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(56) Related Art
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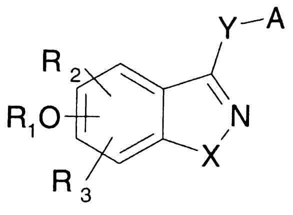
(54) Title: INDAZOLES, BENZISOXAZOLES AND BENZISOTHIAZOLES AND THEIR USE AS ESTROGENIC AGENTS



(I)

(57) Abstract: The present invention relates to compounds of formula (I): in which R_1, R_2, R_3, X, Y and A are as defined in the specification. The compounds are modulators of the estrogen receptors.

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Indazoles, benzisoxazoles and benzisothiazoles, process for preparing them, pharmaceutical compositions and use as estrogenic agents

Field of the invention

The present invention relates to non steroidal compounds with affinity for estrogen receptors. More specifically, the invention relates to indazole, benzisoxazole and benzisothiazole compounds as estrogen receptor subtype modulators and/or selective estrogen receptor modulators (SERM). The present invention also relates to pharmaceutical compositions containing these compounds, and to the use of these compounds in the treatment of estrogen-related diseases.

Background of the invention

The end of the reproductive years of a person's life can often be accompanied by uncomfortable and disruptive symptoms, one of the most common of which is hot flushes. Perimenopause, or premenopause, is the period of years in which normal ovulatory cycles give way to cessation of menses. This time is marked by irregular menstrual cycles. Cycle length begins to increase, and ovulation and fertility decrease. Menopause is typically defined as the point, after the loss of ovarian activity, when permanent cessation of menstruation occurs. In addition, estrogens are involved in various other physiological processes such as the modulation of the immune response and development of cancer (breast, endometrium, colon, prostate). ERα has been proven to be implicated in several diseases, such as breast cancer, and osteoporosis.

It is well established that estrogens play an important role in the development and homeostasis of the reproductive, central nervous, skeletal and cardiovascular systems in both males and females. To date, a plethora of estrogen receptors have been discovered in the brain, involved in various processes such as mood, temperature regulation, sleep, susceptibility to seizure, pain mechanism, and cognitive functions (Toran-Allerand, Endocrinology*,* 2004,145, 1069-1074).

Currently, the estrogen receptor (ER) is a nuclear receptor with two known different subtypes. A new subtype ERβ, different from the known ERα subtype (Green, Nature, 1986, 320, 134-139), was recently discovered (Mosselman et al, FEBS Letters, 1996, 392, 49-53). These subtypes have different biological roles and may have selective and effective clinical uses (Harris H. A., Endocrinology, 2002, 143, 11, 4172-4177). ER subtypes share about 50% identity in the ligand-binding domain (Kuiper et al, Endocrinology, 1998, 139(10), 4252-4263), they have similar Estradiol (E_2) binding affinities and can hetero- or homodimerize (Cowley, J Biol Chem, 1997, 272, 19858-19862) to form a signalling complex (Kuiper et al, Endocrinology, 1997, 138(10), 863-870; Kuiper, Proc. Natl. Acad. Sci. USA, 1996, 93, 5925-5930). ERβ is strongly expressed in a number of tissues including prostate epithelium (Weihua Z, Proc. Natl. Acad. Sci. USA, 2001, 98, 6330-6335), sympathetic ganglia (Zoubina E. V., J. Urol., 2003, 169, 382-385), colon (Witte D., Hum. Pathol., 2001, 32, 940-944), bladder, ovarian granulosa cells (Nilsson S., Physiol. Rev., 2001, 81, 1535-1565), bone marrow (Shim G. J., Proc. Natl. Acad. Sci. USA, 2003, 100, 6694-6699), breast stroma (Cunha G. R., J. Mammary Gland Biol. Neoplasia, 1997, 2, 393-402), lung, intestine, vascular endothelium, dorsal raphe, parts of the brain (Mitra S. W., Endocrinology, 2003, 144, 2055-2067, Krel W., Proc. Natl. Acad. Sci. USA, 2001, 98, 12278-12282). ERα is expressed in breast epithelium (Palmieri C., Endocr. Relat. Cancer, 2002, 9, 1-13), uterus, bone, ovary theca cells (Couse J., Endocr. Rev., 1999, 20, 358-417), prostate stroma (Chu S., Mol. Cell Endocrinol., 1997, 132, 195-199), liver, testis. The finding of compounds with a specific affinity for one or the other subtypes could provide a selective treatment of estrogen-related diseases such as Alzheimer's disease, menopausal complaints (e.g. hot flushes, vaginal dryness, atrophy), cognitive functions (e.g. anxiety, depression, dementia), osteoporosis, estrogen dependant tumours (uterine, breast, colon, or prostate cancers), benign prostatic hyperplasia, bladder control, hearing disorders, stroke, leukaemia, hypertension, obesity, irritable bowel syndrome, or reproductive aspects such as contraception or infertility. ERβ-selective ligands may be therapeutically useful agents to treat chronic intestinal and joint inflammation (Harris et coll., Endocrinology, 2003, 144, 4241-4249).

According to Warembourg M and Leroy D (Brain Res., 2004, 26; 55-66), ERβ was only detected within the rat dorsal raphe nucleus. In contrast, only ERα-immunoreactivity was seen in the septum, and in the magnocellular supraoptic, paraventricular, arcuate, and premammillary nuclei. These observations provide evidence of a distinct neuroanatomical pattern for the two subtypes of the ERs. Localisation of ERβ in serotonin cells show the link between ERβ and the serotoninergic pathway. Finally, Cyr M et al. described (J Psychiatry Neurosci., 2002, 27, 12-27) the effect of a selective estrogen receptor modulator (SERM) such as raloxifen on 5-HT2a receptor.

In conclusion it seems to be relevant to develop ERβ modulators as compounds of interest in the field of schizophrenia, neurodegenerative diseases such a Alzheimer's disease or Parkinson's disease. For the same reasons, ERβ modulators should be of interest as neuroprotective, antidepressant or anxiolytic agents.

However, the two receptors which act as ligand activated transcription factors, were found in a variety of tissues, and differed in their binding pocket only by two amino acids: Leu and Met in ERα, Met and Ile in ERβ. Those similarities could explain that the control of the subtype alpha or beta led to the same pharmacological effect, as it is the case in preclinical model of hot flush phenomena. While ERα modulator decreased the occurrence of hot flushes in a rat preclinical model (Harris et al., Endocrinology, 2002, 143, 4172-4177), selective estrogen receptor modulators such as spiroindene compounds, which were affine for both subtypes, had the same effect on hot flushes (Watanabe et al., J Med Chem, 2003, 46, 3961-3964).

It has also been shown that estrogen receptors can suppress NFKB-mediated transcription in both a ligand-dependent and independent manner (Quaedackers, et al., Endocrinology 2001,142: 1156-1166; Bhat, et al., Journal of Steroid Biochemistry & Molecular Biology 1998, 67: 233-240; Pelzer, et al., Biochemical & Biophysical Research Communications 2001, 286: 1153-7). These data show the link between selective estrogen receptor modulators and NFKB which is implicated in apoptosis and immune/inflammatory response.

Many compounds have been described as estrogen receptor agonists or antagonists as they respectively had a similar activity or blocked the activity of estradiol. Such agonist compounds could be used as contraceptive agents in premenopausal women. Antagonists are widely used therapeutic agents in the treatment of breast cancer (Vogel, Anticancer Drugs, 2003, 14, 265-273) whereas agonists are used in HRT (Hormone Replacement Therapy) in post menauposal women (Burkman, Minerva Ginecol, 2003, 55, 107-116) to treat hot flushes, vaginal atrophy. SERMs are compounds that present mixed activities depending on the tissue (McDonnell, J Soc Gynecol Invest, 2000, 7, S10-S15). SERMs might have utility for the treatment of osteoporosis, cardiovascular diseases and related estrogen receptor diseases.

Estrogen receptors adopt different conformations when binding ligands. Three-dimensional structures of ERα and ERβ have been solved by co-crystallisation with various ligands (Pike A. C. W., EMBO J, 1999, 18, 4608-4618; Shiau A. K., Cell, 1998, 95, 927-937). Each ligand influences receptor ERα or ERβ conformations, leading to distinct biological activities.

Various compounds presented as estrogenic agents have been described in US 2003/0207927 A1 and US 2003/0171412 A1. Indazole derivatives presented as potassium channel blockers are described in WO 2004/043354 and WO 2004/043933. The synthesis of various isoxazoles is described in Ind J Chem 1980, 19B: 571-575. Benzisoxazole intermediates used in the preparation of diuretic compounds are described in Chem Pharm Bull 1991, 39(7): 1760-1772. The synthesis of various benzisothiazoles is described in Tetrahedron 1988, 44(10): 2985-2992.

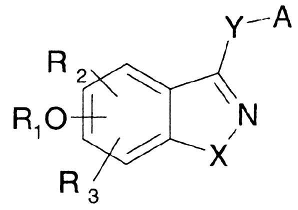
Summary of the invention

One aspect of this invention is to provide indazole, benzisoxazole and benzisothiazole compounds, which have an affinity for the estrogen receptors.

Another aspect of this invention is to provide a pharmaceutical composition containing an indazole, benzisoxazole or benzisothiazole compound as mentioned above.

A further aspect of this invention is to provide the use of an indazole, benzisoxazole, or benzisothiazole compound in the manufacture of a medicament for treating or preventing various diseases mediated by estrogen receptors.

The indazole, benzisoxazole or benzisothiazole compounds of this invention can be represented by the following general formula (I) :



(I)

wherein:

- R_1 is hydrogen or a $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, trifluoromethyl, $-N{=}CR_5R_6$, $-SO_2NR_7R_8$, phenyl, phenyl$(C_1\text{-}C_3)$alkyl or $(C_1\text{-}C_3)$alkyl substituted by a saturated heterocyclic radical, wherein the phenyl is unsubstituted or substituted by at least one substituent selected from the group consisting of a hydroxyl, a halogen, a nitro, a cyano, a $(C_1\text{-}C_3)$alkyl, a $(C_1\text{-}C_3)$alkoxy and a trifluoromethyl; R_1 can also be a salt;
- R_2 and R_3 are each independently hydrogen or a hydroxyl, halogen, nitro, cyano, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, trifluoromethyl, $-NR_7R_8$, $-CONR_7R_8$, $-COR_9$ or $-CO_2R_9$ group; R_2 can also be a phenyl or a saturated or unsaturated heterocycle, wherein the phenyl is unsubstituted or substituted by at least one substituent selected from the group consisting of a hydroxyl, a halogen, a nitro, a cyano, a $(C_1\text{-}C_3)$alkyl, a $(C_1\text{-}C_3)$alkoxy, a trifluoromethyl and a saturated heterocyclic radical;
- X is O, S, SO, SO_2 or NR_4;
- R_4 is hydrogen or a $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, phenyl, phenyl$(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkyl substituted by a saturated heterocyclic radical, $-COR_7$, $-CO_2R_7$ or $-SO_2NR_7R_8$ group, wherein the phenyl is unsubstituted or substituted by at least one substituent selected from the group consisting of a hydroxyl, a halogen, a nitro, a cyano, a $(C_1\text{-}C_3)$alkyl, a $(C_1\text{-}C_3)$alkoxy, a trifluoromethyl, a phenyl$(C_1\text{-}C_3)$alkyl and a phenyl$(C_1\text{-}C_3)$alkoxy;
- Y is direct bond, O, S, SO, SO_2, NR_4, CO, $-(CR_{10}R_{11})_n-$ or $-R_{10}C{=}CR_{11}-$;
- R_5, R_6, R_7 and R_8 are each independently hydrogen or a $(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_6)$cycloalkyl group;
- R_9 is hydrogen, a $(C_1\text{-}C_6)$alkyl, a phenyl or a saturated or unsaturated heterocyclic radical, wherein the phenyl is unsubstituted or substituted by at least one substituent selected from the group consisting of a hydroxyl, a

halogen, a nitro, a cyano, a $(C_1\text{-}C_3)$alkyl, a $(C_1\text{-}C_3)$alkoxy, a trifluoromethyl and a saturated heterocyclic radical;

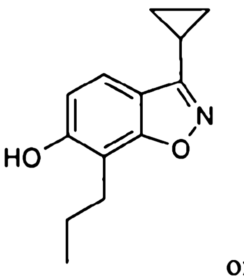
- R_{10} and R_{11} are each independently hydrogen or a cyano, $(C_1\text{-}C_6)$alkyl, -CO-phenyl, -CO(unsaturated heterocyclic radical) or $-CONR_7R_8$ group, wherein the phenyl is unsubstituted or substituted by at least one substituent selected from the group consisting of a hydroxyl, a halogen, a nitro, a cyano, a $(C_1\text{-}C_3)$alkyl, a $(C_1\text{-}C_3)$alkoxy and a trifluoromethyl;
- n is 1 or 2;
- A is a $(C_3\text{-}C_{15})$cycloalkyl or a $(C_3\text{-}C_{15})$cycloalkene, wherein the cycloalkyl or the cycloalkene is unsubstituted or substituted by at least one $(C_1\text{-}C_6)$alkyl;

provided that

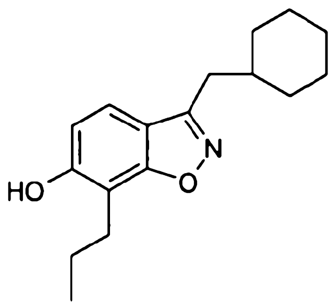
1/ when X is NR_4 where R_4 is H or $(C_1\text{-}C_6)$alkyl and R_1O is 6-OCH_3, then Y is not CO;

2/ when X is O, R_1O is 6-OH or 6-OCH_3, Y is a direct bond and A is cyclopentyl, then (R_2,R_3) or (R_3,R_2) is different from (H, Cl) in position 4,5;

3/ said compound is not



or



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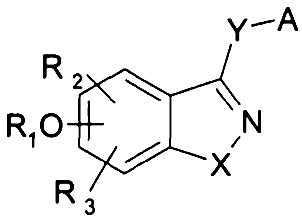
Another aspect of the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cognitive dysfunction:



(I)

wherein:

- R_1 is hydrogen or a $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, trifluoromethyl, $-N{=}CR_5R_6$, $-SO_2NR_7R_8$, phenyl, phenyl$(C_1\text{-}C_3)$alkyl or $(C_1\text{-}C_3)$alkyl substituted by a saturated

- heterocyclic radical, wherein the phenyl is unsubstituted or substituted by at least one substituent selected from the group consisting of a hydroxyl, a halogen, a nitro, a cyano, a $(C_1\text{-}C_3)$alkyl, a $(C_1\text{-}C_3)$alkoxy and a trifluoromethyl; R_1 can also be a salt;
- R_2 and R_3 are each independently hydrogen or a hydroxyl, halogen, nitro, cyano, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, trifluoromethyl, $-NR_7R_8$, $-CONR_7R_8$, $-COR_9$ or $-CO_2R_9$ group; R_2 can also be a phenyl or a saturated or unsaturated heterocycle, wherein the phenyl is unsubstituted or substituted by at least one substituent selected from the group consisting of a hydroxyl, a halogen, a nitro, a cyano, a $(C_1\text{-}C_3)$alkyl, a $(C_1\text{-}C_3)$alkoxy, a trifluoromethyl and a saturated heterocyclic radical;
- X is O, S, SO, SO_2 or NR_4;
- R_4 is hydrogen or a $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, phenyl, phenyl$(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkyl substituted by a saturated heterocyclic radical, $-COR_7$, $-CO_2R_7$ or $-SO_2NR_7R_8$ group, wherein the phenyl is unsubstituted or substituted by at least one substituent selected from the group consisting of a hydroxyl, a halogen, a nitro, a cyano, a $(C_1\text{-}C_3)$alkyl, a $(C_1\text{-}C_3)$alkoxy, a trifluoromethyl, a phenyl$(C_1\text{-}C_3)$alkyl and a phenyl$(C_1\text{-}C_3)$alkoxy;
- Y is direct bond, O, S, SO, SO_2, NR_4, CO, $-(CR_{10}R_{11})_n-$ or $-R_{10}C{=}CR_{11}-$;
- R_5, R_6, R_7 and R_8 are each independently hydrogen or a $(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_6)$cycloalkyl group;
- R_9 is hydrogen, a $(C_1\text{-}C_6)$alkyl, a phenyl or a saturated or unsaturated heterocyclic radical, wherein the phenyl is unsubstituted or substituted by at least one substituent selected from the group consisting of a hydroxyl, a halogen, a nitro, a cyano, a $(C_1\text{-}C_3)$alkyl, a $(C_1\text{-}C_3)$alkoxy, a trifluoromethyl and a saturated heterocyclic radical;
- R_{10} and R_{11} are each independently hydrogen or a cyano, $(C_1\text{-}C_6)$alkyl, -CO-phenyl, -CO(unsaturated heterocyclic radical) or $-CONR_7R_8$ group, wherein the phenyl is unsubstituted or substituted by at least one substituent selected from the group consisting of a hydroxyl, a halogen, a nitro, a cyano, a $(C_1\text{-}C_3)$alkyl, a $(C_1\text{-}C_3)$alkoxy and a trifluoromethyl;
- n is 1 or 2;
- A is a $(C_3\text{-}C_{15})$cycloalkyl or a $(C_3\text{-}C_{15})$cycloalkene, wherein the cycloalkyl or the cycloalkene is unsubstituted or substituted by at least one $(C_1\text{-}C_6)$alkyl.

In the description and claims, the term "(C_1-C_6)alkyl" is understood as meaning a linear or branched hydrocarbon chain having 1 to 6 carbon atoms. A (C_1-C_6)alkyl radical is for example a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl or hexyl radical. Preferred alkyl radicals are those having 1, 2 or 3 carbon atoms.

The term "halogen" is understood as meaning a chlorine, bromine, iodine or fluorine atom.

The term "(C_3-C_{15})cycloalkyl" is understood as meaning a saturated, fused or bridged, mono-, bi- or tricyclic hydrocarbon having 3 to 15 carbon atoms. A monocyclic radical is for example a cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or cyclododecyl radical. A fused, bridged or spiranic, dicyclic or tricyclic radical is for example a norbornyl, bornyl, isobornyl, noradamantyl, adamantyl or spiro[5,5]undecanyl radical. Preferred cycloalkyls are those having 5 to 12 carbon atoms, the cyclopentyl, cyclohexyl, cycloheptyl and adamantyl radicals being especially preferred. A (C_3-C_6)cycloalkyl radical is for example a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl radical.

The term "(C_3-C_{15})cycloalkene" is understood as meaning an unsaturated (C_3-C_{15})cycloalkyl, the latter term being as defined above.

The term "(C_1-C_6)alkoxy" is understood as meaning a group OR in which R is a (C_1-C_6)alkyl as defined above. A (C_1-C_6)alkoxy radical is for example a methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, n-pentyloxy or isopentyloxy radical. Preferred alkoxy radicals are those having 1, 2 or 3 carbon atoms.

In the definition of R_1, a "salt" is understood as meaning an alkali metal salt or alkaline earth metal salt, such as a sodium, potassium, magnesium or calcium salt, or a salt with an ammonium or with an organic amine such as triethylamine, ethanolamine or tris-(2-hydroxyethyl)amine.

The term "heterocycle" or "heterocyclic", is understood as meaning a saturated or unsaturated 5- to 8-membered monocyclic radical containing one or two heteroatoms chosen from O, N and S.

Examples of unsaturated heterocyclic radicals include, but are not limited to, the furyl, imidazolinyl, imidazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinolinyl, isoquinolinyl, thiazolyl, thienyl benzimidazolyl, benzoxazolyl, benzothiazolyl, indolyl and indazolyl radicals.

Examples of saturated heterocyclic radicals include, but are not limited to, the imidazolidinyl, morpholinyl, thiomorpholinyl, piperidyl, piperazinyl, pyrrolidinyl, pyrazolidinyl, tetrahydrofuryl, 2-oxopiperazinyl, 2-oxopiperidyl and 2-oxopyrrolidinyl radicals, the morpholinyl and piperidyl radicals being preferred.

Needless to say, when X is NR_4 and Y and R_2 together form with the indazole ring bearing form a 1H-pyrano[4,3,2-cd]-indazole, one of the carbon atom of the "pyrano moiety" bears substituent A as defined above.

The compounds of formula (I) can form addition salts with acids. Such salts, especially those which are pharmaceutically acceptable, are encompassed by the present invention. Examples of salts include those formed, for example with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, or with organic carboxylic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid.

The present invention also encompasses stereoisomeric forms of the compounds of formula (I).

Preferred compounds of formula (I) include those that fulfil at least one of the following conditions:

- R_1 is hydrogen, a $(C_1\text{-}C_6)$alkyl, a phenyl$(C_1\text{-}C_3)$alkyl, a $(C_1\text{-}C_3)$alkyl substituted by a saturated heterocyclic radical or a $-SO_2NR_7R_8$ group;
- R_2 is hydrogen, hydroxyl, $(C_1\text{-}C_6)$alkyl or halogen;
- R_3 is hydrogen;
- Y is direct bond;
- A is a $(C_3\text{-}C_{15})$cycloalkyl optionally substituted by at least one $(C_1\text{-}C_6)$alkyl;
- R_1O is in position 6- of the ring.

Particularly preferred compounds are those wherein:

- R_1 is hydrogen or a $-SO_2NR_7R_8$ group in which R_7 and R_8 are each independently hydrogen or a $(C_1\text{-}C_6)$alkyl;
- R_2 is hydrogen;
- A is a $(C_3\text{-}C_{12})$cycloalkyl optionally substituted by 1 to 4 $(C_1\text{-}C_6)$alkyls.

The following compounds are also preferred:

a) Compounds where X is NR_4 and

- R_1 is hydrogen or a $(C_1\text{-}C_6)$alkyl, phenyl$(C_1\text{-}C_3)$alkyl or $-SO_2NR_7R_8$ group;
- R_2 and R_3 are each hydrogen;
- R_4 is hydrogen or a $(C_1\text{-}C_6)$alkyl, phenyl, phenyl$(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkyl substituted by a saturated heterocyclic radical, $-SO_2NR_7R_8$ or $-COR_9$ group,

where the phenyl is optionally substituted by at least one substituent selected from the group consisiting of a hydroxyl, a halogen and a phenyl(C_1-C_3)alkoxy;

- Y is a direct bond, $-(CR_{10}R_{11})_n$- or $-R_{10}C=CR_{11}$;
- R_7 and R_8 are each independently hydrogen or a (C_1-C_6)alkyl;
- R_9 is hydrogen or a (C_1-C_6)alkyl;
- R_{10} and R_{11} are each indepently hydrogen, cyano or a $-CONR_7R_8$ group;
- n is 1 or 2;
- A is a (C_3-C_{15})cycloalkyl optionally substituted by at least one (C_1-C_6)alkyl or a phenyl optionally substituted by a hydroxyl or a (C_1-C_3)alkoxy;
- Y and R_2 together with the indazole ring bearing them can also form a 1H-pyrano[4,3,2-cd]indazole;

provided that when R_1 is H or (C_1-C_6)alkyl and Y is a direct bond, then A is not optionally substituted phenyl.

b) Compounds where X is O and

- R_1 is hydrogen or a (C_1-C_6)alkyl, phenyl(C_1-C_3)alkyl, (C_1-C_3)alkyl substituted by a saturated heterocyclic radical or $-SO_2NR_7R_8$ group;
- R_2 is hydrogen, halogen, hydroxyl or (C_1-C_6)alkoxy;
- R_3 is hydrogen;
- Y is a direct bond, $-(CR_{10}R_{11})_n$ or $-CR_{10} = CR_{11}$-;
- R_7 and R_8 are each independently hydrogen or (C_1-C_6)alkyl;
- R_{10} and R_{11} are each indepently hydrogen or cyano;
- n is 1 or 2;
- A is a (C_3-C_{15})cycloalkyl optionally substituted by at least one (C_1-C_6)alkyl or a phenyl optionally substituted by at least one substituent selected from (C_1-C_3)alkoxy, hydroxyl, (C_1-C_3)alkyl and halogen;

provided that

b1/ when R_1 is H or (C_1-C_6)alkyl and Y is a direct bond, then A is not optionally substituted phenyl;

b2/ when R_1O is 6-OH or 6-OCH_3, Y is a direct bond and A is cyclopentyl, then (R_2,R_3) is different from (Cl, H) in position 4,5;

b3/ when X is O, R_1O is 6-OH , R_2 and R_3 are H and Y is CH=CH, then A is not phenyl or 4-methoxyphenyl;

c) Compounds where X is $S(O)_m$ and

- R_1 is hydrogen or a phenyl(C_1-C_3)alkyl or $-SO_2NR_7R_8$ group;
- R_2 and R_3 are each hydrogen, hydroxyl or halogen;
- Y is a direct bond, $-(CR_{10}R_{11})_n$ or $-CR_{10} = CR_{11}$-;
- R_7 and R_8 are each indepently hydrogen or a (C_1-C_6)alkyl;
- R_{10} and R_{11} are each indepently hydrogen or cyano;
- A is a (C_3-C_{15})cycloalkyl optionally substituted by at least one (C_1-C_6)alkyl;
- m is 0, 1 or 2.

In view of their capability to act as agonists or antagonist for estrogen receptors (in other words as SERMs), the compounds of the invention can be used alone or in combination with other active ingredients for the treatment or the prevention of any estrogen-dependent disorder or for the management of estrogen-regulated reproductive functions, in humans (Njar VC and Brodie AM, Drugs, 1999, 58: 233-255) as well as in wild or domestic animals.

The breasts being sensitive targets of estrogen-stimulated proliferation and/or differentiation, SERMs are especially useful in the treatment or prevention of benign breast diseases in women, gynecomastia in men and in benign or malignant breast tumors with or without metastasis both in men and women (A. M. Brodie and V. C. Njar, Steroids, 2000, 65: 171-179 ; K.I. Pritchard, Cancer, 2000, 85, suppl 12: 3065-3072), or in male or female domestic animals.

Due to the involvement of estrogens in the mechanisms of ovulation, implantation and pregnancy, SERMs according to the invention can be used, respectively, for contraceptive, contragestive or abortive purposes in women (A. M. Brodie and V. C. Njar, Drugs, 1999, 58: 233-255) as well as in females of wild or domestic animal species.

The uterus is another reproductive organ responsive to estrogenic stimulation. SERMs are therefore useful to treat or prevent endometriosis, benign uterine diseases or benign or malignant uterine tumors with or without metastasis in women (A. M. Brodie and V. C. Njar, Drugs, 1999, 58: 233-255) or in female domestic animals.

The ovary being the physiological source of estrogen, SERMs can be used to treat abnormal or untimely ovarian estrogen production such as polycystic ovary syndrome or precocious puberty, respectively (Bulun et al., J Steroid Biochem Mol Biol, 1997, 61: 133-139). Ovarian as well as non-ovarian but estrogenproducing benign or malignant tumors with or without metastasis (Sasano H and Harada N, Endocrine Reviews, 1998, 19: 593-607) may also benefit from treatment with SERMs according to the invention.

In males, prostate and testicular tissues are also responsive to estrogenic stimulation (Abney TO, Steroids, 1999, 64: 610-617; Carreau S et al., Int J Androl, 1999, 22: 133-138). Therefore, SERMs can be used to treat or to prevent benign (Sciarra F and Toscano V, Archiv Androl, 2000, 44: 213-220) or malignant prostate tumors with or without metastasis (Auclerc G et al., Oncologist, 2000, 5: 36-44) or to treat, prevent or control spermatogenesis functions or malfunctions, in men as well as in male wild or domestic animals.

Estrogens are also known to be implicated in the regulation of bone turnover; therefore, SERMs may be useful, alone or in combination with other antiresorbtive or proosteogenic agents, in the treatment or prevention of bone disorders according to appropriate therapeutic sequences or regimens.

In addition, estrogens are involved in the regulation of the balance between Th_1 and Th_2 predominant immune functions and may therefore be useful in the treatment or prevention of gender-dependent auto-immune diseases such as lupus, multiple sclerosis, rheumatoid arthritis.

Another aspect of the invention thus consists in a method for the treatment or prevention of the above-mentioned diseases or disorders, wherein a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof is administered to a patient or animal in need of such treatment or prevention. Co-administration with one or more active substances suitable for the treatment or prevention of said diseases or disorders is also encompassed by the present invention.

The compounds of the invention can in particular be used in the following indications:

- treatment of cognitive dysfunction, for instance as neuroprotective, antidepressant or anxiolytic agents.
- treatment of schizophrenia or neurodegenerative diseases such as Alzheimer's disease or Parkinson's disease.
- prevention or treatment of estrogen-dependent disorders, for example hot flushes, osteoporosis, perimenopausal mood, perimenstrual syndromes,

vasomotor related syndromes, vaginal atrophy or dryness, sexual dysfunction such as libido decrease, urinary incontinence, pruritus, local infections of the genital tract. In this case, said compounds can be combined with a sexual endocrine therapeutic agent.

- control or management of reproductive functions, such as male or female fertility, pregnancy, abortion, contraception, delivery, or estrogen-related skin diseases. In this case, said compounds can be combined with a LH-RH agonist or antagonist, an estroprogestative contraceptive, a progestin, an antiprogestin or a prostaglandin.
- prevention or treatment of benign or malignant diseases of the breast, the uterus or the ovary, or of polycystic ovary syndrome. In this case, said compounds can be combined with an antiestrogen, a progestin or a LH-RH agonist or antagonist.
- prevention or treatment of benign or malignant diseases of the prostate or the testis. In this case, said compounds can be combined with an antiandrogen, a progestin, a lyase inhibitor or a LH-RH agonist. If necessary, the compounds of the invention can also be combined with a radiotherapeutic agent; a chemiotherapeutic agent such as a nitrogenated mustard analogue like cyclophosphamide, melphalan, iphosphamide, or trophosphamide; an ethylenimine like thiotepa; a nitrosourea like carmustine; a lysed agent like temozolomide or dacarbazine; an antimetabolite of folic acid like methotrexate or raltitrexed; a purine analogue like thioguanine, cladribine or fludarabine; a pyrimidine analogue like fluorouracil, tegafur or gemcitabine; an alkaloid of vinca or analogue like vinblastine, vincristine or vinorelbine; a podophyllotoxin derivative like etoposide, taxanes, docetaxel or paclitaxel; an anthracycline or analogue like doxorubicin, epirubicin, idarubicin or mitoxantrone; a cytotoxic antibiotic like bleomycin or mitomycin; a platinum compound like cisplatin, carboplatin or oxaliplatin; a monoclonal antibody like rituximab; an antineoplastic agent like pentostatin, miltefosine, estramustine, topotecan, irinotecan or bicalutamide; or with a prostaglandin inhibitor (COX 2/COX 1 inhibitor).
- prevention or treatment of irritable bowel syndrome, Crohn's disease, ulcerative proctitis, colitis or arthritis.

- prevention or treatment of cardiovascular diseases, atherosclerosis, hypertension, restenosis (e.g. for lowering cholesterol, triglycerides, Lp(a), or LDL levels, or modulating HDL level).

As used herein, the term "combined" or "combination" refers to any protocol for the co-administration of a compound of formula (I) and one or more other pharmaceutical substances, irrespective of the nature of the time of administration and the variation of dose over time of any of the substances. The co-administration can for example be parallel, sequential or over an extended period of time.

The compounds of formula (I) or their pharmaceutically acceptable salts may be administered, for example, orally, topically, parenterally, in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and/or vehicles. These dosage forms are given as examples, but other dosage forms may be developed by those skilled in the art of formulation, for the administration of the compounds of formula (I). The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular or intrasternal injections or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle sheep, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients, which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in U.S. Patents N° 4,256,108, 4,166,452 and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active ingredient in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those mentioned above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsion. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents include naturally-occuring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1, 3-butane diol. Acceptable vehicles and solvents that may be employed include water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

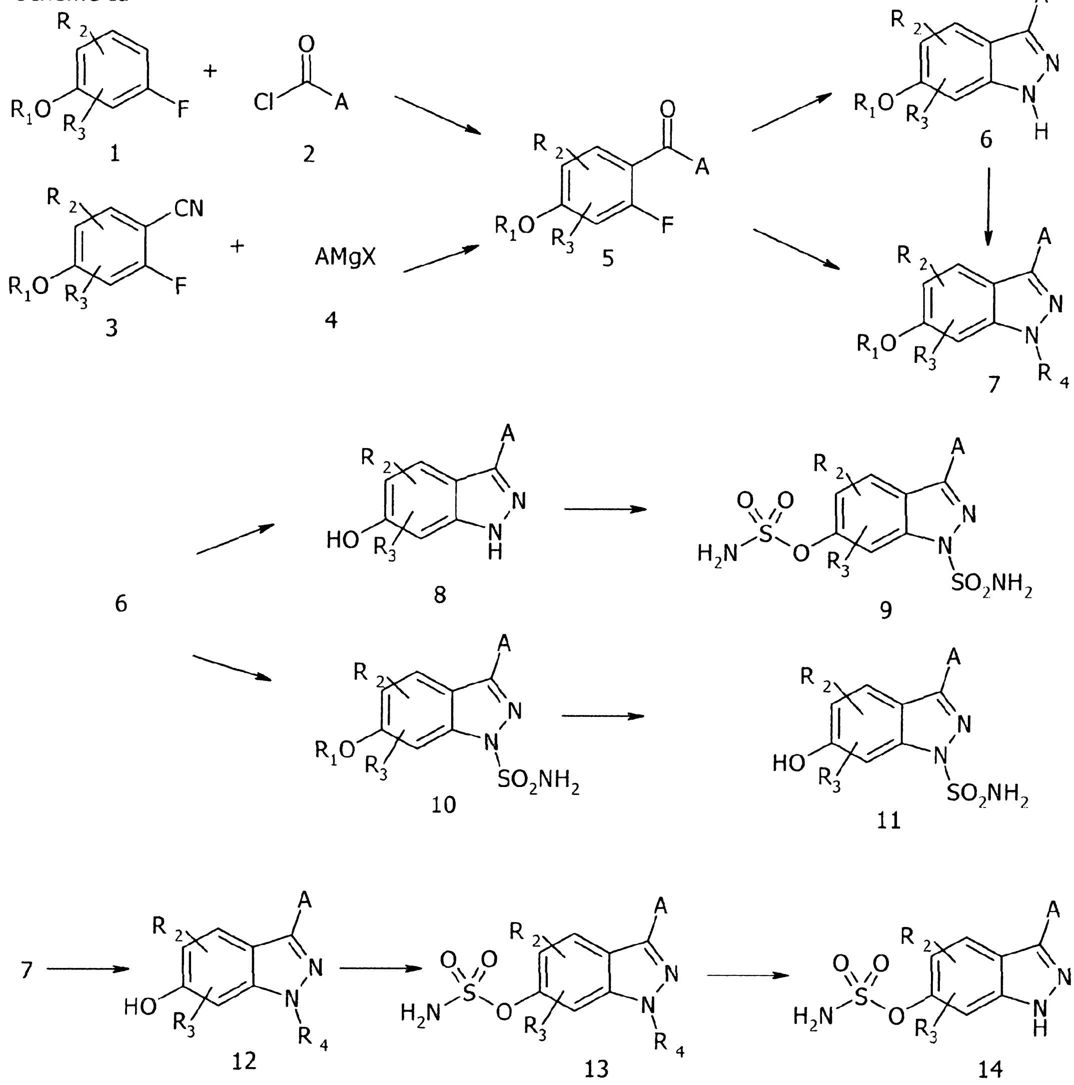
Dosage levels of the order of from about 0.001 mg to about 10 mg/kg of body weight per day are useful in the treatment or prevention of the above-mentioned diseases or disorders, or alternatively about 0.1 mg to about 100 mg per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The indazole derivatives of formula (I) can be prepared according to general schemes Ia, Ib, Ic.

Scheme Ia



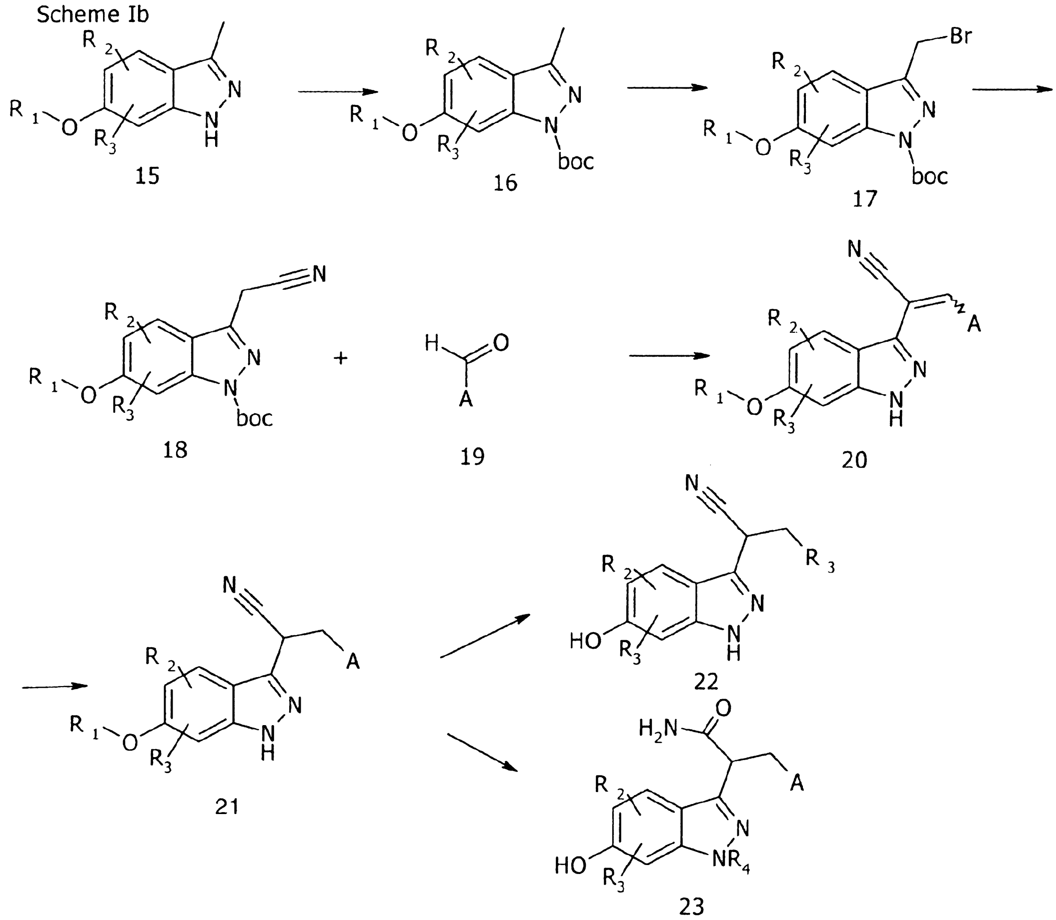
(R_4 = alkyl, X = halogen)

According to scheme Ia fluoroanisole derivative (1) is reacted with a suitable acid chloride of formula (2) by Friedel-Craft reaction following the procedure described by K L Kees (J Med Chem, 29, 11, 1986, 2329-2334) to give ketone (5). This ketone (5) can also be obtained by condensation of alkylmagnesium (4) on fluorobenzonitrile derivative (3) according to H. Shaffer (J Am Chem Soc, 1939, 61, 2175). The ketone (5) is then refluxed in EtOH in the presence of substituted hydrazine or in hydrazine hydrate to afford respectively the cyclised indazoles (6) and (7). The compound (7) can also be prepared by selective N-alkylation of indazole (6) using the conditions described by U. Lerch and

J. König (Synthesis, 1983, 2, 157-8) or the conditions described by J Chung and all (Tetrahedron Letters, 1992, 33, 4717-20).

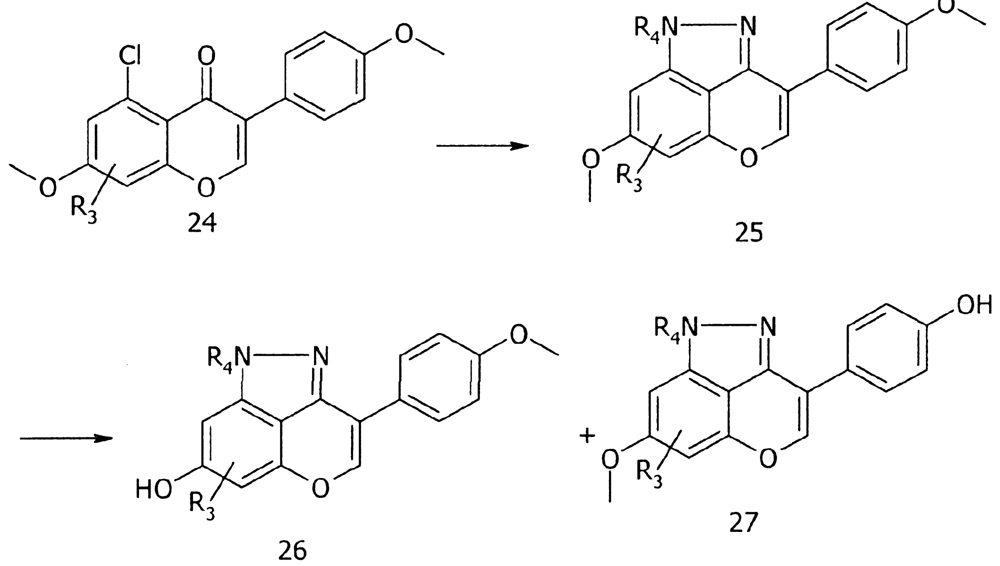
Demethylation of compounds (6) and (7) (if R_1 is methyl) with either tribromoborane using the conditions described by J.F.W. McOmie (Tetrahedron, 1968, 24, 2289-92) or HBr/ AcOH or pyridinium hydrochloride or debenzylation of compounds (6) and (7) (if R_1 is benzyl) with Pd/C with or without PtO_2 using the conditions described by W. H. Hartung (Org. React., VII, 1953, 263) give respectively the hydroxy indazole compounds (8) and (12). Indazole (6) can be directly N-sulfamoylated to give (10) by treatment with sodium hydride and sulfamoyl chloride as described by P. Nussbaumer (J. Med. Chem., 2002, 45, 4310-20), or by reaction with sulfamoyl chloride in dimethylacetamide (DMAc) as described by O. Makoto (Tetrahedron Letters, 2000, 41, 7047-51), then deprotected to obtain sulfamate compound (11). Deprotected indazole (8) can be disulfamoylated to give (9). In the same way, indazole (12) can be reacted with sulfamoyl chloride to give O-sulfamate compound (13) and then deprotected to give (14).

Scheme Ib



According to scheme Ib, the 3-methyl indazole compound (15) prepared using the conditions described by F. Dennler (Tetrahedron, 22, 1966, 3131) was reacted with BOC_2O, TEA and DMAP (T. Ishizuki, Tetrahedron Lett., 28, 1987, 4185) to afford (16). Compound (16) was brominated by Wohl-Ziegler reaction in presence of NBS and benzoyl peroxide following B. R. Henke (J. Med. Chem., 1997, 40, 17, 2706-2725) to give (17). Compound (18) was obtained by reaction of (17) with KCN using the conditions described by Ainsworth (J. Am. Chem. Soc., 1957, 79, 5242-5243). (18) was then reacted with aldehyde (19) in NaH/ DMF or KOH/EtOH to give (20) following the procedure described by M. J. Meyers (J. Med. Chem., 44, 24, 2001, 4230) (BOC deprotection was performed during this reaction). Compound (20) was then reacted with $NaBH_4$ in EtOH to give (21). Demethylation of compound (21) (if R_1 is methyl) with either tribromoborane using the conditions described by J.F.W. McOmie (Tetrahedron, 1968, 24, 2289-92) or HBr/AcOH or pyridinium hydrochloride or debenzylation of compound (21) (if R_1 is benzyl) with Pd/C with or without PtO_2 using the conditions described by W. H. Hartung (Org. React., VII, 1953, 263) gave nitrile compound (22). Demethylation with HBr/ AcOH gave amide compound (23).

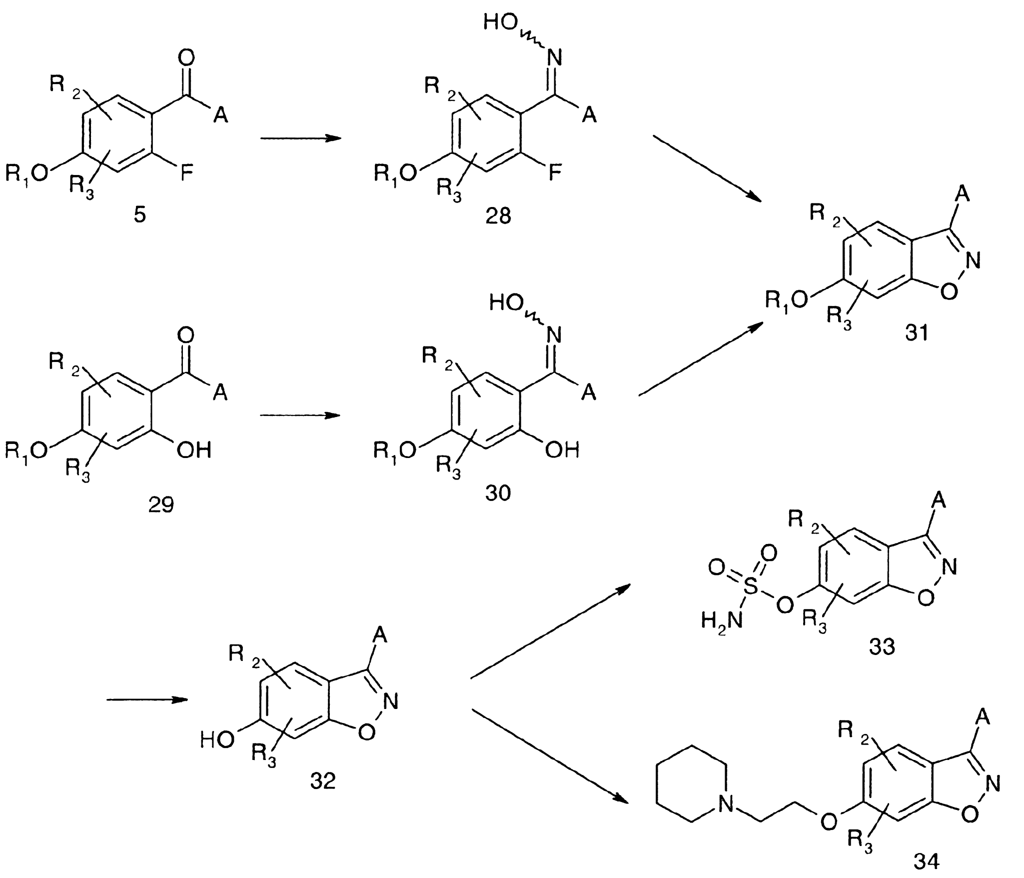
Scheme Ic



According to scheme Ic, compound (24), prepared using the conditions described by M. Kitagawa (Chem. Pharm. Bull., 39, 10, 1991, 2681), was reacted with hydrazine hydrate or alkyl or aryl hydrazine under reflux to give compound (25). Compound (25) was demethylated in the presence of BBr_3 in CH_2Cl_2 using the conditions described by McOmie J.F.W (Tetrahedron, 1968, 24, 2289-92) to give compounds (26) and (27).

The benzisoxazole derivatives of formula (I) can be prepared according to general schemes IIa , IIb, IIc.

Scheme IIa

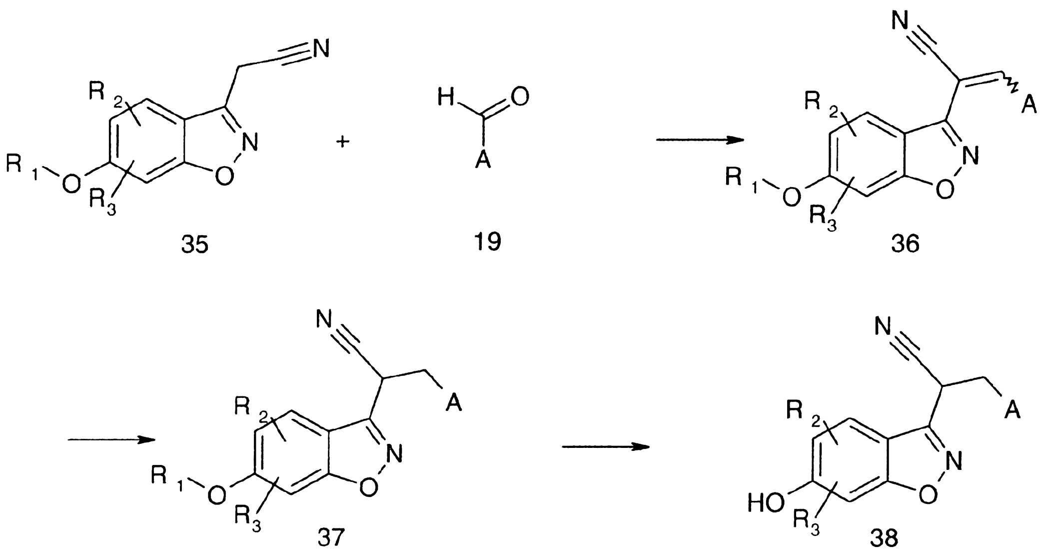


According to scheme IIa, the already described ketone (5) or ketone (29) obtained by Friedel-Craft procedure described by K L Kees (J Med Chem, 29, 11, 1986, 2329-2334) are refluxed in hydroxylamine hydrochloride using the conditions described by Y. Yamanaka (Pestic. Sci., 1998, 54, 3, 223-229) to afford respectively uncyclised oxime (28) and (30). Compound (28) is then cyclised in refluxing NaOH/EtOH solution and compound (30) is cyclised using an intramolecular Mitsunobu reaction (Synthesis, 1981, 1) to afford the corresponding benzisoxazole (31).

Demethylation of compound (31) (if R_1 is methyl) with either tribromoborane using the conditions described by J.F.W. McOmie (Tetrahedron, 1968, 24, 2289-92) or HBr/ AcOH or pyridinium hydrochloride or debenzylation of compounds (31) (if R_1 is benzyl) with Pd/C using conditions described by A. M. Felix (J. Org.

Chem., 43, 1978, 4194) give the hydroxy benzisoxazole compound (32). This compound (32) can be transformed into the corresponding sulfamate (33) by treatment with sodium hydride and sulfamoyl chloride (P. Nussbaumer., J. Med. Chem., 2002, 45, 4310-20), or by reaction with sulfamoyl chloride in dimethylacetamide (DMAc) (O. Makoto, Tetrahedron letters, 2000, 41, 7047-51). Compound (32) can also be transformed into ether compound (34) by reaction with 1-(2-chloroethyl)piperidine using conditions described by M. R. Tremblay (Bioorg. Med. Chem., 1999, 7, 6, 1013-1024).

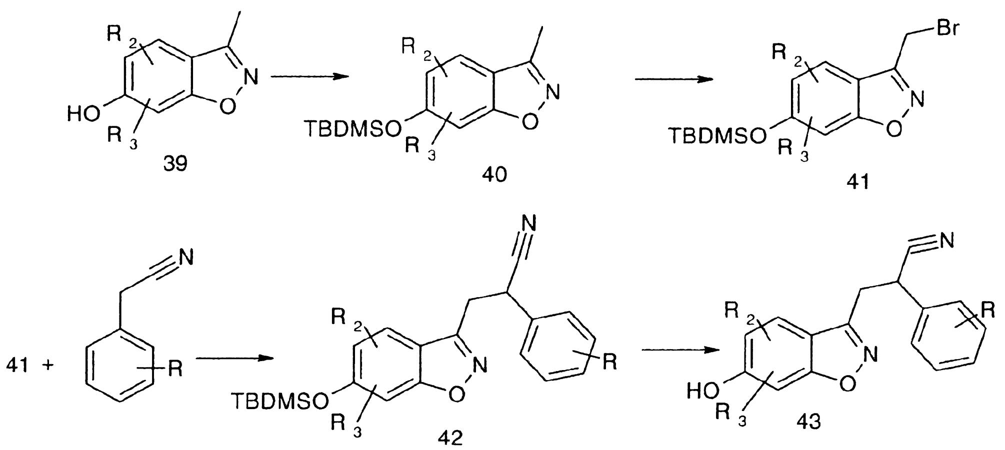
Scheme IIb



According to scheme IIb the benzisoxazole (35) prepared using the conditions described by H. Uno (Chem. Pharm. Bull., 24, 1976, 632) was reacted with aldehyde (19) in NaH/ DMF or KOH/EtOH to give (36). Compound (36) was reacted with $NaBH_4$ in EtOH to give (37).

Demethylation of compound (37) with either tribromoborane using the conditions described by J.F.W. McOmie (Tetrahedron, 1968, 24, 2289-92) or HBr/AcOH or pyridinium hydrochloride gave the hydroxy benzisoxazole compound (38).

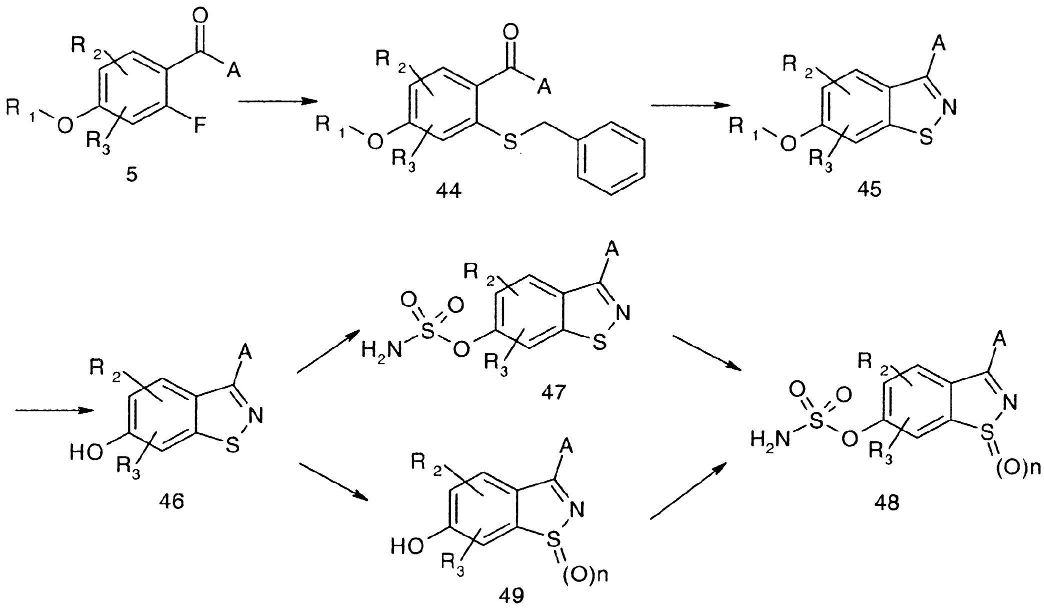
Scheme IIc



According to scheme IIc the benzisoxazole (39) prepared using the conditions described by M. A. Elkasaby (Indian J. Chem. Sect B, 1980, 19, 571) was protected with tert-butyldimethylsilylchloride in imidazole/DMF (P. M. Kendall, J. Org. Chem., 44, 1979, 1421) and the compound (40) obtained was brominated in the presence of NBS and benzoyl peroxide to give (41). Compound (41) was reacted with LDA and substituted phenylacetonitrile to give (42) using the procedure described by E. Teodori (Bioorg. Med. Chem., 7, 9, 1999, 1873-1880). Deprotection of the hydroxyl group in presence of nBu_4F using the conditions described by E. J. Corey (J. Am. Chem. Soc., 94, 1972, 6190) gave compound (43).

The benzisothiazole derivatives of formula (I) can be prepared according to general scheme III.

Scheme III



(n = 1,2)

According to scheme III, ketone (5) was reacted with phenylmethanethiol to give (44). The obtained compound (44) was refluxed in sulfuryl chloride followed by ammoniac treatment to afford cyclised benzisothiazole (45) according to the procedure described by D. M. Fink (Tetrahedron Letters, 1993, 34, 41, 6525-6528). Demethylation of compounds (45) with either tribromoborane using the conditions described by J.F.W McOmie (Tetrahedron, 1968, 24, 2289-92) or HBr/AcOH or pyridinium hydrochloride gave the hydroxy benzisothiazole compounds (46). These compounds (46) can be transformed into the corresponding sulfamates (47) by treatment with sodium hydride and sulfamoyl chloride (P. Nussbaumer, J. Med. Chem., 2002, 45, 4310-20), or by reaction with sulfamoyl chloride in dimethylacetamide (DMAc) (O. Makoto. Tetrahedron letters, 2000, 41, 7047-51).

Oxidation of these compounds (46) and (47) by hydrogen peroxide in trifluoroacetic acid, following the conditions described by S. Grivas and E. Ronne (Acta Chemica Scandinavia, 1995, 49, 225-229), gave respectively the mono and/or dioxidised benzisothiazoles (49) and (48). Compound (49) can be sulfamoylated to give (48).

General schemes I, II and III illustrate the synthesis of compounds (I) in which the substituent R_1O is in position 6- of the heterocyclic ring. It will however be appreciated that compounds (I) where the substituent R_1O is in position 4-, 5- or 7- of the heterocyclic ring can be prepared using the procedures described above.

The following examples are intended to illustrate and not to limit the scope of the invention.

PREPARATION OF ACETOPHENONES (5)

EXAMPLE 1: 4-benzyloxy-2-fluorobenzonitrile

To a mixture of 2-fluoro-4-hydroxy-benzonitrile (98 g, 0.68 mol) and K_2CO_3 (94 g, 0.68 mol) in acetonitrile was added benzyl chloride (86.6 g, 0.68 mol). The mixture was stirred overnight at room temperature and the reaction followed by TLC (toluene/AcOEt 8/2). The mixture was filtered, concentrated under vacuum and crystallized from pentane to give 147 g of solid (95 %).

^{1}H-NMR (DMSO d_6): 5.25 (s,2H), 7.05 (dd,1H), 7.25 (dd,1H), 7.30-7.60 (m,5H), 7.75 (t,1H).

Using the same procedure but replacing 2-fluoro-4-hydroxy-benzonitrile by:

cycloheptyl (2-fluoro-4-hydroxyphenyl) methanone

1-adamantyl (2-fluoro-4-hydroxyphenyl) methanone

the following compounds were respectively obtained:

EXAMPLE 2: cycloheptyl (4-benzyloxy-2-fluorophenyl) methanone

(71 %).

^{1}H-RMN ($CDCl_3$): 1.10-2.00 (m, 12H), 3.50 (m, 1H), 5.17 (s, 2H), 6,85 (dt, 1H), 7.20 (dd, 1H), 7.30-7.60 (m, 6H).

EXAMPLE 3: 1-adamantyl (4-benzyloxy-2-fluorophenyl) methanone

(38%)

^{1}H-NMR (DMSO d_6): 1.30-2.30 (m, 15H), 5.20 (s, 2H), 6.85 (dt, 1H), 7.12 (dd, 1H), 7.20-7.60 (m, 6H).

EXAMPLE 4: cyclopentyl (4-benzyloxy-2-fluorophenyl) methanone

A suspension of magnesium (19 g, 0.79 mol) and iodine (catalytic amount) in THF (20 ml) was refluxed under N_2. A solution of cyclopentylbromide (110 g, 0.738 mol) in THF (400 ml) was added slowly. The mixture was refluxed until all the magnesium was consumed, then cooled to 30°C and added to a solution of 4-benzyloxy-2-fluorobenzonitrile (129 g, 0.56 mol) in THF (600 ml). The reaction was stirred at 50°C overnight then quenched by aqueous NH_4Cl and ice, extracted with ethyl acetate, and washed with brine. The mixture was dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by flash chromatography (heptane/EtOAc 9/1) gave 60 g of product (35 %, as solid).

^{1}H-NMR (DMSO d_6): 1.40-2.00 (m, 8H), 3.58 (m, 1H), 5.20 (s, 2H), 6.85-7.20 (m, 2H), 7.25-7.55 (m, 5H), 7.80 (t, 1H).

Using the same procedure but replacing cyclopentylbromide by cyclohexylchloride, the following compound was obtained:

EXAMPLE 5: cyclohexyl (4-benzyloxy-2-fluorophenyl) methanone

(35%). mp 78°C.

^{1}H-NMR (DMSO d_6): 1.00 to 2.00 (m, 10H), 3.05 (m, 1H), 5.20 (s, 2H), 6.90-7.10 (m, 2H), 7.20-7.60 (m, 5H), 7.75 (t, 1H).

EXAMPLE 6: 1-adamantyl (2-fluoro-4-hydroxyphenyl) methanone

To a mixture of $AlCl_3$ (45 g, 0.337 mol) in 1,2-dichloroethane (DCE, 250 ml) at 0°C was added 1-adamantyl carbonyl chloride (36.6 g, 0.228 mol) in DCE (150 ml). 3-fluorophenol (21 g, 0.183 mol) in DCE (100 ml) was added slowly at 0°C. The reaction was followed by TLC (heptane/toluene 50/50). The mixture was poured onto HCl 2N, extracted with AcOEt, washed with $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by flash chromatography (heptane/toluene 8/2) gave 27 g of 1-adamantyl (2-fluoro-4 -hydroxyphenyl) methanone (48% as solid).

^{1}H-NMR (DMSO, d_6): 1.30 (m, 15H), 5.97 (s, 1H), 6.70 (d,1H), 6.94 (dd, 1H), 7.64 (d, 1H).

Using the same procedure but replacing 1-adamantyl carbonyl chloride by cycloheptane carbonyl chloride, the following compound was obtained:

EXAMPLE 7: cycloheptyl (2-fluoro-4-hydroxyphenyl) methanone

(60 %).

^{1}H-RMN ($CDCl_3$): 1.20-2.00 (m, 12H), 3.58 (m, 1H), 6.70-6.90 (m, 2H), 7.90-8.10 (m, 1H), 12.45 (s, 1H).

Using the same procedure but replacing 1-adamantyl carbonyl chloride by cycloheptane carbonyl chloride and 3-fluorophenol by 3-fluoroanisole, the following compound was obtained:

EXAMPLE 8: cycloheptyl (4-methoxy-2-fluorophenyl) methanone

(45 %).

^{1}H-NMR ($CDCl_3$): 1.40-2.00 (m, 12H), 1.9 (3, 2H), 3.25 (m, 1H), 3.80 (s, 3H), 6.50 (dd, 1H), 6.65 (dd, 1H), 7.75 (t, 1H).

Using the same procedure but replacing 3-fluorophenol by:

3-fluoroanisole

3,5-dimethoxy-chlorobenzene

the following compounds were respectively obtained:

EXAMPLE 9: 1-adamantyl (4-methoxy-2-fluorophenyl) methanone

(15 %).

^{1}H-NMR ($CDCl_3$): 1.50-2.30 (m, 15H), 3.85 (s, 3H), 6.60 (2d, 1H), 6.70 (2d, 1H), 7.70 (t, 1H).

EXAMPLE 10: 1-adamantyl (2-chloro-4,6-dimethoxyphenyl) methanone

(22 %).

^{1}H-NMR ($CDCl_3$, d_1): 1.60-2.10 (m, 15H), 3.75 (s, 3H), 3.80 (s, 3H), 6.35 (s, 1H), 6.50 (s, 1H).

Using the same procedure but replacing 3-fluorophenol by 3,4-dimethoxy -fluorobenzene and 1-adamantyl carbonyl chloride by cyclohexane carbonyl chloride, the following compound was obtained:

EXAMPLE 11: cyclohexyl (2-fluoro-4-hydroxy-5-methoxyphenyl) methanone

^{1}H-NMR (DMSO, d_6): 1.00-2.00 (m, 10H), 3.05 (m, 1H), 3.80 (s, 3H), 6.65 (d, 1H), 7.23 (d, 1H), 10.50 (s, 1H).

PREPARATION OF INDAZOLES (6), (7), (8) and (12)

EXAMPLE 12: 6-benzyloxy-3-cyclopentyl-1H-indazole

A mixture of cyclopentyl (4-benzyloxy-2-fluorophenyl) methanone (40 g, 0.13 mol) in hydrazine hydrate (50 ml) was refluxed overnight. After cooling to room temperature, the solid was filtered, dissolved in EtOAc, then washed with aqueous NH_4Cl and brine. The solution was dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by flash chromatography (toluene/EtOAc 9/1) gave the expected product (13 g , 45 % as solid).

^{1}H-NMR (DMSO d_6): 1.40-2.20 (m, 8H), 3.34 (m, 1H), 5.13 (s, 2H), 6.75 (dd, 1H), 6.90 (d, 1H), 7.20-7.53 (m, 5H), 7.57 (d, 1H), 9.40 (s, 1H).

Using the same procedure but replacing cyclopentyl (4-benzyloxy-2-fluorophenyl) methanone by:

cyclohexyl (4-benzyloxy-2-fluorophenyl) methanone
cycloheptyl (4-benzyloxy-2-fluorophenyl) methanone
1-adamantyl (4-methoxy-2-fluorophenyl) methanone
cycloheptyl (4-methoxy-2-fluorophenyl) methanone

the following compounds were respectively obtained:

EXAMPLE 13: 6-benzyloxy-3-cyclohexyl-1H-indazole

(58 %).

^{1}H-RMN ($CDCl_3$): 1.10-2.10 (m, 10H), 2.95 (m, 1H), 5.15 (s, 2H), 6.75 (dd, 1H), 6.90 (d, 1H), 7.20-7.55 (m, 5H), 7.65 (d, 1H), 12.32 (s, 1H).

EXAMPLE 14: 6-benzyloxy-3-cycloheptyl-1H-indazole

(85 %).

^{1}H-RMN ($CDCl_3$): 1.20-2.10 (m, 12H), 2.55 (m, 1H), 5.07 (s, 2H), 6.45 (dd, 1H), 6.55 (d, 1H), 6.95 (d, 1H), 7,20-7.50 (m, 5H).

EXAMPLE 15 : 3-(1-adamantyl)-6-methoxy-1H-indazole

(30 %).

^{1}H-NMR ($CDCl_3$): 1.50-2,70 (m, 15 H), 3.85 (s, 3H), 6.78 (dd, 1H), 6.88 (d, 1H), 7.57 (d, 1H).

EXAMPLE 16: 3-cycloheptyl-6-methoxy-1H-indazole

(45 %).

^{1}H-NMR ($CDCl_3$): 1.40-2.30 (m, 12H), 3.22 (m, 1H), 3.83 (s, 3H), 6.35 (s, 1H), 6.65-6.90 (m, 2H), 7.58 (d, 1H).

Using the same procedure but replacing hydrazine hydrate by 1-(4-benzyloxyphenyl)hydrazine (prepared following K.J. Duffy, J Med Chem 2001, 44, 22, 3730-3745), the following compound was obtained:

EXAMPLE 17: 6-benzyloxy-3-cyclopentyl-1-(4-benzyloxyphenyl)-1H-indazole

(66%).

^{1}H-RMN (DMSO d_6): 1.15-2.05 (m, 10H), 2.95 (dt, 1H), 3.88 (s, 3H), 5.15 (s, 2H), 6.75 (dd, 1H), 7.12 (d, 1H), 7.25-7.58 (m, 5H), 7.65 (d, 1H).

Using the same procedure but replacing cyclopentyl (4-benzyloxy-2-fluorophenyl) methanone by cyclohexyl (4-benzyloxy-2-fluorophenyl) methanone and hydrazine hydrate by methylhydrazine or benzylhydrazine, the following compound were respectively obtained:

EXAMPLE 18: 6-benzyloxy-3-cyclohexyl-1-methyl-1H-indazole

(66%).

^{1}H-RMN (DMSO d_6): 1.15-2.05 (m, 10H), 2.95 (dt, 1H), 3.88 (s, 3H), 5.15 (s, 2H), 6.75 (dd, 1H), 7.12 (d, 1H), 7.25-7.58 (m, 5H), 7.65 (d, 1H).

EXAMPLE 19: 1-benzyl-6-benzyloxy-3-cyclohexyl-1H-indazole

(76%).

^{1}H-RMN (DMSO d_6): 1.15-2.05 (m, 10H), 2.95 (dt, 1H), 5.10 (s, 2H), 5.15 (s, 2H), 6.75 (dd, 1H), 7.12 (d, 1H), 7.15-7.65 (m, 10H), 7.65 (d, 1H).

EXAMPLE 20: Tertio-butyl-6-benzyloxy-3-cyclohexyl-1H-indazole-1-carboxylate

At 0°C di-tert-butyldicarbonate (36.38 g, 0.166 mol) in acetonitrile (340 ml) was added on a mixture of 6-benzyloxy-3-cyclohexyl-1H-indazole (42.50 g, 0.138 mol), TEA (22 ml, 0.152 mol), acetonitrile (460 ml) and DMAP (3.40 g, 0.027 mol).

The mixture was stirred at room temperature overnight, then concentred under vacuum, diluted with ethyl acetate and washed with water acidified with HCl 2N to pH 2. The mixture was dried over Na_2SO_4, filtered and diluted in diisopropyl ether, the expected product crystallized (44.50 g, yield 79 %).

^{1}H-NMR (DMSO d_6) : 1.15-2.05 (m, 19H), 3.00 (m, 1H), 5.19 (s, 2H), 7.03 (dd, 1H), 7.25-7.45 (m, 5H), 7.69 (d, 1H), 7.78 (d, 2H).

EXAMPLE 21: 6-benzyloxy-3-cyclopentyl-1-(2-piperidin-1-yl-ethyl)-1H-indazole

6-benzyloxy-3-cyclopentyl-1H-indazole was heated for 1 hour with NaOH (1.64g, 41 mmol) and 1-(2-chloroethyl)piperidine in EtOH (60 ml) at 40°C. The reaction was followed by TLC (toluene/dioxane: 7/3), and when completed, the mixture was cooled to room temperature. The mixture was quenched by NH_4Cl, extracted with AcOEt, dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by flash chromatography (toluene/ 1,4-dioxane 7/3) gave the expected product (600 mg, 8% as solid).

^{1}H-RMN (DMSO d_6): 1.40-2.40 (m, 14H), 2.50-2.80 (m, 2H), 3.10-3.60 (m, 5H), 4.30 (t, 2H), 5.15 (s, 2H), 6.70 (dd, 1H), 7.10 (d, 1H), 7.40 (m, 5H), 7.60 (d, 1H).

Using the same procedure but replacing 1-(2-chloroethyl)piperidine by 4-bromobenzylbromide, the following compound was obtained:

EXAMPLE 22: 6-benzyloxy-1-(4-bromobenzyl)- 3-cyclopentyl-1H-indazole

^{1}H-RMN (DMSO d_6): 1.50-2.20 (m, 8H), 3.38 (m, 1H), 5.15 (s, 2H), 5.50 (s, 2H), 6.78 (dd, 1H), 7.05-7.55 (m, 10H), 7.60 (d, 1H).

EXAMPLE 23: 3-cyclopentyl-1H-indazol-6-ol

A mixture of 6-benzyloxy-3-cyclopentyl-1H-indazole (13 g, 0.102 mol), Pd/C (5%, 0.65 g) and PtO_2 (catalytic amount) in ethanol (130 ml) was stirred at room temperature under hydrogen. The reaction was followed by TLC (heptane/EtOAc 50/50). When completed, the mixture was filtered on Celite® and concentrated under vacuum. Crystallization from CH_2Cl_2/pentane gave 7.2 g of white crystals (85 %). mp 175°C.

^{1}H-NMR (DMSO, d_6): 1.40-2.20 (m, 8H), 3.35 (m, 1H), 6.55 (dd, 1H), 6.68 (d, 1H), 7.50 (d, 1H), 9.45 (s, 1H), 12.05 (s,1H).

Using the same procedure but replacing 6-benzyloxy-3-cyclopentyl-1H-indazole by:

6-benzyloxy-3-cyclohexyl-1H-indazole
6-benzyloxy-3-cyclohexyl-1-methyl-1H-indazole
6-benzyloxy-3-cyclopentyl-1-(4-benzyloxyphenyl)-1H-indazole
6-benzyloxy-3-cyclopentyl-1-(2-piperidin-1-yl-ethyl)-1H-indazole
6-benzyloxy-1-(4-bromobenzyl)-3-cyclopentyl-1H-indazole
1-benzyl-6-benzyloxy-3-cyclopentyl-1H-indazole
Tertio-butyl-6-benzyloxy-3-cyclohexyl-1H-indazole-1-carboxylate

the following compounds were respectively obtained:

EXAMPLE 24: 3-cyclohexyl-1H-indazol-6-ol

(85%). mp 147°C.

^{1}H-RMN (DMSO d_6): 1.10-2.10 (m, 10H), 2.90 (m, 1H), 6.55 (dd, 1H), 6.65 (s, 1H), 7.50 (d, 1H), 9.45 (s, 1H), 12.05 (s, 1H).

EXAMPLE 25: 3-cyclohexyl-1-methyl-1H-indazol-6-ol

(75%). mp 205°C.

^{1}H-RMN (DMSO d_6): 1.20-2.00 (m, 10H), 2.92 (dt, 1H), 3.80 (s, 3H), 6.60 (dd, 1H), 6.68 (d, 1H), 7.55 (d, 1H), 9.58 (s, 1H).

EXAMPLE 26: 3-cyclopentyl-1-(4-hydroxyphenyl)-1H-indazol-6-ol

(54%). mp 178°C.

^{1}H-RMN (DMSO d_6): 1.50-2.20 (m, 8H), 3.40 (t, 1H), 6.68 (dd, 1H), 6.83 (d, 1H), 6.90 (d, 2H), 7.38 (d, 2H), 7.59 (d, 1H), 9.60 (s, 1H), 9.68 (s, 1H).

EXAMPLE 27: 3-cyclopentyl-1-(2-piperidin-1-yl-ethyl)-1H-indazol-6-ol, hydrochloride

(90%). mp 120°C.

^{1}H-NMR (DMSO d_6): 1.15-2.30 (m, 14H), 2.90 (m, 2H), 3.20-3.60 (m, 5H), 4.68 (t, 2H), 6.70 (dd, 1H), 6.88 (d, 1H), 7.52 (d, 1H), 10.80 (s, 1H).

EXAMPLE 28: 1-(4-bromobenzyl)-3-cyclopentyl-1H-indazol-6-ol

(90%). mp 147°C.

^{1}H-RMN (DMSO d_6): 1.45-2.30 (m, 8H), 3.35 (m, 1H), 5.40 (s, 2H), 6.60 (d, 1H), 7.00-7.40 (m, 4H), 7.50 (d, 1H), 7.70 (s, 1H).

EXAMPLE 29: 1-benzyl-3-cyclohexyl-1H-indazol-6-ol

(40%) mp 154°C

^{1}H-NMR ($CDCl_3$) : 1.10-2.40 (m, 10H), 3.03 (m, 1H), 5.40 (s, 2H), 5.70 (s, 1H), 6.53 (d, 1H), 6.76 (dd, 1H), 7.00-7.35 (m, 5H), 7.60 (d, 1H).

EXAMPLE 30: Tertio-butyl-3-cyclohexyl-6-hydroxy-1H-indazole-1-carboxylate

(87%) mp 124°C

^{1}H-NMR (DMSO d_6) : 1.20-2.05 (m, 19H), 2.95 (m, 1H), 6.80 (dd, 1H), 7.40 (d, 1H), 7.65 (d, 1H).

EXAMPLE 31: 3-(1-adamantyl)-1H-indazol-6-ol, hydrochloride

A mixture of 3-(1-adamantyl)-6-methoxy-1H-indazole (210 mg, 0.75 mol) in 40 % HBr in acetic acid (10 ml) was heated overnight at 70°C. The mixture was poured onto ice and neutralised with a solution of $NaHCO_3$, then extracted with AcOEt, dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by flash chromatography (heptane/EtOAc 50/50) gave 200 mg of product. The solid was crystallised as HCl salt from Et_2O. The crystals were filtered, washed with ether, and dried to give 160 mg of salt (80 %). mp 140°C.

^{1}H-NMR (DMSO d_6): 1.00-2.60 (m, 15H), 6.65 (d, 1H), 6.75 (s, 1H), 7.55 (d, 1H).

Using the same procedure but replacing 3-(1-adamantyl)-6-methoxy-1H-indazole by 3-cycloheptyl-6-methoxy-1H-indazole, the following compound was obtained:

EXAMPLE 32: 3-cycloheptyl-1H-indazol-6-ol, hydrochloride

(60 %). mp 95°C.

^{1}H-NMR (DMSO d_6): 1.20-2.00 (m, 12H), 3.1 (m, 1H), 6.62 (d, 1H), 6.64 (s, 1H), 7.60 (d, 1H).

PREPARATION OF 1H-INDAZOLE SULFONAMIDES (9), (10), (11), (13) and (14)

EXAMPLE 33: 6-benzyloxy-3-cycloheptyl-1H-indazole-1-sulfonamide

Sulfamoyl chloride (2.9 g, 25 mmol) was added to a solution of 6-benzyloxy-3-cycloheptyl-1H-indazole (6) (4 g, 1.75 mmol) in N,N-dimethylacetamide (40 ml) at 0°C. The mixture was stirred for 3h at 0°C. After extraction with EtOAc, the organic layer was washed with NH_4Cl solution and brine. It was dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by flash chromatography followed by crystallisation from EtOH gave 1.2 g of yellow crystals (24 %).

^{1}H-NMR (DMSO d_6): 1.20-2.00 (m, 12H), 2.58 (m, 1H), 5.05 (s, 2H), 6.65-7.00 (m, 1H), 7.20-7.50 (m, 6H), 7.92 (s, 1H), 8.55 (s, 2H).

Using the same procedure but replacing 6-benzyloxy-3-cycloheptyl-1H-indazole by:

6-benzyloxy-3-cyclohexyl-1H-indazole

3-cyclohexyl-1H-indazol-6-ol

3-cyclohexyl-1-methyl-1H-indazol-6-ol

1-benzyl-3-cyclohexyl-1H-indazol-6-ol

Tertio-butyl-6-benzyloxy-3-cyclohexyl-1H-indazole-1-carboxylate

the following compounds were respectively obtained:

EXAMPLE 34: 6-benzyloxy-3-cyclohexyl-1H-indazole-1-sulfonamide

(100%).

^{1}H-NMR (DMSO d_6): 1.10 to 2.10 (m, 10 H), 3.05 (m, 1H), 5.15 (s, 2H), 7.00 (dd, 1H), 7.25-7.60 (m, 6H), 7.80 (d, 1H), 8.35 (s, 2H).

EXAMPLE 35: 1-(aminosulfonyl)-3-cyclohexyl-1H-indazol-6-yl-sulfamate

(40%). mp 213°C.

^{1}H-NMR (DMSO d_6): 1.20-2.10 (m, 10H), 3.13 (d, 1H), 7.25 (dd, 1H), 7.80 (d, 1H), 8.00 (d, 1H), 8.10 (s, 2H), 8.50 (s, 2H).

EXAMPLE 36: 3-cyclohexyl-1-methyl-1H-indazole-6-sulfonamide

(84%). mp 188°C.

^{1}H-NMR (DMSO d_6): 1.20-2.10 (m, 10H), 3.03 (m, 1H), 3.95 (s, 3H), 6.98 (d, 1H), 7.45 (s, 1H), 7.85 (d, 1H), 8.00 (s, 2H).

EXAMPLE 37: 1-benzyl-3-cyclohexyl-1H-indazol-6-yl-sulfamate

(85%) mp 188°C

^{1}H-NMR (DMSO d_6) : 1.10-2.10 (m, 10H), 3.04 (m, 1H), 5.55 (s, 2H), 7.05 (d, 1H), 7.10 (m, 5H), 5.53 (s, 1H), 7.88 (d, 1H), 8.00 (s, 2H).

EXAMPLE 38: Tertio-butyl-6-[(aminosulfonyl)oxy]-3-cyclohexyl-1H-indazole-1-carboxylate

(46%) mp 128°C

^{1}H-NMR (DMSO d_6) : 1.20-2.10 (m, 19H), 3.10 (m, 1H), 7.23 (dd, 1H), 7.90-8.05 (m, 2H), 8.11 (s, 2H).

Using the same procedure as in Example 21 but replacing 6-benzyloxy-3-cyclopentyl-1H-indazole by:

6-benzyloxy-3-cycloheptyl-1H-indazol-1-sulfonamide

6-benzyloxy-3-cyclohexyl-1H-indazol-1-sulfonamide

the following compounds were respectively obtained:

EXAMPLE 39: 3-cycloheptyl-6-hydroxy-1H-indazole-1-sulfonamide

mp 155°C.

^{1}H-NMR (DMSO d_6): 1.20-2.00 (m, 12H), 2.60 (m, 1H), 6.70 (m, 2H), 6.90 (s, 2H), 7.05 (m, 1H), 7.80 (s, 1H).

EXAMPLE 40: 3-cyclohexyl-6-hydroxy-1H-indazole-1-sulfonamide

mp 162°C.

^{1}H-NMR (DMSO d_6): 1.10-2.10 (m, 10H), 3.00 (m, 1H), 6,78 (dd, 1H), 7.25 (d, 1H), 7.68 (d, 1H), 8.22 (s, 2H), 10.05 (s, 1H).

EXAMPLE 41: 3-cyclohexyl-1H-indazol-6-yl-sulfamate

A mixture of tertio-butyl-6-[(aminosulfonyl)oxy]-3-cyclohexyl-1H-indazole-1-carboxylate (4.00g, 10.12 mmol), water (10 ml), dioxan (30 ml) and few drops of HCl concentred (30%) was stirred overnight and poured into water. The precipitate was collected by filtration to give the expected product. Crystallisation from toluene gave white crystals (1.25 g, 48 %)

^{1}H-NMR (DMSO d_6) : 1.10-2.10 (m, 10H), 3.04 (m, 1H), 6.95 (dd, 1H), 7.35 (d, 1H), 7.83 (d, 1H), 7.96 (s, 2H).

PREPARATION OF 3-BROMOMETHYL-1H-INDAZOLES (16), (17) and (18)

EXAMPLE 42: 1-[(tert-butoxycarbonyl)oxy]-6-methoxy-3-methyl-1H-indazole

Di-tert-butyl-dicarbonate in acetonitrile was mixed at 0°C with 6-methoxy-3-methyl-1H-indazole (prepared following the procedure described by F. Dennler, *Tetrahedron*, 22, 1966, 3131-3139) (26.27 g, 0.162 mol), acetonitrile (200 ml), triethylamine (25 ml, 0.178 mol), DMAP (3.96 g, 0.0324 mol). The mixture was stirred at room temperature overnight. Acetonitrile was concentrated under vacuum. The mixture was extracted with ethylacetate and acidified at pH = 2 with a solution of concentrated HCl, dried over Na_2SO_4, filtered and put in diisopropylether. 23.9 g of the expected product were obtained (as solid, 59 %).

^{1}H-NMR (DMSO d_6): 1.60 (s, 9H), 2.44 (s, 3H), 3.85 (s, 3H), 6.95 (dd, 1H), 7.50 (d, 1H), 7.65 (d, 1H).

EXAMPLE 43: 1-[(tert-butoxycarbonyl)oxy]-6-methoxy-3-bromo-methyl-1H-indazole

1-[(tert-butoxycarbonyl)oxy]-6-methoxy-3-methyl-1H-indazole (25.2 g, 0.096 mol) was dissolved in CCl_4 and mixed with benzoyl peroxide (2.33 g, 9.6 mmol). N-bromosuccinimide (NBS, 18.8 g, 0.109 mol) was slowly added to this mixture and heated under reflux overnight. The mixture was cooled at room temperature, filtered on Celite®, the filtrate was concentrated under vacuum and flashed with toluene. 10.5 g of the expected product were obtained (32 %, as oil).

^{1}H-NMR (DMSO d_6): 1.65 (s, 9H), 3.85 (s, 3H), 4.95 (s, 2H), 7.05 (dd, 1H), 7.55 (s, 1H), 7.80 (d, 1H)

EXAMPLE 44: {1-[(tert-butoxycarbonyl)oxy]-6-methoxy-1H-indazol-3-yl} acetonitrile

KCN (5.73 g, 88 mmol) in 23 ml of H_2O was added dropwise at 0°C to 1-[(tert-butoxycarbonyl)oxy]-6-methoxy-3-bromomethyl-1H-indazole (10.5 g, 30.08 mmol) in 80 ml of ethanol and stirred at room temperature for 1h30. The mixture was poured into water, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4. Concentration and precipitation in diisopropyl ether gave the expected product (4.42 g, 50 % as solid).

^{1}H-NMR (DMSO d6): 1.65 (s, 9H), 3.85 (s, 3H), 4.42 (s, 2H), 7.00 (d, 1H), 7.50 (d, 1H), 7.75 (d, 1H).

PREPARATION OF (1H-INDAZOLE-3-YL)ACETONITRILE (20), (21) and (22)

EXAMPLE 45: 2-(Z/E)-2-(6-methoxy-1H-indazol-3-yl)-3-(4-methoxyphenyl) prop-2-ene nitrile

A solution of KOH at 40 % in 3.5 ml of water and 7.1 ml ethanol was added dropwise to p-anisaldehyde (2.06 ml, 16.9 mmol) and {1-[(tert-butoxycarbonyl)oxy]-6-methoxy-1H-indazol-3-yl}acetonitrile in ethanol. When the reaction was complete, the mixture was filtered to obtain 3.53 g of the expected product (77 % as solid).

^{1}H-NMR (DMSO d_6): 3.35 (s, 1H), 3.85 (s, 3H), 3.90 (s, 3H), 6.70-7.20 (m, 4H), 7.85-8.15 (m, 4H).

Using the same procedure but replacing p-anisaldehyde by cyclohexane carboxaldehyde, the following compound was obtained:

EXAMPLE 46: 2-(Z/E)-3-cyclohexyl-2(6-methoxy-1H-indazol-3-yl) prop-2-enenitrile

(55.4%).

^{1}H-NMR (DMSO d_6): 1.20-1.80 (m, 10H), 2.60-2.75 (m, 1H), 3.80 (s, 3H), 6.85 (dd, 1H), 6.95 (d, 1H), 7.15 (d, 1H), 7.85 (d, 1H), 13.20 (s, 1H).

EXAMPLE 47: 2-(6-methoxy-1H-indazol-3-yl)-3-(4-methoxyphenyl) propanenitrile

To 2-(6-methoxy-1H-indazol-3-yl)-3-(4-methoxyphenyl)prop-2-enenitrile (3.53 g, 11.56 mmol) dissolved in ethanol was added portionwise $NaBH_4$ (0.66 g, 17 mmol). The mixture was stirred at 70°C overnight, then poured into water, acidified with concentrated HCl, extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered and concentrated. The oil was precipitated in ethanol and diisopropyl ether to give the expected product (3.18 g, as a white powder 85.3 %).

^{1}H-NMR (DMSO d_6): 3.56 (s, 3H), 3.60-3.80 (m, 2H), 3.85 (s, 3H), 4.26 (t, 1H), 6.90-7.30 (m, 6H), 7.97 (d, 1H), 11.13 (s, 1H).

Using the same procedure but replacing 2-(Z/E)-2-(6-methoxy-1H-indazol-3-yl)-3-(4-methoxyphenyl)prop-2-enenitrile by 2-(Z/E)-3-cyclohexyl-2-(6-methoxy-1H-indazol-3-yl)prop-2-ene nitrile, the following compound was obtained:

EXAMPLE 48: 3-cyclohexyl-2-(6-methoxy-1H-indazol-3-yl) propanenitrile

(97.5 %).

^{1}H-NMR (DMSO d_6): 0.85-2.45 (m, 13H), 3.80 (s, 3H), 4.65 (t, 1H), 6.75 (dd, 1H), 6.90 (d, 1H), 7.65 (d, 1H), 12.85 (s, 1H).

EXAMPLE 49: 3-cyclohexyl-2-(6-hydroxy-1H-indazol-3-yl) propanenitrile

3-cyclohexyl-2-(6-methoxy-1H-indazol-3-yl) propanenitrile (1.61 g, 5.68 mmol) was dissolved in CH_2Cl_2 and cooled with an ice bath. BBr_3 / CH_2Cl_2 1M (8.6 ml, 8.52 mmol) was added to this mixture, which was stirred at 50°C, then poured onto saturated $NaHCO_3$ solution, extracted with ethylacetate, dried over Na_2SO_4, filtered, concentrated under vacuum and purified by flash chromatography (CH_2Cl_2/MeOH 98/2). Crystallisation from EtOH gave 780 mg of white crystals (51 %). mp 175°C.

^{1}H-NMR (DMSO d_6): 0.80-2.05 (m, 13H), 4.65 (t, 1H), 6.70 (dd, 1H), 6.78 (d, 1H), 7.60 (d, 1H), 9.70 (s, 1H), 12.60 (s, 1H).

PREPARATION OF PROPANAMIDES (23)

Using the same procedure as in Example 27 but replacing 3-(1-adamantyl)-6-methoxy-1H-indazole by:

2-(6-methoxy-1H-indazol-3-yl)-3-(4-methoxyphenyl) propanenitrile

3-cyclohexyl-2-(6-methoxy-1H-indazol-3-yl) propanenitrile

the following compounds were respectively obtained:

EXAMPLE 50: 2-(1-acetyl-6-hydroxy-1H-indazol-3-yl)-3-(4-methoxyphenyl) propanamide

(7.7 %). mp = 152°C.

^{1}H-NMR (DMSO d_6): 2.22 (s, 3H), 3.15 (q, 2H), 3.80 (s, 3H), 4.15 (m, 1H), 6.68 (dd, 1H), 6.80 (d, 1H), 6.85-7.05 (m, 3H), 7.20 (d, 2H), 7.52 (s, 1H), 7.80 (d, 1H), 12.53 (s, 1H).

EXAMPLE 51: 3-cyclohexyl-2-(6-hydroxy-1H-indazol-3-yl) propanamide

(34 %). mp = 199°C.

^{1}H-NMR (DMSO d_6):0.70 -2.10 (m, 13H), 3.90 (t, 1H), 6.55 (d, 1H), 6.75 (s, 1H), 6.83 (s, 1H), 7.45 (s, 1H), 7.65 (d, 1H), 9.50 (s, 1H), 12.20 (s, 1H).

PREPARATION OF THE 1H-PYRANO[4,3,2-cd]INDAZOLES (25), (26) and (27)

EXAMPLE 52: 7-methoxy-3-(4-methoxyphenyl)-1H-pyrano[4,3,2-cd] indazole

Using the same procedure as in Example 12 but replacing cyclopentyl (4-benzyloxy-2-fluorophenyl) methanone by 5-chloro-7-methoxy-3-(4-methoxyphenyl)-4H-chromen-4-one (prepared following Kitagawa *Chem Pharm Bull*, 39, 1991, 2681), the expected product was obtained (as a solid, 84 %).

^{1}H-NMR (DMSO, d_6): 3.60 (s, 3H), 3.80 (s, 3H), 6.60 (d, 2H), 6.80 (d, 2H), 7.10 (d, 1H), 7.30 (d, 1H), 7.80 (s, 1H).

Using the same procedure as in Example 49 but replacing 3-cyclohexyl-2-(6-methoxy-1H-indazol-3-yl) propanenitrile by 7-methoxy-3-(4-methoxyphenyl) -1H-pyrano[4,3,2-cd] indazole, the following compounds were obtained:

EXAMPLE 53: 3-(4-methoxy-phenyl)-1H-pyrano[4,3,2-cd]indazol-7-ol, hydrochloride

(26 %). mp 255°C.

^{1}H-NMR (DMSO d_6): 3.55 (s, 3H), 6.63 (m, 4H), 7.05 (d, 2H), 8.05 (s, 1H), 10.00 (s, 1H).

EXAMPLE 54: 3-(4-hydroxy-phenyl)-1H-pyrano[4,3,2-cd]indazol-7-ol, hydrochloride

(15 %). mp 111°C.

^{1}H-NMR (DMSO d_6): 6.45 (s, 2H), 6.65 (d, 2H), 7.10 (d, 2H), 8.00 (s, 1H), 10.00 (s, 1H).

PREPARATION OF OXIMES (28) and (30)

EXAMPLE 55: 1-adamantyl(2-chloro-4,6-dihydroxyphenyl)methanone

Boron tribromide 1M in CH_2Cl_2 was added to a solution of 1-adamantyl-(2-chloro-4,6-dimethoxyphenyl) methanone (7 g, 21.0 mmoles) and CH_2Cl_2 (30 ml). The mixture was warmed overnight and then poured into water, extracted with ethyl acetate, dried over Na_2SO_4 and concentrated under vacuum to give the expected product (1.9 g, 30 %).

^{1}H-NMR (DMSO d_6): 1.00-1.90 (m, 15H), 6.25 (s, 1H), 6.30 (s, 1H), 10.00 (s, 2H).

EXAMPLE 56: 1-adamantyl(2-chloro-4,6-dihydroxyphenyl) methanone oxime

1-adamantyl-(2-chloro-4,6-dihydroxyphenyl) methanone (1.9 g, 6.2 mmoles), hydroxylamine hydrochloride (100 g) and pyridine (50 ml) were refluxed for 4 h. The mixture was concentrated under vacuum, poured into water, extracted with ethyl acetate, washed with HCl 1N, dried over Na_2SO_4 and concentrated under vacuum to give the crude product. Flash chromatography (AcOEt/toluene 3/7) gave the pure oxime (1 g as a solid, 50%).

^{1}H-NMR (DMSO d_6): 1.50-2.00 (m, 15H), 6.24 (s, 1H), 6.28 (s, 1H).

Using the same procedure but replacing 1-adamantyl-(2-chloro-4,6-dihydroxyphenyl) methanone by:

1-adamantyl-(4-benzyloxy-2-fluorophenyl) methanone

cycloheptyl (4-benzyloxy-2-fluorophenyl) methanone

the following compounds were respectively obtained:

EXAMPLE 57: 1-adamantyl-(4-benzyloxy-2-fluorophenyl) methanone oxime

(32%).

^{1}H-NMR (DMSO d_6): 1.20-2.20 (m, 15H), 5.10 (s, 2H), 6.80 (dt, 1H), 6.90-7.17 (m, 2H), 7.20-7.60 (m, 5H), 10.55 (s, 1H).

EXAMPLE 58: cycloheptyl (4-benzyloxy-2-fluorophenyl) methanone oxime

(60%).

^{1}H-NMR (DMSO d_6): 1.10-2.00 (m, 12H), 2.10-2.20 (m, 1H), 5.10 (s, 2H), 6.67-6.85 (m, 1H), 6.90-7.15 (m, 2H), 7.25-7.50 (m, 5H), 10.47 (s, 1H).

PREPARATION OF BENZISOXAZOLES (31), (32) and (34)

EXAMPLE 59: 6-benzyloxy-3-cyclohexyl-1,2-benzisoxazole

A solution of hydroxylamine hydrochloride (11.7 g) in warm water (100 ml) was poured into a mixture of cyclohexyl (4-benzyloxy-2-fluorophenyl) methanone (20.22 g, 64.7 mmol) and EtOH (54 ml). A solution of sodium hydroxide (11.13 g, 0.278 mol) in water (54 ml) was then added as rapidly as the reflux permitted. The reaction mixture was heated for 12h and then most of the EtOH was removed by distillation. To the residue was added a solution of potassium hydroxide (8.7 g, 0.155 mol) in water (54 ml). The mixture was refluxed for 2 days, then cooled to about 6°C and stirred vigorously. A white solid was obtained, which was thoroughly washed with water and triturated with diisopropyl ether. The benzisoxazole was obtained as a white powder (12.26 g, 62 %) after filtration. mp 110°C.

^{1}H-NMR (DMSO d_6): 1.00-2.10 (m, 10H), 3.05 (m, 1H), 5.20 (s, 2H), 7.00 (dd, 1H), 7.25-7.55 (m, 6H), 7.75 (d, 1H).

Using the same procedure but replacing cyclohexyl (4-benzyloxy-2-fluorophenyl)methanone by cyclohexyl-(2-fluoro-4-hydroxy-5-methoxyphenyl) methanone, the following compound was obtained:

EXAMPLE 60: 3-cyclohexyl-6-hydroxy-5-methoxybenzisoxazole

(50.5 %).

^{1}H-NMR (DMSO d_6): 1.20-2.10 (m, 10H), 3.05 (m, 1H), 3.85 (s, 3H), 6.95 (s, 1H), 7.23 (s, 1H), 9.94 (s, 1H).

EXAMPLE 61: 3-(1-adamantyl)-4-chloro-1,2-benzisoxazol-6-ol

Diethylazodicarboxylate (0.92 g, 1.7 eq) in THF (20 ml) was added to a mixture of 1-adamantyl (2-chloro-4,6-dihydroxyphenyl) methanone oxime (1 g, 3.1 mmoles), triphenyl phosphine (1.4 g, 1.7 eq) in THF (20 ml) at 0°C. The mixture was stirred 2 h at 0°C, poured into water, extracted with ethylacetate, dried over Na_2SO_4 and concentrated under vacuum to give the crude product. Flash chromatography (AcOEt/toluene 1/9) and crystallisation from EtOH yielded the expected product (230 mg, 23 %). mp 215°C.

^{1}H-NMR ($CDCl_3$): 1.50-2.10 (m, 15H), 6.23 (d, 1H), 6.32 (d, 1H).

EXAMPLE 62: 3-(1-adamantyl)-6-benzyloxy-1,2-benzisoxazole

1-adamantyl-(4-benzyloxy-2-fluorophenyl) methanone oxime (2.3 mg, 6 mM) in DMF (30 ml) was added at 0°C dropwise under N_2, to a stirred suspension of NaH (0.61 g, 18 mM, 60 % oil dispersion) in DMF (10 ml). After the complete addition, the reaction mixture was allowed to warm to room temperature and poured into H_2O. The precipitate was collected by filtration to give the expected product (2.06 g, 95 %). mp 132°C.

^{1}H-NMR (DMSO d_6): 1.20-2.45 (m, 15H), 5.22 (s, 2H), 7.00 (d, 1H), 7.30-7.60 (m, 6H), 7.72 (d, 1H).

Using the same procedure but replacing 1-adamantyl-(4-benzyloxy-2-fluorophenyl) methanone oxime by cycloheptyl (4-benzyloxy-2-fluorophenyl) methanone oxime, the following compound was obtained

EXAMPLE 63: 6-benzyloxy-3-cycloheptyl-1,2-benzisoxazole

(90 %). mp 80°C.

^{1}H-NMR (DMSO d_6): 1.30-2.20 (m, 12H), 3.25 (m, 1H), 5.21 (s, 2H), 7.00 (dd, 1H), 7.25-7.60 (m, 6H), 7.75 (d, 1H).

Using the same procedure as in Example 23 but replacing 6-benzyloxy-3-cyclopentyl-1H-indazole by:

3-(1-adamantyl)-6-benzyloxy-1,2-benzisoxazole

6-benzyloxy-3-cycloheptyl-1,2-benzisoxazole

6-benzyloxy-3-cyclohexyl-1,2-benzisoxazole

the following compounds were respectively obtained:

EXAMPLE 64: 3-(1-adamantyl)-1,2-benzisoxazol-6-ol

(47.5 %). mp 215°C.

^{1}H-NMR (DMSO d_6): 1.40-2.20 (m, 13H), 2.35 (s, 2H), 6.80 (dd, 1H), 6.92 (d, 1H), 7.58 (d, 1H), 10.28 (s, 1H).

EXAMPLE 65: 3-cycloheptyl-1,2-benzisoxazol-6-ol

(48 %). mp 156°C.

^{1}H-NMR (DMSO d_6): 1.20-2.20 (m, 12H), 3.18 (m, 1H), 6.80 (d, 1H), 6.90 (s, 1H), 7.65 (d, 1H), 10.25 (s, 1H).

EXAMPLE 66: 3-cyclohexyl-1,2-benzisoxazol-6-ol

(37%). mp 181°C.

^{1}H-NMR (DMSO d_6): 1.10-2.10 (m, 10H), 3.02 (dt, 1H), 6.80 (dd, 1H), 6.90 (s, 1H), 7.68 (d, 1H), 10.25 (s, 1H).

EXAMPLE 67: 3-cyclohexyl-1,2-benzisoxazol-5,6-diol

Using the same procedure as in Example 49 but replacing 3-cyclohexyl-2-(6-methoxy-1H-indazol-3-yl) propanenitrile by 3-cyclohexyl-6-hydroxy-5-methoxybenzisoxazole, the expected product was obtained (48.4 %). mp 177°C.

^{1}H-NMR (DMSO d_6): 1.20-2.05 (m, 10H), 3.05 (dt, 1H), 6.92 (s, 1H), 7.05 (s, 1H), 9.55 (br s , 2H).

EXAMPLE 68: 3-cyclohexyl-6-(2-piperidin-1-yl-ethoxy)-1,2-benzisoxazole

A mixture of 3-cyclohexyl-1,2-benzisoxazol-6-ol (2.69 g, 12 mmol), 1-(2-chloroethyl)-piperidine hydrochloride (2.39 g, 13 mmol) and K_2CO_3 (3.59 g, 26 mmol) in CH_3CN (30 ml) was heated at reflux for 3h and stirred at room temperature overnight. The reaction mixture was poured into H_2O and extracted with EtOAc. The organic extract was washed with brine, dried (Na_2SO_4) and concentrated to give a residue (3.78 g). This residue was purified by flash chromatography (toluene/1,4-dioxane 8/2). Crystallisation from EtOH gave white crystals (0.53 g, 13.4 %). mp 69°C.

^{1}H-NMR (DMSO d_6): 1.20-2.10 (m, 16H), 2.30-2.50 (m, 4H), 2.70 (t, 2H), 2.95-3.05 (dt, 1H), 4.15 (t, 2H), 6.95 (dd, 1H), 7.25 (d, 1H), 7.75 (d, 1H).

EXAMPLE 69: Trihydroxybenzoin

Resorcinol (100 g, 0.91 mol) and 4-hydroxyphenylacetic acid (138.4 g, 0.91 mol) were dissolved into BF_3Et_2O (346 ml, 2.73 mol) under N_2. The mixture was stirred and heated at 50-60°C. After complete reaction, the mixture was cooled to room temperature and poured into a large volume of iced water. The crude product was filtered off and dried to yield trihydroxybenzoin (70 %). mp 211°C.

^{1}H-NMR (Acetone d_6): 4.12 (s, 2H), 6.78 (d, 2H), 6.91 (d, 1H), 7.13 (d, 2H), 7.54-7.6 (m, 2H), 8.21 (s, 1H), 8.35 (s, 1H), 8.70 (s, 1H).

EXAMPLE 70: 1-[2-hydroxy-4-(tetrahydro-2H-pyran-2-yloxy)phenyl]-2-[4-(tetrahydro-2H-pyran-2-yloxy)phenyl]ethanone

To a cooled (0-5°C) suspension of trihydroxybenzoin (100 g, 0.41 mol) and, as a catalyst, TsOH (0.062 g) in toluene (350 ml), a solution of dihydropyran (DHP) (150 ml, 1.64 mol) was slowly added. The reaction mixture became homogenous and was stirred at room temperature for 1h. Triethylamine was added and the solvent was evaporated under reduced pressure. The brown oil crystallized upon trituration with hot isopropanol (1.2 l) and a white solid was collected (182 g, 90 %).

^{1}H-NMR ($CDCl_3$): 1.40-2.05 (m, 12H), 3.40-3.60 (m, 2H), 3.65-3.90 (m, 2H), 4.05 (s, 2H), 5.30 (t, 1H), 5.40 (t, 1H), 6.46 (dd, 1H), 6.54 (d, 1H), 6.94 (d, 2H), 7.10 (d, 2H), 7.68 (d, 1H), 12.52 (s, 1H).

EXAMPLE 71: 1-[2-hydroxy-4-tetrahydro-2H-pyran-2-yloxy)phenyl]-2-[4-(tetrahydro-2H-pyran-2-yloxy)phenyl]ethanone oxime

A mixture of 1-[2-hydroxy-4-(tetrahydro-2H-pyran-2-yloxy)]-2-[4-(tetrahydro-2H-pyran-2-yloxy) phenyl]ethanone (5 g, 12 mmol) and H_2NOH, HCl (8.59 g, 12.3 mmol) was stirred for 24h in pyridine (65 ml) at room temperature. The reaction mixture was poured into a large volume of 99/1 H_2O/triethylamine and was then extracted with EtOAc. The organic solution was washed with brine. After drying over Na_2SO_4, EtOAc was evaporated. The residue was purified by flash column chromatography (toluene/1,4-dioxane 90/1 + TEA 1 %) to provide a colorless oil (5.05 g, 97 %).

^{1}H-NMR (DMSO d_6): 1.30-2.00 (m, 12H), 3.40-3.60 (m, 2H), 3.60-3.80 (m, 2H), 4.12 (s, 2H), 5.38 (t, 1H), 5.45 (t, 1H), 6.48 (d, 1H), 6.50 (s, 1H), 6.93 (d, 2H), 7.05-7.30 (m, 3H), 7.40 (d, 1H), 11.63 (s, 1H), 11.85 (s, 1H).

EXAMPLE 72: 6-(tetrahydro-2H-pyran-2-yloxy)-3-[4-(tetrahydro-2H-pyran-2-yloxy) benzyl]-1,2-benzisoxazole

Using the same procedure as in Example 61 but replacing 1-adamantyl-(2-chloro-4,6-dihydroxyphenyl) methanone oxime by 1-[2-hydroxy-4-(tetrahydro-2H-pyran-2-yloxy)phenyl]-2-[4-(tetrahydro-2H-pyran-2-yloxy)phenyl]ethanone oxime, the expected product was obtained (25 %).

^{1}H-NMR (DMSO d_6): 1.40-2.10 (m, 12H), 3.40 –3.85 (m, 4H), 4.25 (s, 2H), 5.39 (s, 1H), 5.61 (s, 1H), 6.90-7.10 (m, 3H), 7.20-7.35 (m, 3H), 7.55 (d, 1H)

EXAMPLE 73: 3-(4-hydroxybenzyl)-1,2-benzisoxazol-6-ol

6-(tetrahydro-2H-pyran-2-yloxy)-3-[4-(tetrahydro-2H-pyran-2-yloxy)benzyl]-1, 2-benzisoxazole (3.85 mmol) and paratoluenesulfonic acid (APTS, catalytic amount) were dissolved in methanol (20 ml). After reaction at 60-70°C for 3h, the reaction mixture was cooled to room temperature and poured into satured $NaHCO_3$ and extracted with EtOAc. After washing (H_2O) and drying ($MgSO_4$), the extract was concentrated. The crude product was purified by flash chromatography (toluene/1,4-dioxane 8/2) and crystallised to give an off-white crystal (0.58 g, 31%). mp 178°C.

^{1}H-NMR (DMSO d_6): 4.11 (s, 2H), 6.69 (d, 2H), 6.75 (dd, 1H), 6.90 (d, 1H), 7.13 (d, 2H), 7.48 (d, 1H), 9.80 (s, 2H).

PREPARATION OF BENZISOXAZOLE SULFAMATE (33)

Using the same procedure as in Example 33 but replacing 6-benzyloxy-3-cycloheptyl-1H-indazole by:

3-(1-adamantyl)-1,2-benzisoxazol-6-ol

3-cycloheptyl-1,2-benzisoxazol-6-ol

3-cyclohexyl-1,2-benzisoxazol-6-ol

the following compounds were respectively obtained:

EXAMPLE 74: 3-(1-adamantyl)-1,2-benzisoxazol-6-yl sulfamate

(82 %). mp 87°C.

^{1}H-NMR (DMSO d_6): 1.50-2.45 (m, 15H), 7.28 (dd, 1H), 7.63 (d, 1H), 7.96 (d, 1H), 8.15 (s, 2H).

EXAMPLE 75: 3-cycloheptyl-1,2-benzisoxazol-6-yl sulfamate

(54 %). mp 82°C.

^{1}H-NMR (DMSO d_6): 1.40-2.10 (m, 12H), 3.32 (m, 1H), 7.30 (d, 1H), 7.60 (d, 1H), 8.05 (d, 1H), 8.15 (s, 2H).

EXAMPLE 76: 3-cyclohexyl-1,2-benzisoxazol-6-yl sulfamate

(46 %). mp 145°C.

^{1}H-NMR (DMSO d_6): 1.20-2.20 (m, 10H), 3.15 (dt, 1H), 7.25 (dd, 1H), 7.62 (d, 1H), 8.05 (d, 1H), 8.15 (s, 2H).

PREPARATION OF BENZISOXAZOLES (36) (37) and (38)

EXAMPLE 77: 2-(Z/E)-(6-methoxy-1,2-benzisoxazol-3-yl)-3-(4-methoxyphenyl)prop-2-enenitrile

A solution of 40 % KOH/H_2O (3 ml) and EtOH (4,8 ml) was added slowly to a heterogenous mixture of (6-methoxy-1,2-benzisoxazol-3-yl)acetonitrile (2.4 g, 12.7 mmoles), prepared following H. Uno (*Chem. Pharm. Bull.*, 24 (4), 632-643, 1976), 4-methoxybenzaldehyde (1.1 eq, 14 mmoles, 1.8 g) and EtOH (24 ml) at room temperature. The mixture was stirred at room temperature for 1h and the precipitate was filtered under vacuum, washed with water and EtOH, to give pure 2-(Z/E)-(6-methoxy-1,2-benzisoxazol-2-yl)-3-(4-methoxy-phenyl)-prop-2-enenitrile (3.15 g, 81 %).

^{1}H-NMR (acetone d_6) = 3.94 (s, 3H), 3.97 (s, 3H), 7.08 (dd, 1H), 7.15 (d, 2H), 8.05-8.30 (m, 4H).

Using the same procedure but replacing 4-methoxybenzaldehyde by 4-hydroxybenzaldehyde the following compound was obtained:

EXAMPLE 78: 2-(Z/E)-3-(4-hydroxyphenyl)-2-(6-methoxy-1,2-benzisoxazol-3-yl)prop-2-enenitrile

(86 %). mp > 380°C.

^{1}H-NMR (DMSO d_6): 3.85 (s, 3H), 6.15 (d, 2H), 7.00 (d, 1H), 7.25 (s, 1H), 7.70 (s, 3H), 8.00 (d, 1H).

EXAMPLE 79: 2-(6-methoxy-1,2-benzisoxazol-3-yl)-3-(4-methoxyphenyl) propanenitrile

$NaBH_4$ (1.05 eq, 0.2 g, 5.15 mmoles) was added to an heterogenous solution of 2-(Z/E)-(6-methoxy-1,2-benzisoxazol-3-yl)-3-(4-methoxy-phenyl)prop-2-enenitrile

(1.5 g, 4.9 mmoles) and EtOH (20 ml). The mixture was heated at 50°C for 1 h, and acidified at pH 1 with HCl 1N, extracted with AcOEt, dried over Na_2SO_4 and concentrated under vacuum to give pure 2-(6-methoxy-1,2-benzisoxazol-3-yl)-3-(4-methoxyphenyl) propanenitrile (1.5 g, 100 %).

^{1}H-NMR ($CDCl_3$) = 3.35 (d, 2H), 3.80 (s, 3H), 3.90 (s, 3H), 4.45 (t, 1H), 6.84 (d, 2H), 6.93 (dd, 1H), 7.02 (d, 1H), 7.04 (d, 2H), 7.50 (d, 1H).

EXAMPLE 80: 2-(6-hydroxy-1,2-benzisoxazol-3-yl)-3-(4-hydroxyphenyl) propanenitrile

To a solution of 2-(6-methoxy-1,2-benzisoxazol-3-yl)-3-(4-methoxyphenyl)propanenitrile (1.5 g, 4.9 mmoles) in CH_2Cl_2 (100 ml) under N_2, was added BBr_3 1M in CH_2Cl_2 (4 eq, 20 ml). The mixture was refluxed for 2h, poured into water and extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated under vacuum to give the crude product. Purification by flash chromatography (CH_2Cl_2/MeOH 98/2) and crystallisation from EtOH yielded the expected crystals (850 mg, 62 %). mp 214°C.

^{1}H-NMR (DMSO d_6): 3.25 (m, 2H), 5.10 (t, 1H), 6.65 (d, 2H), 6.90 (d, 1H), 7.00 (d, 2H), 7.06 (s, 1H), 7.70 (d, 1H), 9.35 (s, 1H), 10.50 (s, 1H).

Using the same procedure as in Example 77 but replacing 4-methoxybenzaldehyde by:

3-fluoro-4-methoxybenzaldehyde
4-methoxy-2-methyl-benzaldehyde
3-methoxy-benzaldehyde
4-fluorobenzaldehyde
cyclohexanal
3,4-dimethoxybenzaldehyde

and then using the same procedures as described in Examples 79 and 80, the following compounds were respectively obtained:

EXAMPLE 81: 2-(6-hydroxy-1,2-benzisoxazol-3-yl)-3-(3-fluoro-4-hydroxyphenyl)- propanenitrile

(56 %). mp 201°C.

^{1}H-NMR (DMSO d_6) : 3.25 (m, 2H), 5.15 (t, 1H), 6.70-7.20 (m, 5H), 7.72 (d, 1H), 9.82 (s, 1H), 10.55 (s, 1H).

EXAMPLE 82: 2-(6-methoxy-1,2-benzisoxazol-3-yl)-3-(4-hydroxy-2-methylphenyl)- propanenitrile

(15 %). mp 131°C.

^{1}H-NMR (acetone d_6): 2.11 (s, 3H), 3.28 (d, 2H), 3.80 (s, 3H), 4.72 (t, 1H), 6.40-6.60 (m, 2H), 6.85 (dd, 1H), 7.00 (d, 1H), 7.10 (d, 1H), 8.09 (s, 1H).

EXAMPLE 83: 2-(6-hydroxy-1,2-benzisoxazol-3-yl)-3-(3-hydroxyphenyl) propanenitrile

(20%).

^{1}H-NMR (acetone d_6): 3.25-3.60 (m, 2H), 4.90 (t, 1H), 6.60-7.25 (m, 6H), 7.70 (d, 1H), 8.80 (br s,1H).

EXAMPLE 84: 2-(6-hydroxy-1,2-benzisoxazol-3-yl)-3-(4-fluorophenyl) propanenitrile

(35%). mp 152°C.

^{1}H-NMR (DMSO d_6): 2.40-2.70 (m, 2H), 3.95 (t, 1H), 4.25 (s, 1H), 5.90-6.50 (m, 6H), 6.70 (d, 1H).

EXAMPLE 85: 2-(6-hydroxy-2-benzisoxazol-3-yl)-3-cyclohexyl-propanenitrile

(63 %). mp 111°C.

^{1}H-NMR (acetone d_6): 0.80-2.10 (m, 13H), 4.56 (dd, 1H), 6.90 (dd, 2H), 7.02 (d, 1H), 7.67 (d, 1H), 9.38 (s, 1H).

EXAMPLE 86: 2-(6-hydroxy-1,2-benzisoxazol-3-yl)-3-(3, 4-dihydroxyphenyl) propanenitrile

(56 %). mp 154°C.

^{1}H-NMR (DMSO d_6): 3.00-3.35 (m, 2H), 5.06 (t, 1H), 6.50 (dd, 1H), 6.55-6.75 (m, 2H), 6.90 (dd, 1H), 7.00 (dd, 1H), 7.70 (d, 1H), 8.90 (br s, 1H).

PREPARATION OF BENZISOXAZOLES (40) (41) (42) and (43)

EXAMPLE 87: 3-methyl-6-[(tert-butyl(dimethyl)silyl)oxy]-1, 2-benzisoxazole

3-methyl-1,2-benzisoxazol-6-ol (10 g, 67 mmoles) (prepared following M.A. Elkasaby, *Indian J. Chem.*, 1987, 26, 620) and DMF (50 ml) were added to a mixture of tert-butyldimethylsilyl chloride (1.05 eq, 10.6 g), imidazole (2.5 eq, 11.4 g) and DMF (100 ml) under N_2. The mixture was then stirred at room temperature for 1h, poured into water and extracted with ethyl acetate, dried over Na_2SO_4, filtered and concentrated under vacuum to give a crude product. Flash chromatography (AcOEt/Toluene 18/85 with 0.1 % TEA) gave 6-[(tert-butyl(dimethyl)silyl) oxy]-3-methyl-1,2-benzisoxazole (17.1 g, 97 %).

^{1}H-NMR ($CDCl_3$ d_1): 0.20 (s, 6H), 1.00 (s, 9H), 2.60 (s, 3H), 6.80 (dd, 1H), 6.95 (d, 1H), 7.45 (d, 1H).

EXAMPLE 88: 3-(bromomethyl)-6-[(tert-butyl(dimethyl)silyl)oxy]-1, 2-benzisoxazole

NBS (12.7 g, 71.5 mmoles) and benzyl peroxide (1.6 g, 6.5 mmoles) were added to a mixture of 3-methyl-6-[(tert-butyl(dimethyl)silyl)oxy]-1,2-benzisoxazole (17.1 g, 65 mmoles) and CCl_4 (200 ml). The mixture was refluxed overnight and the precipitate was filtered, washed with CCl_4 and purified by flash chromatography (AcOEt/Toluene 1/9 with 0.1 % TEA) to give 3-(bromomethyl)-6-[(tert-butyl(dimethyl)silyl)oxy]-1,2-benzisoxazole (15.1 g, 68 %).

^{1}H-NMR ($CDCl_3$ d_1): 0.25 (s, 6H), 1.00 (s, 9H), 4.57 (s, 2H), 6.88 (dd, 1H), 7.02 (d, 1H), 7.55 (d, 1H).

EXAMPLE 89: 3-(6-[(tert-butyl)silyl)oxy]-1,2-benzisoxazol-3-yl)-2-(4-methoxyphenyl) propanenitrile

A solution of n-BuLi 2.0M in THF (9.7 mmoles) was slowly added to a solution of diisopropylamine (1.3 ml, 1.05 eq) and dry THF (10 ml) at -20°C under N_2. The mixture was stirred for 30 min at -20°C, then 4-methoxybenzonitrile (1.3 g, 8.8 mmoles) and dry THF (10 ml) were slowly added at -78°C. The mixture was stirred for 30 min at -78°C, then 3-(bromomethyl)-6-[(tert-butyl(dimethyl)silyl)oxy]-1,2-benzisoxazole (3 g, 8.8 mmoles) and dry THF (10 ml) were slowly added. The mixture was then stirred for 30 min at room temperature, poured into water, extracted with AcOEt, dried over Na_2SO_4, and purified by flash chromatography (AcOEt/Heptane 2/8 with 0.1 % TEA) to give 3-(6-[(tert-butyl)dimethylsilyl)oxy]-1,2-benzisoxazol-3-yl)-2-(4-methoxyphenyl) propanenitrile (1 g, 28 %).

^{1}H-NMR ($CDCl_3$ d_1): 0.20 (s, 6H), 1.00 (s, 9H), 3.25-3.65 (m, 2H), 3.70-4.48 (t, 1H), 6.80-7.60 (m, 7H).

EXAMPLE 90: 3-(6-hydroxy-1,2-benzisoxazol-3-yl)-2-(4-methoxyphenyl)propanenitrile

A solution of nBu_4F 1N in THF was added to a mixture of 3-(6-[(tert-butyl)silyl)oxy]-1,2-benzisoxazol-3-yl)-2-(4-methoxyphenyl)propanenitrile (1.0 g, 2.45 mmoles) in dry THF (20 ml) at room temperature. The mixture was then stirred at room temperature for 2h and then poured into water and extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude product was purified by flash chromatography (AcOEt/Toluene 2/8) and crystallisation from MeOH/cyclohexane yielded the expected product (210 mg, 30 %).

^{1}H-NMR (DMSO d_6) = 3.00-3.50 (m, 2H), 5.05 (t, 1H), 6.60 (d, 2H), 6.90 (dd, 1H), 7.00 (d,2H), 7.05 (s, 1H), 7.70 (d, 1H), 9.40 (s, 1H), 10.50 (s, 1H).

PREPARATION OF BENZISOTHIAZOLES (45) and (46)

EXAMPLE 91: cyclohexyl (4-benzyloxy-2-benzylthiophenyl) methanone

A solution of phenylmethanethiol (2.35 ml, 20 mmoles) in THF (10 ml) was slowly added to a mixture of potassium tert-butoxide (2.24 g, 20 mmoles) in THF (80 ml) under N_2 at room temperature. The mixture was stirred for 15 min at room temperature and cyclohexyl (4-benzyloxy-2-fluorophenyl) methanone (6.5 g, 20 mmoles) in THF (10 ml) was slowly added. The mixture was heated for 2h at 50°C and poured into an aqueous solution of NH_4Cl, extracted with ethyl acetate, dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography (Heptane/AcOEt 90/10 with 0.1 % TEA) to give cyclohexyl (4-benzyloxy-2-benzylthiophenyl) methanone (8.3 g, 100 %).

^{1}H-RMN (DMSO d_6): 1.00-1.85 (m, 10H), 3.10-3.30 (m, 1H), 4.15 (s, 2H), 5.19 (s, 1H), 6.85 (dd, 1H), 7.05 (d, 1H), 7.15-7.60 (m, 10H), 7.90 (d, 1H).

EXAMPLE 92: 6-benzyloxy-3-cyclohexyl-1,2-benzisothiazole

Sulfuryl chloride (1.77 ml, 2.2 mmoles) was slowly added to a solution of cyclohexyl (4-benzyloxy-2-benzylthiophenyl) methanone (8.77 g, 21 mmoles) in CH_2Cl_2 (80 ml) at 0°C. The mixture was stirred for 2h at room temperature and then concentrated under vacuum. THF (80 ml) was added to the mixture and then EtOH (80 ml) saturated with ammoniac was slowly added at 0°C. The mixture was stirred overnight at room temperature, poured into water, extracted with ethyl acetate, dried over Na_2SO_4, filtered and concentrated under vacuum to give a crude product. Flash chromatography (heptane/AcOEt 98/2) gave 6-benzyloxy-3-cyclohexyl-1,2-benzisothiazole (3.55 g, 52 %).

^{1}H-NMR (DMSO d_6): 1.10 to 2.00 (m, 10H), 3.25 (dt, 1H), 5.20 (s, 2H), 7.12 (dd, 1H), 7.25 to 7.55 (m, 5H), 7.75 (d, 1H), 8.02 (d, 1H).

EXAMPLE 93: 3-cyclohexyl-1,2-benzisothiazol-6-ol

A solution of boron tribromide 1M in CH_2Cl_2 (11.9 ml, 11.9 mmoles) was slowly added to a solution of 6-benzyloxy-3-cyclohexyl-1,2-benzisothiazole (3.5 g, 10 mmoles) in CH_2Cl_2 (50 ml) at 0°C. The mixture was stirred at room temperature for 15 min and poured into water. The precipitate was filtered, dried and crystallised from EtOH to give pure 3-cyclohexyl-1,2-benzisothiazol-6-ol (940 mg, 40.3 %). mp 190°C.

^{1}H-NMR (DMSO d_6): 1.10 to 2.10 (m, 10H), 3.20 (dt, 1H), 6.95 (dd, 1H), 7.40 (d, 1H), 7.93 (d, 1H), 10.18 (s, 1H).

Using the same procedures as in Examples 91 to 93 but replacing cyclohexyl (4-benzyloxy-2-fluorophenyl) methanone by cyclopentyl (4-benzyloxy-2-fluorophenyl) methanone, the following compound was obtained:

EXAMPLE 94: 3-cyclopentyl-1,2-benzisothiazol-6-ol

mp 130°C.

^{1}H-NMR (DMSO d_6): 1.50 to 2.20 (m, 8H), 3.62 (m, 1H), 6.95 (dd, 1H), 7.35 (d, 1H), 7.92 (d, 1H), 10.18 (s, 1H).

PREPARATION OF BENZISOTHIAZOLE SULFAMATES (47) and (48)

EXAMPLE 95: 3-cyclohexyl-1,2-benzisothiazol-6-yl sulfamate

Sulfamoyl chloride (780 mg, 6.76 mmol) was added by portions to a mixture of 3-cyclohexyl-1,2-benzisothiazol-6-ol (790 mg, 3.38 mmoles) and dimethylacetamide (15 ml) at 0°C. The mixture was stirred for 30 min at 0°C and then at room temperature overnight, poured into water and extracted with ethyl acetate, dried over Na_2SO_4 and concentrated under vacuum.

The crude product was purified by flash chromatography (Toluene/1,4-dioxan 9/1) and crystallised from EtOH/pentane to give the expected product (620 mg, 59 %). mp 150°C.

^{1}H-NMR (DMSO d_6): 1.20 to 2.05 (m, 10H), 3.30 (m, 1H), 7.40 (dd, 1H), 8.10 (d, 1H), 8.15 (s, 2H), 8.25 (d, 1H).

Using the same procedure but replacing 3-cyclohexyl-1,2-benzisothiazol-6-ol by 3-cyclopentyl-1,2-benzisothiazol-6-ol, the following compound was obtained:

EXAMPLE 96: 3-cyclopentyl-1,2-benzisothiazol-6-yl sulfamate

mp 132°C.

^{1}H-NMR (DMSO d_6): 1.55 to 2.25 (m, 8H), 3.65-3.85 (m, 1H), 7.4 (dd, 1H), 8.10 (s, 1H), 8.15 (s, 2H), 8.23 (d, 1H).

EXAMPLE 97: 3-cyclohexyl-1,1-dioxido-1,2-benzisothiazol-6-yl sulfamate

Hydrogen peroxide (0.6 ml) was slowly added to a mixture of sulfamic acid, 3-cyclohexyl-1,2-benzisothiazol-6-yl-ester (1 g, 3.2 mmoles), trifluoroacetic acid (2 ml) and dichloromethane (20 ml) at room temperature. The mixture was then stirred for 2h and then poured into water. The precipitate was filtered and purified by flash chromatography (Toluene/1,4-dioxan 85/15) to give after crystallisation a solid (70 mg, 6 %). mp 170°C.

^{1}H-NMR (DMSO d_6): 1.10 to 2.20 (m, 10H), 7.25 (dd, 1H), 8.07 (d, 1H), 8.25 (s, 1H), 8.43 (s, 1H).

PHARMACOLOGICAL TEST RESULTS

SUBTYPE ESTROGEN RECEPTOR BINDING *IN VITRO*

The method was derived from those described for rat uterus (Botella J. et al, J Endocrinol Invest, 1990, 13: 905-910) and human Ishikawa cell (Botella J., J Steroid Biochem Molec Biol, 1995, 55: 77-84) estrogen receptors. Relative binding affinities (RBA) were determined by competitive radiometric binding assays, using purified full-length recombinant human ERα and ERβ (PanVera, Madison, WI). Receptors were incubated in Tris buffer (10mM Tris, 2 mM DTT, 1 mg/BSA, 10 % Glycerol, pH 7.5 with HCl) at 4 °C for 18-20 hours with 2 nM of [^{3}H]-E_2 with or without increasing concentrations of test compound from 1 nM to 10 µM. Non-specific binding was measured in the presence of a 500-fold excess of unlabeled E_2. Separation of bound and free ^{3}H-E_2 fractions was achieved with dextran (0.25 %) coated charcoal (2.5 %) in Tris-EDTA buffer. After shaking for a few seconds and centrifugation at 1500 g and 4°C for 10 minutes, 150 µl/well of Optiphase 'Super Mix' scintillation liquid was mixed with 50 µl of supernatant of each sample and the radioactivity was measured in a MicroBeta counter (Wallac, Turku, Finland). Data were evaluated by a sigmoidal dose-response curve (Prism, GraphPad Software Inc.) to estimate the concentration of competitor at half-maximal specific binding (IC_{50}). RBA of each competitor was calculated as the ratio of IC_{50}s of E_2 and competitor, and the RBA value for E_2 was arbitrarily set at 100 %. The selectivity for ERα and ERβ was obtained from the ratio R of the IC_{50} for ERα to the IC_{50} for ERβ for each test compound.

Table 1: Estrogen Receptor α and β binding assays

Compound	ER	IC_{50} (nM)			RBA (%)			n	R (IC_{50}s)
		Mean	±	S.E.M	Mean	±	S.E.M		α/β
E_2	α	1.6	±	0.1	100.0	±		59	0.8
	β	2.1	±	0.1	100.0	±		59	
Ex 23	α	1332.0	±	267.8	0.2	±	0.05	4	31.9
	β	41.8	±	7.1	10.4	±	4.0	4	
Ex 24	α	159.1	±	23.7	1.2	±	0.2	9	15.6
	β	10.2	±	0.9	24.6	±	4.3	9	
Ex 31	α	119.0	±	45.2	3.1	±	0.8	4	3.3
	β	36.2	±	18.7	17.7	±	5.1	4	
Ex 35	α	2686.0	±	593.0	0.1	±	0.02	4	10.8
	β	248.0	±	48.7	0.9	±	0.1	4	
Ex 40	α	1483.0	±	1177.6	0.1	±	0.02	5	7.9
	β	187.6	±	34.0	1.0	±	0.2	5	
Ex 65	α	75.3	±	5.4	2.5	±	0.6	4	3.7
	β	20.2	±	4.2	13.2	±	3.1	4	
Ex 66	α	260.0	±	40.1	1.1	±	0.2	4	5.8
	β	44.6	±	7.7	9.4	±	3.1	4	

Compound	ER	IC$_{50}$ (nM)			RBA (%)			n	R (IC$_{50}$s)
		Mean	±	S.E.M	Mean	±	S.E.M		αβ
Ex 73	α	2912.3	±	317.8	0.1	±	0.0	3	6.0
	β	484.8	±	157.7	1.0	±	0.3	4	
Ex 80	α	67.5	±	5.0	3.4	±	0.4	8	9.0
	β	7.5	±	0.7	43.0	±	7.8	8	
Ex 81	α	139.3	±	33.9	2.4	±	0.7	4	9.7
	β	14.4	±	5.3	35.9	±	14.0	4	
Ex 84	α	2300.8	±	445.6	0.1	±	0.03	4	18.7
	β	122.9	±	25.9	2.5	±	0.4	4	
Ex 86	α	1894.0	±	364.8	0.2	±	0.03	4	14.1
	β	134.8	±	31.0	2.4	±	0.4	4	
Ex 93	α	88.6	±	11.7	1.3	±	0.2	4	2.3
	β	37.8	±	5.4	5.1	±	0.8	4	

n = number of assays

ESTROGENIC AND ANTI-ESTROGENIC ACTIVITIES *IN VITRO*

The estrogenic and anti-estrogenic potentials of new compounds were evaluated using the induction of alkaline phosphatase (APase) activity, an estrogen specific response in human endometrial adenocarcinoma Ishikawa cells (Botella J., J Steroid Biochem Molec Biol, 1995, 55: 77-84; Littlefield et al., Endocrinology, 1990, 127: 2757-2762).

Ishikawa cells were routinely grown as monolayers in Dulbecco's Modified Eagle's medium (DMEM) containing 4 mM Glutamax I and supplemented with 10 % of decomplemented fetal calf serum (dFCS) and antibiotics. They were maintained in a humidified atmosphere of 5 % CO_2 and 95 % air, at 37 ± 0.1° C. Stocks were performed once a week to maintain continuous exponential growth.

For studies, Ishikawa cells were plated into 96-well microplates. The next day, the medium was changed to a phenol red-free DMEM containing 5 % dFCS stripped of endogenous estrogens by dextran coated charcoal treatment. Twenty-four hours later, the medium was renewed and the relevant controls and test compounds, diluted appropriately in estrogen-free DMEM, were added either alone (estrogenic effect) or with 10^{-8} M E_2 (anti-estrogenic effect) to the plated cells and incubated for four days. For each compound, the tested concentrations ranged from 10^{-12} M to 10^{-5} M, and the final vehicle concentration did not exceed 0.1 %.

At the end of the incubation period, APase activity was assayed by a method involving the hydrolysis of p-nitrophenyl phosphate to p-nitrophenol at pH 9.8 and spectrophotometric determination of the product at 405 nm.

In brief, the microplates were first rinsed twice with cold phosphate buffered solution and then placed at -80° C for at least 15 minutes. After thawing at room temperature for 5-10 minutes, the plates were put on ice and 50 µl ice-cold solution containing 5 mM p-nitrophenyl phosphate was added to each well. The plates were warmed to room temperature to allow for the development of the enzymatic reaction (t_0). After a 15 to 60 minute incubation period, the intensity of the yellow color generated by the production of p-nitrophenol was measured into each well at 405 nm using a microplate reader (Wallac, model 1420 Victor[2]).

For each tested concentration, APase activity, reflected by absorbance, was first expressed as fold increase over control (FI) and then as percentage of E_2 activity (10^{-8} M) chosen equal to 100 %. Sigmoidal dose-response curves were plotted and EC_{50} (estrogenic effect) and IC_{50} (anti-estrogenic effect) values were calculated for each compound.

Table 2: Estrogenic and anti-estrogenic activities *In vitro*

Compound	Estrogenic activity				Anti-estrogenic activity			
	EC_{50} (nM)	±	S.E.M	n	IC_{50} (nM)	±	S.E.M	n
E_2	0.1	±	0.05	3		±		
Ex 23	1695	±	168	4	ND	±		1
Ex 24	136.3	±	1.2	4	ND	±		1

Compound	Estrogenic activity				Anti-estrogenic activity			
	EC_{50} (nM)	±	S.E.M	n	IC_{50} (nM)	±	S.E.M	n
Ex 31	30.8	±	0.5	4	ND	±		1
Ex 35	373.8	±	43.0	3	ND	±		1
Ex 40	131.9	±	4.7	4	ND	±		1
Ex 65	51.7	±	6.2	4	ND	±		1
Ex 66	220.6	±	14.0	4	ND	±		1
Ex 73	ND	±		4	ND	±		1
Ex 80	147.3	±	39.9	4	ND	±		4
Ex 81	ND	±		4	ND	±		1
Ex 84	322.5	±	20	4	ND	±		2
Ex 86	ND	±		4	ND	±		1
Ex 93	123.8	±	8.9	4	-	±		1

n = number of assays; ND = not detected; - not determined

PROLIFERATIVE ACTIVITY *IN VITRO*

The proliferative effect of the compounds of the invention was evaluated on human breast cancer cell line MCF-7 by measuring the number of viable cells after 6 days of treatment.

MCF-7 cells were routinely cultured as monolayers in Dulbecco's modified Eagle's medium (DMEM) containing 4 mM Glutamax and 4.5 g/l glucose and supplemented with 5 % (v/v) decomplemented fetal calf serum (dFCS) and antibiotics.

Cells were plated at 2.10^6 cells/75 cm^2 flasks and incubated at 37° C in a humidified atmosphere containing 5 % CO_2. They were passaged once weekly to maintain continuous exponential growth. Forty eight hours before the start of an experiment, near-confluent cells were changed to a phenol red free DMEM containing 5 % steroid-stripped dFCS by dextran coated charcoal treatment (DCC-DMEM). On the day of the experiment, cells were harvested by brief exposure to trypsin and plated in DCC-DMEM in 96-well microplates at a density of 4.10^3 cells/well. The next day, the medium was renewed and test compounds, diluted appropriately in estrogen-free DMEM, were added and incubated for six days. For each compound, the tested concentrations ranged from 10^{-12} M to 10^{-5} M and the final vehicle concentration did not exceed 0.1 % (v/v). At the end of the incubation period, cell proliferation was evaluated by quantitation of the cellular ATP content which signals the presence of metabolically active cells.

ATP assay

The assay, based on the ATP-dependent luciferase reaction, enables generation of a luminescent signal proportional to the amount of ATP present. As there is a linear relationship between the amount of ATP and the number of viable cells present in culture, the luminescent signal allowed to precisely evaluate cell proliferation (Crouch, S.P.M. et al. J. Immunol. Meth., 1993, 160, 81; Kangas, L. et al. Med. Biol. 1984, 62, 338; Petty, R.D. et al. J. Biolum. Chemilum. 1995, 10, 29).

In brief, the microplates were inverted to discard the culture medium and 100 µl of fresh medium was added into each well. The microplates were equilibrated at room temperature for approximately 30 minutes. 100 µl of luciferase reagent was added into each well and contents were mixed for 2 minutes to induce cell lysis. The plates were incubated at room temperature for 10 minutes to stabilize luminescence signal.

Luminescence was recorded using a microplate reader (Wallac, model 1420 Victor[2]) and results were expressed as percentage of the control luminescence. Sigmoidal dose-response curves were plotted and EC_{50} values were calculated for each compound in order to evaluate their proliferative potency.

Table 3: Proliferative activities in MCF-7 cells

Compound	Cell proliferation					
	EC_{50} (nM)	±	S.E.M	n	Effect at 10^{-8} M (% of control)	Effect at 10^{-6} M (% of control)
E_2	0.01	±	0	4	211.6	204.7
Ex 23	376.5	±	70.1	3	81.7	175.7
Ex 24	18.5	±	1.8	3	89.9	142.8
Ex 31	3.7	±	0.7	4	138.8	146.3
Ex 35	58.2	±	15.0	4	94.4	162.6
Ex 40	11.5	±	2.8	4	106.9	151.7
Ex 65	27.6	±	2.0	4	123.1	259.5
Ex 66	25.4	±	4.0	4	100.3	148.7
Ex 73	365.1	±	126.1	4	94.2	133.7
Ex 80	45.2	±	25.6	4	109.5	147.2
Ex 81	634.8	±	284.9	4	86.8	117.3
Ex 84	77.9	±	4.1	4	97.0	285.8
Ex 86	465.7	±	34.0	4	85.6	139.4
Ex 93	16.1	±	2.6	4	115.8	155.8

ESTROGENIC ACTIVITY *IN VIVO*

Prepubescent female rats were orally treated at 3 mg/rat/day for 3 days. On the day following the last treatment, uteri were removed and wet weights were recorded.

The results are expressed as % of stimulation of uterus weight in comparison with vehicles.

The compounds of examples 23, 31, 35, 66, 73, 84, 86 and 93 exhibited a marked selectivity for the human recombinant estrogen receptor β and a weak estrogenic effect in alkaline phosphatase activity in the Ishikawa cell model.

These compounds were accordingly selected to check their *in vitro* estrogenicity. The aim of this study was to test these compounds in comparison with tamoxifen (TAM), with an ERβ selective standard agonist: DPN or 2,3-bis-(4 -hydroxyphenyl)propionitrile (Meyers M J, J Med Chem 2001, 44; 24, 4230-4251) and with an ERα selective standard agonist: PPT or 1,3,5-tris-(4-hydroxyphenyl) -4-propyl-1H-pyrazole (Stauffer S R, J Med Chem 2000, 43; 4934-4947), when 17β-estradiol (E2) at 3 mg/rat/day p.o. is taken as the standard reference.

Table 4: Estrogenic activity of in vitro selected compounds

Compound	% stimulation vs vehicle	Number of animals
DPN	358	8
E_2	526	8
Ex 23	12	8
Ex 24	101	8
Ex 31	468	6
Ex 35	38	8
Ex 40	41	8
Ex 65	84	8
Ex 66	31	8
Ex 73	52	8
Ex 80	70	8
Ex 81	49	8
Ex 84	24	8
Ex 86	25	8
Ex 93	88	8
PPT	96	6
TAM	206	8

These results show that the compound of Example 23 is a potent ligand to estrogen receptor beta, with a weak *in vivo* estrogenic activity after oral administration.

DOSE-RELATED UTEROTROPHIC ACTIVITY *IN VIVO*

Prepubescent female rats were orally treated with 0.3; 1; 3 or 10 mg/rat/day for 3 days. On the day following the last treatment, uteri were removed and wet weights were recorded.

The results are expressed as % of stimulation of uterus weight in comparison with vehicles. 17β-estradiol (E2) at 3 mg/rat/day p.o. is taken as the standard reference.

<u>Table 5</u>: Dose-related uterotrophic activity *in vivo*

Compound	Dosage (mg/rat/day)	% stimulation vs vehicle	Number of animals
E_2	3	333	8
Ex 23	0.3	-13	8
Ex 23	1	-5	8
Ex 23	3	-4	8
Ex 23	10	20	8

The compound of example 23 has been selected as a potential good candidate for treating estrogenic dependent diseases because of the lack of uterotrophicity up to a 3 mg/animal/day dosage, after oral administration.

EFFECT OF COMPOUNDS ON HOT FLUSH MODEL *IN VIVO*

According to Berendsen et al. (Eur. J. Pharmacol., 2003, 482; 329-33), tail skin temperature of ovariectomized rats may serve as a useful tool for selection of compounds that are of potential use in the treatment of hot flushes in postmenopausal women. The aim of this study was to evaluate the effect of the compound of Example 23 over 4 days on tail skin temperature in ovariectomized rats. 17β-estradiol, the standard reference, was administered by oral route at 1 mg/rat/day over 13 consecutive days (Watanabe N. et al, 2003). Twenty IOPS Wistar female rats from Charles River France, weighing 176 to 200 g on arrival, were used for the study. Rats were accommodated in groups of four in stainless steel mesh cages. After implantation of telemetric transmitters (TA10TA-F40, Data Sciences International) until the end of the study, they were housed in groups of two in macrolon cages and maintained on a 14-10 hours light/dark cycle. Standard environmental conditions for this species were regularly controlled. Animals were allowed free access to a specific estrogen-free diet of Harlan Teklad 2016 pellets from HARLAN. They were allowed free access to filtered and softened tap water. Water was dispensed ad libitum via automatic deliveries in metallic cages and in plastic bottles in macrolon cages. Rats were then ovariectomized and left undisturbed for at least 2 weeks. After this hormonal rest period, tail skin temperature was monitored during the same period and animals were randomized into 3 groups based on mean temperature. The first group was "ovariectomy control group", the second group was "estradiol group" to confirm the estrogen activity on tail temperature and the third group was "Ex 23 group" to test the activity of this product on temperature. Body weights were then recorded on the first day of treatment and at the end of study.

The Results are expressed as % of stimulation of uterus weight in comparison with vehicles. 17β-estradiol (E2) at 3 mg/rat/day is taken as the standard reference.

Table 6: Effect of Ex 23 on tail skin temperature (TST) in ovariectomized rats

Compound	Dosage (mg/rat/day)	TST Variation day 1 vs day 0 (C°)	TST Variation day 4 vs day 0 (C°)	TST Variation day 7 vs day 0 (C°)	n
vehicle	-	-0.6	-0.6	-0.7	4
E_2	3	-4.8	-3.5	-5.6	4
Ex 23	0.3	-0.8	-2.1	-1.9	10

The compound of example 23 decreased tail skin temperature of ovariectomized rat, without deleterious side-effects on uteri, unlike estradiol activity on body weight or uteri (as seen below).

Table 7: Effect of Ex 23 on body weight and uteri, after one week treatment

Compound	Dosage (mg/rat/day)	Uteri weight (% increase vs vehicle)	Body weights (% increase vs vehicle)	n
vehicle	-	-	-	4
E_2	3	273	- 10	4
Ex 23	0.3	- 2.6	+ 4.4	10

EFFECT OF COMPOUNDS ON BONE AND CARDIOVASCULAR PARAMETERS IN VIVO

The ovariectomized rat is a mandatory model for preclinical evaluation of new compounds used for the prevention of bone loss (osteoporosis). Female Wistar - derived OFA strain rats from IFFA CREDO (France) were ovariectomized or sham operated as intact control. Upon arrival, they were housed in metal hanging cages in groups of 3 or 4 per cage and had ad libitum access to food and water for one week. After a one week acclimation period, daily dosing was carried out with the compound of interest or 17β-estradiol.

During the study, plasma samples were taken to allow lipid parameter assay: triglycerides, free cholesterol, total cholesterol, HDL, LDL, VLDL, apoliporotein A and B100; bone metabolism parameters such as: DPD, Ca^{2+}, collagen type I and II C-telopeptide fragments; and urinary bone markers such as Ca^{2+}, and inorganic phosphate. All assays were carried out following the manufacturer's recommendations.

To allow bone mineral density measurement of individual lumbar segments, lumbar high resolution or whole body dual energy X-ray absorptiometry procedures were carried out during the study on isoflurane anesthetized animals.

ANTIDEPRESSANT ACTIVITY OF COMPOUNDS

Antidepressant effect of estradiol was recently reported in studies using ER β KO mice model. In addition, ER β localization in dorsal *raphe nucleus* area in rat has been described. The gold standard test for antidepressant potency of compound consist in the forced swimming test, in this experiment antidepressants could be distinguished from psychostimulants which decreased immobility at doses which increased general activity. In order to investigate the putative antidepressant potency of the compounds reported here, the forced swimming test was performed according to the following design. The animals were housed six per cage under standard colony conditions, with a 12 h light/dark cycle and *ad libitum* food and water. They were allowed to acclimatize to the colony for at least 7 days prior to any experimentation. For subcutaneous administration, the compound of Example 23 was dissolved in olive oil and diluted to the desired concentration on the day of administration. For positive control, intraperitoneal (i.p.) injection of desipramine was done. Desipramine was dissolved in double-distilled water (10 mg/kg). The experiments were conducted 30 min after the positive control drug treatment (only for desipramine treatment). Other compounds, ie: estradiol and the compound of Example 23 were daily injected subcutaneously in rats, during a 7 days period. Acquisition were performed on day 8 (24 h after the last administration of items) and day 9

(48h after estradiol or compound 23 administration), respectively. Data aquired 24 hours after the last administration consisted in the "naïve animal group", these animals had never been previously tested in the device. Data aquired 48 hours after a last administration of compounds consisted in "trained animal group".

<u>Table 8</u>: Effect of Ex 23 onto immobility duration in stress conditions

Compound	Dosage (mg/rat/day)	Naïve animals (s.)	Trained animals (s.)	n
vehicle	-	133.7±28.6	178.1±25.5	11
desipramine	30	Not tested	2.6±1.5***	11
E2	0.007	22.5±7.1***	79.2±23.0*	11
Ex 23	2.8	45.2±15.6*	160.7±44.1	12

(acquisition during a 10 minutes test, items or desipramine vs vehicle, $p<0.05$, $p<0.001$)

On the 8th, the forced swim test was performed. This study was carried out in rats according to the methods described by Porsolt (Eur. J. Pharm., 1978). Briefly, rats were placed individually in glass cylinders (height: 40 cm, diameter: 18 cm) containing 25 cm of water at 25 °C. Ten minutes later, rats were removed and dried before being returned to their home cages. The animals were replaced in the cylinders 24 h later, and the procedure was repeated, and a 10-min observation period was recorded.

The model was validated by desipramine activity found in the test. Results shown the confirmation of the antidepressor potency of estradiol, 24h and 48h after administration. the compound of Example 23 exhibited a antidepressor activity when animals were first-in-the-test 24h after administration, while in trained animal group 48h after administration, the antidepressor potency of the compound of Example 23 disappeared.

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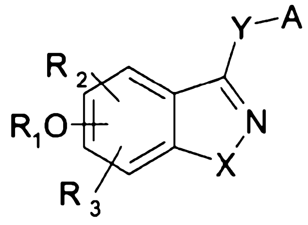
The claims defining the invention are as follows:

1. A compound of formula (I)



(I)

or an acid addition salt or a stereoisomeric form thereof, wherein:

- R_1 is hydrogen or a $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, trifluoromethyl, $-N{=}CR_5R_6$, $-SO_2NR_7R_8$, phenyl, phenyl$(C_1\text{-}C_3)$alkyl or $(C_1\text{-}C_3)$alkyl substituted by a saturated heterocyclic radical, wherein the phenyl is unsubstituted or substituted by at least one substituent selected from the group consisting of a hydroxyl, a halogen, a nitro, a cyano, a $(C_1\text{-}C_3)$alkyl, a $(C_1\text{-}C_3)$alkoxy and a trifluoromethyl; R_1 can also be a salt;
- R_2 and R_3 are each independently hydrogen or a hydroxyl, halogen, nitro, cyano, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, trifluoromethyl, $-NR_7R_8$, $-CONR_7R_8$, $-COR_9$ or $-CO_2R_9$ group; R_2 can also be a phenyl or a saturated or unsaturated heterocycle, wherein the phenyl is unsubstituted or substituted by at least one substituent selected from the group consisting of a hydroxyl, a halogen, a nitro, a cyano, a $(C_1\text{-}C_3)$alkyl, a $(C_1\text{-}C_3)$alkoxy, a trifluoromethyl and a saturated heterocyclic radical;
- X is O, S, SO, SO_2 or NR_4;
- R_4 is hydrogen or a $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, phenyl, phenyl$(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkyl substituted by a saturated heterocyclic radical, $-COR_7$, $-CO_2R_7$ or $-SO_2NR_7R_8$ group, wherein the phenyl is unsubstituted or substituted by at least one substituent selected from the group consisting of a hydroxyl, a halogen, a nitro, a cyano, a $(C_1\text{-}C_3)$alkyl, a $(C_1\text{-}C_3)$alkoxy, a trifluoromethyl, a phenyl$(C_1\text{-}C_3)$alkyl and a phenyl$(C_1\text{-}C_3)$alkoxy;
- Y is direct bond, O, S, SO, SO_2, NR_4, CO, $-(CR_{10}R_{11})_n-$ or $-R_{10}C{=}CR_{11}-$;
- R_5, R_6, R_7 and R_8 are each independently hydrogen or a $(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_6)$cycloalkyl group;
- R_9 is hydrogen, a $(C_1\text{-}C_6)$alkyl, a phenyl or a saturated or unsaturated heterocyclic radical, wherein the phenyl is unsubstituted or substituted by at least one substituent

selected from the group consisting of a hydroxyl, a halogen, a nitro, a cyano, a $(C_1$-$C_3)$alkyl, a $(C_1$-$C_3)$alkoxy, a trifluoromethyl and a saturated heterocyclic radical;

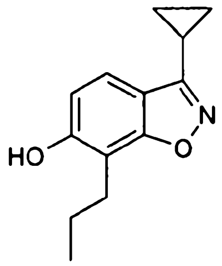
- R_{10} and R_{11} are each independently hydrogen or a cyano, $(C_1$-$C_6)$alkyl, -CO-phenyl, -CO(unsaturated heterocyclic radical) or -$CONR_7R_8$ group, wherein the phenyl is unsubstituted or substituted by at least one substituent selected from the group consisting of a hydroxyl, a halogen, a nitro, a cyano, a $(C_1$-$C_3)$alkyl, a $(C_1$-$C_3)$alkoxy and a trifluoromethyl;
- n is 1 or 2;
- A is a $(C_3$-$C_{15})$cycloalkyl or a $(C_3$-$C_{15})$cycloalkene, wherein the cycloalkyl or the cycloalkene is unsubstituted or substituted by at least one $(C_1$-$C_6)$alkyl;

provided that:

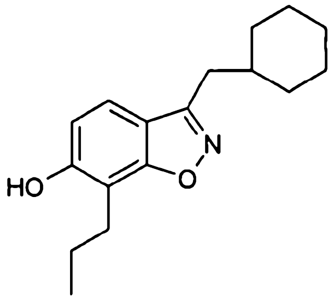
1/ when X is NR_4 where R_4 is H or $(C_1$-$C_6)$alkyl and R_1O is 6-OCH_3, then Y is not CO;

2/ when X is O, R_1O is 6-OH or 6-OCH_3, Y is a direct bond and A is cyclopentyl, then (R_2,R_3) or (R_3,R_2) is different from (H, Cl) in position 4,5;

3/ said compound is not



or



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2. A compound according to claim 1 or an acid addition salt thereof, wherein R_1 is hydrogen, a $(C_1$-$C_6)$alkyl, a phenyl$(C_1$-$C_3)$alkyl, a $(C_1$-$C_3)$alkyl substituted by a saturated heterocyclic radical or a -$SO_2NR_7R_8$ group.

3. A compound according to claim 1 or 2 or an acid addition salt thereof, wherein R_2 is hydrogen, hydroxyl, $(C_1$-$C_6)$alkyl or halogen.

4. A compound according to one of claims 1 to 3 or an acid addition salt thereof, wherein R_3 is hydrogen.

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5. A compound according to one of claims 1 to 4 or an acid addition salt thereof, wherein Y is a direct bond.

6. A compound according to one of claims 1 to 5 or an acid addition salt thereof, wherein A is a $(C_3\text{-}C_{15})$cycloalkyl optionally substituted by at least one $(C_1\text{-}C_6)$alkyl.

7. A compound according to one of claims 1 to 6 or an acid addition salt thereof, wherein R_1O is in position 6- of the ring.

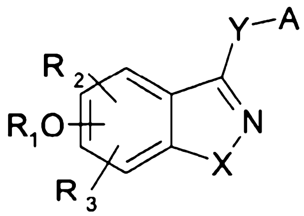
8. A compound according to one of claims 1 to 6 or an acid addition salt thereof, which is selected from
3-cyclopentyl-1H-indazol-6-ol,
3-cyclohexyl-1H-indazol-6-ol,
1-(aminosulfonyl)-3-cyclohexyl-1H-indazol-6-yl-sulfamate,
3-cyclohexyl-6-hydroxy-1H-indazole-1-sulfonamide.

9. A compound according to one of claims 1 to 8 or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance.

10. A compound according to one of claims 1 to 8 or a pharmaceutically acceptable salt thereof for use as an active substance modulating estrogen receptors.

11. A pharmaceutical composition comprising (i) a compound according to one of claims 1 to 8 or a pharmaceutically acceptable salt thereof and (ii) a pharmaceutically acceptable excipient.

12. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cognitive dysfunction:



(I)

wherein:

- R_1 is hydrogen or a (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, trifluoromethyl, $-N{=}CR_5R_6$, $-SO_2NR_7R_8$, phenyl, phenyl(C_1-C_3)alkyl or (C_1-C_3)alkyl substituted by a saturated heterocyclic radical, wherein the phenyl is unsubstituted or substituted by at least one substituent selected from the group consisting of a hydroxyl, a halogen, a nitro, a cyano, a (C_1-C_3)alkyl, a (C_1-C_3)alkoxy and a trifluoromethyl; R_1 can also be a salt;
- R_2 and R_3 are each independently hydrogen or a hydroxyl, halogen, nitro, cyano, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_6)alkoxy, trifluoromethyl, $-NR_7R_8$, $-CONR_7R_8$, $-COR_9$ or $-CO_2R_9$ group; R_2 can also be a phenyl or a saturated or unsaturated heterocycle, wherein the phenyl is unsubstituted or substituted by at least one substituent selected from the group consisting of a hydroxyl, a halogen, a nitro, a cyano, a (C_1-C_3)alkyl, a (C_1-C_3)alkoxy, a trifluoromethyl and a saturated heterocyclic radical;
- X is O, S, SO, SO_2 or NR_4;
- R_4 is hydrogen or a (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, phenyl, phenyl(C_1-C_3)alkyl, (C_1-C_3)alkyl substituted by a saturated heterocyclic radical, $-COR_7$, $-CO_2R_7$ or $-SO_2NR_7R_8$ group, wherein the phenyl is unsubstituted or substituted by at least one substituent selected from the group consisting of a hydroxyl, a halogen, a nitro, a cyano, a (C_1-C_3)alkyl, a (C_1-C_3)alkoxy, a trifluoromethyl, a phenyl(C_1-C_3)alkyl and a phenyl(C_1-C_3)alkoxy;
- Y is direct bond, O, S, SO, SO_2, NR_4, CO, $-(CR_{10}R_{11})_n-$ or $-R_{10}C{=}CR_{11}-$;
- R_5, R_6, R_7 and R_8 are each independently hydrogen or a (C_1-C_6)alkyl or (C_3-C_6)cycloalkyl group;
- R_9 is hydrogen, a (C_1-C_6)alkyl, a phenyl or a saturated or unsaturated heterocyclic radical, wherein the phenyl is unsubstituted or substituted by at least one substituent selected from the group consisting of a hydroxyl, a halogen, a nitro, a cyano, a (C_1-C_3)alkyl, a (C_1-C_3)alkoxy, a trifluoromethyl and a saturated heterocyclic radical;
- R_{10} and R_{11} are each independently hydrogen or a cyano, (C_1-C_6)alkyl, -CO-phenyl, -CO(unsaturated heterocyclic radical) or $-CONR_7R_8$ group, wherein the phenyl is unsubstituted or substituted by at least one substituent selected from the group consisting of a hydroxyl, a halogen, a nitro, a cyano, a (C_1-C_3)alkyl, a (C_1-C_3)alkoxy and a trifluoromethyl;
- n is 1 or 2;

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- A is a (C_3-C_{15})cycloalkyl or a (C_3-C_{15})cycloalkene, wherein the cycloalkyl or the cycloalkene is unsubstituted or substituted by at least one (C_1-C_6)alkyl.

13. Use of a compound of formula (I) as defined in claim 12, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prevention or treatment of estrogen-dependent disorders, wherein said compound can be used in combination with a sexual endocrine therapeutic agent.

14. Use of a compound of formula (I) as defined in claim 12, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the control or management of reproductive functions, wherein said compound can be used in combination with a LH-RH agonist or antagonist, an estroprogestative contraceptive, a progestin, an antiprogestin or a prostaglandin.

15. Use of a compound of formula (I) as defined in claim 12, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prevention or treatment of benign or malignant diseases of the breast, the uterus or the ovary, or of polycystic ovary syndrome, wherein said compound can be used in combination with an antiestrogen, a progestin or a LH-RH agonist or antagonist.

16. Use of a compound of formula (I) as defined in claim 12, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prevention or treatment of benign or malignant diseases of the prostate or the testis, wherein said compound can be used in combination with an antiandrogen, a progestin, a lyase inhibitor or a LH-RH agonist or antagonist.

17. A method of preventing or treating a disease where modulation of estrogen receptors is required, which comprises administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I) as defined in claim 12, or a pharmaceutically acceptable salt thereof.

18. Use or method according to one of claims 12 to 17, wherein the compound of formula (I) fulfils at least one of the following conditions:

- R_1 is hydrogen, a (C_1-C_6)alkyl, a phenyl(C_1-C_3)alkyl, a (C_1-C_3)alkyl substituted by a saturated heterocyclic radical or a $-SO_2NR_7R_8$ group;
- R_2 is hydrogen, hydroxyl, (C_1-C_6)alkyl or halogen;
- R_3 is hydrogen;
- Y is direct bond;
- A is a (C_3-C_{15})cycloalkyl optionally substituted by at least one (C_1-C_6)alkyl;
- R_1O is in position 6- of the ring.

19. The method of claim 17 or claim 18 wherein the compound of Formula I or pharmaceutically acceptable salts thereof is administered in combination with a sexual endocrine therapeutic agent.

20. The method of claim 17 or claim 18 wherein the compound of Formula I or pharmaceutically acceptable salt thereof is administered in combination with a LH-RH agonist or antagonist, and estroprogestative contraceptive, a progestin, an antiprogestin or a prostaglandin.

Dated 4 November, 2011

Laboratoire Theramex

Patent Attorneys for the Applicant/Nominated Person

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