention are compounds of formula (I):

\[
\text{X} \quad \text{R}_1
\]

\[
\text{R}_2 \quad \text{R}_3 \quad \text{R}_4
\]

\[
\text{OH}
\]

wherein

X is oxygen, sulphur, NH, NOH, or NOMe;

R is a group selected from aryl and heteroaryl, optionally substituted by one or more substituents selected from

- hydrogen,
- halogen,
- \(\text{CF}_3\),
- linear or branched \(\text{C}_1-\text{C}_6\) alkyl,

- OR5 and
- NR6R7, wherein R5, R6 and R7 are independently hydrogen or linear or branched \(\text{C}_1-\text{C}_6\) alkyl;

R1 is a group selected from
- linear or branched C1-Ce alkyl,
- \((CH_2)_m\)-OR2, wherein \(m\) is an integer between 1 and 3 and R2 is selected from hydrogen and linear C1-C3 alkyl,
- C3-C6 cycloalkyl, and
- N(R3)OR4, wherein R3 and R4 are independently hydrogen or linear or branched C1-C3 alkyl, and pharmaceutically acceptable salts thereof.

According to a first preferred embodiment of the invention in said compounds of formula (I) R1 is selected from:
- linear or branched C1-C6 alkyl,
- \((CH_2)_m\)-OR2 wherein m is 1 and R2 is linear C1-C3 alkyl,
- C3-C6 cycloalkyl, or
- N(R3)OR4, wherein R3 and R4 are as defined above.

Particularly preferred compounds of the invention according to this embodiment are compounds of formula (I) wherein R1 is
- linear or branched C1-C6 alkyl,
- \((CH_2)_m\)-OR2 wherein m is 1 and R2 is CH3,
- cyclopropyl,
- or
- N(R3)OR4, wherein R3 and R4 are independently C1-C3 alkyl, preferably CH3.

According to a second preferred embodiment of the invention, also in combination with the preceding embodiment, in the above compounds of formula (I), R1 is not methyl.

Particularly preferred compounds according of this embodiment are compounds wherein R1 is selected from the group consisting of ethyl, isopropyl, isobutyl, CH2OCH3, cyclopropyl and N(CH3)OCH3.

According to a third preferred embodiment of the invention, also in combination with the first embodiment, R1 is selected from the group consisting of methyl, ethyl, isopropyl, isobutyl, CH2OCH3, cyclopropyl and N(CH3)OCH3.

According to a further preferred embodiment of the invention, also in combination with the first and third embodiment, in the above compounds of formula (I) when R1 is methyl, R is not selected from 3-pyridyl, 4-chlorophenyl, 4-trifluoromethylphenyl, 3-thiophenyl, 3-thiazolyl-(2-methyl), phenyl, thiazole, 2-4-difluorophenyl, 4-methoxyphenyl and 2-methylthiazole.

According to another preferred embodiment of the invention, also in combination with any of the preceding embodiments, X is oxygen.

According to a further preferred embodiment of the invention, also in combination with any of the preceding embodiments, said aryl is phenyl and said heteroaryl is a 5- or 6-membered heteroaryl containing from 1 to 3 heteroatoms selected from N, O and S. Preferably, said 5- or 6-membered heteroaryl is selected from the group consisting of thiophenyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, oxadiazolyl, oxazolyl and pyridinyl.
According to a further preferred embodiment of the invention, also in combination with any of the preceding embodiments, in said compounds of formula (I), wherein R is aryl, the aryl is optionally substituted with a group selected from:

- halogen, preferably selected from Br and F;
- linear or branched C1-C3 alkyl, preferably CH3;
- OR5 and NR6R7, wherein R5, R6 and R7 are independently hydrogen or linear C1-C3 alkyl.

Preferred identities of OR5 and NR6R7 are OH, NH2 and NHCH3, respectively.

According to a further preferred embodiment of the invention, also in combination with any of the preceding embodiments, in said compounds of formula (I), wherein R is heteroaryl, this is optionally substituted with linear or branched C1-C6 alkyl, preferably with CH3.

Particularly preferred compounds of formula (I) of the invention are those wherein R is selected from the group consisting of 3-fluorophenyl, 4-fluorophenyl, 2-bromophenyl, 3-bromophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-aminophenyl, 4-aminophenyl, 3-methylaminophenyl, 4-methylaminophenyl, thiophen-2yl, furan-2yl, pyrrol-2yl, 1H-imidazol-5yl, 1-methyl-imidazol-5yl, pyrazol-4yl, 1,2,4-oxadiazol-3yl, pyridin-2yl, pyridin-3yl and pyridin-4yl.

Particularly preferred compounds of formula (I) according to the invention are selected from:

1-[2-(3-fluorophenyl)-4-hydroxy-1,3-thiazol-5-yl]propan-1-one (compound n. 1)
2-(3-fluorophenyl)-4-hydroxy-N-methoxy-N-methyl-1,3-thiazole-5-carboxamide (compound n. 3)
1-(2-(3-fluorophenyl)-4-hydroxythiazol-5-yl)ethanone (compound n. 4)
1-[2-(3-fluorophenyl)-4-hydroxy-1,3-thiazol-5-yl]-2-methylpropan-1-one (compound n. 5)
4-hydroxy-N-methoxy-N-methyl-2-(thiophen-2-yl)-1,3-thiazole-5-carboxamide (compound n. 6)
1-[4-hydroxy-2-(thiophen-2-yl)-1,3-thiazol-5-yl]propan-1-one (compound n. 7)
4-hydroxy-N-methoxy-N-methyl-2-(2-methylphenyl)-1,3-thiazole-5-carboxamide (compound n. 8)
1-[4-hydroxy-2-(2-methylphenyl)-1,3-thiazol-5-yl]propan-1-one (compound n. 9)
2-(2-bromophenyl)-4-hydroxy-N-methoxy-N-methyl-1,3-thiazole-5-carboxamide (compound n. 10)
1-[2-(2-bromophenyl)-4-hydroxy-1,3-thiazol-5-yl]propan-1-one (compound n. 11)
4-hydroxy-2-(2-hydroxyphenyl)-N-methoxy-N-methyl-1,3-thiazole-5-carboxamide (compound n. 12)
1-[2-(2-hydroxyphenyl)-4-hydroxy-1,3-thiazol-5-yl]propan-1-one (compound n. 13)
1-[2-(3-bromophenyl)-4-hydroxy-1,3-thiazol-5-yl]propan-1-one (compound n. 14)
1-[2-(furan-2-yl)-4-hydroxy-1,3-thiazol-5-yl]propan-1-one (compound n. 15)
1-[4-hydroxy-2-(1H-pyrrol-2-yl)-1,3-thiazol-5-yl]propan-1-one (compound n. 16)
1-[4-hydroxy-2-(1-methyl-1H-pyrrol-2-yl)-1,3-thiazol-5-yl]propan-1-one (compound n. 17)
1-[4-hydroxy-2-(1-methyl-1H-imidazol-5-yl)-1,3-thiazol-5-yl]propan-1-one (compound n. 18)
1-[4-hydroxy-2-(1H-imidazol-5-yl)-1,3-thiazol-5-yl]propan-1-one (compound n. 19)
1-[4-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,3-thiazol-5-yl]propan-1-one (compound n. 20)
1-[4-hydroxy-2-(thiophen-2-yl)-1,3-thiazol-5-yl]butan-1-one (compound n. 21)
1-[4-hydroxy-2-(thiophen-2-yl)-1,3-thiazol-5-yl]-3-methylbutan-1-one (compound n. 22)
1-[4-hydroxy-2-(1,2,4-oxadiazol-3-yl)-1,3-thiazol-5-yl]propan-1-one (compound n. 23)
1-[4-hydroxy-2-(1,2-oxazol-5-yl)-1,3-thiazol-5-yl]propan-1-one (compound n. 24)
1-[4-hydroxy-2-(pyridin-4-yl)-1,3-thiazol-5-yl]propan-1-one (compound n. 26)
1-[4-hydroxy-2-(2-hydroxyphenyl)-N-methoxy-N-methyl-1,3-thiazole-5-carboxamide
4

Thus, assay was reached at 3 hours after treatment (about 50% of inhibition on both the parameters), see Example 47 below.

Most particularly preferred compounds of formula (I) according to the invention are selected from:

sodium 2-(3-fluorophenyl)-5-propanoyl-1,3-thiazol-4-olate (compound n. 2)
2-(3-fluorophenyl)-4-hydroxy-N-methoxy-N-methyl-1,3-thiazole-5-carboxamide (compound n. 3)
4-hydroxy-2-(2-hydroxyphenyl)-N-methoxy-N-methyl-1,3-thiazole-5-carboxamide (compound n. 12) and
1-[4-hydroxy-2-(3-fluorophenyl)-1,3-thiazol-5-yl]propan-1-one (compound n. 28).

As it will be described in details in Example 46, the present inventors have found that the above compounds 1-

45 are potent antagonists of TRPM8.

In details, all of the above compounds have been tested in a high-throughput screening (HTS) cellular-based

12)

40)

28).

Thus, a second object of the present invention are the above compounds of formula (I) for use as antagonists of

TRPM8, preferably of human TRPM8.

Oral administration of a compound of formula (I) representative of the present invention significantly attenuated
cold and mechanical alldynia at 3 hours and 5 hours post-dose. The maximal activity was reached at 3 hours
after treatment (about 50% of inhibition on both the parameters), see Example 47 below.
Moreover, the same representative compound showed a high selectivity versus a wide range of selected GPCRs as well as towards TRPV1, TRPV4 and TRPA1 thus confirming its selective mechanism of action, see Example 48 below. 

Finally, as reported in Example 49 below, the tested compound shows no effect towards any human cytochrome isoform thus excluding potential drug drug interaction. In addition, none effect was observed towards hERG channel thus excluding potential cardiotoxic effect during the clinical development. The low logD values of the tested compound makes it particularly suitable when ip, iv and ives applications are required, especially in the treatment of urological disorders. At the same time, the relatively high plasma half-life and the high oral bioavailability could makes it the ideal candidate for the treatment of chronic diseases, like inflammatory and neuropathic pain. 

Thus, the above disclosed compounds of the invention are particularly suitable to be used in therapy. Accordingly, a third object of the present invention are the above compounds of formula (I) for use as medicaments. 

A fourth object of the present invention are the above compounds of formula (I) for use in the prevention, reduction of the risk of, amelioration and/or treatment of a disease associated with activity of TRPM8, preferably a disease deriving from overexpression and/or hyperactivity of TRPM8 receptor. 

According to the present invention, by "overexpression and/or hyperactivity of TRPM8 receptor" it is meant an expression and/or activity of TRPM8 receptor higher than at physiological level. 

According to the present invention, by "disease that is associated with activity of TRPM8" it is preferably meant a disease selected from pain, itch, irritable bowel diseases, cold induced and/or exacerbated respiratory disorders, ischaemia, neurodegeneration, stroke, urological disorders, and psychiatric disorders. 

Preferably, said pain is selected from chronic pain, cancer pain, neuropathic pain, which is meant to include cold allodynia and diabetic neuropathy, postoperative pain, osteoarthritic pain, rheumatoid arthritic pain, neuralgia, neuropathies, fibromyalgia, algesia, nerve injury, migraine, headaches.

Preferably, said cold-induced and/or exacerbated respiratory disorder is selected from cold-induced and/or exacerbated pulmonary hypertension, COPD and asthma.

Preferably, said urological disorders are selected from painful bladder syndrome, interstitial cystitis, detrusor overactivity (also known as overactive bladder), urinary incontinence, neurogenic detrusor overactivity (also known as detrusor hyperflexia), idiopathic detrusor overactivity (also known as detrusor instability), benign prostatic hyperplasia, lower urinary tract disorders and lower urinary tract symptoms.

Preferably, said psychiatric disorders are selected from anxiety and depression. 

A fifth object of the present invention are pharmaceutical compositions comprising the at least one of the above said compounds of formula (I) in combination with pharmaceutically acceptable excipients and/or diluents. 

According to a preferred embodiment said pharmaceutical composition is for the prevention, reduction of the risk of, amelioration and/or treatment of a disease associated with activity of TRPM8, preferably a diseasease deriving from overexpression and/or hyperactivity of TRPM8 receptor.
According to a preferred embodiment, said pharmaceutical composition contains at least one of the above compounds of formula (I) as the sole active principle(s). According to an alternative preferred embodiment, said pharmaceutical composition contains at least one of the above compounds of formula (I) in association with at least one other active principle.

According to a further preferred embodiment of the invention, also in combination with the preceding embodiments, the pharmaceutical compositions may be for intravesical, intravenous, topical or oral administration.

The compounds of the invention of formula (I) are conveniently formulated in pharmaceutical compositions using conventional techniques and excipients such as those described in "Remington's Pharmaceutical Sciences Handbook" MACK Publishing, New York, 18th ed., 1990.

A sixth object of the present invention is a therapeutic method for the prevention, reduction of the risk of, amelioration and/or treatment of said disease associated with activity of TRPM8, preferably a disease deriving from overexpression and/or hyperactivity of TRPM8 receptor, comprising administering the above compound of formula (I) in a subject in need thereof.

The compounds of the invention can be administered as the sole active principles or in combination with other therapeutically active compounds.

The administration of the compounds of the invention can be effected by intravesical instillation, by intravenous injection, as a bolus, in dermatological preparations (creams, lotions, sprays and ointments), by inhalation as well as orally in the form of capsules, tablets, syrup, controlled-release formulations and the like.

The average daily dose depends on several factors such as the severity of the disease, the condition, age, sex and weight of the patient. The dose will vary generally from 1 to 1500 mg of compounds of formula (I) per day optionally divided in multiple administrations.

The present invention shall be illustrated by means of the following examples which are not construed to be viewed as limiting the scope of the invention.

**Examples**

**Synthesis of preferred compounds**

The compounds listed in Table I have been synthetised following the procedures described in the following examples.

**Materials and methods**

All reagents were purchased from Sigma-Aldrich, Fluorochem and Alfa Aesar and used without further purification. Nuclear magnetic resonance (NMR) spectra were recorded in the indicated solvent with tetramethylsilane (TMS) as internal standard on a Bruker Avance3 400 MHz instrument. Chemical shifts are reported in parts per million (ppm) relative to the internal standard. Abbreviations are used as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublets of doublet, bs = broad signal. Coupling constants (J values) are given in hertz (Hz). Analytical HPLC-MS spectra were recorded on a Thermo Finnigan Surveyor coupled with a Thermo Finnigan LCQ DECA XP-PLUS apparatus and equipped with a C18 (10 µM, 4.6mm X 150mm) Phenomenex Gemini reverse phase column. The eluent mixture consisted of 10 mM (pH 4.2)
ammonium formate/formic acid buffer and acetonitrile used according the gradient from 90:10 to 10:90 at a flow rate of 0.200 mL/min. All MS experiments were performed using electrospray ionization (ESI) in positive and negative ion mode.

All reactions were monitored by thin layer chromatography (TLC) carried out on Grace Resolv Davisil silica gel plates 250 μm thick, 60 F254, visualized by using UV (254 nm) or stains such as KMnO4, p-anisaldehyde, and eerie ammonium molybdate (CAM). Chromatographic purifications were carried out on silica gel columns with Grace Resolv Davisil silica 60. All organic solutions were dried over anhydrous \( \text{NH}_2\text{C}_2 \) or \( \text{MgSO}_4 \) and concentrated on a rotary evaporator. All compounds used for biological assays are at least of 98% purity based

on HPLC analytical results monitored with 220 and 254 nm wavelengths, unless otherwise noted.

**General procedure**

Example 1

**Synthesis of 3-fluorobenzene-carbothioamide (Intermediate a)**

A 100 mL round-bottomed flask equipped with condenser and magnetic stirrer was charged with 3-fluorobenzoamide (2.0 g, 14.4 mmol), which was dissolved in 30 mL of THF, then Lawesson’s reagent was added to the solution (3.5 g, 8.64 mmol). The mixture was heated to 60 °C and stirred overnight; the transformation was monitored by TLC (Eluent: n-hexane / EtOAc 7:3). The solution was cooled at room temperature and the solvent removed by vacuum distillation.

The crude was purified by flash chromatography (Eluent: n-hexane / EtOAc 7:3) from which 3-fluorobenzene-carbothioamide was obtained as a yellow solid (2.0 g, 12.9 mmol, Y = 89%).

**1H-NMR (CDCl3):** 7.80-7.55 (bs, 1H, \( \text{NH}_2 \)), 7.66-7.60 (m, 2H), 7.44-7.37 (m, 1H), 7.27-7.20 (m, 1H), 7.30-7.00 (bs, 1H, \( \text{NH}_2 \)).

MS (ES+) m/z: 156.1 m/z [M+H]+.

**Synthesis of ethyl 2-(3-fluorophenyl)-4-hydroxy-3-thiazole-5-carboxylate (Intermediate b)**

A microwave vial equipped with a magnetic stirrer was charged with 3-fluorobenzene-carbothioamide (0.5 g, 3.22 mmol) dissolved in dry ethanol (8 mL), diethylbromomalonate was added (0.055 mL, 3.22 mmol) and the vial tightly stoppered. The solution was irradiated in a microwave apparatus at 100°C for 30 minutes. Ethyl 2-(3-fluorophenyl)-4-hydroxy-3-thiazole-5-carboxylate was obtained as a yellow solid after crystallization from ethanol (0.439 g, 1.64 mmol, Y = 51%).

**1H-NMR (CDCl3):** 9.94 (bs, 1H, \( \text{OH} \)), 7.80-7.70 (m, 2H), 7.49-7.41 (m, 1H), 7.2-7.17 (m, 1H), 4.43 (q, 2H, \( J=7.1 \text{ Hz} \)), 1.42 (t, 3H, \( J=7.1 \text{ Hz} \)).

MS (ES+) m/z: 267.81 [M+H]+.

**Synthesis of ethyl 2-(3-fluorophenyl)-4-methoxy-3-thiazole-5-carboxylate (Intermediate c)**

A 25 mL round-bottomed flask equipped with a magnetic stirrer was charged with Ethyl 2-(3-fluorophenyl)-4-hydroxy-3-thiazole-5-carboxylate (0.100 g, 0.374 mmol) which was dissolved in dry THF (3 mL) and DMF (2.5 mL), the solution was treated with NaH (60-65% Oil dispersion, 0.022 g, 1.5 eq) and methyl iodide (0.140 mL, 7 eq.) and stirred overnight at room temperature. The reaction was quenched in water and extracted in ethyl acetate (20 mL, 3 times), the organics were collected and washed with saturated sodium bicarbonate and brine
then anhydrified over dry sodium sulphate. The crude was purified over silica gel (Eluent: n-hexane/ethyl acetate 9:1). Ethyl 2-(3-fluorophenyl)-4-methoxy-1,3-thiazole-5-carboxylate was obtained as a yellow solid (0.053 g, 0.19 mmol, Y = 50%).

\[ \text{ESI}^+ \text{m/z: 297.32 [M+H]^+}. \]

\[ \text{H-NMR (CDCl}_3\text{): } \delta \text{ 7.69-7.25 (m, 2H), 7.47-7.41 (m, 1H), 7.23-7.16 (m, 1H), 4.36 (q, 2H, J=7.2 Hz), 4.25 (s, 3H), 1.39 (t, 3H, J=7.2 Hz).} \]

Synthesis of 2-(3-fluorophenyl)-4-methoxy-1,3-thiazole-5-carboxylic acid (Intermediate d)

A 25 mL round-bottomed flask equipped with a magnetic stirrer was charged with Ethyl 2-(3-fluorophenyl)-4-methoxy-1,3-thiazole-5-carboxylate (0.097 g, 0.344 mmol) which was dissolved in ethanol (3 mL) and water (0.020 mL). Then KOH was added (0.193 g, 3.44 mmol) and the solution was stirred overnight at room temperature. The mixture was diluted in water (15 mL), acidified with HCl 2N to pH 2 and extracted in ethyl acetate (20 mL x 2). The organic layers were collected and washed with water and brine, then anhydrified over dry sodium sulphate. 2-(3-fluorophenyl)-4-methoxy-1,3-thiazole-5-carboxylic acid was obtained as yellow solid (0.077 g, 0.304 mmol, Y = 88%).

\[ \text{ESI}^+ \text{m/z: 252.25 [M-H]^-.} \]

Synthesis of 2-(3-fluorophenyl)-4-methoxy-1,3-thiazole-5-carbonyl chloride (Intermediate e)

A 25 mL round-bottomed flask equipped with a magnetic stirrer and a water cooled condenser was charged with 2-(3-fluorophenyl)-4-methoxy-1,3-thiazole-5-carboxylic acid (0.049 g, 0.193 mmol) and 5 mL of dry DCM at room temperature. The solution was treated with an excess of thionyl chloride (0.028 mL, 0.387 mmol) and a catalytic amount of DMF (0.002 mL) then refluxed for 2.5 hours. The solution was cooled then volatiles were removed under reduced pressure. The oily residue was stripped a few times with toluene to further remove residual thionyl chloride. 2-(3-fluorophenyl)-4-methoxy-1,3-thiazole-5-carbonyl chloride as pale yellow oil was obtained (0.052 g, 0.0193 mmol, Y = 95%) and used without further purification.

Synthesis of 2-(3-fluorophenyl)-N,4-dimethoxy-N-methyl-1,3-thiazole-5-carboxamide (Intermediate f)

In a 25 mL round-bottomed flask equipped with a magnetic stirrer, 2-(3-fluorophenyl)-4-methoxy-1,3-thiazole-5-carbonyl chloride (0.052 g, 0.193 mmol) was dissolved in dry DCM (5 mL) and cooled to 0°C with an ice bath. This solution was treated with a mixture of N,O-dimethylhydroxylamine hydrochloride (0.038 g, 0.386 mmol), triethylamine (0.1 mL) and DCM (2 mL), and stirred at the same temperature for 45 minutes. As checked by LC-MS, the reaction was complete thus it was quenched and worked up as it follows: the mixture was dilute with DCM (50 mL) and washed with water (10 mL x 2) and brine (10 mL) dried over anhydrous sodium sulphate and the solvent vacuum distilled. 2-(3-fluorophenyl)-N,4-dimethoxy-N-methyl-1,3-thiazole-5-carboxamide (0.060 g, 0.20 mmol, Y = 95%) was obtained as an oily solid and used in the next synthetic step.

\[ \text{ESI}^+ \text{m/z: 297.32 [M+H]^+.} \]
Synthesis of 1-[2-(3-fluorophenyl)-4-methoxy-1,3-thiazol-5-yl]propan-1-one (Intermediate g)

A 10 mL round-bottomed flask equipped with a magnetic stirrer was charged with 2-(3-fluorophenyl)-N-4-dimethoxy-N-methyl-1,3-thiazole-5-carboxamide (0.066 g, 0.223 mmol) and 2.5 mL of dry THF was refrigerated to -78°C. The solution was treated at the same temperature ethylmagnesium chloride (0.17 mL, 0.334 mmol) then stirred at -60°C for 1.5 hours. The cooling system was removed and the reaction quenched at room temperature with saturated aqueous ammonium chloride solution (10 mL). The mixture was extracted with ethyl acetate (20 mL x 2), the organics were collected and washed twice with water (20 mL x 2) and once with brine (20 mL). The organic phase was then anhydried and the solvents vacuum removed. The crude was purified over silica gel by flash chromatography. 1-[2-(3-fluorophenyl)-4-methoxy-1,3-thiazol-5-yl]propan-1-one was obtained as a pale yellow solid (0.056 g, 0.211 mmol, Y = 95%).

1H-NMR (CDCl3): δ 7.75-7.70 (m, 2H), 7.48-7.41 (m, 1H), 7.23-7.3. 16 (m, 1H), 4.25 (s, 3H), 2.95 (q, 2H, J = 7.3 Hz), 1.21 (t, 3H, J = 7.3 Hz).

MS (ES+) m/z: 266.30 [M+H]+.

Synthesis of 1-[2-(3-fluorophenyl)-4-hydroxy-1,3-thiazol-5-yl]propan-1-one (1)

A 10 mL round-bottomed flask equipped with a magnetic stirrer was charged with 1-[2-(3-fluorophenyl)-4-methoxy-1,3-thiazol-5-yl]propan-1-one (0.042 g, 0.158 mmol) and dissolved at room temperature in dry DCM (4 mL) then refrigerated to 0°C with an ice bath. The solution was treated at this temperature with boron tribromide 1M in dichloromethane (0.39 mL, 0.390 mmol) then stirred for 30 minutes. The reaction was diluted with DCM (20 mL) and stirred with water (10 mL) for 10 minutes. The organic layer was separated and anhydried over anhydrous sodium sulphate, the solvent was distilled and the crude purified over silica gel. 1-[2-(3-fluorophenyl)-4-hydroxy-1,3-thiazol-5-yl]propan-1-one was obtained as a yellow solid (0.029 g, 0.115 mmol, Y = 73%)

1H-NMR (CDCl3): δ 11.90 (bs, 1H, OH), 7.83-7.79 (m, 1H), 7.79-7.74 (m, 1H), 7.51-7.43 (m, 1H), 7.28-7.21 (m, 1H), 2.80 (q, 2H, J = 7.3 Hz), 1.30 (t, 3H, J = 7.3 Hz).

MS (ES+) m/z: 252.12 [M+H]+, MS (ES+) m/z: 250.11 [M-1].

Example 2

Synthesis of sodium 2-(3-fluorophenyl)-5-propanoyl-1,3-thiazol-4-olate (2)

A 25 mL round-bottomed flask equipped with a magnetic stirrer was charged with 1-[2-(3-fluorophenyl)-4-hydroxy-1,3-thiazol-5-yl]propan-1-one (0.034 g, 0.135 mmol) and dissolved at room temperature in methanol (6 mL). The solution was then treated with an equivalent of NaOH (0.135 mL, 0.135 mmol, 1M in methanol) and stirred for 30 minutes. The volatiles were vacuum distilled and the title compound was obtained as an off-white solid in quantitative yield (0.037 g, 0.135 mmol).

1H-NMR (DMSO-d6): δ 7.69-7.66 (m, 1H), 7.63-7.60 (m, 1H), 7.53-7.47 (m, 1H), 7.32-7.29 (m, 1H), 2.77 (q, 2H, J = 7.4 Hz), 0.97 (t, 3H, J = 7.4 Hz).

MS (ES+) m/z: 252.25 [M+H]+.

Example 3

Synthesis of 1-[2-(3-fluorophenyl)-4-hydroxythiazol-5-yl]ethanone (4)
Starting from 3-fluorobenzenecarbothioamide (0.10 g, 0.70 mmol) prepared as described in Example 1 -
intermediate a, the general procedure for the thiazoles synthesis was applied to obtain 2-(3-fluorophenyl)-N,4-
dimethoxy-N-methyl-1 ,3-thiazole-5-carboxamide (Weinreb's amide). The latter was subjected to the same
synthetic conditions specified in the general procedure using methylmagnesium chloride to obtain 1-(2-(3-
fluorophenyl)-4-methoxythiazol-5-yl)ethanone, which was then deprotected with boron tribromide to obtain the
title compound as an off-white solid (0.030 g, 0.13 mmol, Y = 87 %).

1H-NMR (CDCl3): δ 7.85-7.71 (m, 2H), 7.55-7.40 (m, 1H), 7.30-7.19 (m, 1H), 2.50 (s, 3H).

MS (ES+) m/z: 238.0 [M+H]+.

Example 4

Synthesis of 1-[2-(3-fluorophenyl)-4-hydroxy-1 ,3-thiazol-5-yl]-2-methylpropan-1-one (5)

Starting from 3-fluorobenzenecarbothioamide (0.070 g, 0.45 mmol) prepared as described in Example 1 -
intermediate a, the general procedure for the thiazoles synthesis was applied to obtain 2-(3-fluorophenyl)-N,4-
dimethoxy-N-methyl-1 ,3-thiazole-5-carboxamide (Weinreb's amide). The latter was subjected to the same
synthetic conditions specified in the general procedure using isopropylmagnesium chloride to obtain 1-[2-(3-
fluorophenyl)-4-methoxy-1 ,3-thiazol-5-yl]-2-methylpropan-1-one, which was then deprotected with boron
tribromide to obtain the title compound as a yellow solid (0.021 g, 0.08 mmol, Y = 88 %).

1H-NMR (CDCl3): δ 7.85-7.71 (m, 2H), 7.55-7.40 (m, 1H), 7.30-7.19 (m, 1H), 2.50 (m, 1H), 1.30 (d, 6H, J=7.0
Hz).

MS (ES+) m/z: 266.0 [M+H]+.

Example 5

Synthesis of 1-[4-hydroxy-2-(thiophen-2-yl)-1 ,3-thiazol-5-yl]propan-1-one (7)

Starting from thiophene-2-carbothioamide (0.074 g, 0.52 mmol) prepared as described in Example 1 -
intermediate a, the general procedure for the thiazoles synthesis was applied to obtain N,4-dimethoxy-N-methyl-
2-(thiophen-2-yl)-1 ,3-thiazole-5-carboxamide (Weinreb's amide). The latter was subjected to the same synthetic
conditions specified in the general procedure using ethylmagnesium chloride to obtain 1-[4-methoxy-2-
(thiophen-2-yl)-1 ,3-thiazol-5-yl]propan-1-one which was then deprotected with boron tribromide to obtain the
title compound as a yellow solid (0.022 g, 0.09 mmol, Y = 88 %).

1H-NMR (CDCl3): δ 7.70 (s, 1H), 7.52 (s, 1H), 7.11 (s, 1H), 2.70 (q, 2H, J = 7.1 Hz), 1.28 (t, 3H, J = 7.1 Hz).

MS (ES+) m/z: 240.1 [M+H]+.

Example 6

Synthesis of 1-[4-hydroxy-2-(2-methylphenyl)-1 ,3-thiazol-5-yl]propan-1-one (9)

Starting from 2-methylbenzenecarbothioamide (0.152 g, 1.0 mmol) prepared analogously to what described in
Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain N,4-
dimethoxy-N-methyl-2-(2-methylphenyl)-1 ,3-thiazole-5-carboxamide (Weinreb's amide). The latter was
subjected to the same synthetic conditions specified in the general procedure using ethylmagnesium chloride
to obtain 1-[4-methoxy-2-(2-methylphenyl)-1 ,3-thiazol-5-yl]propan-1-one which was then deprotected with boron
tribromide to obtain the title compound as a brown solid (0.044 g, 0.18 mmol, Y = 89 %).
Example 7

**Synthesis of 1-[2-(2-bromophenyl)-4-hydroxy-3-thiazol-5-yl]propan-1-one (11)**

Starting from 2-bromobenzencarbothioamide (0.053 g, 0.15 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain 2-(2-bromophenyl)-N,4-dimethoxy-N-methyl-3-thiazole-5-carboxamide (Weinreb's amide). The latter was subjected to the same synthetic conditions specified in the general procedure using ethylmagnesium chloride to obtain 1-[2-(2-bromophenyl)-4-methoxy-3-thiazol-5-yl]propan-1-one which was then deprotected with boron tribromide to obtain the title compound as a yellow solid (0.018 g, 0.06 mmol, Y = 87 %).

**H-NMR (CDCl3): δ 8.35-8.28 (m, 1H), 7.75-7.65 (m, 1H), 7.50-7.37 (m, 1H), 7.37-7.28 (m, 1H), 2.80 (q, 2H, J=7.0 Hz), 1.28 (t, 3H, J=7.0 Hz).**

MS (ES+) m/z; 312.1 [M+H]+.

Example 8

**Synthesis of 1-[2-(2-hydroxyphenyl)-4-hydroxy-3-thiazol-5-yl]propan-1-one (13)**

Starting from 2-methoxybenzencarbothioamide (0.061 g, 0.35 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure was applied for the thiazoles synthesis to obtain N,4-dimethoxy-2-(2-methoxyphenyl)-N-methyl-3-thiazole-5-carboxamide (Weinreb’s amide). The Weinreb’s amide was subjected to the same synthetic conditions specified in the general procedure using ethylmagnesium chloride to obtain 1-[4-methoxy-2-(2-methoxyphenyl)-3-thiazol-5-yl]propan-1-one which was then deprotected with boron tribromide (4 equivalents) to obtain the title compound as a yellow solid (0.016 g, 0.07 mmol, Y = 95 %).

**H-NMR (CDCl3): δ 12.27 (s, 1H, OH), 11.55 (s, 1H, OH), 7.69-7.61 (m, 1H), 7.40-7.30 (m, 1H), 7.08-6.98 (m, 1H), 6.93-6.86 (m, 1H), 2.77 (q, 2H, J=7.0 Hz), 1.26 (t, 3H, J=7.0 Hz).**

MS (ES+) m/z; 250.1 [M+H]+.

Example 9

**Synthesis of 1-[2-(3-bromophenyl)-4-hydroxy-3-thiazol-5-yl]propan-1-one (14)**

Starting from 3-bromobenzencarbothioamide (0.20 g, 0.92 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain 2-(3-bromophenyl)-N,4-dimethoxy-N-methyl-3-thiazole-5-carboxamide (Weinreb’s amide). The latter was subjected to the same synthetic conditions specified in the general procedure using ethylmagnesium chloride to obtain 1-[2-(3-bromophenyl)-4-methoxy-3-thiazol-5-yl]propan-1-one which was then deprotected with boron tribromide to obtain the title compound as a white solid (0.055 g, 0.17 mmol, Y = 95 %).

**H-NMR (CDCl3): δ 11.89 (bs, 1H, OH), 8.23-8.18 (m, 1H), 7.89-7.91 (m, 1H), 7.69-7.63 (m, 1H), 7.41-7.34 (m, 1H), 2.80 (q, 2H, J=7.0 Hz), 1.30 (t, 3H, J=7.0 Hz).**

MS (ES+) m/z; 312.1 [M+H]+.
Synthesis of 1-[2-(furan-2-yl)-4-hydroxy-1,3-thiazol-5-yl]propan-1-one (15)

Starting from furan-2-carbothioamide (0.101 g, 0.79 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain 2-(furan-2-yl)-N,4-dimethoxy-N-methyl-1,3-thiazole-5-carboxamide (Weinreb's amide). The latter was subjected to the same synthetic conditions specified in the general procedure using ethylmagnesium chloride to obtain 1-[2-(furan-2-yl)-4-methoxy-1,3-thiazol-5-yl]propan-1-one which was then deprotected with boron tribromide to obtain the title compound as a yellow solid (0.034 g, 0.15 mmol, Y = 90%).

$^1$H-NMR (CDCl$_3$): δ 7.60 (s, 1H), 7.15 (d, 1H, J = 3.6 Hz), 6.52 (d, 1H, J = 3.6 Hz), 2.95 (q, 2H, J = 7.3 Hz), 1.21 (t, 3H, J=7.3 Hz).

MS (ES$^+$) m/z: 223.2 [M+H]$^+$.

Example 11

Synthesis of 1-[4-hydroxy-2-(1H-pyrrol-2-yl)-1,3-thiazol-5-yl]propan-1-one (16)

Starting from 1H-pyrrole-2-carbothioamide (0.103 g, 0.82) prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain N,4-dimethoxy-N-methyl-2-(1 H-pyrrol-2-yl)-1,3-thiazole-5-carboxamide (Weinreb's amide). The latter was subjected to the same synthetic conditions specified in the general procedure using ethylmagnesium chloride to obtain 1-[4-methoxy-2-(1H-pyrrol-2-yl)-1,3-thiazol-5-yl]propan-1-one which was then deprotected with boron tribromide to obtain the title compound as a yellow solid (0.034 g, 0.15 mmol, Y = 93%).

$^1$H-NMR (CDCl$_3$): δ 11.89 (bs, 1H, OH), 8.10 (vbs, 1HNH), 7.10-6.80 (m, 2H), 6.20-6.05 (m, 1H), 2.95 (q, 2H, J = 7.3 Hz), 1.21 (t, 3H, J=7.3 Hz).

MS (ES$^+$) m/z: 223.2 [M+H]$^+$.

Example 12

Synthesis of 1-[4-hydroxy-2-(1-methyl-1H-pyrrol-2-yl)-1,3-thiazol-5-yl]propan-1-one (17)

Starting from 1-methyl-1 H-pyrrole-2-carbothioamide (0.105 g, 0.75 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain N,4-dimethoxy-N-methyl-2-(1-methyl-1 H-pyrrol-2-yl)-1,3-thiazole-5-carboxamide (Weinreb's amide). The latter was subjected to the same synthetic conditions specified in the general procedure using ethylmagnesium chloride to obtain 1-[4-methoxy-2-(1-methyl-1 H-pyrrol-2-yl)-1,3-thiazol-5-yl]propan-1-one which was then deprotected with boron tribromide to obtain the title compound as a yellow solid (0.034 g, 0.14 mmol, Y = 91%).

$^1$H-NMR (CDCl$_3$): δ 11.51 (bs, 1H, OH), 7.10-6.95 (m, 1H), 6.95-6.75 (m, 1H), 6.19-6.05 (m, 1H), 3.73 (s, 3H), 2.95 (q, 2H, J = 7.3 Hz), 1.21 (t, 3H, J=7.3 Hz).

MS (ES$^+$) m/z: 237.3 [M+H]$^+$.

Example 13

Synthesis of 1-[4-hydroxy-2-(1-methyl-1H-imidazol-5-yl)-1,3-thiazol-5-yl]propan-1-one (18)

Starting from 1-methyl-1 H-imidazole-5-carbothioamide (0.203 g, 1.44 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain
N,4-dimethoxy-N-methyl-2-(1-methyl-1H-imidazol-5-yl)-1,3-thiazole-5-carboxamide (Weinreb’s amide). The latter was subjected to the same synthetic conditions specified in the general procedure using ethylmagnesium chloride to obtain 1-[4-methoxy-2-(1-methyl-1H-imidazol-5-yl)-1,3-thiazole-5-carboxamide (Weinreb’s amide). The latter was then deprotected with boron tribromide to obtain the title compound as a yellow solid (0.065 g, 0.27 mmol, Y = 94%)

1H-NMR (CDCl3): δ 11.65 (bs, 1H, OH), 7.91-7.70 (m, 1H), 7.52-7.40 (m, 1H), 3.33 (s, 3H), 2.95 (q, 2H, J= 7.3 Hz), 1.21 (t, 3H, J=7.3 Hz).

MS (ES+) m/z: 238.4 [M+H]+.

Example 14

Synthesis of 1-[4-hydroxy-2-(1H-imidazol-5-yl)-1,3-thiazole-5-y1]propan-1-one (19)

Starting from 1H-imidazol-5-carbothioamide (0.198 g, 1.56 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain 2-(1H-imidazol-5-yl)-N,4-dimethoxy-N-methyl-1,3-thiazole-5-carboxamide (Weinreb’s amide). The latter was subjected to the same synthetic conditions specified in the general procedure using ethylmagnesium chloride to obtain 1-[4-methoxy-2-(1H-imidazol-5-yl)-1,3-thiazole-5-y1]propan-1-one which was then deprotected with boron tribromide to obtain the title compound as a yellow solid (0.062 g, 0.28 mmol, Y = 89%)

1H-NMR (CDCl3): δ 8.20-8.10 (m, 1H); 7.40-7.30 (m, 1H), 2.95 (q, 2H, J= 7.3 Hz), 1.20 (t, 3H, J=7.3 Hz).

MS (ES+) m/z: 224.4 [M+H]+.

Example 15

Synthesis of 1-[4-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,3-thiazole-5-y1]propan-1-one (20)

Starting from 1-methyl-1H-pyrazol-4-carbothioamide (0.211 g, 1.49 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain N,4-dimethoxy-N-methyl-2-(1-methyl-1H-pyrazol-4-yl)-1,3-thiazole-5-carboxamide (Weinreb’s amide). The latter was subjected to the same synthetic conditions specified in the general procedure using ethylmagnesium chloride to obtain 1-[4-methoxy-2-(1-methyl-1H-pyrazol-4-yl)-1,3-thiazole-5-y1]propan-1-one which was then deprotected with boron tribromide to obtain the title compound as a yellow solid (0.064 g, 0.27 mmol, Y = 92%)

1H-NMR (CDCl3): δ 11.51 (vbs, 1H, OH), 7.90-8.75 (m, 1H); 7.65-7.45 (m, 1H), 3.70 (s, 3H), 2.95 (q, 2H, J=7.3 Hz), 1.20 (t, 3H, J=7.3 Hz).

MS (ES+) m/z: 238.5 [M+H]+.

Example 16

Synthesis of 1-[4-hydroxy-2-(thiophen-2-yl)-1,3-thiazole-5-y1]butan-1-one (21)

Starting from thiophene-2-carbothioamide (0.20 g, 1.39 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain N,4-dimethoxy-N-methyl-2-(thiophen-2-yl)-1,3-thiazole-5-carboxamide (Weinreb’s amide). The latter was subjected to the same synthetic conditions specified in the general procedure using propylmagnesium chloride to obtain
1-[4-methoxy-2-(thiophen-2-yl)-1,3-thiazol-5-yl]butan-1-one which was then deprotected with boron tribromide to obtain the title compound as a yellow solid (0.067 g, 0.26 mmol, Y = 95 %).

$^1$H-NMR (CDCl$_3$): $\delta$ 11.37 (vbs, 1H, OH), 7.80-7.60 (m, 2H); 7.22-7.09 (m, 1H), 2.51 (t, 2H, J=7.5 Hz), 1.71 (m, 2H), 0.92 (t, 3H, J=7.4 Hz).

MS (ES$^+$) m/z: 254.4 [M+H]$^+$.  

**Example 17**

**Synthesis of 1-[4-hydroxy-2-(thiophen-2-yl)-1,3-thiazol-5-yl]butan-1-one** (22)

Starting from thiophene-2-carbothioamide (0.150 g, 1.04 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazolos synthesis was applied to obtain N,4-dimethoxy-N-methyl-2-(thiophen-2-yl)-1,3-thiazol-5-yl-carboxamide (Weinreb's amide). The latter was subjected to the same synthetic conditions specified in the general procedure using isobutylmagnesium chloride to obtain 1-[4-methoxy-2-(thiophen-2-yl)-1,3-thiazol-5-yl]butan-1-one which was then deprotected with boron tribromide to obtain the title compound as a yellow solid (0.053 g, 0.20 mmol, Y = 95 %).

$^1$H-NMR (CDCl$_3$): $\delta$ 11.45 (vbs, 1H, OH), 7.80-7.60 (m, 2H); 7.22-7.09 (m, 1H), 2.49 (d, 2H, J= 7.3 Hz), 1.90-1.70 (m, 1H), 0.89 (d, 6H, J=7.2 Hz).

MS (ES$^+$) m/z: 268.2 [M+H]$^+$.  

**Example 18**

**Synthesis of 1-[4-hydroxy-2-[1,2,4-oxadiazol-3-yl]-1,3-thiazol-5-yl]propan-1-one** (23)

Starting from 1,2,4-oxadiazole-3-carbothioamide (0.151 g, 1.16 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazolos synthesis was applied to obtain N,4-dimethoxy-N-methyl-2-[1,2,4-oxadiazol-3-yl]-1,3-thiazol-5-yl-carboxamide (Weinreb's amide). The latter was subjected to the same synthetic conditions specified in the general procedure using ethylmagnesium chloride to obtain 1-[4-methoxy-2-[1,2,4-oxadiazol-3-yl]-1,3-thiazol-5-yl]propan-1-one which was then deprotected with boron tribromide to obtain the title compound as a yellow solid (0.049 g, 0.22 mmol, Y = 88 %).

$^1$H-NMR (CDCl$_3$): $\delta$ 11.62 (bs, 1H, OH), 8.45 (s, 1H), 2.95 (q, 2H, J= 7.3 Hz), 1.20 (t, 3H, J=7.3 Hz).

MS (ES$^+$) m/z: 226.1 [M+H]$^+$.  

**Example 19**

**Synthesis of 1-[4-hydroxy-2-[1,2-oxazol-5-yl]-1,3-thiazol-5-yl]propan-1-one** (24)

Starting from 1,2-oxazol-5-carbothioamide (0.148 g, 1.15 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazolos synthesis was applied to obtain N,4-dimethoxy-N-methyl-2-[1,2-oxazol-5-yl]-1,3-thiazol-5-yl-carboxamide (Weinreb's amide). The latter was subjected to the same synthetic conditions specified in the general procedure using ethylmagnesium chloride to obtain 1-[4-methoxy-2-[1,2-oxazol-5-yl]-1,3-thiazol-5-yl]propan-1-one which was then deprotected with boron tribromide to obtain the title compound as a yellow solid (0.048 g, 0.22 mmol, Y = 89 %).

$^1$H-NMR (CDCl$_3$): $\delta$ 11.41 (bs, 1H, OH), 7.51 (d, 1H, J=3.1 Hz), 6.80 (d, 1H, J=3.1 Hz), 2.96 (q, 2H, J=7.3 Hz), 1.22 (t, 3H, J=7.3 Hz).

MS (ES$^+$) m/z: 225.3 [M+H]$^+$.  

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Example 20

Synthesis of 1-[4-hydroxy-2-(pyridin-3-yl)-1,3-thiazol-5-yl]propan-1-one (25)

Starting from pyridine-3-carbothioamide (0.186 g, 1.34 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain N,4-dimethoxy-N-methyl-2-(pyridin-3-yl)-1,3-thiazole-5-carboxamide (Weinreb’s amide). The latter was subjected to the same synthetic conditions specified in the general procedure using ethylmagnesium chloride to obtain 1-[4-methoxy-2-(pyridin-3-yl)-1,3-thiazol-5-yl]propan-1-one which was then deprotected with boron tribromide to obtain the title compound as a yellow solid (0.060 g, 0.26 mmol, Y = 89%).

1H-NMR (CDCl3): δ 11.56 (bs, 1H, OH), 9.15-9.00 (m, 1H), 8.75-8.65 (m, 1H), 8.35-8.25 (m, 1H), 7.66-7.56 (m, 1H), 2.94 (q, 2H, J = 7.3 Hz), 1.20 (t, 3H, J=7.3 Hz).

MS (ES+) m/z: 235.3 [M+H]+.

Example 21

Synthesis of 1-[4-hydroxy-2-(pyridin-4-yl)-1,3-thiazol-5-yl]propan-1-one (26)

Starting from pyridine-4-carbothioamide (0.175 g, 1.27 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain N,4-dimethoxy-N-methyl-2-(pyridin-4-yl)-1,3-thiazole-5-carboxamide (Weinreb’s amide). The latter was subjected to the same synthetic conditions specified in the general procedure using ethylmagnesium chloride to obtain 1-[4-methoxy-2-(pyridin-4-yl)-1,3-thiazol-5-yl]propan-1-one which was then deprotected with boron tribromide to obtain the title compound as a yellow solid (0.054 g, 0.23 mmol, Y = 92%).

1H-NMR (CDCl3): δ 11.56 (bs, 1H, OH), 9.15-9.00 (m, 2H), 8.55-8.65 (m, 2H), 2.94 (q, 2H, J = 7.3 Hz), 1.20 (t, 3H, J=7.3 Hz).

MS (ES+) m/z: 235.3 [M+H]+.

Example 22

Synthesis of 1-[4-hydroxy-2-(pyridin-2-yl)-1,3-thiazol-5-yl]propan-1-one (27)

Starting from pyridine-2-carbothioamide (0.214 g, 1.55 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain N,4-dimethoxy-N-methyl-2-(pyridin-2-yl)-1,3-thiazole-5-carboxamide (Weinreb’s amide). The latter was subjected to the same synthetic conditions specified in the general procedure using ethylmagnesium chloride to obtain 1-[4-methoxy-2-(pyridin-2-yl)-1,3-thiazol-5-yl]propan-1-one which was then deprotected with boron tribromide to obtain the title compound as a yellow solid (0.065 g, 0.28 mmol, Y = 91%).

1H-NMR (CDCl3): δ 11.56 (bs, 1H, OH), 8.75-8.65 (m, 1H), 8.15-8.05 (m, 1H), 7.95-7.85 (m, 1H), 7.66-7.56 (m, 1H), 2.94 (q, 2H, J = 7.3 Hz), 1.20 (t, 3H, J=7.3 Hz).

MS (ES+) m/z: 235.3 [M+H]+.

Example 23

Synthesis of 1-[4-hydroxy-2-(3-hydroxyphenyl)-1,3-thiazol-5-yl]propan-1-one (28)
Starting from 3-methoxybenzenecarbothioamide (0.105 g, 0.63 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure was applied for the thiazoles synthesis to obtain N,4-dimethoxy-2-(3-methoxyphenyl)-N-methyl-1,3-thiazole-5-carboxamide (Weinreb’s amide).

The Weinreb’s amide was subjected to the same synthetic conditions specified in the general procedure using ethylmagnesium chloride to obtain 1-[4-methoxy-2-(3-methoxyphenyl)-1,3-thiazol-5-yl]propan-1-one which was then deprotected with boron tribromide (4 equivalents) to obtain the title compound as a yellow solid (0.029 g, 0.12 mmol, Y = 91 %).

$^1$H-NMR (CDCl$_3$): δ 12.37 (s, 1H, OH), 11.45 (s, 1H, OH), 7.70-7.10 (m, 4H), 2.82 (q, 2H, J=7.3 Hz), 1.17 (t, 3H, J=7.3 Hz).

MS (ES$^+$) m/z: 250.3 [M+H$^+$].

Example 24

Synthesis of 1-[4-hydroxy-2-(4-hydroxyphenyl)-1,3-thiazol-5-yl]propan-1-one (29)

Starting from 4-methoxybenzenecarbothioamide (0.026 g, 1.23 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure was applied for the thiazoles synthesis to obtain N,4-dimethoxy-2-(4-methoxyphenyl)-N-methyl-1,3-thiazole-5-carboxamide (Weinreb’s amide).

The Weinreb’s amide was subjected to the same synthetic conditions specified in the general procedure using ethylmagnesium chloride to obtain 1-[4-methoxy-2-(4-methoxyphenyl)-1,3-thiazol-5-yl]propan-1-one which was then deprotected with boron tribromide (4 equivalents) to obtain the title compound as a yellow solid (0.058 g, 0.23 mmol, Y = 90 %).

$^1$H-NMR (CDCl$_3$): δ 12.41 (s, 1H, OH), 11.55 (s, 1H, OH), 7.75-7.10 (m, 4H), 2.82 (q, 2H, J=7.3 Hz), 1.17 (t, 3H, J=7.3 Hz).

MS (ES$^+$) m/z: 250.3 [M+H$^+$].

Example 25

Synthesis of 1-[4-hydroxy-2-(3-methylphenyl)-1,3-thiazol-5-yl]propan-1-one (30)

Starting from 3-methylbenzenecarbothioamide (0.086 g, 0.57 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain N,4-dimethoxy-N-methyl-2-(3-methylphenyl)-1,3-thiazole-5-carboxamide (Weinreb’s amide). The latter was subjected to the same synthetic conditions specified in the general procedure using ethylmagnesium chloride to obtain 1-[4-methoxy-2-(3-methylphenyl)-1,3-thiazol-5-yl]propan-1-one which was then deprotected with boron tribromide to obtain the title compound as a yellow solid (0.027 g, 0.10 mmol, Y = 96 %).

$^1$H-NMR (CDCl$_3$): δ 11.55 (s, 1H, OH), 7.70-7.47 (m, 2H), 7.45-7.10 (m, 2H), 2.80 (q, 2H, J=7.3 Hz), 2.32 (s, 3H), 1.15 (t, 3H, J=7.3 Hz).

MS (ES$^+$) m/z: 248.4 [M+H$^+$].

Example 26

Synthesis of 1-[4-hydroxy-2-(4-methylphenyl)-1,3-thiazol-5-yl]propan-1-one (31)

Starting from 4-methylbenzenecarbothioamide (0.087 g, 0.58 mmol), prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain N,4-
dimethoxy-N-methyl-2-(4-methylphenyl)-1,3-thiazole-5-carboxamide (Weinreb's amide). The latter was subjected to the same synthetic conditions specified in the general procedure using ethylmagnesium chloride to 1-[4-methoxy-2-(4-methylphenyl)-1,3-thiazol-5-yl]propan-1-one which was then deprotected with boron tribromide to obtain the title compound as a yellow solid (0.027 g, 0.1 mmol, Y = 95%).

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1H-NMR (CDCl3): 8.11.55 (bs, 1H, OH), 7.85-7.70 (m, 2H), 7.35-7.05 (m, 2H), 2.80 (q, 2H, J=7.3 Hz), 1.15 (t, 3H, J=7.3 Hz).

MS (ES+) m/z: 248.2 [M+H]+.

Example 27

Synthesis of 1-[2-(3-aminophenyl)-4-hydroxy-1,3-thiazol-5-yl]propan-1-one (32)

Starting from 3-nitrobenzenecarbothioamide (0.235 g, 1.35 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain N,4-dimethoxy-N-methyl-2-(3-nitrophenyl)-1,3-thiazole-5-carboxamide (Weinreb's amide). The latter was subjected to the same synthetic conditions specified in the general procedure using ethylmagnesium chloride to obtain 1-[4-methoxy-2-(3-nitrophenyl)-1,3-thiazol-5-yl]propan-1-one.

The compound was then dissolved in methanol and mixed with 5 equivalents of stannous chloride dihydrate thus irradiated in a microwaves apparatus for 30 minutes at 100°C.

After complete reduction of the nitro group, acid base extraction and work-up, the 1-[2-(3-aminophenyl)-4-methoxy-1,3-thiazol-5-yl]propan-1-one was obtained pure. The latter was subjected to deprotection conditions with boron tribromide affording the title compound as a yellow solid (0.033 g, 0.13 mmol, last two steps Y = 51%).

1H-NMR (CDCl3): 8.111.72 (bs, 1H, OH), 7.74 (bs, 1H, NH), 7.22 (bs, 1H, NH), 7.20-6.89 (m, 3H), 6.72-6.60 (m, 1H), 2.80 (q, 2H, J=7.3 Hz), 1.15 (t, 3H, J=7.3 Hz).

MS (ES+) m/z: 249.3 [M+H]+.

Example 28

Synthesis of 1-[2-(4-aminophenyl)-4-hydroxy-1,3-thiazol-5-yl]propan-1-one (33)

Starting from 4-nitrobenzenecarbothioamide (0.234 g, 1.35 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain N,4-dimethoxy-N-methyl-2-(4-nitrophenyl)-1,3-thiazole-5-carboxamide (Weinreb's amide). The latter was subjected to the same synthetic conditions specified in the general procedure using ethylmagnesium chloride to obtain 1-[4-methoxy-2-(4-nitrophenyl)-1,3-thiazol-5-yl]propan-1-one. The compound was dissolved in methanol, mixed with 5 equivalents of stannous chloride dihydratethus and irradiated in a microwaves apparatus for 30 minutes at 100°C.

After complete reduction of the nitro group, acid extraction and work-up, the 1-[2-(4-aminophenyl)-4-methoxy-1,3-thiazol-5-yl]propan-1-one was obtained pure for subsequent deprotection with boron tribromide affording the title compound as a yellow solid (0.032 g, 0.12 mmol, last two steps Y = 49%).

1H-NMR (CDCl3): 8.111.63 (bs, 1H, OH), 7.75-7.45 (m, 2H; bs 1H, NH), 6.89 (bs, 1H, NH) 6.65-6.40 (m, 2H), 2.80 (q, 2H, J=7.3 Hz), 1.15 (t, 3H, J=7.3 Hz).
MS (ES\textsuperscript{+}) m/z: 249.4 [M+H]\textsuperscript{+}.

Example 29

Synthesis of 1-{4-hydroxy-2-[3-(methylamino)phenyl]-1,3-thiazol-5-yl}propan-1-one (34)

Starting from 3-(bromo)benzenecarbothioamide (0.429 g, 1.98 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain 2-(3-bromophenyl)-N,4-dimethoxy-N-methyl-1,3-thiazole-5-carboxamide (Weinreb's amide). The latter compound was subjected to the same synthetic conditions specified in the general procedure using ethylmagnesium chloride to obtain 1-[2-(3-bromophenyl)-4-methoxy-1,3-thiazol-5-yl]propan-1-one. The bromo aryl thiazole derivative was then dissolved in anhydrous toluene and treated with 5 equivalents of sodium tert-butoxide, 1.5 equivalents of methylamine, 0.1 equivalents of 2-(di-tertbutyolphosphino)biphenyl, 0.05 equivalents of tris(dibenzylidene-acetone)dipalladium(0) and sealed in a vial thus irradiated in a microwaves apparatus at 100°C for an hour. After chromatography, 1-[4-methoxy-2-[3-(methylamino)phenyl]-1,3-thiazol-5-yl]propan-1-one was obtained and then deprotected with boron tribromide to obtain the title compound as a yellow solid (0.020 g, 0.08 mmol, last two steps Y = 21 %).

\textsuperscript{1}H-NMR (CDCl\textsubscript{3}): δ, 11.60 (bs, 1H, OH), 7.25-6.90 (m, 3H), 6.75-6.65 (m, 1H), 4.35 (vbs, 1H, NH), 3.05 (s, 3H), 2.93 (q, 2H, J= 7.3 Hz), 1.25 (t, 3H, J=7.3 Hz).

MS (ES\textsuperscript{+}) m/z: 263.4 [M+H]\textsuperscript{+}.

Example 30

Synthesis of 1-{4-hydroxy-2-[4-(methylamino)phenyl]-1,3-thiazol-5-yl}propan-1-one (35)

Starting from 4-(bromo)benzenecarbothioamide (0.50 g, 2.32 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain 2-(4-bromophenyl)-N,4-dimethoxy-N-methyl-1,3-thiazole-5-carboxamide (Weinreb's amide). The latter was subjected to the same synthetic conditions specified in the general procedure using ethylmagnesium chloride to obtain 1-[2-(4-bromophenyl)-4-methoxy-1,3-thiazol-5-yl]propan-1-one. The bromo aryl thiazole derivative was then dissolved in anhydrous toluene and treated with 5 equivalents of sodium tert-butoxide, 1.5 equivalents of methylamine, 0.1 equivalents of 2-(di-tertbutyolphosphino)biphenyl, 0.05 equivalents of tris(dibenzylidene-acetone)dipalladium(0) and sealed in a vial thus irradiated in a microwaves apparatus at 100°C for an hour. After chromatography 1-[4-methoxy-2-[4-(methylamino)phenyl]-1,3-thiazol-5-yl]propan-1-one was obtained and then O-demethylated by the action of boron tribromide affording the title compound as a yellow solid (0.015 g, 0.06 mmol, last two steps Y = 13 %).

\textsuperscript{1}H-NMR (CDCl\textsubscript{3}): δ, 11.60 (bs, 1H, OH), 7.72-7.43 (m, 2H), 6.63-6.39 (m, 2H), 4.35 (vbs, 1H, NH), 3.07 (s, 3H), 2.96 (q, 2H, J= 7.3 Hz), 1.23 (t, 3H, J=7.3 Hz).

MS (ES\textsuperscript{+}) m/z: 263.4 [M+H]\textsuperscript{+}.

Example 31

Synthesis of 1-[2-(4-fluorophenyl)-4-hydroxy-1,3-thiazol-5-yl]propan-1-one (36)

Starting from 4-fluorobenzencarbothioamide (0.122 g, 0.78 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain 2-(4-
fluorophenyl)-N,4-dimethoxy-N-methyl-1,3-thiazole-5-carboxamide (Weinreb's amide). The latter was subjected to the same synthetic conditions specified in the general procedure using ethylmagnesium chloride to obtain 1-(4-fluorophenyl)-4-methoxy-1,3-thiazol-5-yl]propan-1-one which was then deprotected with boron tribromide to obtain the title compound as a yellow solid (0.037 g, 0.15 mmol, Y = 91 %).

1H-NMR (CDCl3): δ 11.85 (bs, 1H, OH), 7.95-7.80 (m, 2H), 7.29-7.10 (m, 2H), 2.80 (q, 2H, J=7.3 Hz), 1.30 (t, 3H, J=7.3 Hz).

MS (ES') m/z: 252.12 [M+H]+, MS (ES') m/z: 250.11 [M-H].

Example 32

Synthesis of 1-[2-(3-fluorophenyl)-4-hydroxy-1,3-thiazol-5-yl]butan-1-one (37)

Starting from 3-fluorobenzencarbothioamide (0.124 g, 0.80 mmol) prepared as described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain 2-(3-fluorophenyl)-N,4-dimethoxy-N-methyl-1,3-thiazole-5-carboxamide (Weinreb's amide). The latter was subjected to the same synthetic conditions specified in the general procedure using propylmagnesium chloride to obtain 1-[2-(3-fluorophenyl)-4-methoxy-1,3-thiazol-5-yl]butan-1-one, which was then deprotected with boron tribromide to obtain the title compound as a light yellow solid (0.028 g, 0.10 mmol, Y = 81 %).

1H-NMR (CDCl3): δ 11.90 (bs, 1H, OH), 7.85-7.71 (m, 2H), 7.50-7.40 (m, 1H), 7.27-7.19 (m, 1H), 2.72 (t, 2H, J=7.3 Hz), 1.83 (q, 2H, J=7.3 Hz), 1.05 (t, 3H, J=7.3 Hz).

MS (ES') m/z: 266.30 [M+H]+.

Example 33

Synthesis of 1-[2-(3-fluorophenyl)-4-hydroxy-1,3-thiazol-5-yl]-3-methylbutan-1-one (38)

Starting from 3-fluorobenzencarbothioamide (0.112 g, 0.72 mmol) prepared as described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain 2-(3-fluorophenyl)-N,4-dimethoxy-N-methyl-1,3-thiazole-5-carboxamide (Weinreb's amide). The latter was subjected to the same synthetic conditions specified in the general procedure using isobutylmagnesium chloride to obtain 1-[2-(3-fluorophenyl)-4-methoxy-1,3-thiazol-5-yl]-3-methylbutan-1-one, which was then deprotected with boron tribromide to obtain the title compound as an yellow solid (0.033 g, 0.12 mmol, Y = 73 %).

1H-NMR (CDCl3): δ 12.10 (bs, 1H, OH), 7.83-7.73 (m, 2H), 7.50-7.43 (m, 1H), 7.28-7.21 (m, 1H), 2.62 (d, 2H, J=7.3 Hz), 2.34 (m, 1H), 1.05 (d, 6H, J=7.3 Hz).

MS (ES') m/z: 280.23 [M+H]+.

Example 34

Synthesis of 1-[2-(3-fluorophenyl)-4-hydroxy-1,3-thiazol-5-yl]-2-methoxyethanone (39)

1-[2-(3-fluorophenyl)-4-methoxy-1,3-thiazol-5-yl]ethanone (0.200 g, 0.79 mmol), prepared as described in Example 3, was dissolved in 10 mL of dry DCM and N-bromosuccinimide (0.142 g, 0.79 mmol) was added. The resulting mixture was stirred for 3h at room temperature. The solvent was evaporated under vacuum distillation to obtain 2-bromo-1-[2-(3-fluorophenyl)-4-methoxy-1,3-thiazol-5-yl]ethanone which was used without further purification. The compound was then dissolved in 5 mL of glacial acetic acid, sodium acetate (0.65 g, 7.9 mmol) was added and the mixture was heated at 120°C for 2h. The solution was diluted with 30 mL of water and
washed with diethyl ether (20 mL x 3). 2-[2-(3-fluorophenyl)-4-methoxy-1,3-thiazol-5-yl]-2-oxoethyl acetate was purified by flash chromatography (n-hexane : ethyl acetate 9:1 as eluent). The latter compound was dissolved in 10 mL of 1,4-dioxane and 2 mL of NaOH 2M were added. The solution was stirred at room temperature for 2h. The solution was diluted with 10 mL of HCl 2M and the compound extracted with ethyl acetate. 1-[2-(3-fluorophenyl)-4-methoxy-1,3-thiazol-5-yl]-2-methoxyethanone was obtained as orange oil in 65% yield. The latter compound (0.089 g, 0.33 mmol) was dissolved in 5 mL of dry DMF and 0.016 g (0.66 mmol) of NaH (60% w/w) were added at 0°C. Then 41 µL (0.66 mmol) of methyl iodide were added and the solution was stirred at room temperature for 5h. The mixture was quenched with 10 mL of saturated NH4Cl and the compound was extracted with ethyl acetate. The crude was purified by flash chromatography with n-hexane : ethyl acetate 9:1 as eluent to obtain 1-[2-(3-fluorophenyl)-4-methoxy-1,3-thiazol-5-yl]-2-methoxyethanone in quantitative yield. 1-[2-(3-fluorophenyl)-4-methoxy-1,3-thiazol-5-yl]-2-methoxyethanone was dissolved at room temperature in dry DCM (4 mL) then refrigerated to 0°C with an ice bath. The solution was treated at this temperature with boron tribromide 1M in dichloromethane (0.66 mL, 0.66 mmol) then stirred for 30 minutes. The reaction was diluted with DCM (10 mL) and stirred with water (10 mL) for 10 minutes. The organic layer was separated and anhydried over anhydrous sodium sulphate, the solvent was distilled and the crude purified over silica gel.

1-[2-(3-fluorophenyl)-4-hydroxy-1,3-thiazol-5-yl]-2-methoxyethanone was obtained as a yellow solid (0.019 g, 0.071 mmol, Y = 43 %).

1H-NMR (CDCl3): δ 7.83-7.71 (m, 2H), 7.42-7.35 (m, 1H), 7.28-7.21 (m, 1H), 2.85 (s, 2H), 2.37 (s, 3H).

MS (ES+): m/z: 268.21 [M+H]+.

Example 35
Synthesis of 1-[2-(3-fluorophenyl)-4-hydroxy-1,3-thiazol-5-yl]propane-1-thione (40)

1-[2-(3-fluorophenyl)-4-methoxy-1,3-thiazol-5-yl]propane-1-thione (0.120 g, 0.45 mmol), prepared as described in Example 1 - intermediate g, was dissolved in 5 mL of dry THF. Lawesson’s reagent (0.273 g, 0.675 mmol) was added and the resulting mixture was heated at 130°C in a sealed tube for 2h. The solution was cooled at room temperature and the solvent removed by vacuum distillation. The crude was purified by flash chromatography (n-hexane : ethyl acetate 85:15 as eluent) to obtain 1-[2-(3-fluorophenyl)-4-methoxy-1,3-thiazol-5-yl]propane-1-thione as a yellow oil (0.037 mg, 0.13 mmol, Y = 29 %). The latter compound was deprotected with boron tribromide as described for compound 1 to obtain the title compound as a yellow solid (0.030 g, 0.11 mmol, Y = 86 %).

1H-NMR (CDCl3): δ 11.81 (bs, 1H, OH), 7.81-7.76 (m, 1H), 7.71-7.64 (m, 1H), 7.61-7.53 (m, 1H), 7.28-7.20 (m, 1H), 2.85 (q, 2H, J = 7.3 Hz), 1.51 (t, 3H, J = 7.3 Hz).

MS (ES+): m/z: 268.35. 12 [M+H]+.

Example 36
Synthesis of 2-(3-fluorophenyl)-4-hydroxy-N-methoxy-N-methyl-1,3-thiazole-5-carboxamide (3)

Starting from 3-fluorobenzencarbonothioamide (0.055 g, 0.35 mmol), prepared as described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain 2-(3-fluorophenyl)-N,4-dimethoxy-N-methyl-1,3-thiazole-5-carboxamide (Weinreb's amide). The latter was then directly deprotected
with boron tribromide to obtain the 2-(3-fluorophenyl)-4-hydroxy-N-methoxy-N-methyl-1,3-thiazole-5-carboxamide as a pale yellow solid (0.019 g, 0.07 mmol, Y = 95%).

1H-NMR (CDCl3): δ 7.85-7.70 (m, 2H), 7.45-7.35 (m, 1H), 7.25-7.19 (m, 1H), 3.85 (s, 3H), 3.37 (s, 3H).

MS (ES1+) m/z: 283.9 [M+H]+.

Example 37

Synthesis of 4-hydroxy-N-methoxy-N-methyl-2-(thiophen-2-yl)-1,3-thiazole-5-carboxamide (6)

Starting from thiophene-2-carbothioamide (0.081 g, 0.57 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain N,4-dimethoxy-N-methyl-2-(thiophen-2-yl)-1,3-thiazole-5-carboxamide (Weinreb's amide). The latter was directly deprotected with boron tribromide to obtain the title compound as an off-white solid (0.030 g, 0.11 mmol, Y = 95%).

1H-NMR (CDCl3): δ 7.68 (s, 1H), 7.48 (s, 1H), 7.08 (s, 1H), 3.80 (s, 3H), 3.35 (s, 3H).

MS (ES1+) m/z: 271.1 [M+H]+.

Example 38

Synthesis of 4-hydroxy-N-methoxy-N-methyl-2-(methylphenyl)-1,3-thiazole-5-carboxamide (8)

Starting from 2-methylbenzene carbothioamide (0.103 g, 0.68 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain N,4-dimethoxy-N-methyl-2-(methylphenyl)-1,3-thiazole-5-carboxamide (Weinreb's amide). The latter was directly deprotected with boron tribromide to obtain the title compound as an off-white solid (0.037 g, 0.13 mmol, Y = 95%).

1H-NMR (CDCl3): δ 12.10 (s, 1H, OH), 7.84-7.78 (m, 1H), 7.41-7.20 (m, 3H), 3.80 (s, 3H), 3.38 (s, 3H), 2.62 (s, 3H).

MS (ES1+) m/z: 279.9 [M+H]+.

Example 39

Synthesis of 2-(2-bromophenyl)-4-hydroxy-N-methoxy-N-methyl-1,3-thiazole-5-carboxamide (10)

Starting from 2-bromobenzene carbothioamide (0.051 g, 0.15 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure for the thiazoles synthesis was applied to obtain 2-(2-bromophenyl)-N,4-dimethoxy-N-methyl-1,3-thiazole-5-carboxamide (Weinreb's amide). The latter was directly deprotected with boron tribromide to obtain the title compound as a white solid (0.021 g, 0.06 mmol, Y = 95%).

1H-NMR (CDCl3): δ 12.00 (s, 1H, OH), 8.35-8.21 (m, 1H), 7.78-7.68 (m, 1H), 7.50-7.37 (m, 1H), 7.37-7.22 (m, 1H), 3.83 (s, 3H), 3.39 (s, 3H).

MS (ES1+) m/z: 343.04 [M+H]+.

Example 40

Synthesis of 4-hydroxy-2-(2-hydroxyphenyl)-N-methoxy-N-methyl-1,3-thiazole-5-carboxamide (12)

Starting from 2-methoxybenzene carbothioamide (0.120 g, 0.72 mmol) prepared analogously to what described in Example 1 - intermediate a, the general procedure was applied for the thiazoles synthesis to obtain N,4-dimethoxy-2-(2-methoxyphenyl)-N-methyl-1,3-thiazole-5-carboxamide (Weinreb's amide).
The Weinreb’s amide was directly deprotected with boron tribromide (4 equivalents) to obtain the title compound as a yellow solid (0.040 g, 0.14 mmol, Y = 95%).

1H-NMR (CDCl$_3$): $\delta$ 12.29 (s, 1H, OH), 11.60 (s, 1H, OH), 7.70-7.62 (m, 1H), 7.41-7.32 (m, 1H), 7.10-7.02 (m, 1H), 6.95-6.89 (m, 1H), 3.83 (s, 3H), 3.38 (s, 3H).

MS (ES$^+$) m/z: 281.1 [M+H$^+$].

**Example 41**

**Synthesis of 2-(3-fluorophenyl)-4-hydroxy-A/-methoxy-A/-methyl-1,3-thiazole-5-carbothioamide (41)**

2-(3-fluorophenyl)-W,4-dimethoxy-W-methyl-1,3-thiazole-5-carboxamide (0.100 g, 0.34 mmol), prepared as described in Example 1 - intermediate 1, was dissolved in 5 mL of dry THF. Lawesson’s reagent (0.361 g, 0.51 mmol) was added and the resulting mixture was heated at 70°C in for 2h. The solution was cooled at room temperature and the solvent removed by vacuum distillation. The crude was purified by flash chromatography (n-hexane : ethyl acetate 85:15 as eluent) to obtain 2-(3-fluorophenyl)-A/-4-dimethoxy-N- methyl-1,3-thiazole-5-carbothioamide as a yellow oil (0.072 g, 0.23 mmol, Y = 68%). The latter compound was deprotected with boron tribromide as described for compound 1 to obtain the title compound as a yellow solid (0.057 g, 0.19 mmol, Y = 85%).

1H-NMR (CDCl$_3$): $\delta$ 7.83-7.79 (m, 2H), 7.44-7.35 (m, 1H), 7.26-7.20 (m, 1H), 3.95 (s, 3H), 3.45 (s, 3H).

MS (ES$^+$) m/z: 299.20 [M+H$^+$].

**Example 42**

**Synthesis of 2-(3-fluorophenyl)-5-[1 E]-N-methoxypropanimidoyl]-1,3-thiazol-4-ol (42)**

To a solution of methyl 2-chloro-3-oxopentanoate (0.200 g, 1.215 mmol) in 5 mL of ethanol, methoxyamine hydrochloride (0.152 g, 1.823 mmol) and ammonium acetate (0.149 g, 1.823 mmol) were added and the resulting mixture was stirred at room temperature for 4h. The mixture was diluted with water (10 mL) and extracted with ethyl ether (20 mL). The organic phase was then anhydried over dry sodium sulphate and the solvent removed by vacuum distillation. The crude was dissolved in 5 mL of ethanol and trasfered into a microwave vial; then 0.093 g (0.60 mmol) of 3-fluorobenzencarbothioamide were added. The vial was sealed and irradiated at 100 °C for 60 minutes. The solution was cooled at room temperature and the solvent removed by vacuum distillation. The crude was purified by flash chromatography (n-hexane : ethyl acetate 90:10 as eluent) to obtain 2-(3-fluorophenyl)-5-[1 E]-N-methoxypropanimidoyl]-1,3-thiazol-4-ol as a yellow solid (0.066 mg, 0.23 mmol, Y = 39%).

1H-NMR (CDCl$_3$): $\delta$ 10.45 (bs, 1H, OH), 7.75-7.65 (m, 2H), 7.45-7.38 (m, 1H), 7.18-7.11 (m, 1H), 4.00 (s, 3H), 2.68 (q, 2H, J= 7.3 Hz), 1.22 (t, 3H, J=7.3 Hz).

MS (ES$^+$) m/z: 281.12 [M+H$^+$].

**Example 43**

**Synthesis of 2-(3-fluorophenyl)-5-propanimidoyl-1,3-thiazol-4-ol (43)**

To a solution of methyl 2-chloro-3-oxopentanoate (0.107 g, 0.650 mmol) in 1.5 mL of ethanol, O-(Trimethylsilyl) hydroxylamine (0.120 g, 0.975 mmol) and ammonium acetate (0.125 g, 1.625 mmol) were added and the resulting mixture was stirred at room temperature for 1h. The crude was trasfered into a microwave vial then
0.052 g (0.650 mmol) of 3-fluorobenzenecarbothioamide were added. The vial was sealed and irradiated at 120 °C for 50 minutes. The solution was cooled at room temperature and the solvent removed by vacuum distillation. The crude was purified by flash chromatography (dichloromethane : methanol 99:1 as eluent) to obtain 2-(3-fluorophenyl)-5-propanimidoyl-1 ,3-thiazol-4-ol as a yellow solid (0.078 mg, 0.31 mmol, Y = 48 %).

1H-NMR (CDCl3): δ 10.50 (bs, 1H, OH), 7.87-7.79 (m, 2H), 7.51-7.43 (m, 1H), 7.26-7.20 (m, 1H), 2.60 (q, 2H, J= 7.3 Hz), 1.42 (t, 3H, J=7.3 Hz).

MS (ES⁺) m/z: 251.34 [M+H]⁺.

Example 44

Synthesis of 2-(3-fluorophenyl)-5-[(1 E)-N-hydroxypropanimidoyl]-1 ,3-thiazol-4-ol (44)

A solution of 0.040 g (0.143 mmol) of 2-(3-fluorophenyl)-5-[(1 E)-N-methoxypropanimidoyl]-1 ,3-thiazol-4-ol (example 42) in dry dichloromethane (5 mL) was then refrigerated to 0°C with an ice bath. The solution was treated at this temperature with boron tribromide 1M in dichloromethane (0.36 mL, 0.36 mmol) then stirred for 30 minutes. The reaction was diluted with DCM (5 mL) and stirred with water (5 mL) for 10 minutes. The organic layer was separated and anhydried over anhydrous sodium sulphate, the solvent was distilled and the crude purified over silica gel.

2-(3-fluorophenyl)-5-[(1 E)-N-hydroxypropanimidoyl]-1 ,3-thiazol-4-ol was obtained as an orange solid (0.031 g, 0.18 mmol, Y = 83 %)

1H-NMR (CD3OD): δ 7.81-7.78 (m, 1H), 7.77-7.73 (m, 1H), 7.50-7.22 (m, 2H), 2.81 (q, 2H, J= 7.3 Hz), 1.54 (t, 3H, J=7.3 Hz).

MS (ES⁺) m/z: 267.22 [M+H]⁺.

Example 45

Synthesis of cyclopropyl[2-(3-fluorophenyl)-4-hydroxy-1 ,3-thiazol-5-yl]methanone (45)

Starting from 3-fluorobenzenecarbothioamide (0.085 g, 0.55 mmol) prepared as described in Example 1 intermediate a, the general procedure for the thioazoles synthesis was applied to obtain 2-(3-fluorophenyl)-N,4-dimethoxy-N-methyl-1 ,3-thiazole-5-carboxamide (Weinreb’s amide). The latter was subjected to the same synthetic conditions specified in the general procedure using cyclopropylmagnesium bromide to obtain cyclopropyl[2-(3-fluorophenyl)-4-methoxy-1 ,3-thiazol-5-yl]methanone which was then deprotected with boron tribromide to obtain the title compound as a light brown solid (0.121 g, 0.46 mmol, Y = 81 %).

1H-NMR (CDCl3): δ 11.50 (bs, 1H, OH), 7.83-7.78 (m, 2H), 7.53-7.41 (m, 1H), 7.29-7.21 (m, 1H), 2.38 (m, 1H), 0.95-0.88 (m, 2H), 0.63-0.55 (m, 2H).

MS (ES⁺) m/z: 264.40 [M+H]⁺.

Example 46

Evaluation of in vitro activity

a. Cloning, sequencing, transfection and selection of positive clones expressing human TRPM8

A functional cell-based assay for the identification of TRPM8 receptor antagonists, optimised to allow high throughput screening at FLIPR^TeSTA, was developed in HEK293 cells by stable pure clone selection and functional characterization with a fluorescent calcium sensitive dye.
TRPM8 was cloned into the multiple cloning site of pcDNA3 mammalian expression vector; the obtained construct pcDNA3/hTRPM8 was fully sequence verified and used for the transfection of HEK293 cell line. HEK293 cells stably transfected with TRPM8 gene were maintained in Minimum essential medium. The cells were transfected with the pcDNA3/hTRPM8 vector by electroporation and then selected with medium containing 0.8 mg/ml G418 for 10-15 days.

The following commercial compounds were used as TRPM8 channel reference compound to test HEK293/hTRPM8 cell line for both agonist and antagonist activity:

**Activators**: Menthol (SIGMA cat.# M2772) WS-3, (N-Ethyl-5-methyl-2-(1-methylethyl)cyclohexanecarboxamide) (SIGMA cat.# W345501)

**Blocker**: Capsazepine (SIGMA cat.# C191)

The experimental activities were performed using FLIPR instruments.

The functional clones were selected at FLIPR 384 on the basis of 1 mM menthol response. Two best responder clones were selected, diluted at a cell density of 1 cell/well and analysed at FLIPR 384 with 1 mM menthol.

The TRPM8 receptor was analysed for the response to reference agonist, menthol, using a calcium-dependent fluorescence signal.

Patch clamp recordings were also obtained in voltage-clamp configuration on HEK/TRPM8 clones in order to verify the receptor pharmacology and to determine the agonist dose-response curve and \( EC_{50} \) value. HEK293 cells were maintained at room temperature on an fire-polished borosilicate glass pipettes having 1.5-2.5 M\( \Omega \) resistance were used to record currents following drug application. Menthol application induced a dose-dependent inward current in a selected HEK/hTRPM8 clone (calculated \( EC_{50} \) value = 58 \( \mu \)M). No menthol-induced currents were recorded in not transfected HEK293 cells.

In order to determine the capsazepine antagonist activity on menthol agonist response and to verify the antagonist response stability throughout different days of experiments, the selected clone of TRPM8 was analysed after 24h at FLIPR 384 in presence of variable concentrations of antagonist (from 100 nM to 316 \( \mu \)M).

The selected clone showed very good stability and reproducibility of the antagonist activity (calculated \( IC_{50} \) value = 20 \( \mu \)M).

Summarizing, the best clone was characterized for: 1- pharmacology: agonist \( EC_{50} \) and antagonist \( IC_{50} \) determination over different experiments;

2- optimal cell density and seeding time;

3- DMSO sensitivity;

4- ligand stability;

5- patch clamp analysis.

b. Screening set up for the identification of TRPM8 antagonists

The following commercial compounds were used as ligands:

**Activator**: Cooling Agent 10 (Takasago CAS N. 87061-04-9)

**Blocker**: Capsazepine (SIGMA cat # D_5879)

The experimental activities were performed using FLIPR instruments.
HEK293 cells stably transfected with TRPM8 gene were maintained in Minimum essential medium. The TRPM8 cell line was analysed for the response to a library of compounds using a Ca²⁺ mobilization-dependent fluorescence signal in 384 wells microtiter plate format. The analysis was performed using the FLIPRTETRA (MDC) with the ICCD Camera.

The execution of the assay involved the use of three microtiter plates:

1. **Assay plate**, containing cells loaded with dye and prepared as follows:

Cells were seeded at 15000 c/well in Poly-D-Lysine coated 384 wells Microtiter Plates in complete medium (25µL/well).

24h after seeding, the cell plates were washed with Tyrode assay buffer by the Microplate Washer and 10µL of Tyrode assay buffer was left in each well.

Cells were then loaded with 10 µL/well of the Fluo-4 NW dye solution by CyBi®-Well pipettor. Each bottle of Fluo4-N W dye (Molecular Probes cat. #F36206, component A) was re-suspended in 8mL of Tyrode assay buffer and supplemented with 100 µL of water-soluble probenecid (MolecularProbes cat.#F36206, component B). Dye loaded cell plates were incubated for 1 h at room temperature.

2. **Compound Dilution Plate**, containing diluted test compounds, formulated as follows:

Column 1: wells containing Assay Buffer plus DMSO 0.5% final

Column 2: wells alternating Max Signal Control in first injection (Maximum Response: Cooling Agent 10 at EC100, 100 µM) and Min Signal Control in first injection (Assay buffer plus 0.5% DMSO final);

Columns 3-22: wells containing Assay Buffer plus 0.5% DMSO final. To these wells the compounds to be tested were added at 3x concentration.

Column 23: alternating wells of Max Signal Control in second injection (Assay buffer) and Min Signal Control in second injection (Antagonist Capsazepine IC100, 50 µM) in Assay buffer plus 0.5% DMSO final;

Column 24: wells containing Capsazepine (Antagonist) at 8 concentrations in duplicate at final concentrations of 50µM, 25µM, 6.25µM, 3.15µM, 1.56µM, 780 nM, 309 nM in Assay buffer plus 0.5% DMSO final.

3. **Activator Plate**, containing agonist Cooling Agent 10 at EC80, formulated as follows:

Column 1: Cooling Agent 10 (Agonist) at 8 concentrations dose response in duplicate at final concentrations of 100µM, 31.6µM, 16µM, 8µM, 4µM, 2µM, 1µM, 0.5µM, 0.25µM, 0.125µM in Assay buffer;

Columns 2-24: Cooling Agent 10 (Agonist) at EC80 (3 fold concentrated, 20µM final) in Assay buffer.

The test was carried out according to a procedure comprising the following steps:

1. The samples contained in the wells of the Compound Plate were added to the corresponding wells of the Assay Plate by the FLIPRTETRA, thus resulting in the addition in Columns 3-22 of the test compounds at 3x concentration to the cells of the assay plates. No mixing was performed in the assay wells and the signal of the emitted fluorescence was recorded for 300 seconds.

2. The samples contained in the wells of the Activator Plate were added to the corresponding wells of the Assay Plate by the FLIPRTETRA, thus resulting in the addition in Columns 3-22 of the Assay Plate of the agonist compound in addition to the test compounds. The signal of the emitted fluorescence was recorded for 180 seconds.
Columns 1, 2, 23 and 24 were used as control. In particular: the "Max Signal Control in first injection" indicates the Cooling Agent 10 agonist response at EC100. "Max Signal Control in the second injection" indicates the agonist at EC50 (10 μM) in presence of pre-injected Assay buffer, the "Min Signal Control in first injection" corresponds to Assay buffer injection and "Min Signal Control in the second injection" indicates the agonist at EC50 (20 μM) in presence of pre-injected reference antagonist Capsazepine at IC100 (50 μM).

During the Target Activation (TA) phase, the injection of the reference agonist at EC50 gave an increase of fluorescent signal in MAX Signal control wells in which the assay buffer in CA was preinjected, while the response was completely inhibited in MIN Signal control wells due to the preinjection of the reference inhibitor Capsazepine.

The goal of the assay was to find antagonists of TRPM8 activity; to this aim the change of fluorescent signal during TA phase was measured.

Several parameters were computed and analyzed (μ-factor, Interplate variability, Intraplate variability, Day to Day variability, Antagonist Dose response and IC50 determination, Agonist Dose response and EC50 determination).

As for the antagonist Dose response and IC50 determination, capsazepine (reference antagonist) was included as control and the IC50 values of all the assayed compounds were calculated.

Compounds 1-45 were tested and all showed an IC50 value below 2 μM; the majority of the compounds having an IC50 below 0.1 μM, some of them having an IC50 below 0.03 μM.

**Example 47**

**Evaluation of in vivo activity**

Chronic Constriction Model of Pain

Neuropathic pain behavior will be induced by ligation of the sciatic nerve according to the method described by Bennett GJ et al., Pain. 33: 87-107, 1988. Briefly, male Sprague-Dawley rats will be anaesthetized (100 mg/kg ketamine and 10 mg/kg xylazine i.p.) and the left sciatic nerve will be exposed at the level of the thigh by blunt dissection through the biceps femoris. Proximal to the sciatic's trifurcation, about 12 mm of nerve will be freed of adhering tissue and four ligatures will be loosely tied around it with about 1 mm spacing so that the epineural circulation will be preserved. The length of nerve thus affected was 6-8 mm long. The animals will be allowed to recover and used the day after the surgery. Sham animals represent rats operated but not ligated.

The study was performed in order to determine antiallodynic effects of compound 2. On day 7 and 14 following ligation, neuropathic rats were received a single dose of compound 2; 1, 3 and 5h following treatment, mechanical and cold allodynia were evaluated using Dynamic Plantar Aesthesiometer (DPA) and drop of acetone.

All data were presented as the mean ± SEM. Analysis of data was conducted using GraphPad Prism 4.01 . Statistical analysis was performed by two-way ANOVA followed by Dunnett's test for multiple comparisons, as appropriate. Statistical significance was set at p<0.05.
Oral administration of compound 2 at the dose of 10mg/kg on day 7 and on day 14 after nerve-induced injury, significantly attenuated cold and mechanical allodynia at 3 hours and 5 hours post-dose. The maximal activity was reached at 3 hours after treatment (about 50% of inhibition on both the parameters, Fig. 1a, 1b, 2a and 2b) according to its pharmacokinetic profile.

Example 48

Selectivity analysis
a. GPCRs Selectivity

Compound 2 was tested to evaluate the activity towards cloned human GPCRs (G-protein coupled receptors) using radioligand binding assays. The compound was tested at 10 µM in duplicate and the results are summarized in Table 1.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Cmpd 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>human Muscarinic M₂</td>
<td>inactive</td>
</tr>
<tr>
<td>human Muscarinic M₃</td>
<td>inactive</td>
</tr>
<tr>
<td>human Adrenergic β₁</td>
<td>inactive</td>
</tr>
<tr>
<td>human Adrenergic β₂</td>
<td>inactive</td>
</tr>
<tr>
<td>human Adrenergic α₁A</td>
<td>inactive</td>
</tr>
<tr>
<td>human Adrenergic α₂A</td>
<td>inactive</td>
</tr>
<tr>
<td>human Serotoninergic 5-HT₁A</td>
<td>inactive</td>
</tr>
<tr>
<td>human Histamine H₁</td>
<td>inactive</td>
</tr>
<tr>
<td>human Histamine H₂</td>
<td>inactive</td>
</tr>
<tr>
<td>human Cannabinoid CB₁</td>
<td>inactive</td>
</tr>
<tr>
<td>human Cannabinoid CB₂</td>
<td>inactive</td>
</tr>
<tr>
<td>human Bradykinin B₁</td>
<td>inactive</td>
</tr>
<tr>
<td>human Bradykinin B₂</td>
<td>inactive</td>
</tr>
<tr>
<td>human Dopamine D₂₅</td>
<td>inactive</td>
</tr>
<tr>
<td>human Dopamine D₃</td>
<td>inactive</td>
</tr>
<tr>
<td>human Opioid δ₂ (DOP)</td>
<td>inactive</td>
</tr>
<tr>
<td>human Opioid κ (KOP)</td>
<td>inactive</td>
</tr>
<tr>
<td>human Opioid μ (MOP)</td>
<td>inactive</td>
</tr>
<tr>
<td>human Opioid NOP (ORL1)</td>
<td>inactive</td>
</tr>
<tr>
<td>human NK1</td>
<td>inactive</td>
</tr>
</tbody>
</table>

As it is possible to note from Table 1, compound 2 shows a high selectivity versus a wide range of selected GPCRs (including muscarinic M₃, CB₂, BK₁, alpha e beta adrenergic) that are well known to be involved in the...
pain control. These data support that the observed in vivo efficacy of compound 2 and in general of all the compounds of the invention is potential strongly dependent on the TRPM8 blockage,

b. Ion Channel Selectivity.

In order to address more specifically the potential selectivity issues, a counterassay was carried out for compound 2 against TRPV1 and TRPV4 ion channels, both involved in the nociception (Jhaveri MD, et al 2005. Eur. J. Neurosci. 22 (2): 361-70, Brierley SM et al, 2008, Gastroenterology. 2008 Jun; 134(7):2059-69) and towards TRPA1. The results are summarized in Table 2.

The ability of compound 2 to act as an antagonist of TRPV1 was evaluated with a calcium influx assay. The signal elicited in the presence of the positive control agonist (capsaicin) was set to 100% and the signal in the presence of the antagonist (ruthenium red) was set to 0. In parallel, the ability of compound 2 to act as an antagonist of TRPV4 was evaluated with a calcium influx assay. The signal elicited in the presence of the positive control agonist (GSK1016790A) was set to 100% and the signal in the presence of the antagonist (ruthenium red) was set to 0. The ability of compound 2 to act as an antagonist of TRPA1 was evaluated with a calcium influx assay. The signal elicited in the presence of the positive control agonist (allyl isothiocyanate, AITC) was set to 100% and the signal in the presence of the antagonist (ruthenium red) was set to 0.

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC$_{50}$ (TRPV1)</th>
<th>IC$_{50}$ (TRPV4)</th>
<th>IC$_{50}$ (TRPA1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>$&gt; 10^5 M$</td>
<td>$&gt; 10^5 M$</td>
<td>$&gt; 10^5 M$</td>
</tr>
</tbody>
</table>

The data strongly highlight the great selectivity of compound 2 towards TRPV1, TRPV4 and TRPA1 thus confirming its selective mechanism of action.

Example 49

ADME and PK evaluation

The ADME properties and the pharmacokinetic profile of compound 2 were evaluated. The results are summarized in Table 3 and Table 4:

<table>
<thead>
<tr>
<th>Log D$_{7.4}$</th>
<th>0.440</th>
</tr>
</thead>
<tbody>
<tr>
<td>pKa</td>
<td>4.18</td>
</tr>
<tr>
<td>hERG (IC50)</td>
<td>$&gt; 1$ mM</td>
</tr>
<tr>
<td>CYP450 Inhibition (IC50 at 10 µM)</td>
<td>CYP3A4 , CYP1A2, CYP2D6, CYP2C9, CYP2C19 &gt; 30 µM</td>
</tr>
<tr>
<td>Plasma Protein Binding</td>
<td>human 98.71% - rat 97.50%</td>
</tr>
<tr>
<td>CLint(rat)</td>
<td>29.4 µL/min/mg</td>
</tr>
<tr>
<td>Rat Plasma Stability (%) remaining</td>
<td>98.2% at 30min, 80.3 at 60min</td>
</tr>
</tbody>
</table>
Table 4

<table>
<thead>
<tr>
<th>Compound</th>
<th>intravenous administration</th>
<th>oral administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CL (mL/min/kg)</td>
<td>Vds (L/kg)</td>
</tr>
<tr>
<td>2 $^a$</td>
<td>6.81</td>
<td>1.78</td>
</tr>
</tbody>
</table>

$^a$ IV 5 mg/kg; PO 10 mg/kg

Compound 2 shows no effect towards any human cytochrome isoform at the maximal concentration of 10 μM thus excluding potential drug-drug interaction. In addition, none effect was observed towards hERG channel thus excluding potential cardiotoxic effect during the clinical development.

The low logD values of compound 2 makes it particularly suitable when ip, iv and ives applications are required, especially in the treatment of urological disorders. At the same time, the relatively high plasma half-life (2.94 h) and the high oral bioavailability (F = 100%) could makes it the ideal candidate for the treatment of chronic diseases, like inflammatory and neuropathic pain.
<table>
<thead>
<tr>
<th>Compound Number</th>
<th>Structure</th>
<th>Chemical Name</th>
<th>IC50 (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>1-[2-(3-fluorophenyl)-4-hydroxy-1,3-thiazol-5-yl]propan-1-one</td>
<td>0.032</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>Sodium 2-(3-fluorophenyl)-5-propanoyl-1,3-thiazol-4-olate</td>
<td>0.028</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>2-(3-fluorophenyl)-4-hydroxy-N-methoxy-N-methyl-1,3-thiazole-5-carboxamide</td>
<td>0.018</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>1-(2-(3-fluorophenyl)-4-hydroxythiazol-5-yl)ethanone</td>
<td>0.958</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Structure 5" /></td>
<td>1-[2-(3-fluorophenyl)-4-hydroxy-1,3-thiazol-5-yl]-2-methylpropan-1-one</td>
<td>0.299</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6.png" alt="Structure 6" /></td>
<td>4-hydroxy-N-methoxy-N-methyl-2-(thiophen-2-yl)-1,3-thiazole-5-carboxamide</td>
<td>0.156</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7.png" alt="Structure 7" /></td>
<td>1-[4-hydroxy-2-(thiophen-2-yl)-1,3-thiazol-5-yl]propan-1-one</td>
<td>0.596</td>
</tr>
<tr>
<td>8</td>
<td><img src="image8.png" alt="Structure 8" /></td>
<td>4-hydroxy-N-methoxy-N-methyl-2-(2-methylphenyl)-1,3-thiazole-5-carboxamide</td>
<td>0.086</td>
</tr>
<tr>
<td>No.</td>
<td>Chemical Structure</td>
<td>Compound Formula</td>
<td>Log P Value</td>
</tr>
<tr>
<td>-----</td>
<td>-------------------</td>
<td>-----------------</td>
<td>-------------</td>
</tr>
<tr>
<td>9</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>1-[4-hydroxy-2-(2-methylphenyl)-1,3-thiazol-5-yl]propan-1-one</td>
<td>0.411</td>
</tr>
<tr>
<td>10</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>2-(2-bromophenyl)-4-hydroxy-N-methoxy-N-methyl-1,3-thiazole-5-carboxamide</td>
<td>0.435</td>
</tr>
<tr>
<td>11</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>1-[2-(2-bromophenyl)-4-hydroxy-1,3-thiazol-5-yl]propan-1-one</td>
<td>0.912</td>
</tr>
<tr>
<td>12</td>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>4-hydroxy-2-(2-hydroxyphenyl)-N-methoxy-N-methyl-1,3-thiazole-5-carboxamide</td>
<td>0.006</td>
</tr>
<tr>
<td>13</td>
<td><img src="image5.png" alt="Structure 5" /></td>
<td>1-[2-(2-hydroxyphenyl)-4-hydroxy-1,3-thiazol-5-yl]propan-1-one</td>
<td>0.112</td>
</tr>
<tr>
<td>14</td>
<td><img src="image6.png" alt="Structure 6" /></td>
<td>1-[2-(3-bromophenyl)-4-hydroxy-1,3-thiazol-5-yl]propan-1-one</td>
<td>1.73</td>
</tr>
<tr>
<td>15</td>
<td><img src="image7.png" alt="Structure 7" /></td>
<td>1-[2-(furan-2-yl)-4-hydroxy-1,3-thiazol-5-yl]propan-1-one</td>
<td>0.236</td>
</tr>
<tr>
<td>16</td>
<td><img src="image8.png" alt="Structure 8" /></td>
<td>1-[4-hydroxy-2-(1H-pyrrol-2-yl)-1,3-thiazol-5-yl]propan-1-one</td>
<td>0.123</td>
</tr>
<tr>
<td>17</td>
<td><img src="image9.png" alt="Structure 9" /></td>
<td>1-[4-hydroxy-2-(1-methyl-1H-pyrrol-2-yl)-1,3-thiazol-5-yl]propan-1-one</td>
<td>0.323</td>
</tr>
<tr>
<td>18</td>
<td><img src="image10.png" alt="Structure 10" /></td>
<td>1-[4-hydroxy-2-(1-methyl-1H-imidazol-5-yl)-1,3-thiazol-5-yl]propan-1-one</td>
<td>0.112</td>
</tr>
<tr>
<td></td>
<td>Molecular Structure</td>
<td>Chemical Formula</td>
<td>Log P</td>
</tr>
<tr>
<td>---</td>
<td>---------------------</td>
<td>-----------------</td>
<td>---------</td>
</tr>
<tr>
<td>19</td>
<td><img src="image19" alt="Structure 19" /></td>
<td>1-[4-hydroxy-2-(1H-imidazol-5-yl)-1,3-thiazol-5-yl]propan-1-one</td>
<td>0.302</td>
</tr>
<tr>
<td>20</td>
<td><img src="image20" alt="Structure 20" /></td>
<td>1-[4-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,3-thiazol-5-yl]propan-1-one</td>
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<td>21</td>
<td><img src="image21" alt="Structure 21" /></td>
<td>1-[4-hydroxy-2-(thiophen-2-yl)-1,3-thiazol-5-yl]butan-1-one</td>
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<td><img src="image22" alt="Structure 22" /></td>
<td>1-[4-hydroxy-2-(thiophen-2-yl)-1,3-thiazol-5-yl]-3-methylbutan-1-one</td>
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<td><img src="image23" alt="Structure 23" /></td>
<td>1-[4-hydroxy-2-(1,2,4-oxadiazol-3-yl)-1,3-thiazol-5-yl]propan-1-one</td>
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<td><img src="image24" alt="Structure 24" /></td>
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<td>0.123</td>
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<td>0.356</td>
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<td><img src="image26" alt="Structure 26" /></td>
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<td><img src="structure35.png" alt="" /></td>
<td>1-{4-hydroxy-2-[4-(methylamino)phenyl]-1,3-thiazol-5-yl}propan-1-one</td>
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<td>1-(2-(3-fluorophenyl)-4-hydroxythiazol-5-yl)isobutan-1-one</td>
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<td><img src="structure41.png" alt="" /></td>
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<td><img src="image1.png" alt="Structure 1" /></td>
<td>2-(3-fluorophenyl)-5-[(1E)-N-methoxypropanimidoxy]-1,3-thiazol-4-ol</td>
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<td><img src="image2.png" alt="Structure 2" /></td>
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<td><img src="image3.png" alt="Structure 3" /></td>
<td>2-(3-fluorophenyl)-5-[(1E)-N-hydroxypropanimidoxy]-1,3-thiazol-4-ol</td>
<td>1.36</td>
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<td><img src="image4.png" alt="Structure 4" /></td>
<td>cyclopropyl[2-(3-fluorophenyl)-4-hydroxy-1,3-thiazol-5-yl]methanone</td>
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CLAIMS

1. A compound of formula (I):

\[
\text{(I)}
\]

wherein

X is oxygen, sulphur, NH, NOH, or NOMe;

R is a group selected from aryl and heteroaryl, optionally substituted by one or more substituents selected from:

- hydrogen,
- halogen,
- \( \text{CF}_3 \),
- linear or branched \( \text{C}_1-\text{C}_6 \) alkyl,
- OR5 and
- NR6R7, wherein R5, R6 and R7 are independently hydrogen or linear or branched \( \text{C}_1-\text{C}_6 \) alkyl;

R1 is a group selected from:

- linear or branched \( \text{C}_1-\text{C}_6 \) alkyl,
- \( (\text{CH}_2)^m \text{OR}_2 \), wherein m is an integer between 1 and 3 and R2 is selected from hydrogen and linear \( \text{C}_1-\text{C}_3 \) alkyl,
- \( \text{C}_3-\text{C}_6 \) cycloalkyl, and
- N(R3)OR4, wherein R3 and R4 are independently hydrogen or linear or branched \( \text{C}_1-\text{C}_3 \) alkyl,

and pharmaceutically acceptable salts thereof, for use as a medicament.

2. A compound for use according to claim 1, wherein

X is oxygen.

3. A compound for use according to claim 1 or 2 wherein

R is phenyl or a 5- or 6-membered heteroaryl containing from 1 to 3 heteroatoms selected from N, O and S, preferably, said 5- or 6-membered heteroaryl is selected from the group consisting of thiophenyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, oxadiazolyl, oxazolyl and pyridinyl.

4. A compound for use according to claims 1 to 3 wherein

R is aryl optionally substituted with a group selected from:

- halogen, preferably selected from Br and F,
- linear or branched \( \text{C}_1-\text{C}_3 \) alkyl, preferably \( \text{CH}_3 \),
- OR5 and NR6R7, wherein R5, R6 and R7 are independently hydrogen or linear \( \text{C}_1-\text{C}_3 \) alkyl, preferably OH, \( \text{NH}_2 \) or \( \text{NHCH}_3 \), respectively.
5. A compound for use according to claims 1 to 4 wherein

R is heteroaryl and the heteroaryl is optionally substituted with linear or branched C1-C6 alkyl, preferably with CH3.

6. A compound for use according to claims 1 to 5 wherein

R is selected from the group consisting of 3-fluorophenyl, 4-fluorophenyl, 2-bromophenyl, 3-bromophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-aminophenyl, 4-aminophenyl, 3-methyaminophenyl, 4-methylaminophenyl, thiophen-2-yl, furan-2-yl, pyrrol-2-yl, 1H-imidazol-5-yl, 1-methyl-imidazol-5-yl, pyrazol-4-yl, 1,2,4-oxadiazol-3yl, 1,2-oxazol-5yl, pyridin-2yl, pyridin-3yl and pyridin-4yl.

7. A compound for use according to claims 1 to 6 wherein

R1 is
- linear or branched C1-C6 alkyl,
- \((CH_2)_m\)OR2 wherein m is 1 and R2 is linear C1-C3 alkyl,
- C3-C6 cycloalkyl, or
- N(R3)OR4, wherein R3 and R4 are as defined in claim 1.

8. A compound for use according to claims 1 to 7 wherein

R1 is
- linear or branched C1-C6 alkyl,
- \((CH_2)_m\)OR2 wherein m is 1 and R2 is CH3,
- cyclopropyl,
- or
- N(R3)OR4, wherein R3 and R4 are independently C1-C3 alkyl, preferably CH3.

9. A compound for use according to claims 1 to 8 wherein

R1 is selected from the group consisting of:
- Metyl, ethyl, isopropyl, isobutyl, CH2OCH3, cyclopropyl or-N(CH3)OCH3.

10. A compound of formula (I):

![Chemical structure](image)

wherein

- X is oxygen, sulphur, NH, NOH, or NOMe;
- R is a group selected from aryl and heteroaryl, optionally substituted by one or more substituents selected from
  - hydrogen,
- halogen,
- $\text{CF}_3$,
- linear or branched $C_1$-$C_6$ alkyl,
- OR5 and
- $\text{NR}_6R_7$, wherein R5, R6 and R7 are independently hydrogen or linear or branched $C_1$-$C_6$ alkyl;

R1 is a group selected from
- linear or branched $C_1$-$C_6$ alkyl,
- $(\text{CH}_2)_m$-OR2, wherein m is an integer between 1 and 3 and R2 is selected from hydrogen and linear $C_1$-$C_3$ alkyl,
- $C_3$-$C_6$ cycloalkyl, and
- $\text{N}(\text{R}_3)$OR4, wherein R3 and R4 are independently hydrogen or linear or branched $C_1$-$C_3$ alkyl, and pharmaceutically acceptable salts thereof, with the proviso that when R1 is methyl, R is not selected from 3-pyridyl, 4-chlorophenyl, 4-trifluoromethylphenyl, 3-thiazolyl-(2-methyl), phenyl, thiazole, 2,4-difluorophenyl, 4-methoxyphenyl and 2-methylthiazole.

11. A compound according to claims 10, wherein R1 is different from methyl.

12. A compound according to claims 10, selected from:
- 1-[2-(3-fluorophenyl)-4-hydroxy-1,3-thiazol-5-yl]propan-1-one (compound n. 1)
- sodium 2-(3-fluorophenyl)-5-propanoyl-1,3-thiazol-4-olate (compound n. 2)
- 2-(3-fluorophenyl)-4-hydroxy-N-methoxy-N-methyl-1,3-thiazole-5-carboxamide (compound n. 3)
- 1-(2-(3-fluorophenyl)-4-hydroxythiazol-5-yl)ethanone (compound n. 4)
- 1-[2-(3-fluorophenyl)-4-hydroxy-1,3-thiazol-5-yl]-2-methylpropan-1-one (compound n. 5)
- 4-hydroxy-N-methoxy-N-methyl-2-(thiophen-2-yl)-1,3-thiazol-5-carboxamide (compound n. 6)
- 1-[4-hydroxy-2-(thiophen-2-yl)-1,3-thiazol-5-yl]propan-1-one(compound n. 7)
- 4-hydroxy-N-methoxy-N-methyl-2-(2-methylphenyl)-1,3-thiazole-5-carboxamide(compound n. 8)
- 1-[4-hydroxy-2-(furan-2-yl)-1,3-thiazol-5-yl]propan-1-one (compound n. 9)
- 2-(2-bromophenyl)-4-hydroxy-N-methoxy-N-methyl-1,3-thiazole-5-carboxamide (compound n.10)
- 1-[2-(2-bromophenyl)-4-hydroxy-1,3-thiazol-5-yl]propan-1-one (compound n. 11)
- 4-hydroxy-2-(2-hydroxyphenyl)-N-methoxy-N-methyl-1,3-thiazole-5-carboxamide (compound n. 12)
- 1-[2-(2-hydroxyphenyl)-4-hydroxy-1,3-thiazol-5-yl]propan-1-one (compound n. 13)
- 1-[2-(3-bromophenyl)-4-hydroxy-1,3-thiazol-5-yl]propan-1-one (compound n. 14)
- 1-[4-hydroxy-2-(1H-pyrrol-2-yl)-1,3-thiazol-5-yl]propan-1-one (compound n. 15)
- 1-[4-hydroxy-2-(1H-pyrrol-2-yl)-1,3-thiazol-5-yl]propan-1-one (compound n. 16)
- 1-[4-hydroxy-2-(1-methyl-1H-pyrrol-2-yl)-1,3-thiazol-5-yl]propan-1-one (compound n. 17)
- 1-[4-hydroxy-2-(1-methyl-1H-imidazol-5-yl)-1,3-thiazol-5-yl]propan-1-one (compound n. 18)
- 1-[4-hydroxy-2-(1H-imidazol-5-yl)-1,3-thiazol-5-yl]propan-1-one (compound n. 19)
- 1-[4-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,3-thiazol-5-yl]propan-1-one (compound n. 20)
- 1-[4-hydroxy-2-(thiophen-2-yl)-1,3-thiazol-5-yl]butan-1-one (compound n. 21)
1. [4-hydroxy-2-(thiophen-2-yl)-1,3-thiazol-5-yl]-3-methylbutan-1-one (compound n. 22)
2. [4-hydroxy-2-(1,2,4-oxadiazol-3-yl)-1,3-thiazol-5-yl]propan-1-one (compound n. 23)
3. [4-hydroxy-2-(1,2-oxazol-5-yl)-1,3-thiazol-5-yl]propan-1-one (compound n. 24)
4. [4-hydroxy-2-(pyridin-3-yl)-1,3-thiazol-5-yl]propan-1-one (compound n. 25)
5. [4-hydroxy-2-(pyridin-4-yl)-1,3-thiazol-5-yl]propan-1-one (compound n. 26)
6. [4-hydroxy-2-(pyridin-2-yl)-1,3-thiazol-5-yl]propan-1-one (compound n. 27)
7. [4-hydroxy-2-(3-fluorophenyl)-1,3-thiazol-5-yl]propan-1-one (compound n. 28)
8. [4-hydroxy-2-(3-fluorophenyl)-1,3-thiazol-5-yl]propan-1-one (compound n. 29)
9. [4-hydroxy-2-(3-fluorophenyl)-1,3-thiazol-5-yl]propan-1-one (compound n. 30)
10. [4-hydroxy-2-(4-fluorophenyl)-1,3-thiazol-5-yl]propan-1-one (compound n. 31)
11. [4-hydroxy-2-(4-fluorophenyl)-1,3-thiazol-5-yl]propan-1-one (compound n. 32)
12. [4-hydroxy-2-(4-fluorophenyl)-1,3-thiazol-5-yl]propan-1-one (compound n. 33)
13. [4-hydroxy-2-(4-fluorophenyl)-1,3-thiazol-5-yl]propan-1-one (compound n. 34)
14. [4-hydroxy-2-(4-fluorophenyl)-1,3-thiazol-5-yl]propan-1-one (compound n. 35)
15. [4-hydroxy-2-(4-fluorophenyl)-1,3-thiazol-5-yl]propan-1-one (compound n. 36)
16. [4-hydroxy-2-(4-methylphenyl)-1,3-thiazol-5-yl]propan-1-one (compound n. 37)
17. [4-hydroxy-2-(4-methylphenyl)-1,3-thiazol-5-yl]propan-1-one (compound n. 38)
18. [4-hydroxy-2-(4-methylphenyl)-1,3-thiazol-5-yl]propan-1-one (compound n. 39)
19. [4-hydroxy-2-(4-methylphenyl)-1,3-thiazol-5-yl]propan-1-one (compound n. 40)
20. [4-hydroxy-2-(4-methylphenyl)-1,3-thiazol-5-yl]propan-1-one (compound n. 41)
21. [4-hydroxy-2-(4-methylphenyl)-1,3-thiazol-5-yl]propan-1-one (compound n. 42)
22. [4-hydroxy-2-(4-methylphenyl)-1,3-thiazol-5-yl]propan-1-one (compound n. 43)
23. [4-hydroxy-2-(4-methylphenyl)-1,3-thiazol-5-yl]propan-1-one (compound n. 44).

13. A compound according to claim 12 selected from:

sodium 2-(3-fluorophenyl)-5-propanoyl-1,3-thiazol-4-olate (compound n. 2)

2. (3-fluorophenyl)-4-hydroxy-N-methoxy-N-methyl-1,3-thiazole-5-carboxamide (compound n. 3)
3. 4-hydroxy-2-(2-hydroxyphenyl)-N-methoxy-N-methyl-1,3-thiazole-5-carboxamide (compound n. 12) and
4. [4-hydroxy-2-(3-fluorophenyl)-1,3-thiazol-5-yl]propan-1-one (compound n. 28).

14. A compound as claimed in any one of claims 1 to 13, for use in the prevention and/or treatment of a disease selected from the group consisting of itch, irritable bowel diseases, cold-induced and/or exacerbated respiratory disorders ischaemia, pain, urological disorders, stroke, psychiatric disorders and neurodegeneration.

15. A compound as claimed in claim 14, wherein said disease is selected from chronic pain, neuropathic pain, postoperative pain, cancer pain, osteoarthritic pain, rheumatoid arthritis, neuralgia, fibromyalgia, neuropathies, fibromyalgia, algesia, nerve injury, migraine, headache, itch, irritable bowel disease, , painful bladder syndrome, interstitial cystitis, detrusor overactivity, urinary incontinence, neurogenic detrusor overactivity, idiopathic detrusor overactivity, benign prostatic hyperplasia, lower urinary tract disorders and lower
urinary tract symptoms, anxiety, depression and cold-induced/or exacerbated pulmonary hypertension, COPD
and asthma.
16. A pharmaceutical composition comprising as the active ingredient at least one compound according to any
one of claims 1 to 13 in combination with pharmaceutically acceptable excipients and/or diluents.
INTERNATIONAL SEARCH REPORT

PCT/EP2015/064146

A. CLASSIFICATION OF SUBJECT MATTER
C07D417/04 C07D263/42
A61K31/426 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>EP 2 606 888 AI (DOMPE SPA [IT]) 26 June 2013 (2013-06-26) page 35; table IV</td>
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<td>ARCADI, ANTONIO; ATTANASI, ORAZIO A.; GUIDI, BARBARA ET AL: &quot;2-Substituted 5-acetyl-4-thiazolyl triazoles as useful building blocks for the preparation of functionalized thi azoles&quot;, EUR. JOURN. ORG. CHEM., 1999, XP002734666, page 3117 - page 3126; compounds la-g table IV</td>
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Date of the actual completion of the international search 4 September 2015

Date of mailing of the international search report 21/09/2015

Name and mailing address of the ISA:
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NL - 2280 HV Rijswijk
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Fax: (+31-70) 340-3016

Authorized officer
Menegaki, Fotini

Form PCT/ISA/210 (second sheet) (April 2005)
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<td>ARCADI, ANTONIO; ATTANASI, ORAZIO A.; GUIDI, BARBARA; ROSSI, ELISABETTA ET AL: &quot;Pyrido[3,4-c] thi azole through palladium-catalyzed coupling of 2-substituted 5-acetyl-4-thiazolyl triflates with alkynes/annulati on reactions&quot;, CHEMISTRY LETTERS, CHEMICAL SOCIETY OF JAPAN, vol. 28, no. 1, 1999, pages 59-60, XP002734668, page 59; compounds 1a-g</td>
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