INDOLES USEFUL IN THE TREATMENT OF ANDROGEN-RECEPTOR RELATED DISEASES

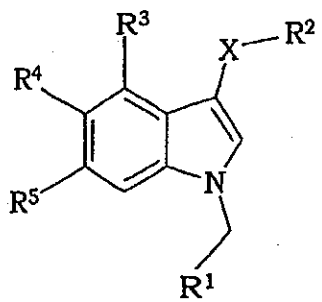
The invention relates to indole derivatives, their preparation and their use for the treatment of androgen-receptor related conditions, disorders or diseases and other androgen related treatments.

Compounds possessing androgenic activity are useful in the treatment of men with low endogenous levels of circulating androgenic hormones or men with suppressed androgenic effects. Such treatments are prescribed to older men, to hypogonadal men or men treated with progestagens for male contraception. In addition, potent androgens suppress spermatogenesis and can be used as male contraceptives.

It is thus important to obtain compounds with high affinity for the androgen receptor. Non-steroidal compounds with high affinity for the androgen receptor are particularly useful since they may have different tissue distribution characteristics than steroidal androgens and can be designed by proper choice of substituents to be more or less selective for certain tissues. For example, an action in the brain is usually prevented when compounds are strongly hydrophilic or carry an ionic charge.

Disclosed are non-steroidal compounds with affinity for the androgen receptor. These compounds are potentially useful for the treatment of androgen-receptor related disorders or disorders which can be treated with androgens.

In a first aspect, there is provided a compound having the formula I.



wherein

X is S, SO or SO_2;

R^1 is a 5- or 6-membered monocyclic, hetero- or homocyclic, saturated or unsaturated ring structure optionally substituted with one or more substituents selected from the group consisting of halogen, CN, (1C-4C)fluoroalkyl, nitro, (1C-4C)alkyl, (1C-4C)alkoxy or (1C-4C)fluoroalkoxy;

R^2 is 2-nitrophenyl, 2-cyanophenyl, 2-hydroxymethyl-phenyl, pyridin-2-yl, pyridin-2-yl-N-oxide, 2-benzamide, 2-benzoic acid methyl ester or 2-methoxyphenyl;

R^3 is H, halogen or (1C-4C)alkyl;

R^4 is H, OH, (1C-4C)alkoxy, or halogen;

R^5 is H, OH, (1C-4C)alkoxy, NH_2, CN, halogen, (1C-4C)fluoroalkyl, NO_2, hydroxy(1C-4C)alkyl, CO_2H, CO_2(1C-6C)alkyl, or R^5 is NHR^6, wherein R^6 is (1C-6C)acyl optionally substituted with one or more halogens, $S(O)_2$(1C-4C)alkyl, or $S(O)_2$aryl optionally substituted with (1C-4C)alkyl or one or more halogens, or R^5 is $C(O)N(R^8,R^9)$, wherein R^8 and R^9 each independently are H, (3C-6C)cycloalkyl, or CH_2R^{10}, wherein R^{10} is H, (1C-5C)alkyl, (1C-5C)alkenyl, hydroxy(1C-3C)alkyl, (1C-4C)alkylester of carboxy(1C-4C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, (mono- or di(1C-4C)alkyl)aminomethyl, (mono- or di(1C-4C)alkyl)aminocarbonyl, or a 3-, 4-, 5- or 6-membered monocyclic, homo- or heterocyclic, aromatic or non-aromatic ring, or R^8 and R^9 form together with the N a heterocyclic 5- or 6-membered saturated or unsaturated ring optionally substituted with (1C-4C)alkyl;

or a salt or hydrate form thereof.

In a second aspect, there is provided a compound as defined above for use in therapy.

In a third aspect, there is provided a pharmaceutical composition comprising a compound as defined above and a pharmaceutically acceptable carrier.

In a fourth aspect, there is provided a use of a compound as defined above for the manufacture of a medicament for the treatment of androgen-receptor related disorders, androgen related disorders and androgen insufficiency.

In one embodiment R^1 is a 5- or 6-membered monocyclic, hetero- or homocyclic, saturated or unsaturated ring structure optionally substituted with one or more substituents selected from the group consisting of halogen, CN, CF_3, nitro, methoxy, trifluoromethoxy or methyl; R^2 is 2-nitrophenyl, 2-cyanophenyl, 2-hydroxymethyl-phenyl, pyridin-2-yl, pyridin-2-yl-N-oxide, 2-benzamide, 2-benzoic acid methyl ester or 2-methoxyphenyl; R^3 is H, halogen or (1C-2C)alkyl; R^4 is H or F.

In another embodiment R^5 is H, OH, (1C-4C)alkoxy, CN, halogen, (1C-4C)fluoroalkyl, NO_2, hydroxy(1C-4C)alkyl, CO_2(1C-6C)alkyl, or R^5 is NHR^6, wherein R^6 is (1C-6C)acyl optionally substituted with one or more halogens, $S(O)_2$(1C-4C)alkyl, or $S(O)_2$aryl optionally substituted with (1C-4C)alkyl or one or more halogens, or

R^5 is C(O)N(R^8,R^9), wherein R^8 and R^9 each independently are H, (3C-6C)cycloalkyl, or CH_2R^{10}, wherein R^{10} is H, (1C-5C)alkyl, (1C-5C)alkenyl, hydroxy(1C-3C)alkyl, (1C-4C)alkylester of carboxy(1C-4C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, (mono- or di(1C-4C)alkyl)aminomethyl, (mono- or di(1C-4C)alkyl)-aminocarbonyl, or a 3-, 4-, 5- or 6-membered monocyclic, homo- or heterocyclic, aromatic or non-aromatic ring, or R^8 and R^9 form together with the N a heterocyclic 5- or 6-membered saturated or unsaturated ring optionally substituted with (1C-4C)alkyl.

In yet another embodiment R^3 is H or halogen; R^4 is H; R^5 is H, OH, (1C-4C)alkoxy, CN, F, Cl, CF_3, NO_2, hydroxy(1C-4C)alkyl, CO_2(1C-6C)alkyl, or R^5 is NHR^6, wherein R^6 is (1C-3C)acyl optionally substituted with one or more halogens or R^5 is C(O)N(R^8,R^9), wherein R^8 and R^9 each independently are H, (3C-5C)cycloalkyl, or CH_2R^{10}, wherein R^{10} is H, (1C-5C)alkyl, (1C-5C)alkenyl, hydroxy(1C-3C)alkyl, (1C-2C)alkylester of carboxy(1C-2C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, (mono- or di(1C-4C)alkyl)aminomethyl, (mono- or di(1C-4C)alkyl)aminocarbonyl, (3C-5C)cycloalkyl, or a 5-membered heterocyclic ring.

In yet another embodiment X is S or SO_2; R^2 is 2-nitrophenyl, 2-hydroxymethyl-phenyl, 2-benzamide, 2-methoxyphenyl, 2-cyanophenyl or pyridin-2-yl; R^3 is H or F; R^5 is H, OH, (1C-2C)alkoxy, CN, F, Cl, CF_3, NO_2, hydroxy(1C-4C)alkyl, CO_2(1C-4C)alkyl, or R^5 is NHR^6, wherein R^6 is formyl, acetyl, fluoroacetyl, difluoroacetyl, or trifluoroacetyl, or R^5 is C(O)N(R^8,R^9), wherein R^8 is H, and R^9 is H, cyclopropyl or R^9 is CH_2R^{10}, wherein R^{10} is H, (1C-2C)alkyl, hydroxy(1C-2C)alkyl, methoxy(1C-2C)alkyl, cyclopropyl.

In yet another embodiment X is S; R^1 is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, pyrimidin-5-yl, pyrimidin-4-yl, pyrazin-2-yl, 3-fluorophenyl, 3-cyanophenyl, or 3-nitrophenyl; R^2 is 2-nitrophenyl, 2-hydroxymethyl-phenyl, 2-methoxyphenyl, 2-cyanophenyl or pyridin-2-yl; R^3 is H; R^5 is OH, (1C-2C)alkoxy, CN, CF_3, NO_2, hydroxy(1C-4C)alkyl, CO_2(1C-4C)alkyl, or NHR^6, wherein R^6 is formyl, acetyl, fluoroacetyl, difluoroacetyl, or trifluoroacetyl.

In yet another embodiment R^1 is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, pyrimidin-5-yl, pyrimidin-4-yl, or pyrazin-2-yl; R^2 is 2-nitrophenyl, or 2-hydroxymethyl-phenyl; R^5 is OH, (1C-2C)alkoxy, CN, hydroxy(1C-4C)alkyl, or NHR^6, wherein R^6 is formyl, acetyl, fluoroacetyl, difluoroacetyl, or trifluoroacetyl.

In yet another embodiment R^1 is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, pyrimidin-5-yl, or pyrimidin-4-yl; R^2 is 2-nitrophenyl; R^5 is OH, (1C-2C)alkoxy, CN, or NHR^6, wherein R^6 is formyl, acetyl, fluoroacetyl, difluoroacetyl, or trifluoroacetyl.

In a specific embodiment the subject invention provides the compounds 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indole, 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carbonitrile, 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carbonitrile-hydrochloride, 3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indole-6-carbonitrile, 3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-4-ylmethyl-1*H*-indole-6-carbonitrile, *N*-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-2-fluoro-acetamide, and *N*-[3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indol-6-yl]-formamide.

In another embodiment X is S; R^1 is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, 3-fluorophenyl, 3-cyanophenyl, or 3-nitrophenyl; R^2 is 2-nitrophenyl, 2-hydroxymethyl-phenyl, 2-methoxyphenyl, 2-cyanophenyl or pyridin-2-yl; R^3 is H;
R^5 is $C(O)N(R^8,R^9)$, wherein R^8 is H, and R^9 is H, or CH_2R^{10}, wherein R^{10} is H, (1C-2C)alkyl, hydroxy(1C-2C)alkyl, or methoxy(1C-2C)alkyl.

In yet another embodiment R^1 is 3,5-difluorophenyl, pyridin-2-yl, or pyridin-3-yl; R^2 is 2-nitrophenyl, or 2-hydroxymethyl-phenyl; R^5 is $C(O)N(R^8,R^9)$, wherein R^8 is H, and R^9 is CH_2R^{10}, wherein R^{10} is H, or (1C-2C)alkyl.

In a specific embodiment the subject invention provides the compound 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid methylamide.

In yet another embodiment X is S; R^1 is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, 3-fluorophenyl, 3-cyanophenyl, or 3-nitrophenyl; R^2 is 2-nitrophenyl, 2-hydroxymethyl-phenyl, 2-methoxyphenyl, 2-cyanophenyl or pyridin-2-yl; R^3 is H; R^5 is $C(O)N(R^8,R^9)$, wherein R^8 and R^9 each independently are H or CH_2R^{10}, wherein R^{10} is H, (1C-5C)alkyl, (1C-5C)alkenyl, hydroxy(1C-3C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, or (mono- or di(1C-4C)alkyl)aminomethyl.

In yet another embodiment R^1 is 3,5-difluorophenyl, pyridin-2-yl, or pyridin-3-yl; R^2 is 2-nitrophenyl, or 2-hydroxymethyl-phenyl; R^5 is $C(O)N(R^8,R^9)$, wherein R^8 and R^9 each independently are H, or CH_2R^{10}, wherein R^{10} is H, (1C-5C)alkyl, hydroxy(1C-3C)alkyl, or (1C-3C)alkoxy(1C-3C)alkyl.

In a specific embodiment the subject invention provides the compound 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid dimethylamide.

In those cases that a compound of the invention contains a basic amine function, the compound may be used as a free base or as a pharmaceutically acceptable salt such as hydrochloride, acetate, oxalate, tartrate, citrate, phosphate, maleate or fumarate.

A compound according to the invention is a compound as defined above, a salt thereof, a hydrate thereof or a prodrug thereof.

The terms used in this description have the following meaning:
alkyl is a branched or unbranched alkyl group, for example methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, hexyl, and the like;
fluoroalkyl is an alkyl group substituted with one or more fluorine atoms;
cycloalkyl is a cyclized unbranched alkyl group, such as cyclopropyl, cyclobutyl, cyclopentyl and the like;
alkenyl is a branched or unbranched alkenyl group, such as ethenyl, 2-butenyl, etc.;
alkoxy is a branched or unbranched alkyloxy group, for example methyloxy, ethyloxy, propyloxy, isopropyloxy, butyloxy, sec-butyloxy, tert-butyloxy and the like;
fluoroalkoxy is a alkoxy group substituted with one or more fluorine atoms;
aryl is a mono- or polycyclic, homo- or heterocyclic aromatic ring system, such as phenyl, naphtyl or pyridyl; a monocyclic ring with 6 atoms is preferred for use;
acyl is a (substituent-)carbonyl group, such as an aroyl or alkanoyl;

aroyl is arylcarbonyl such as a benzoyl group;
alkanoyl means a formyl or alkylcarbonyl group such as formyl, acetyl and propanoyl;
carboxy is a -COOH substituent, making the compound an organic acid;
carboxylate is a salt of a carboxyl substituent.
The prefixes (1C-4C), (2C-4C) etc. have the usual meaning to restrict the meaning of the indicated group to those with 1 to 4, 2 to 4 etc. carbon atoms;
halogen refers to fluorine, chlorine, bromine and iodine.

The androgen receptor affinity and efficacy of the compounds according to the invention make them suitable for use in the treatment of androgen-receptor related disorders, disorders which can be treated with androgens, and in diagnostic methods focussed on the amount and/or location of androgen receptors in various tissues. For the latter purpose it can be preferred to make labelled variants of the compounds according to the invention. Typical androgen receptor-related treatments are those for male contraception and male or female hormone replacement therapy. Thus the invention also pertains to a method of treatment of androgen insufficiency, by administering to a male or female human or animal an effective amount of any of the compounds of the subject invention. The subject invention also lies in the use of any of its compounds for the preparation of a medicine for treating androgen insufficiency. In the context of the invention, the term "androgen insufficiency" is to be understood to pertain to all kinds of diseases, disorders, and symptoms in which a male or a female suffers from too low a testosterone level, such as in hypogonadal men or boys. In particular, the androgen insufficiency to be treated by a compound of the invention is the reduction of the testosterone level which a male individual incurs as a result of age (the compound of the invention is then used for male hormone replacement therapy), or when he is subject to male contraception. In the context of male contraception, the compound of the invention especially serves to neutralise the effect of regimens of male hormone contraception in which a sterilitant such as a progestagen or LHRH (luteinizing hormone releasing hormone) is administered regularly, *e.g.* daily, or it is used as the sole male contraceptive substance.

Thus, the subject invention provides any one of the compounds of the subject invention for use in therapy.

The subject invention further encompasses a pharmaceutical composition comprising a compound of the subject invention and a pharmaceutically acceptable carrier. In an embodiment of the subject invention, the pharmaceutical composition is for the

treatment of a disorder selected from the group consisting of an androgen-receptor related disorder, an androgen related disorder and androgen insufficiency.

The subject invention further provides a use of a compound of the invention for the manufacture of a medicament for the treatment of androgen-receptor related disorders, androgen related disorders and androgen insufficiency.

The subject invention further envisions a method of treating a disorder selected from the group consisting of an androgen-receptor related disorder, an androgen related disorder and androgen insufficiency comprising administering a pharmaceutically effective amount of a compound according to the invention to a subject in need thereof.

The compounds of the invention may further be useful for the treatment of osteoporosis, as well as other bone disorders, bone fraction repair, sarcopenia, frailty, skin aging, male hypogonadism, female sexual dysfunction, postmenopausal symptoms, atherosclerosis, aplastic anemia, muscular atrophy, lipodystrophy, reduced muscle strength and function, side effects of chemotherapy, chronic fatigue syndrome, benign prostate hyperplasia (BPH), cachexia, chronic catabolic state, cognitive impairment, male contraception, and others.

The compounds of the invention may be administered in conjunction with estrogens, progestogen and other androgens.

The compounds of the invention can be produced by various methods known in the art of organic chemistry in general. More specifically the routes of synthesis as illustrated in the following schemes and examples can be used. In the schemes and examples the following abbreviations were used:

DMF = dimethylformamide
mCPBA = *meta* chloro perbenzoic acid
THF = tetrahydofuran
TBTU = 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
DIPEA = diisopropylethylamine
EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

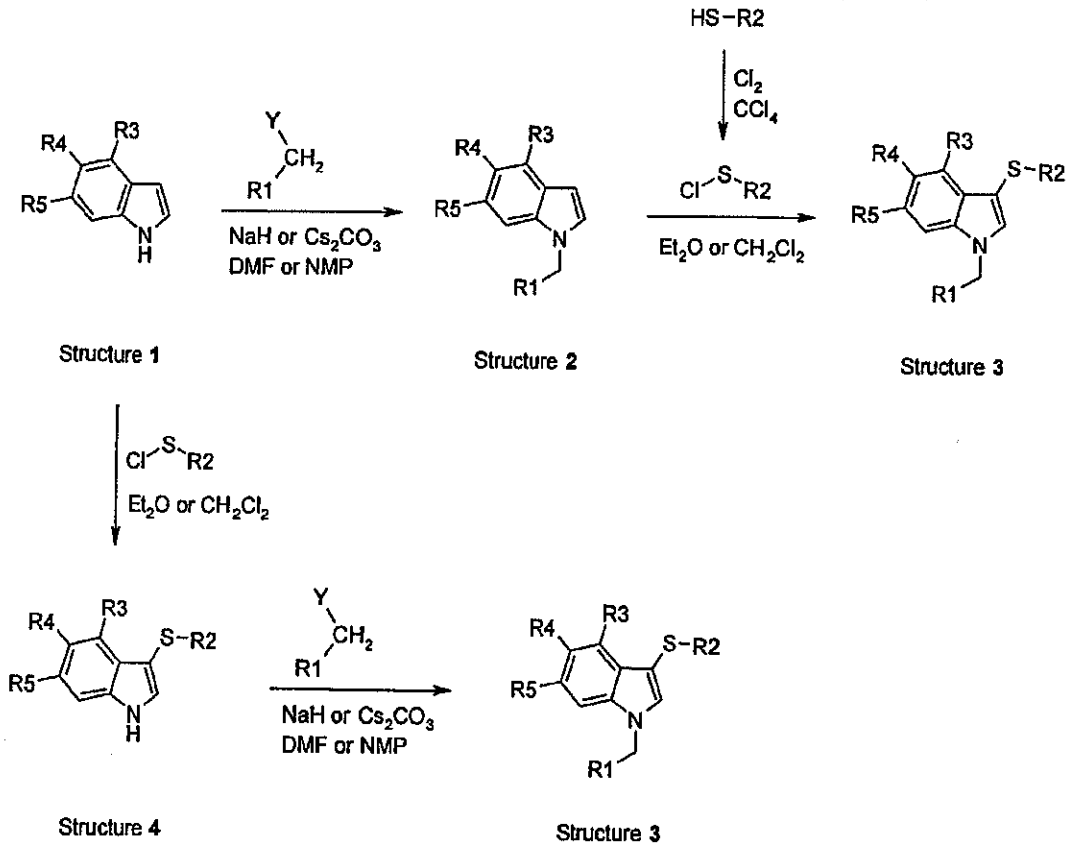
HOBt = 1-hydroxybenzotriazole
NMM = N-methylmorpholine
SPE = solid phase extraction
RP-SPE = reversed phase solid phase extraction
DMSO = dimethylsulfoxide
DCM = dichloromethane
DHT = 5α-dihydrotestosterone
NMP = 1-methyl-2-pyrrolidinone
DMS = dimethyl sulfide

With regard to nomenclature the following trivial names are used interchangeably for substituents R^1 and R^2:

Trivial name	Official name
2-pyridyl	pyridin-2-yl
3-pyridyl	pyridyl-3-yl
4-pyridyl	pyridyl-4-yl
3,5-pyrimidyl	pyrimidin-5-yl
2,4-pyrimidyl	pyrimidin-4-yl
2,5-pyrazyl	pyrazin-2-yl
etc.	

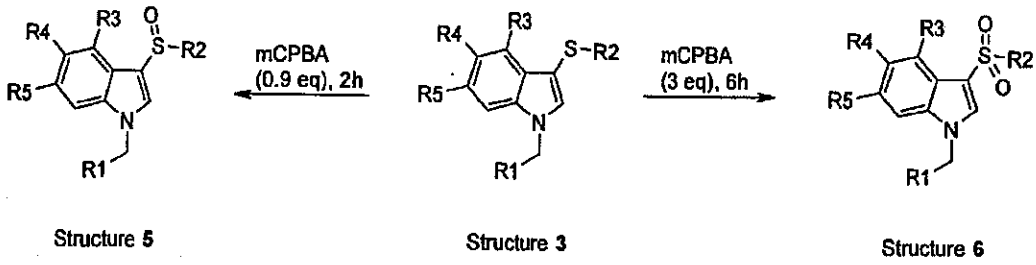
In each of the Schemes I-VII the meanings of the symbols correspond to the definitions given in the previous paragraphs.

Substituted indole compounds of structure **3** were prepared in two steps from the correctly substituted indoles of structure **1**, via two different routes. In the first route a correctly substituted indole of structure **1** is N-alkylated with a halide of type R^1CH_2Y, where Y is a halogen, mesylate or tosylate, with NaH or Cs_2CO_3 as a base in DMF or NMP at 0°C to room temperature, to give a compound of structure **2**. Structure **2** is then sulfanylated at the C-3 position of the indole ring by reaction with a sulfenyl chloride in either CH_2Cl_2 or diethyl ether at room temperature, to give structure **3**. In the second route the two steps of the first route are reversed: the correctly substituted indole of structure **1** is first sulfanylated at the C-3 position of the indole to give structure **4**, followed by N-alkylation with R^1CH_2Y to give structure **3** (Scheme I).



Scheme I

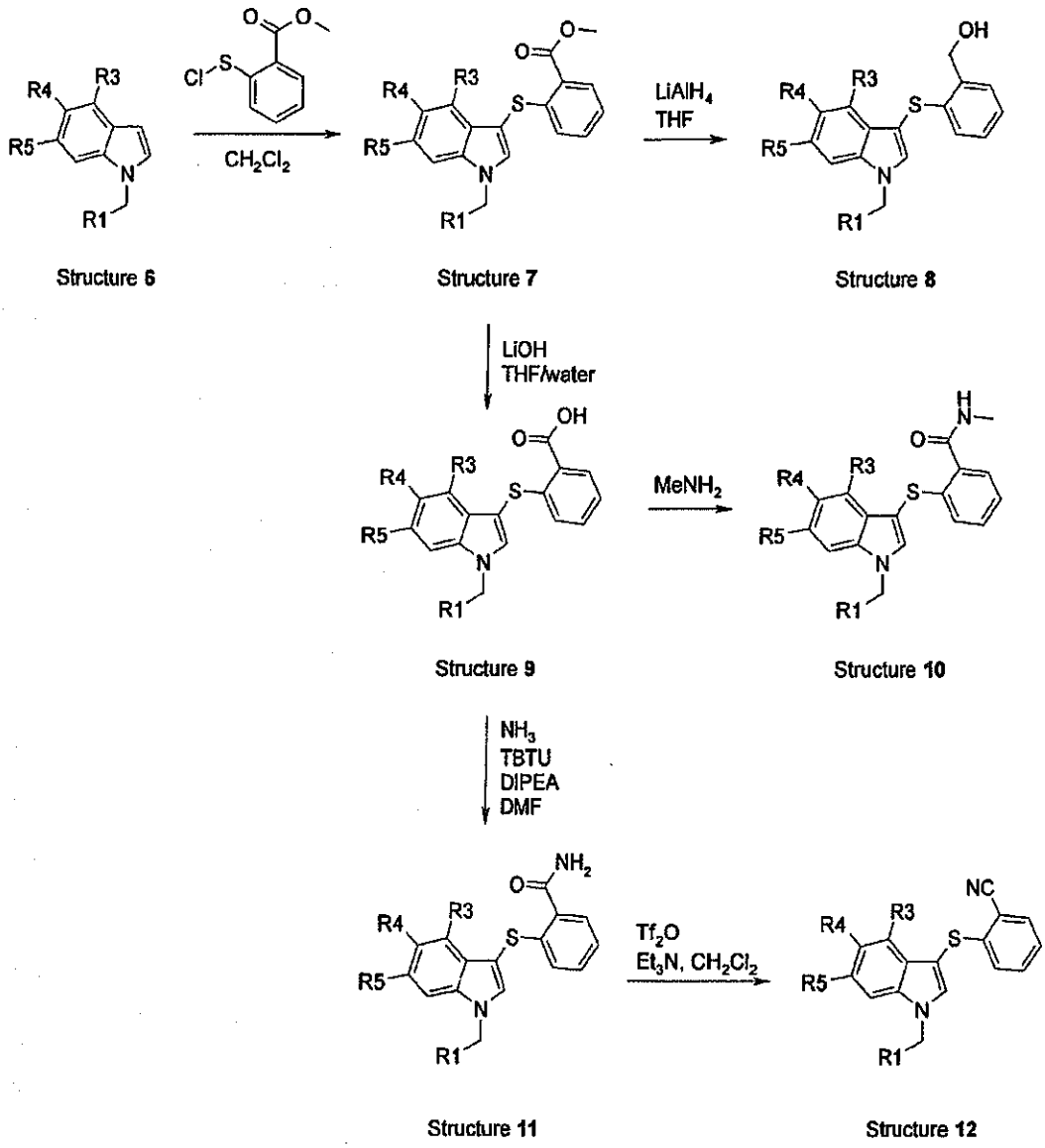
Sulfoxides of structure **5** can be obtained by oxidation of the corresponding sulfide (Structure **3**) by reaction with e.g. 0.9 equivalents of mCPBA. Sulfones of structure **6** can be obtained by oxidation of the corresponding sulfide (Structure **3**) by reaction with e.g. 3 equivalents of mCPBA (Scheme **II**).



Scheme II

Scheme **III** describes the synthesis of compounds of structure **3**, in which the R^2 group is a phenyl ring substituted on the 2-position with either CO_2Me (Structure **7**), CH_2OH

(Structure **8**), CO_2H (Structure **9**), CONHMe (Structure **10**), $CONH_2$ (Structure **11**) or CN (Structure **12**).



Structure **6** Structure **7** Structure **8**

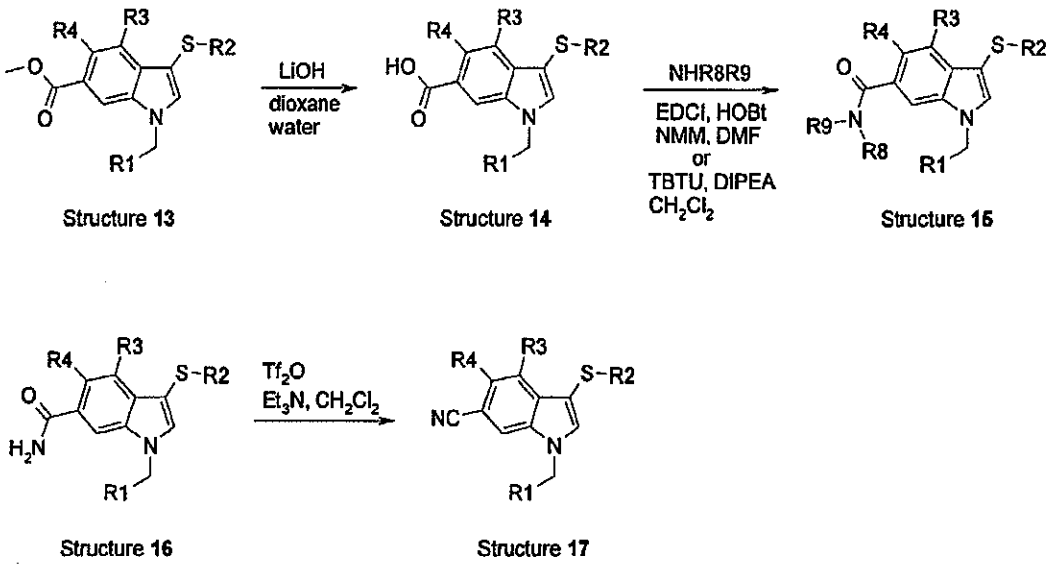
Structure **9** Structure **10**

Structure **11** Structure **12**

Scheme III

In the first step a substituted indole of structure **6** is sulfanylated at the 3-position with 2-(carboxymethyl)-phenylsulfenyl chloride, which was prepared from methylthiosalicylate and chlorine gas, to give a compound of structure **7**. Reduction of the methyl ester moiety of compounds of structure **7** with $LiAlH_4$ gave the corresponding hydroxymethyl compounds of structure **8**. Saponification of the methyl

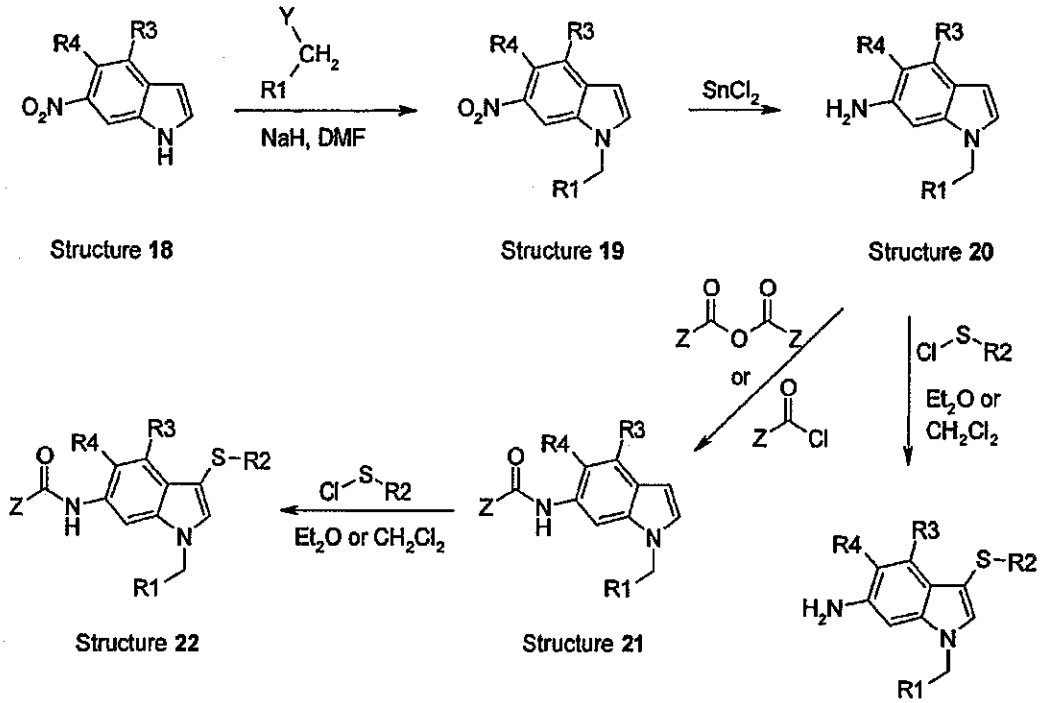
ester moiety of compounds of structure **7** with lithium hydroxide gave the corresponding carboxylic acid compounds of structure **9**. The carboxylic acid moiety of compounds of structure **9** can be converted to the corresponding carboxamide by reaction with an amine, TBTU and DIPEA in DMF at room temperature. By this method structure **10** was obtained when methylamine was used as the amine and structure **11** was obtained when NH_3 was used as the amine. Dehydration of the benzamide moiety of structure **11** with Tf_2O and triethylamine in CH_2Cl_2 afforded the corresponding benzonitrile compound of structure **12** (Scheme III).



Scheme IV

Scheme **IV** describes the synthesis of compounds of structure **3**, in which the indole ring is substituted at the 6-position with either CO_2Me (Structure **13**), CO_2H (Structure **14**), $CONR^8R^9$ (Structure **15**), $CONH_2$ (Structure **16**) or CN (Structure **17**). Saponification of the methyl ester moiety of structure **13** with lithium hydroxide afforded the corresponding carboxylic acid of structure **14**. The carboxylic acid moiety of structure **14** can be converted to the corresponding carboxamides of structures **15** and **16** by reaction with an amine or amine salt, in the presence of EDCI and HOBt in a mixture of NMM and DMF or in the presence of TBTU and DIPEA in CH_2Cl_2 at room temperature. Dehydration of the benzamide moiety of structure **16** with Tf_2O and

triethylamine in CH_2Cl_2 afforded the corresponding benzonitrile compound of structure **17** (Scheme **IV**).

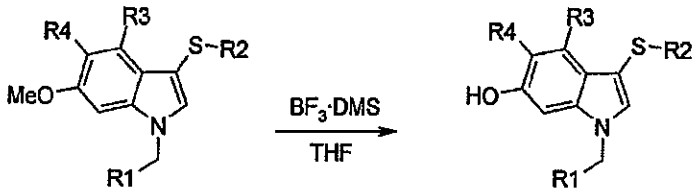


Scheme V

Scheme **V** describes the synthesis of compounds of structure **22** containing an acylated amine functionality on the 6-position of the indole ring. These compounds can be synthesised from 6-nitro indoles of structure **18** in 4 steps. In the first step the indole of structure **18** is alkylated on the nitrogen atom by reaction of a halide of type R^1CH_2Y, in which Y is halogen, mesylate or tosylate, with NaH as a base in DMF to give compounds of structure **19**. In the second step the nitro group of structure **19** is reduced to an amine group by $SnCl_2$ to give structure **20**. Subsequent acylation of the amine group with an acid chloride of type ZCOCl afforded structure **21**, which was then sulfanylated at the 3-position of the indole ring by reaction with a sulfenyl chloride in either CH_2Cl_2 or Et_2O as a solvent, at room temperature, to give compounds of structure

22. Direct sulfanylation of a compound of structure **20** with a sulfenyl chloride afforded structure **23**

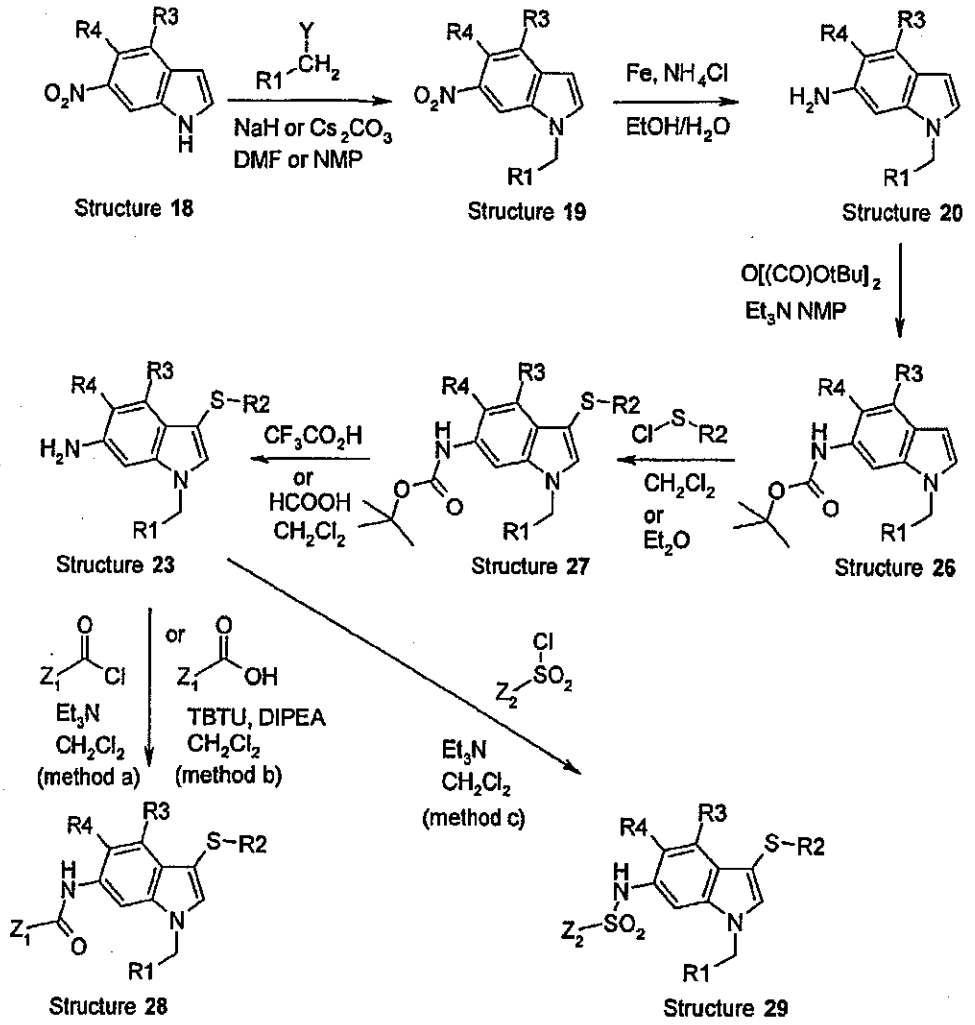
In Scheme **VI** is decribed how methyl ethers of structure **24** can be cleaved with e.g. BF_3·DMS in THF at room temperature to hydroxy compounds of structure **25**.



Structure **24** Structure **25**

Scheme VI

Scheme **VII** describes the synthesis of compounds containing either an acylated amine functionality (structure **28**) or a sulfonamide functionality (structure **29**) at the 6-position of the indole ring. These compounds can be prepared from 6-nitro indoles of structure **18** in 6 steps. In the first step the indole of structure **18** is alkylated on N-1 by reaction of a halide of type R^1CH_2Y, in which Y is a halogen, mesylate or tosylate, with NaH or Cs_2CO_3 as a base in either NMP or DMF to give compounds of structure **19**. In the second step the nitro group of structure **19** is reduced to an amine group with Fe and NH_4Cl in an ethanol/water mixture to give structure **20**. Subsequent acylation of the amine group with di-*tert*-butyl dicarbonate afforded structure **26** which was then sulfanylated at the 3-position of the indole ring by reaction with a sulfenyl chloride in either CH_2Cl_2 or Et_2O to give compounds of structure **27**. Then the amide functionality at the 6-position of the indole was cleaved with trifluoroacetic acid or HCOOH to give amines of structure **23**. These amines can be converted into amides of structure **28** by reaction with either triethylamine and an acid chloride in CH_2Cl_2 (method a) or an acid, TBTU and DIPEA in CH_2Cl_2 (method b). Sulfonamides of structure **29** can be prepared by reaction of amines of structure **23** with sulfonyl chlorides (method c).



Scheme VII

The present invention also relates to a pharmaceutical composition comprising the non-steroidal compound according to the invention mixed with a pharmaceutically acceptable auxiliary, such as described in the standard reference Gennaro *et al*, *Remmington: The Science and Practice of Pharmacy*, (20th ed., Lippincott Williams & Wilkins, 2000, see especially Part 5: Pharmaceutical Manufacturing). Suitable auxiliaries are made available in e.g. the Handbook of Pharmaceutical Excipients (2nd Edition, Editors A. Wade and P.J. Weller; American Pharmaceutical Association; Washington; The Pharmaceutical Press; London, 1994). The mixture of a compound according to the invention and a pharmaceutically acceptable auxiliary may be

compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically suitable liquids the compounds can also be applied as an injection preparation in the form of a solution, suspension, emulsion, or as a spray, e.g. nasal spray. For making dosage units, e.g. tablets, the use of conventional additives such as fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used. The compounds of the invention may also be included in an implant, a vaginal ring, a patch, a gel, and any other preparation for sustained release.

Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like, or mixtures thereof used in suitable amounts.

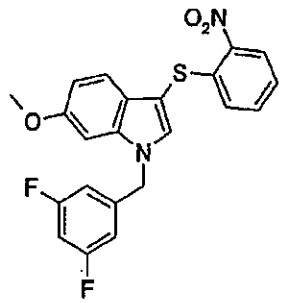
The dosage amounts of the present compounds will be of the normal order for pharmaceutically active compounds, e.g. of the order of 0.001 to 50 mg/kg body weight of the recipient per administration. The recipient can be a human or an animal in need of an androgen receptor-related treatment or an androgen treatment.

The invention is illustrated by the following examples.

Examples

Example 1

1-(3,5-Difluoro-benzyl)-6-methoxy-3-(2-nitro-phenylsulfanyl)-1*H*-indole (Compound 63, Structure 3 of Scheme I, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^5=OMe)



General method 1: N-alkylation of a (un)substituted indole of structure **1** to give N-alkylated indole of structure **2**, followed by 3-sulfanylation to give substituted indoles of structure **3** (Scheme **I**).

(a) 1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indole (Structure **2** of Scheme I, where R^1 = 3,5-difluorophenyl, R^3=R^4=H, R^5=OMe)

Under a nitrogen atmosphere: to a cooled (0°C) solution of 6-methoxyindole (863 mg, 5.86 mmol) in DMF (40 mL) was added NaH (60% in oil; 281 mg, 7.03 mmol) in small portions over a 3 minute period. The resulting green suspension was stirred at 0°C for 10 min. Then 3,5-difluorobenzyl bromide (0.91 mL, 7.03 mmol) was added. The mixture was stirred at 0°C for 1 h and then at room temperature for another 21 h. Ethyl acetate (50 mL) was added and the mixture was washed with 3% aqueous citric acid (3x50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give a green oil (1.43 g). The crude product was purified over a 20 g silica SPE cartridge (ethyl acetate/heptane 1:9) to give the title compound as a colourless oil (1.23 g, yield = 77%).

LCMS: 4.01 min (96.3%, MH^+ = 274); TLC (ethyl acetate/heptane 1:4): R_f = 0.46; ^1H NMR ($CDCl_3$): δ 3.80 (s, 3H, OCH_3), 5.24 (s, 2H, NCH_2Ar), 6.51 (dd, 1H, J1 = 3.5 Hz,

J2 = 0.8 Hz), 6.57-6.60 (m, 2H), 6.65 (d, 1H, J = 3.1 Hz), 6.66-6.72 (m, 1H), 6.81 (dd, 1H, J1 = 8.6 Hz, J2 = 3.1 Hz), 7.01 (d, 1H, J = 3.5 Hz), 7.53 (d, 1H, J = 8.6 Hz).

(b) 1-(3,5-Difluoro-benzyl)-6-methoxy-3-(2-nitro-phenylsulfanyl)-1*H*-indole (Compound 63 , Structure 3 of Scheme I, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^5=OMe)

To a solution of 1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indole (900 mg, 3.29 mmol) in diethyl ether (20 mL) was added dropwise at room temperature a suspension of 2-nitrobenzenesulfenyl chloride (627 mg, 3.31 mmol) in diethyl ether (10 mL) over a period of 2 min. After stirring at room temperature for 1 h ethyl acetate (50 mL) was added and the mixture was washed with saturated $NaHCO_3$ solution (2x50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give an orange-red oil (1.54 g). The crude product was crystallised from toluene/acetone to give the title compound as orange-red crystalline solid (900 mg, yield = 64%).

LCMS: 4.25 min (100%, MH^+ = 427); HPLC: 4.86 min (98.7%); ^{1}H NMR ($CDCl_3$): δ 3.82 (s, 3H, OCH_3), 5.32 (s, 2H, NCH_2Ar), 6.63-6.69 (m, 2H), 6.72-6.79 (m, 1H), 6.75 (d, 1H, J = 2.7 Hz), 6.85 (dd, 1H, J1 = 8.2 Hz, J2 = 2.7 Hz), 6.98 (dd, 1H, J1 = 6.7 Hz, J2 = 1.2 Hz), 7.16-7.20 (m, 1H), 7.26-7.30 (m, 1H) 7.34 (s, 1H), 7.39 (d, 1H, J = 8.2 Hz), 8.27 (dd, 1H, J1 = 8.2 Hz, J2 = 1.6 Hz).

According to General method 1 the following compounds were prepared:

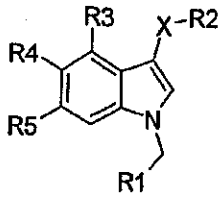


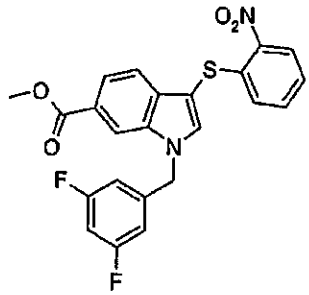
Table 1 Compounds synthesised according to General Method 1

Compound number	X	R^1	R^2	R^3	R^4	R^5	MWt	LCMS (MH+)	LCMS ret. Time[a] (min)
21	S	3,5-difluorophenyl	2-methoxyphenyl	H	H	OMe	411.47	446[c]	5.14[b]
22	S	3,5-difluorophenyl	2-nitrophenyl	H	H	Br	475.32	476	4.89
23	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CF3	464.41	465	5.34[b]
24	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CH2OH	426.44	Nd	3.88[b]
25	S	3,5-difluorophenyl	2-nitrophenyl	H	H	Cl	430.86	431	4.89
50	S	3,5-difluorophenyl	2-nitrophenyl	H	H	F	414.40	415	4.79
51	S	3,5-difluorophenyl	2-nitrophenyl	F	H	H	414.40	415	4.72
52	S	3,5-difluorophenyl	2-nitrophenyl	H	H	H	396.41	397	4.22
53	S	3,5-difluorophenyl	2-nitrophenyl	H	F	H	414.40	415	4.75
54	S	3,5-difluorophenyl	2-nitrophenyl	Cl	H	H	430.86	431	5.14[b]
55	S	3,5-difluorophenyl	2-nitrophenyl	Me	H	H	410.44	411	5.24[b]
56	S	3,5-difluorophenyl	2-nitrophenyl	H	OH	H	412.41	413	4.50[b]
60	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NO2	441.41	442	4.7
61	S	3,5-difluorophenyl	2-nitrophenyl	H	H	OH	412.41	413	4.54[b]
63	S	3,5-difluorophenyl	2-nitrophenyl	H	H	OMe	426.45	274[d]	4.01
66	S	3,5-difluorophenyl	2-pyridyl-N-oxide	H	H	OMe	398.43	399	3.96
90	S	phenyl	2-nitrophenyl	H	H	H	360.43	361	4.19
91	S	phenyl	2-nitrophenyl	H	OMe	H	390.46	391	4.14
92	S	phenyl	2-nitrophenyl	H	H	OMe	390.46	391	4.12

a) 7 min LCMS method was used, unless stated otherwise. b) 10 min LCMS method was used. c) M+Cl. nd = not detected. d) =$[M\text{-}S(PhNO_2)]H^+$.

Example 2

1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid methyl ester (Compound **31** , Structure **3** of Scheme **I**, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^5=CO_2Me)



(a) 1*H*-Indole-6-carboxylic acid methyl ester (Structure **1** of Scheme **I**, where R^3=R^4=H, R^5=CO_2Me)

To a solution of 1*H*-Indole-6-carboxylic acid (1.500 g, 9.31 mmol) in methanol (50 mL) was added concentrated H_2SO_4 (550 µL, 10.24 mmol). The mixture was stirred overnight at reflux temperature. The mixture was then neutralised to pH 7 by addition of saturated aqueous $NaHCO_3$ and the mixture was extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a yellow powder. The product was recrystallised from heptane/ethyl acetate to give the title compound as green/yellow crystals (688 mg, yield = 53%)

^{1}H NMR ($CDCl_3$): δ 3.94 (s, 3H, CH_3OCO), 6.60 (m, 1H), 7.37 (t, 1H, J = 4.7 Hz), 7.66 (d, 1H, J = 8.2 Hz), 7.82 (dd, 1H, J1 = 8.2 Hz, J2 = 1.0 Hz), 8.18 (s, 1H), 8.73 (s, 1H, NH)

(b) 1-(3,5-Difluoro-benzyl)-1*H*-indole-6-carboxylic acid methyl ester (Structure **2** of Scheme **I**, where R^1 = 3,5-difluorophenyl, R^3=R^4=H, R^5=CO_2Me)

Under a nitrogen atmosphere: to a solution of 1*H*-indole-6-carboxylic acid methyl ester (367 mg, 2.09 mmol) in DMF (10 mL) was added NaH (60% in oil, 101 mg, 2.52 mmol) at room temperature. After stirring for 15 min 1-bromomethyl-3,5-difluoro-benzene (325 µL, 2.51 mmol) was added and the mixture was stirred at room temperature for 4 h. The reaction was quenched with 3% aqueous citric acid (10 mL)

and ethyl acetate (30 mL) was added. The mixture was washed with 3% aqueous citric acid (3x20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil (702 mg). The crude product was purified over a 20 g silica SPE cartridge (ethyl acetate/heptane 1:9) to give the title compound as a colourless oil, which slowly crystallised on standing (530 mg, yield = 84%).

LCMS: 4.08 min (99%, $MH^+ = 302$); ^1H NMR ($CDCl_3$): δ 3.92 (3, 3H, CO_2CH_3), 5.37 (s, 2H, NCH_2Ar), 6.54-6.60 (m, 2H), 6.64 (d, 1H, J = 3.1 Hz), 6.67-6.74 (m, 1H), 7.27 (d, 1H, J = 3.1 Hz), 7.68 (d, 1H, J = 8.6 Hz), 7.83 (d, 1H, J = 8.6 Hz), 8.01 (s, 1H).

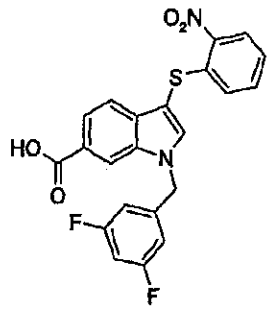
(c) 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid methyl ester (Compound **31** , Structure **3** of Scheme **I**, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^5=CO_2Me)

To a solution of 1-(3,5-Difluoro-benzyl)-1*H*-indole-6-carboxylic acid methyl ester (330 mg, 1.10 mmol) in dichloromethane (30 mL) was added at room temperature a solution of 2-nitrobenzenesulfenyl chloride (210 mg, 1.11 mmol) in dichloromethane (10 mL). The mixture was stirred at room temperature for 4 days. The reaction mixture was concentrated and the crude product was purified over a 20 g silica SPE cartridge (ethyl acetate/heptane 1:5 to 1:2) to give the title compound as a yellow solid (392 mg, yield = 78%).

HPLC: 4.60 min (97.8%); ^1H NMR ($CDCl_3$): δ 3.93 (s, 3H, CO_2CH_3), 5.45 (s, 2H, NCH_2Ar), 6.63-6.69 (m, 2H), 6.74-6.80 (m, 1H), 6.88 (dd, 1H, J1 = 8.2 Hz, J2 = 1.2 Hz), 7.18-7.23 (m, 1H), 7.26-7.30 (m, 1H), 7.57 (d, 1H, J = 7.8 Hz), 7.58 (s, 1H), 7.89 (dd, 1H, J1 = 7.8 Hz, J2 = 1.2 Hz), 8.12 (s, 1H), 8.28 (dd, 1H, J1 = 7.8Hz, J2 = 1.2 Hz).

Example 3

1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid (Compound **30** , Structure **14** of Scheme **IV**, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H)

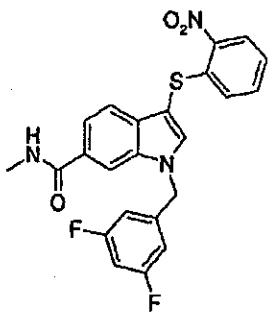


To a solution of 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid methyl ester (150.0 mg, 0.33 mmol) in dioxane (20 mL) and water (15 mL) was added $LiOH.H_2O$ (83.1 mg, 2.0 mmol) in 5 ml water. The reaction mixture was stirred overnight at 60°C. The mixture was then acidified to pH 4 by addition of 15% aqueous HCl and the mixture was extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a yellow powder. The product was recrystallised from heptane/ethyl acetate to give the title compound as yellow/orange crystals (129.3 mg, y = 89%)

^{1}H NMR (DMSO): δ 5.62 (s, 2H, CH_2Ar), 6.85 (dd, 1H, J1 = 8.6 Hz, J2 = br), 7.05 (m, 2H, br), 7.20 (m, 1H, br), 7.32-7.38 (m, 1H), 7.40 (d, 1H, J = 8.2 Hz), 7.44-7.50 (m, 1H), 7.68 (dd, 1H, J1 = 8.6 Hz, J2 = br), 7.97 (s, 1H, COOH), 8.20 (s, 1H), 8.26 (s, 1H), 8.28 (d, 1H, J = 8.2)

Example 4

1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid methylamide (Compound 47, Structure **15** of Scheme **IV**, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=R^8=H, R^9=Me)



General method 2: amidation of 6-carboxyl indoles of structure **14** to give 6-carboxamideindoles of structure **15** (Scheme **IV**).

Under nitrogen atmosphere: to a solution of 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid (25.1 mg, 57.0 µmol) in dry DMF (10mL) was added NMM (1 mL), HOBt (9.60 mg, 62.7 µmol), EDCI (12.1 mg, 62.7 µmol), and methylammonium chloride (19.2 mg, 285 µmol). The reaction mixture was stirred overnight at room temperature and then poured into ice water. The resulting precipitate was filtered and the residue was washed with excess water followed by little heptane. The product was dried *in vacuo* at 40°C to give the title compound as a yellow solid (15.2 mg, y = 60%).

LCMS: 4.31 min (100.0%, MH^+ = 454); ^{1}H NMR (DMSO): δ 2.80(d, 3H, J = 4.3, C<u>H</u>$_3$NHCO), 5.63 (s, 2H, C<u>H</u>$_2$Ar), 6.86 (dd, 1H, J1 = 8.2 Hz, J2 = 1.0 Hz), 7.04 (m, 2H), 7.20 (m, 1H), 7.33-7.37 (m, 1H), 7.41 (d, 1H, 8.6 Hz), 7.46-7.50 (m, 1H), 7.64 (dd, 1H, J1 = 8.2 Hz, J2 = 1.0 Hz), 8.15 (s, 1H), 8.25 (s, 1H), 8.27 (dd, 1H, J1 = 8.6 Hz, J2 = 1.0 Hz), 8.40 (m, 1H, MeN<u>H</u>CO).

According to General method 2 the following compounds were prepared:

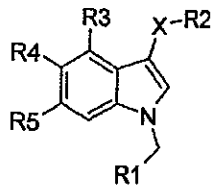


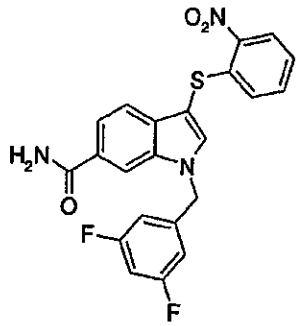
Table 2 Compounds synthesised according to General Method 2

Compound number	X	R^1	R^2	R^3	R^4	R^5	MWt	LCMS (MH+)	LCMS ret. Time[a] (min)
27	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO(1-pyrrolidinyl)	493.53	494	4.66
28	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO(4-morpholinyl)	509.53	510	4.50
29	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO[1-(4-methylpiperazinyl)]	522.57	523	3.81
32	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONEt2	495.55	496	4.82
34	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2(2-furanyl)	519.53	520	4.74
35	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2(3-pyridyl)	530.55	531	3.94
36	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2CH2NMe2	510.56	511	3.90
37	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2CH2OH	483.49	484	4.21
38	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2CH2OMe	497.52	498	4.48
39	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2CO2Me	511.50	512	4.51
40	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2CONMe2	524.55	525	4.33
41	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2cPr	493.53	494	4.75
42	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2iPr	495.55	496	4.85
43	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2Ph	529.56	530	4.90
44	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHcPr	479.50	480	4.57
45	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHEt	467.49	468	4.56
46	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHiPr	481.52	482	4.71
47	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHMe	453.47	454	4.31
48	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHnPr	481.52	482	4.75
49	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONMe2	467.49	468	4.30[b]

a) 7 min LCMS method was used, unless stated otherwise. b) 10 min LCMS method was used.

Example 5

1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid amide (Compound **33** , Structure **16** of Scheme **IV**, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H)

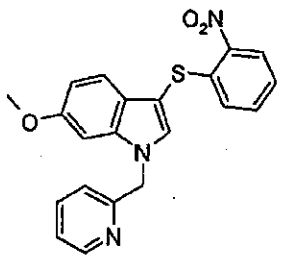


The title compound was prepared according to General method 2, using 51.1 mg (116 µmol) carboxylic acid, 19.5 mg (128 µmol) HOBt, 24.6 mg (128 µmol) EDCI and 31.1 mg (581 µmol) ammonium chloride. The title compound was obtained as a yellow solid (9,0 mg; 18%).

LCMS: 4.16 min (100.0%, MH^+ = 440); ^{1}H NMR ($CDCl_3$): δ 5.46 (s, 2H, CH_2Ar), 6.65 (m, 2H), 6.77 (m, 1H), 6.88 (dd, 1H, J1 = 8.2 Hz, J2 = 1.0 Hz)), 7.21 (m, 1H), 7.29 (m, 1H), 7.51 (dd, 1H, J1 = 7.8 Hz, J2 = 1.0 Hz), 7.57 (d, 1H, J = 7.7 Hz), 7.58 (s, 1H), 8.05 (s, 1H), 8.29 (dd, 1H, J1 = 8.2 Hz, J2 = 1.0 Hz).

Example 6

6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole (Compound **9** , Structure **3** of Scheme **I**, where R^1 = 2-pyridyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^5=OMe)



General method 3: 3-sulfanylation of a (un)substituted indole of structure **1** to give substituted indoles of structure **4**, followed by indole-*N*-alkylation to give N-alkylated indole structure **3** (Scheme **I**).

(a) 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1*H*-indole (Structure **4** of Scheme **I**, where R^2 = 2-nitrophenyl, R^1=R^3=R^4=H, R^5=OMe)

To a solution of 6-methoxyindole (1.5 g, 10.2 mmol) in Et_2O (100 mL) was added a solution of 2-nitrobenzenesulfenyl chloride (1.93 g, 10.2 mmol) in 50 mL Et_2O dropwise, over a 4 minute period. The resulting yellow solution was stirred at room temperature for 1 h. The solvent was evaporated and the crude product was purified over a silica column (heptane/ethyl acetate 9:1) to give the title compound (3.054 g, yield = 97%).

HPLC : 3.72 min. purity 96.7%, TLC (heptane/ethyl acetate 1:1): R_f = 0.6;

^{1}H NMR ($CDCl_3$): δ 3.87 (s, 3H, OCH3), 6,84 (dd, 1H, J1 = 7.8 Hz, J2 = 3,13 Hz), 6.97 (m, 2H), 7.16 (t, 1H, J = 7.8Hz), 7.25 (t, 1H, J = 7.8Hz), 7.36 (d, 1H, J = 7.8 Hz), 7.44 (d, 1H, J = 2.0 Hz), 8.26 (d, 1H, J = 7.8 Hz), 8.45 (s, 1H, NH).

(b) 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole (Compound **9**, Structure **3** of Scheme **I**, where R^1 = 2-pyridyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^5=OMe)

To a solution of 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1*H*-indole (1.5 g, 5 mmol) in DMF (150 mL) was added NaH (60% in oil; 500 mg, 12.5 mmol) in small portions, over a 4 minute period. The resulting dark solution was stirred for 5 min. at room temperature. Then 2-picolyl chloride hydrochloride (984 mg, 6 mmol) was added in small portions, over a 2 minute period. During stirring at room temperature (2h) the colour of the solution slightly changed from dark to yellow. Ethyl acetate (100 mL) was added and the mixture was washed with 2% aqueous citric acid (2x100 mL) and water (100 mL). The organic phase was dried (MgSO4) and the solvent was evaporated. The crude product was purified by crystallisation (ethyl acetate/heptane) to give the title compound (1.437 g, yield = 74%).

HPLC : 10.3 min, purity 99.6%, TLC (heptane/ethyl acetate 1:1): R_f = 0.3;

^{1}H NMR ($CDCl_3$): δ 3.80 (s, 3H, OCH3), 5.47 (s, 2H, NCH_2), 6.82 (m, 2H), 6.88 (d, 1H, J = 7.8 Hz), 7.01 (dd, 1H, J1 = 7.8 Hz, J2 = 1,6 Hz), 7.15-7.19 (m, 1H), 7.25 (m,

2H), 7.37 (d, 1H, j = 8.6 Hz), 7.60-7.64 (m, 1H), 8.26 (dd, 1H, J1 = 7.8 Hz, J2 = 1.6 Hz), 8.63 (d, 1H, J = 5.88 Hz).

According to General method 3 the following compounds were prepared:

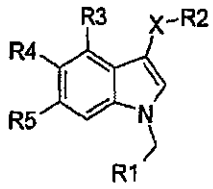


Table 3 Compounds synthesised according to General Method 3

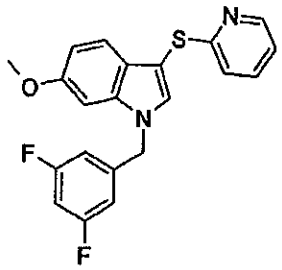
Compound number	X	R^1	R^2	R^3	R^4	R^5	MWt	LCMS (MH+)	LCMS ret. Time[a] (min)
1	S	2,5-difluorophenyl	2-nitrophenyl	H	H	OMe	426.44	427	4.07
2	S	2,fluoro,3-methylphenyl	2-nitrophenyl	H	H	OMe	422.48	423	4.23
3	S	2-chlorophenyl	2-nitrophenyl	H	H	OMe	424.91	425	4.17
4	S	2-cyanophenyl	2-nitrophenyl	H	H	OMe	415.47	416	3.97
5	S	2-fluorophenyl	2-nitrophenyl	H	H	OMe	408.45	409	4.10
6	S	2-methyl,3-nitrophenyl	2-nitrophenyl	H	H	OMe	449.48	450	4.10
7	S	2-methylphenyl	2-nitrophenyl	H	H	OMe	404.49	405	4.16
8	S	2-nitrophenyl	2-nitrophenyl	H	H	OMe	435.46	436	4.08
9	S	2-pyridyl	2-nitrophenyl	H	H	OMe	391.45		10.30[b]
11	S	2-tetrahydropyranyl	2-nitrophenyl	H	H	OMe	398.48	399	4.68
12	S	2-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	458.46	459	4.29
13	S	3-(5-methylisoxazolyl)	2-nitrophenyl	H	H	OMe	395.44	396	4.66
14	S	3,4-dichlorophenyl	2-nitrophenyl	H	H	OMe	459.35	459	4.33
15	S	3,5-dichlorophenyl	2-nitrophenyl	H	H	OMe	459.35	459	4.36
67	S	3-chlorophenyl	2-nitrophenyl	H	H	OMe	424.91	425	4.34
68	S	3-cyanophenyl	2-nitrophenyl	H	H	OMe	415.47	416	3.92
69	S	3-fluoro,5-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	476.45	477	4.42
70	S	3-fluoro,6-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	476.45	477	4.27
71	S	3-fluorophenyl	2-nitrophenyl	H	H	OMe	408.45	409	4.22

Compound number	X	R^1	R^2	R^3	R^4	R^5	MWt	LCMS (MH+)	LCMS ret. Time[a] (min)
72	S	3-methoxyphenyl	2-nitrophenyl	H	H	OMe	420.49	421	4.04
73	S	3-methylphenyl	2-nitrophenyl	H	H	OMe	404.49	405	4.16
74	S	3-nitrophenyl	2-nitrophenyl	H	H	OMe	435.46	436	4.00
75	S	3-pyridyl	2-nitrophenyl	H	H	OMe	391.45	392	3.28
76	S	3-trifluoromethyl,4-chlorophenyl	2-nitrophenyl	H	H	OMe	492.90	493	4.33
77	S	3-trifluoromethyloxyphenyl	2-nitrophenyl	H	H	OMe	474.46	475	4.43
78	S	3-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	458.46	459	4.21
79	S	4-(2-methylthiazolyl)	2-nitrophenyl	H	H	OMe	411.50	412	4.39
80	S	4-(3,5-dimethylisoxazolyl)	2-nitrophenyl	H	H	OMe	409.46	410	4.49
81	S	4-chlorophenyl	2-nitrophenyl	H	H	OMe	424.91	425	4.22
82	S	4-cyanophenyl	2-nitrophenyl	H	H	OMe	415.47	416	3.93
83	S	4-fluorophenyl	2-nitrophenyl	H	H	OMe	408.45	409	4.07
84	S	4-methoxyphenyl	2-nitrophenyl	H	H	OMe	420.49	421	4.03
85	S	4-methylphenyl	2-nitrophenyl	H	H	OMe	404.49	405	4.19
86	S	4-morpholinyl	2-nitrophenyl	H	H	OMe	413.50	414	3.54
87	S	5-(2-chlorothiazolyl)	2-nitrophenyl	H	H	OMe	431.92	432	4.61
88	S	5-(2-chlorothiophenyl)	2-nitrophenyl	H	H	OMe	430.93	431	4.92
89	S	cyclohexyl	2-nitrophenyl	H	H	OMe	396.51	397	5.11

a) 7 min LCMS method was used unless stated otherwise. b) a 20 min run on an HPLC system was used.

Example 7

1-(3,5-Difluoro-benzyl)-6-methoxy-3-(pyridin-2-ylsulfanyl)-1*H*-indole (Compound **65**, Structure **3** of Scheme **I**, where R^1 = 3,5-difluorophenyl, R^2 = 2-pyridyl, R^3=R^4=H, R^5=OMe)



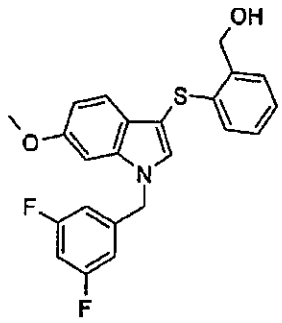
Under a nitrogen atmosphere: to a cooled (-10°C) solution of 2-mercaptopyridine (25 mg, 0.22 mmol) in CCl_4 (2 mL) was passed Cl_2-gas during a period of 1 minute. The solvent was evaporated and a solution of 1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indole (25 mg, 0.09 mmol) in Et_2O (2 mL) was added dropwise. The reaction mixture was concentrated and the crude product was purified by preparative LCMS to give the title compound (7.77 mg, yield = 23%).

LCMS : 3.95 min (100%, MH^+ 383); TLC (heptane/ethyl acetate 1:1): R_f=0.6;

^{1}H-NMR ($CDCl_3$) : δ 2.23 (s, 1H, NH), 3.82 (s, 1H, OCH_3), 6.65 (m, 2H), 6.73 (d, 1H, J = 2.7 Hz), 6.73-6.78 (m, 1H), 6.80 (d, 1H, J = 7.8 Hz), 6.87 (dd, 1H, J1 = 7.8 Hz, J2 = 1.6 Hz), 7.00 (ddd, 1H, J1 = 9.8 Hz, J2 = 4.7 Hz, J3 = 0.8 Hz), 7.35 (s, 1H), 7.42 (ddd, 1H, J1 = J2 = 7.8 Hz, J3 = 1.6 Hz), 7.50 (d, 1H, 8.6 Hz), 8.46 (d, 1H, J = 4.7 Hz).

Example 8

{2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-phenyl}-methanol (Compound **16**, Structure **8** of Scheme **III**, where R^1 = 3,5-difluorophenyl, R^3=R^4=H, R^5=OMe)



a) 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester (Compound **19** , Structure **7** of Scheme **III**, where R^1 = 3,5-difluorophenyl, R^3=R^4=H, R^5=OMe)

Chlorine gas was bubbled through CCl_4 (5 mL) at -10°C for 3 min. Then a solution of methylthiosalicylate (91 µL, 0.66 mmol) in CCl_4 (2 mL) was added. The mixture was stirred at -10°C for 5 min and then at room temperature for 15 min. The mixture was concentrated and redissolved in CH_2Cl_2 (5 mL). To this solution a solution of 1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indole (121 mg, 0.443 mmol) in CH_2Cl_2 (3 mL) was added dropwise. The mixture was stirred at room temperature for 2 h and was concentrated. The crude product was purified by column chromatography (ethyl acetate/heptane 1:9) to give the title compound as a white solid (161 mg, 83% yield). LCMS: 4.72 min (MH^+ = 440); ^{1}H-NMR ($CDCl_3$) : δ 3.82 (s, 3H, $ArOCH_3$), 3.99 (s, 3H, CO_2CH_3), 5.30 (s, 2H, CH_2Ar), 6.62-6.69 (m, 2H), 6.71-6.77 (m, 2H), 6.83 (dd, 1H, J1 = 8.6 Hz, J2 = 2.4 Hz), 6.87 (dd, 1H, J1 = 8.4 Hz, J2 = 1.2 Hz), 7.06-7.11 (m, 1H, 7.15-7.20 (m, 1H), 7.30 (s, 1H), 7.44 (d, 1H, J = 8.6 Hz), 8.02 (dd, 1H, J1 = 8.0 Hz, J2 = 1.2 Hz).

b) {2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-phenyl}-methanol (Compound **16** , Structure **8** of Scheme **III**, where R^1 = 3,5-difluorophenyl, R^3=R^4=H, R^5=OMe)

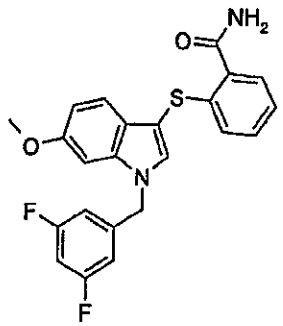
Under a nitrogen atmosphere: to a solution of 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester (13.5 mg, 0.031 mmol) in THF (2 mL) was added $LiAlH_4$ (1.0 M in THF, 0.040 mL, 0.040 mmol). The mixture was stirred at room temperature for 3 h. Then ethyl acetate (25 mL) was added and the mixture was washed with 3% aqueous citric acid (2x25 mL) and brine (25 mL). The organic phase was dried ($MgSO_4$) and concentrated to give a colourless oil (15 mg). The crude product

was purified by prep. HPLC to give the title compound as a colourless oil (5.6 mg, 44% yield).

LCMS: 4.47 min (95.6%, $MH^+ = 412$); ^{1}H-NMR ($CDCl_3$) : δ 3.49 (s, 1H, OH), 3.81 (3, 3H, OCH_3), 4.92 (s, 2H, $C\underline{H_2}OH$), 5.28 (s, 2H, CH_2Ar), 6.62-6.66 (m, 2H), 6.70-6.77 (m, 2H), 6.83 (dd, 1H, J1 = 8.8 Hz, J2 = 2.4 Hz), 6.89 (dd, 1H, J1 = 8.0 Hz, J2 = 1.2 Hz), 7.02-7.07 (m, 1H), 7.08-7.13 (m, 1H), 7.29 (s, 1H), 7.38 (dd, 1H, J1 = 8.0 Hz, J2 = 1.2 Hz), 7.44 (d, 1H, J = 8.8 Hz).

Example 9

2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzamide (Compound **18**, Structure **11** of Scheme **III**, where R^1 = 3,5-difluorophenyl, R^3=R^4=H, R^5=OMe)



a) 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzoic acid (Structure **9** of Scheme **III**, where R^1 = 3,5-difluorophenyl, R^3=R^4=H, R^5=OMe)

To a solution of 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester (97 mg, 0.221 mmol) in THF (10 mL) was added a solution of $LiOH \cdot H_2O$ (71 mg, 1.69 mmol) in water (10 mL). The mixture was stirred at room temperature for 17 h and then at 60°C for 24 h and was then acidified with 3% aqueous citric acid. Ethyl acetate (50 mL) was added and the mixture was washed with 3% aqueous citric acid (2x50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$) and concentrated to give a yellow solid (104 mg). The crude product was recrystallised from ethyl acetate/heptane to give the title compound as a yellow powder (49 mg, 52% yield).

LCMS: 4.37 min (MH^+ = 426); ^{1}H-NMR ($CDCl_3$) : δ 3.77 (s, 3H, OCH_3), 5.51 (s, 2H, CH_2Ar), 6.69 (d, 1H, J = 8.0 Hz), 6.76 (dd, 1H, J1 = 8.4 Hz, J2 = 2.4 Hz), 6.98-7.04 (m, 2H), 7.11-7.15 (m, 1H), 7.16-7.25 (m, 4H), 7.83 (s, 1H), 7.92 (dd, 1H, J1 = 8.0Hz, J2 = 1.6 Hz).

General method 4: Reaction of an amine with a carboxylic acid of structure **9**, with TBTU and DIPEA, to give amides of structure **3**, in which R^2 = phenyl-2-carboxamide , exemplified by compounds of structure **10** and **11** (Scheme **III**).

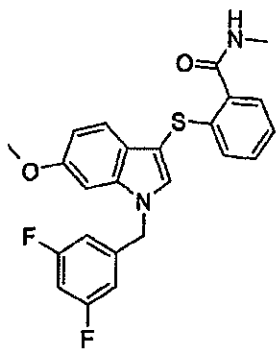
b) 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzamide (Compound **18**, Structure **11** of Scheme **III**, where R^1 = 3,5-difluorophenyl, R^3=R^4=H, R^5=OMe)

Through a solution of 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzoic acid (36 mg, 0.085 mmol), TBTU (28 mg, 0.087 mmol) and DIPEA (30 µL, 0.172 mmol) in DMF (1 mL) was bubbled NH_3 gas for 10 min. The mixture was then stirred at room temperature for 3 days. Then 3% aqueous citric acid (0.4 mL) was added and the crude reaction mixture was purified over a RP-SPE cartridge (2g sorbent; 25% aqueous methanol to 100% methanol) to give a white solid (34 mg). The crude product was purified by column chromatography (ethyl acetate) to give the title compound as a colourless oil, which solidifies on standing (31 mg, yield: 86%).

LCMS: 4.20 min (MH^+ = 425); ^{1}H-NMR ($CDCl_3$) : δ 3.81 (s, 3H, OCH_3), 5.39 (s, 2H, CH_2Ar), 6.05 (s, br, 1H, NH), 6.28 (s, br, 1H, NH), 6.61-6.67 (m, 2H), 6.70-6.72 (m, 1H), 6.73-6.77 (m, 1H), 6.83 (dd, 1H, J1 = 8.8 Hz, J2 = 2.0 Hz), 6.92 (dd, 1H, J1 = 8.0 Hz, J2 = 1.2 Hz), 7.07-7.17 (m, 2H), 7.31 (s, 1H), 7.45 (d, 1H, J = 8.8 Hz), 7.60 (dd, 1H, J1 = 8.0 Hz, J2 = 1.2 Hz).

Example 10

2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-*N*-methyl-benzamide (Compound **17**, Structure **10** of Scheme **III**, where R^1 = 3,5-difluorophenyl, R^3=R^4=H, R^5=OMe)

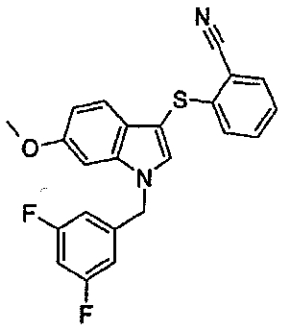


According to general **method 4** compound **17** was synthesised from methylamine.

LCMS: 4.07 min (MH^+ = 439).

Example 11

2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzonitrile (Compound 20, Structure 12 of Scheme III, where R^1 = 3,5-difluorophenyl, R^3=R^4=H, R^5=OMe)

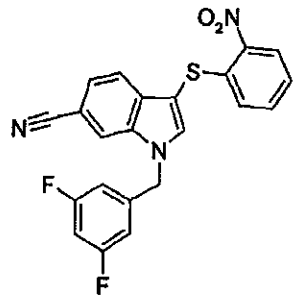


To a cooled (0°C) solution of 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzamide (8 mg, 0.019 mmol) and Et_3N (10 µL, 0.072 mmol) in CH_2Cl_2 (1.5 mL) was added Tf_2O (6 µL, 0.036 mmol). The mixture was stirred at 0°C for 2 h and then at room temperature for 22 h. Water (25 mL) was added and the mixture was extracted with CH_2Cl_2 (2x25 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to give a brown oil (25 mg). The crude product was purified by column chromatography (ethyl acetate/heptane 1:2) to give the title compound as a pale pink oil (3 mg, yield: 39%).

LCMS: 4.57 min (MH^+ = 407); ^{1}H-NMR ($CDCl_3$): δ 3.82 (s, 3H. OCH_3), 5.30 (s, 2H, CH_2Ar), 6.62-6.67 (m, 2H), 6.71-6.73 (m, 1H), 6.74-6.78 (m, 1H), 6.86 (dd, 1H, J1 = 8.8 Hz, J2 = 2.0 Hz), 6.91 (d, 1H, J = 8.4 Hz), 7.11-7.15 (m, 1H), 7.26-7.30 (m, 1H), 7.37 (s, 1H), 7.46 (d, 1H, J = 8.8 Hz), 7.57-7.60 (m, 1H).

Example 12

1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carbonitrile (Compound 26, Structure 17 of Scheme IV, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H)

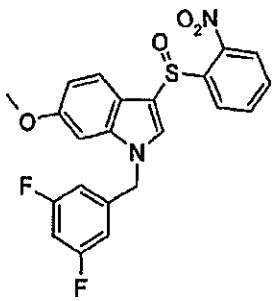


To a cooled (0°C) suspension of 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid amide (15 mg, 0.034 mmol) and Et_3N (10 µL, 0.072 mmol) in CH_2Cl_2 (1.5 mL) was added Tf_2O (13 µL, 0.077 mmol). The mixture was stirred at 0°C for 2 h and then at room temperature for 20 h. Water (25 mL) was added and the mixture was extracted with CH_2Cl_2 (2x25 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to give the title compound as a yellow solid (13 mg, yield: 91%).

LCMS: 4.55 min (MH^+ = not detectable); ^{1}H-NMR ($CDCl_3$): δ 5.42 (s, 2H, CH_2Ar), 6.63-6.69 (m, 2H), 6.78-6.85 (m, 2H), 7.21-7.25 (m, 1H), 7.28-7.33 (m, 1H), 7.44 (dd, 1H, J1 = 8.4 Hz, J2 = 1.2 Hz), 7.62 (d, 1H, J = 8.4 Hz), 7.66 (s, 1H), 8.29 (dd, 1H, J1 = 8.4 Hz, J2 = 1.6 Hz).

Example 13

1-(3,5-Difluoro-benzyl)-6-methoxy-3-(2-nitro-benzenesulfinyl)-1*H*-indole (Compound 64, Structure **5** of Scheme **II**, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^5=OMe)



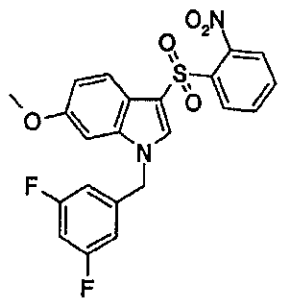
To a solution of 1-(3,5-Difluoro-benzyl)-6-methoxy-3-(2-nitro-phenylsulfanyl)-1*H*-indole (40 mg, 0.09 mmol) in CH_2Cl_2 (4 mL) was added meta-chloroperbenzoic acid (14.5, 0.08 mmol). The solution was stirred at room temperature for 2 h. The solvent

was evaporated and the crude product was purified by prep LC-MS to give the title compound (14.3 mg, yield = 34%).

HPLC : 4.13 min, purity 100%; TLC (heptane/ethyl acetate 1:1) : Rf = 0.4; ^{1}H NMR ($CDCl_3$): δ 3.66 (s, 3H, OCH3), 5.12 (s, 2H), 6.57 (m, 3H), 6.75 (m, 2H), 7.47 (d, 1H, J = 7.8 Hz), 7.52 (s, 1H), 7.66-7.70 (m, 1H), 8.28-8.32 (m, 1H), 8.23 (dd, 1H, J1 = 7.8 Hz, J2 = 1.9 Hz), 8.80 (dd, 1H, J1 = 7.8 Hz, J2 = 3.1 Hz).

Example 14

1-(3,5-Difluoro-benzyl)-6-methoxy-3-(2-nitro-benzenesulfonyl)-1*H*-indole (Compound **62**, Structure 6 of Scheme II, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^5=OMe)

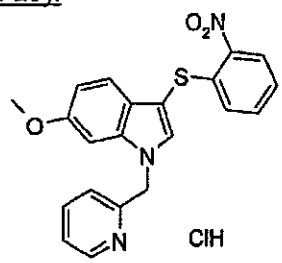


To a solution of 1-(3,5-Difluoro-benzyl)-6-methoxy-3-(2-nitro-phenylsulfanyl)-1*H*-indole (40 mg, 0.09 mmol) in CH_2Cl_2 (4 mL) was added meta-chloroperbenzoic acid (46.5 mg, 0.27 mmol). The solution was stirred at room temperature for 6 h. The solvent was evaporated and the crude product was purified by LC-MS to give the title compound (14.5 mg, yield = 34%).

HPLC: 4.38 min. purity 100%; TLC (heptane/ethyl acetate 1:1) : Rf = 0.6; ^{1}H NMR ($CDCl_3$): δ 3.71 (s, 3H, OCH3), 5.25 (s, 2H), 6.58 (d, 1H, J = 3.1), 6.62 (m, 1H), 6.07-6.11 (m, 1H), 6.88 (dd, 1H, J1 = 7.8 Hz, J2 = 3.1 Hz), 7.63 (m, 4H), 7.72 (d, 1H, J = 7.8 Hz), 7.83 (s, 1H), 8.37 (dd, 1H, J1 = 7.8 Hz, J2 = 1.9 Hz).

Example 15

6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole monohydrochloride (Compound **10**).

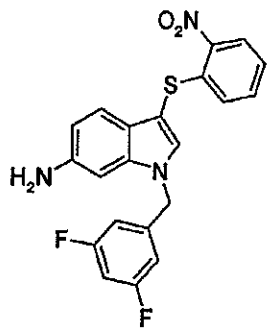


To a solution of 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole in methylene chloride was passed HCl-gas till the organic salt crystallised. The title compound was isolated by filtration.

LC-MS : 4.04 min (MH^+ = 392); ^1H NMR (DMSO): δ 3.78 (s, 3H, OCH3), 5.78 (s, 2H, NCH_2), 6.77 (dd, 1H, J1 = 7.8 Hz, J2 = 2.0 Hz), 6.93 (dd, 1H, J1 = 7.8 Hz, J2 = 0.8 Hz), 7.22 (d, 1H, J = 7.8 Hz), 7.26 (d, 1H, J = 2.0 Hz), 7.34 (m, 2H), 7.48-7.52 (m, 1H), 7.59 (t, 1H, J = 7.0 Hz), 7.96 (s, 1H), 8.08 (t, 1H, J = 7.0 Hz), 8.27 (dd, 1H, J1 = 7.8 Hz, J2 = 1.6 Hz), 8.74 (d, 1H, J = 6.7 Hz).

Example 16

1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-ylamine (Compound **57**, Structure **23** of Scheme **V**, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H)



a) 1-(3,5-Difluoro-benzyl)-6-nitro-1*H*-indole (Structure **19** of Scheme **V**, where R^1 = 3,5-difluorophenyl, R^3=R^4=H)

To a solution of 6-nitroindole (162 mg, 1.0 mmol) in DMF (4 mL) was added NaH (60% dispersion on oil; 80 mg, 2.0 mmol). The resulting dark solution was stirred at room temperature for 15 minutes. 3,5-difluorobenzyl bromide (129 µL, 1,1 mmol) was added. The reaction mixture was stirred overnight, poured into acidified water and extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*.

The product was purified over a SiO_2 column (heptane/ethyl acetate 9:1) to give the title compound as a yellow solid (270 mg, yield = 94%).

LCMS: 5.54 min (100.0%, MH^+ = 289); ^1H NMR ($CDCl_3$): δ 5.40 (s, 2H, CH_2Ar), 6.58 (m, 2H), 6.71 (d, 1H, J = 3.5 Hz), 6.75 (m, 1H), 7.26 (s, 1H), 7,41 (d, 1H, J = 3.5 Hz), 7.71 (d, 1H, J = 8.3 Hz), 8.05 (dd, 1H, J1 = 8.3 Hz, J2 = 2.0 Hz), 8.21 (d, 1H, J = 2.0 Hz).

b) 1-(3,5-Difluoro-benzyl)-1*H*-indol-6-ylamine (Structure **20** of Scheme **V**, where R^1 = 3,5-difluorophenyl, R^3=R^4=H)

To a solution of 1-(3,5-Difluoro-benzyl)-6-nitro-1*H*-indole (144 mg, 0.5 mmol) in ethanol (20 mL) was added hydrochloric acid 37% (80 µL) and $SnCl_2.2H_2O$ (600 mg). The reaction mixture was stirred at 60 °C for 40 h and was then concentrated *in vacuo*. The residue was poured into ethyl acetate and a concentrated $NaHCO_3$-solution was added. The two-layer phase system was filtered over decalite to get rid of the tin salts and the filtrate was twice extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The product was purified over a SiO_2 column (heptane/ethyl acetate 9:1) to give the title compound as a colourless oil (89 mg, yield = 69%).

LCMS: 3.20 min (97.7%, $MH^+ = 259$); ^1H NMR ($CDCl_3$): δ 5.12 (s, 2H, $C\underline{H}_2Ar$), 6.52 (m, 2H), 6.56 (d, 1H, J = 3.5 Hz), 6.63 (m, 1H), 7.97 (dd, 1H, J1 = 8.3 Hz, J2 = 2.0 Hz), 7.13 (d, 1H, J = 3.5 Hz), 7,17 (d, 1H, J = 2.0 Hz), 7.55 (d, 1H, J = 8.3 Hz).

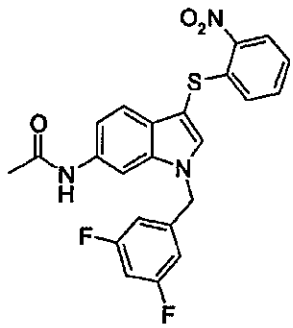
c) 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-ylamine (Compound 57, Structure **23** of Scheme V, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H)

To a solution of 1-(3,5-Difluoro-benzyl)-1*H*-indol-6-ylamine (25 mg, 0.1 mmol) in DCM (4 mL) was added 2-nitrobenzenesulfenyl chloride. The resulting yellow solution was stirred at room temperature for 1 hour. The mixture was concentrated *in vacuo* and purified over a SiO_2 column (heptane/ethyl acetate 9:1) to give the title compound as an orange solid (11.6 mg, yield = 28%).

LCMS: 5.11 min (100.0%, $MH^+ = 412$); ^1H NMR ($CDCl_3$): δ 5.22 (s, 2H, $C\underline{H}_2Ar$), 6.56 (m, 2H), 6.65 (m, 1H), 6.84 (dd, 1H, J1 = 8.2 Hz, J2 = 1.2 Hz), 7.00 (dd, 1H, J1 = 8.2 Hz, J2 = 1.2 Hz), 7.19 (m, 1H), 7.30 (d, 1H, J = 1.2 Hz), 7.31 (s, 1H), 7.37 (d, 1H, J = 8.2 Hz) 7.49 (m, 1H), 8.27 (dd, 1H, J1 = 8.2 Hz, J2 = 1.2 Hz).

Example 17

N-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-acetamide (Compound **58**, Structure **22** of Scheme **V**, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, Z = methyl)



General method 5: Reaction of an acid anhydride with a 6-aminoindole of structure **20** to give compounds of structure **21**, followed by sulfanylation of the indole 3-position to give compounds of structure **22** (Scheme **V**).

a) *N*-[1-(3,5-Difluoro-benzyl) -1*H*-indol-6-yl]-acetamide (Structure **21** of Scheme **V**, where R^1 = 3,5-difluorophenyl, R^3=R^4=H, Z = methyl)

To a solution of 1-(3,5-Difluoro-benzyl)-1*H*-indol-6-ylamine (25 mg, 0.1 mmol) in DCM (4 mL) was added pyridine (25 µL) and acetic anhydride (9.8 µL, 0.11 mmol) and stirred overnight at room temperature. The reaction mixture was poured into 10 mL of water and neutralised with $NaHCO_3$ and extracted twice with DCM. De combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give the crude compound as a off white solid (23.3 mg, yield = 84%). The product was used without further purification.

LCMS: 4.10 min (97.4%, MH^+ = 301); ^{1}H NMR ($CDCl_3$): δ 2.18 (s, 3H, CH_3CON), 5.28 (s, 2H, CH_2Ar), 6.53 (d, 1H, J = 3.1), 6.58 (m, 2H), 6.68 (m, 1H), 6.87 (dd, 1H, J1 = 8.3 Hz, J2 = 1.6 Hz), 7.07 (d, 1H, J = 3.1 Hz), 7,55 (d, 1H, J = 8.3 Hz), 7.90 (s, 1H).

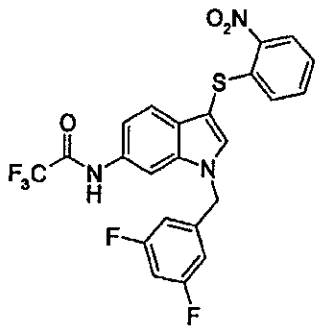
b) *N*-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-acetamide (Compound **58**, Structure **22** of Scheme **V**, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, Z = methyl)

To a solution of *N*-[1-(3,5-Difluoro-benzyl)-1*H*-indol-6-yl]-acetamide (23.3 mg, 0.08 mmol) in diethyl ether (4 mL) was added 2-nitrobenzenesulfenyl chloride (14.7 mg,

0.09 mmol). The resulting yellow solution was stirred overnight at room temperature. The mixture was concentrated *in vacuo* and purified over a SiO_2 column (heptane/ethyl acetate 9:1) to give the title compound as a yellow solid (35.0 mg, yield = 96%).
LCMS: 4.26 min (98.6%, MH^+ = 454); ^1H NMR (DMSO): δ 2.03 (s, 3H, CH_3CON), 5.51 (s, 2H, CH_2Ar), 6.89 (dd, 1H, J = 8.3 Hz, J2 = 1.2 Hz), 6.95 (m, 2H), 7.17 (dd, 1H, J1 = 8.3 Hz, J2 = 2.0 Hz), 7.19 (m, 1H), 7.27 (d, 1H, J = 8.3 Hz), 7,34 (m, 1H), 7.49 (m, 1H), 7.97 (d, 1H, J = 1.2 Hz), 8.02 (s, 1H), 8.27 (dd, 1H, J1 = 8.3 Hz, J2 = 1.2 Hz).

Example 18

N-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-2,2,2-trifluoro-acetamide (Compound **59**, Structure **22** of Scheme **V**, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, Z = trifluoromethyl)

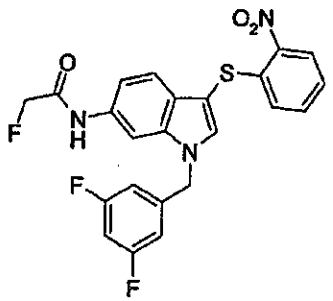


According to General method 5, step a): *N*-[1-(3,5-Difluoro-benzyl)-1*H*-indol-6-yl]-2,2,2-trifluoro-acetamide was prepared using 1-(3,5-Difluoro-benzyl)-1*H*-indol-6-ylamine (17.7 mg, 69 µmol), pyridine (17 µL) and trifluoroacetic anhydride (9,68 µL, 70 µmol). The compound was purified over a SiO_2 column (heptane/ethyl acetate 9:1) to give the title compound as a white solid (10.9 mg, yield = 61%).
LCMS: 4.41 min (82.1%, MH^+ = 355)
According to General method 5, step b): *N*-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-2,2,2-trifluoro-acetamide was prepared using *N*-[1-(3,5-Difluoro-benzyl)-1*H*-indol-6-yl]-2,2,2-trifluoro-acetamide (10.9 mg, 31 µmol) and 2-nitrobenzenesulfenyl chloride (5.7 mg, 37 µmol). The compound was purified over an HPLC column ($MeCN/H_2O$) to give the title compound as a yellow solid (10.2 mg, yield = 65%).
LCMS: 4.65 min (89.0%, MH^+ = 508); ^1H NMR (DMSO): δ 5.56 (s, 2H, CH_2Ar), 6.87 (dd, 1H, J = 8.3 Hz, J2 = 1.2 Hz), 7.01 (m, 2H), 7.20 (m, 1H), 7.35 (m, 1H), 7.37 (dd,

1H, J1 = 8.3 Hz, J2 = 2.0 Hz), 7.39 (d, 1H, J = 8.3 Hz), 7.49 (m, 1H), 7,50 (d, 1H, J = 2.0 Hz), 8.15 (s, 1H), 8.28 (dd, 1H, J1 = 8.3 Hz, J2 = 2.0 Hz).

Example 19

Compound 97: *N*-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-2-fluoro-acetamide, structure 28 of Scheme VII, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, Z^1= monofluoromethyl.



a) 1-(3,5-Difluoro-benzyl)-6-nitro-1*H*-indole, structure 19 of Scheme VII, where R^1 = 3,5-difluorophenyl, R^2=R^3=R^4=H.

To a solution of 6-nitro-1*H*-indole (19.5 g, 120 mmol) in NMP (500 mL) was added at 0 °C cesium carbonate (39.1 g, 120 mmol). After stirring for 30 min at 0 °C 3,5-difluorobenzyl bromide (30.0 g, 144 mmol) was added and the mixture was allowed to warm to room temperature and stirred for 18 hrs. The mixture was poured into saturated aqueous ammonium chloride (1 L) and extracted with ethyl acetate (2 x 500 mL). The combined organic layers were washed with H_2O (2 x 500 mL) and brine (500 mL) and dried (Na_2SO_4) and concentrated to give the title compound (65 g, yellow solid) which was used without furter purification.

b) 1-(3,5-Difluoro-benzyl)-1*H*-indol-6-ylamine, structure 20 of Scheme VII, where R^1 = 3,5-difluorophenyl, R^2=R^3=R^4=H.

EtOH 96% (1L) was added to 1-(3,5-difluoro-benzyl)-6-nitro-1*H*-indole and the mixture was stirred at 60 °C until all material was dissolved. 37% HCl (37 mL) was added followed by tin(II)chloride dihydrate (268 g, 1.19 mol) and stirring was continued at 60 °C for 18 hrs. After the mixture was cooled to room temperature the solvent was removed under reduced pressure. Ethyl acetate (800 mL) was added and the mixture was poured into saturated aqueous $NaHCO_3$ (1 L) and filtered over kieselguhr. The layers were separated and the organic layer was washed with H_2O (2 x 500 mL) and

brine (500 mL), dried (Na_2SO_4) and concentrated to afford the the title compound (54 g, brown oil/solid) which was used without further purification.

c) [1-(3,5-Difluoro-benzyl)-1*H*-indol-6-yl]-carbamic acid *tert*-butyl ester, structure **26** of Scheme **VII**, where R^1 = 3,5-difluorophenyl, R^2=R^3=R^4=H.

1-(3,5-Difluoro-benzyl)-1*H*-indol-6-ylamine was dissolved in NMP (1 L) and triethylamine (34 mL, 242 mmol) was added followed by di-*tert*-butyl dicarbonate (53 g, 242 mmol) and the mixture was stirred at room temperature for 18 hrs. The mixure was poured into saturated aqueous $NaHCO_3$ (1.5 L) and extracted with ethyl acetate (3 x 750 mL). The combined organic layers were washed with H_2O (1 L) and brine (1 L), dried (Na_2SO_4) and concentrated. The crude product was purified using column chromatography (heptane/ethyl acetate 4:1) to afford the title compound (39 g, 109 mmol, 91% (three steps), white solid).

d) [1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-carbamic acid *tert*-butyl ester, structure **27** of Scheme **VII**, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H.

To a solution of [1-(3,5-difluoro-benzyl)-1*H*-indol-6-yl]-carbamic acid *tert*-butyl ester (39 g, 109 mmol) in diethylether (750 mL) was added 2-nitrobenzenesulfenyl chloride (20.4 g, 109 mmol) and the reaction mixture was stirred at room temperature for 18 hrs. The mixture was poured into saturated aqueous $NaHCO_3$ (1 L) and extracted with ethyl acetate (2 x 300 mL). The combined organic layers were washed with H_2O (400 mL) and brine (400 mL), dried and concentrated to afford the title compound (56 g, yellow solid) which was used without further purification.

e) 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-ylamine, structure **23** of Scheme **VII**, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H.

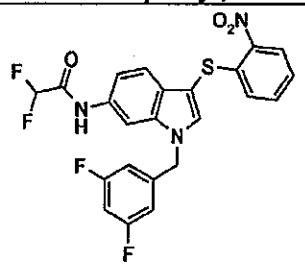
[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-carbamic acid *tert*-butyl ester was dissolved in CH_2Cl_2 (1 L) and under nitrogen atmosphere trifluoroacetic acid (48 mL, 624 mmol) was added dropwise at room temperature. After stirring for 1 h another portion of trifluoroacetic acid (48 mL, 624 mmol) was added and the reaction mixture was stirred for an additional hour. The mixture was diluted with CH_2Cl_2 (500 mL) and H_2O (1 L) and 3N NaOH solution was added until the pH of the mixture was 11-12. The layers were separated and the organic layer was washed with H_2O (500 mL) and brine (500 mL), dried (Na_2SO_4) and concentrated to afford the crude product. The

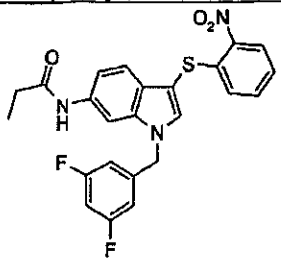
product was purified using column chromatography (heptane/ethylacetate 1:1) to give the title compound (28 g, 68 mmol, 63 % (two steps), red/brown solid).

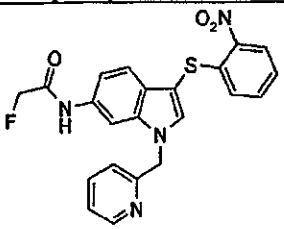
General method 6: Reaction of an acid chloride (method a), carboxylic acid (method b) or sulfonyl chloride (method c) with a 6-aminoindole of structure **23** to give compounds of structure **28** and **29** (Scheme **VII**).
Method a, b and c can all be carried out using the same procedure which is examplified below for method a.

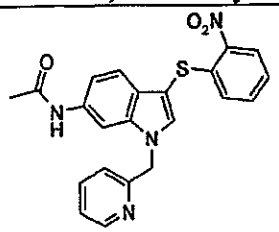
To a solution of 1-(3,5-difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-ylamine (300 mg, 0.73 mmol) in CH_2Cl_2 (7 mL) was added at 0 °C triethylamine (0.12 mL, 0.87 mmol). Subsequently monofluoroacetyl chloride (50 µL, 0.73 mmol) was added and the mixture was stirred at room temperature for 18 hrs. The mixture was concentrated and purified using flash column chromatography (CH_2Cl_2/MeOH 99:1) to afford compound **97** (317 mg, 0.67 mmol, 92%, yellow solid).
^{1}H NMR (DMSO) δ 4.82 (s, 1H), 5.03 (s, 1H), 5.52 (s, 2H), 6.89 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 6.98-7.01 (m, 2H), 7.20 (tt, 1H, J1 = 9.5 Hz, J2 = 3.0 Hz), 7.28-7.32 (m, 2H), 7.33-7.37 (m, 1H), 7.46-7.51 (m, 1H), 7.98 (s, 1H), 8.08 (s, 1H), 8.27 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 10.15 (s, 1H).

According to **general method 6** the following compounds were prepared:

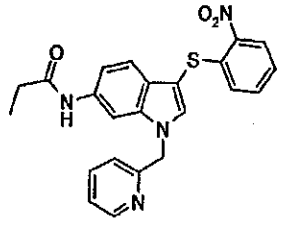
Compound **98**: *N*-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-2,2-difluoro-acetamide, structure **28** of Scheme **VII**, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, Z^1= difluoromethyl. Method a was used.	
	^{1}H-NMR (DMSO): δ 5.55 (s, 2H), 6.23-6.50 (m, 1H), 6.88 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 6.97-7.03 (m, 2H), 7.20 (tt, 1H, J1 = 9.5 Hz, J2 = 3.0 Hz), 7.30-7.38 (m, 3H), 7.46-7.51 (m, 1H), 7.98 (d, 1H, J = 1.1 Hz), 8.12 (s, 1H), 8.28 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 10.80 (s, 1H).

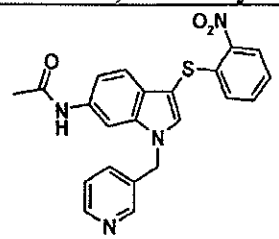
Compound 99: *N*-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-propionamide, structure **28** of Scheme **VII**, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, Z^1= ethyl. Method b was used.	
	^{1}H-NMR (DMSO): δ 1.07 (t, 3H, J = 7.6 Hz), 2.31 (q, 2H, J = 7.6 Hz), 5.51 (s, 2H), 6.89 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 6.93-6.97 (m, 1H), 7.16-7.23 (m, 3H), 7.27 (d, 1H, J = 8.4 Hz), 7.32-7.37 (m, 1H), 7.46-7.51 (m, 1H), 8.01 (d, 1H, J = 1.1 Hz), 8.02 (s, 1H), 8.27 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 9.92 (s, 1H).

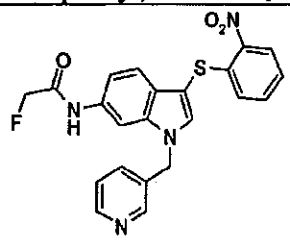
Compound **100**: 2-Fluoro-*N*-[3-(2-nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indol-6-yl]-acetamide, structure **28** of Scheme **VII**, where R^1 = 2-pyridyl, R^2 = 2-nitrophenyl, R^3=R^4=H, Z^1= monofluoromethyl. Method a was used.	
	^{1}H-NMR ($CDCl_3$): δ 4.88 (s, 1H), 5.00 (s, 1H), 5.51 (s, 2H), 6.94-6.99 (m, 2H), 7.06 (dd, 1H, J1 = 7.6 Hz, J2 = 1.5 Hz), 7.18 (td, 1H, J1 = 8.4 Hz, J2 = 1.5 Hz), 7.22-7.29 (m, 2H), 7.46 (d, 1H, J = 8.4 Hz), 7.55 (s, 1H), 7.64 (td, 1H, J1 = 8.4 Hz, J2 = 1.5 Hz), 8.02 (s, 1H), 8.05 (d, 1H, J = 2.2 Hz), 8.27 (dd, 1H, J1 = 7.6 Hz, J2 = 1.5 Hz), 8.62 (d, 1H, J = 4.6 Hz).

Compound **101**: *N*-[3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indol-6-yl]-acetamide, structure **28** of Scheme **VII**, where R^1 = 2-pyridyl, R^2 = 2-nitrophenyl, R^3=R^4=H, Z^1= methyl. Method a was used.	
	^{1}H-NMR ($CDCl_3$): δ 1.80 (s, 3H), 5.48 (s, 2H), 6.92-6.98 (m, 3H), 7.15-7.30 (m, 4H), 7.40 (d, 1H, J = 7.6 Hz), 7.51 (s, 1H), 7.63 (td, 1H, J1 = 7.6 Hz, J2 = 2.2 Hz), 8.04 (d, 1H, J = 1.5 Hz), 8.26 (dd, 1H, J1 = 7.6 Hz, J2 = 1.5 Hz), 8.61 (d, 1H, J = 4.6 Hz).

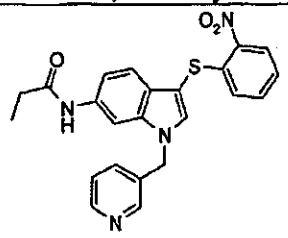
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Compound **102**: *N*-[3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indol-6-yl]-propionamide, structure **28** of Scheme **VII**, where R^1 = 2-pyridyl, R^2 = 2-nitrophenyl, R^3=R^4=H, Z^1= ethyl). Method b was used.	
	^{1}H-NMR ($CDCl_3$): δ 1.25 (t, 3H, J = 7.6 Hz), 2.41 (q, 2H, J = 7.6 Hz), 5.49 (s, 2H), 6.92-6.98 (m, 3H), 7.15-7.27 (m, 4H), 7.40 (d, 1H, J = 8.4 Hz), 7.51 (s, 1H), 7.63 (td, 1H, J1 = 7.6 Hz, J2 = 1.5 Hz), 8.12 (d, 1H, J = 1.5 Hz), 8.26 (dd, 1H, J1 = 7.6 Hz, J2 = 1.5 Hz), 8.61 (d, 1H, J = 4.6 Hz).

Compound **103**: *N*-[3-(2-Nitro-phenylsulfanyl)-1-pyridin-3-ylmethyl-1*H*-indol-6-yl]-acetamide, structure **28** of Scheme **VII**, where R^1 = 3-pyridyl, R^2 = 2-nitrophenyl, R^3=R^4=H, Z^1= methyl. Method a was used.	
	^{1}H NMR ($CDCl_3$) δ 2.20 (s, 3H), 5.40 (s, 2H), 6.86 (dd, 1H, J1 = 7.6 Hz, J2 = 2.2 Hz), 6.72 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 7.16-7.20 (m, 1H), 7.24-7.31 (m, 3H), 7.40 (d, 1H, J = 8.4 Hz), 7.42 (s, 1H), 7.49-7.52 (m, 1H), 8.15 (d, 1H, J = 2.2 Hz), 8.26 (dd, 1H, J1 = 8.4 Hz, J2 = 2.2 Hz), 8.55 (d, 1H, J = 3.0 Hz), 8.58 (dd, 1H, J1 = 8.4 Hz, J2 = 2.2 Hz).

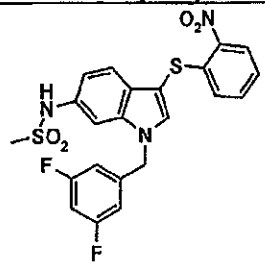
Compound **104**: 2-Fluoro-*N*-[3-(2-nitro-phenylsulfanyl)-1-pyridin-3-ylmethyl-1*H*-indol-6-yl]-acetamide, structure **28** of Scheme **VII**, where R^1 = 3-pyridyl, R^2 = 2-nitrophenyl, R^3=R^4=H, Z^1= monofluoromethyl. Method a was used.	
	^{1}H NMR ($CDCl_3$) δ 4.88 (s, 1H), 5.00 (s, 1H), 5.42 (s, 2H), 6.92 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 7.00 (dd, 1H, J1 = 8.4 Hz, J2 = 1.8 Hz), 7.17-7.21 (m, 1H), 7.25-7.32 (m, 2H), 7.44-7.47 (d, 1H, J = 7.6 Hz), 7.45 (s, 1H), 7.49-7.53 (m, 1H), 8.04 (d, 1H, J = 4.6 Hz), 8.15 (d, 1H, J = 1.8 Hz), 8.27 (dd, 1H, J1 = 8.4 Hz, J2 = 1.8 Hz), 8.56 (d, 1H, J = 3.0 Hz), 8.58 (dd, 1H, J1 = 4.6 Hz, J2 = 1.2 Hz).

Compound **105**: *N*-[3-(2-Nitro-phenylsulfanyl)-1-pyridin-3-ylmethyl-1*H*-indol-6-yl]-propionamide, structure **28** of Scheme **VII**, where R^1 = 3-pyridyl, R^2 = 2-nitrophenyl, R^3=R^4=H, Z^1= ethyl. Method b was used.



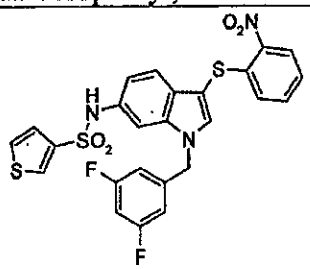
^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3H, J = 7.6 Hz), 2.42 (q, 2H, J = 7.6 Hz), 5.39 (s, 2H), 8.68 (dd, 1H, J1 = 8.4 Hz, J2 = 1.8 Hz), 6.91 (dd, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 7.15-7.20 (m, 1H), 7.24-7.30 (m, 3H), 7.38-7.41 (m, 2H), 7.48-7.52 (m, 1H), 8.23 (d, 1H, J = 1.8 Hz), 8.27 (dd, 1H, J1 = 8.4 Hz, J2 = 1.8 Hz), 8.55 (d, 1H, J = 3.0 Hz), 8.57 (dd, 1H, J1 = 4.6 Hz, J2 = 1.1 Hz).

Compound **106**: *N*-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-methanesulfonamide, structure **29** of Scheme **VII**, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, Z^2= Me. Method c was used.

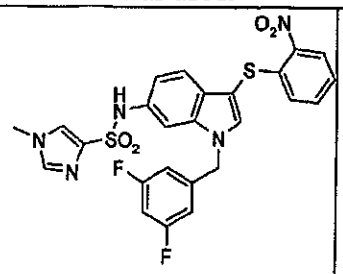


^{1}H-NMR (DMSO): δ 2.95 (s, 3H), 5.54 (s, 2H), 6.90 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 6.98-7.04 (m, 3H), 7.20 (tt, 1H, J1 = 9.5 Hz, J2 = 3.0 Hz), 7.31-7.37 (m, 2H), 7.41 (d, 1H, J = 1.5 Hz), 7.47-7.52 (m, 1H), 8.08 (s, 1H), 8.27 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 9.65 (s, 1H).

Compound **107**: Thiophene-3-sulfonic acid [1-(3,5-difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-amide, structure **29** of Scheme **VII**, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, Z^1= 3-thiophene. Method c was used.

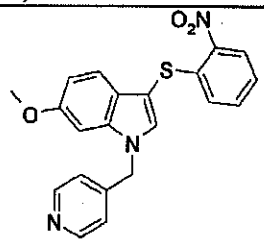


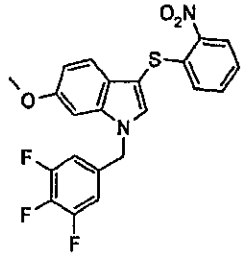
^{1}H-NMR (DMSO): δ 5.50 (s, 2H), 6.85 (m, 2H), 6.92-6.97 (m, 2H), 7.13 (dd, 1H, J1 = 5.0, J2 = 1.1 Hz), 7.19-7.26 (m, 2H), 7.31 (d, 1H, J = 2.2 Hz), 7.32-7.36 (m, 1H), 7.45-7.50 (m, 1H), 7.61 (dd, 1H, J1 = 5.0 Hz, J2 = 3.0 Hz), 7.97 (dd, 1H, J1 = 3.0 Hz, J2 = 1.1 Hz), 8.05 (s, 1H), 8.26 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 10.20 (s, 1H).

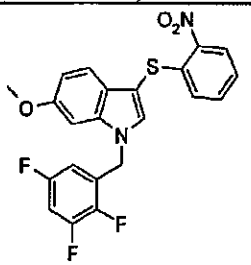
Compound **108**: 1-Methyl-1*H*-imidazole-4-sulfonic acid [1-(3,5-difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-amide, structure **29** of Scheme **VII**, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, Z^2= 4-(1-methyl)-imidazole. Method c was used.	
	^{1}H-NMR (DMSO): δ 3.60 (s, 3H), 5.46 (s, 2H), 6.86 (dd, 1H, J1 = 7.6 Hz, J2 = 0.7 Hz), 6.92 (dd, 1H, J1 = 7.6 Hz, J2 = 1.5 Hz), 6.96-7.01 (m, 2H), 7.19 (d, 1H, J = 7.6 Hz), 7.23 (tt, 1H, J1 = 9.5 Hz, J2 = 3.0 Hz), 7.31-7.36 (m, 2H), 7.45-7.49 (m, 1H), 7.66-7.69 (m, 2H), 8.02 (s, 1H), 8.26 (dd, 1H, J1 = 7.6 Hz, J2 = 0.7 Hz), 10.20 (s, 1H).

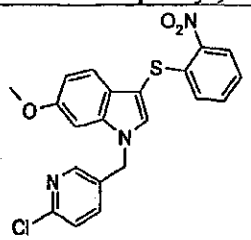
Example 20

According to **general method 3** the following compounds were prepared:

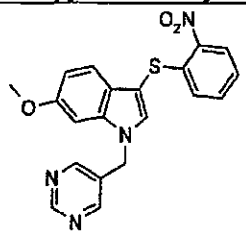
Compound **93**: 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyridin-4-ylmethyl-1*H*-indole, structure **3** of scheme **I**, where R^1 = 4-pyridyl, R^2 = 2-nitrophenyl, R^3 = R^4 = H, R^5 = OMe. NaH and DMF were used.	
	^{1}H NMR ($CDCl_3$): δ 3.80 (s, 3H, OCH_3), 5.37 (s, 2H, NCH_2Ar), 6.71 (d, 1H, J = 2.7 Hz), 6.86 (dd, 1H, J1 = 8.4 Hz, J2 = 2.7 Hz), 7.00 (dd, 1H, J1 = 8.4 Hz, J2 = 1.5 Hz), 7.04 (m, 2H), 7.19 (td, 1H, J1 = 7.6 Hz, J2 = 1.5 Hz), 7.29 (td, 1H, J1 = 7.6 Hz, J2 = 1.5 Hz), 7.36 (s, 1H), 7.40 (d, 1H, J = 8.4 Hz), 8.27 (dd, 1H, J1 = 7.6 Hz, J2 = 1.5 Hz), 8.59 (m, 2H).

Compound **94**: 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-(3,4,5-trifluoro-benzyl)-1*H*-indole, structure **3** of scheme **I**, where R^1 = 3,4,5-difluorophenyl, R^2 = 2-nitrophenyl, $R^3 = R^4$ = H, R^5 = OMe. Cs_2CO_3 and NMP were used.	
	^{1}H-NMR ($CDCl_3$): δ 3.83 (s, 3H, OCH_3), 5.28 (s, 2H, NCH_2Ar), 6.72 (d, 1H, J = 2.2 Hz), 6.75 (d, 1H, J = 7.6 Hz), 6.77 (d, 1H, J = 7.6 Hz), 6.86 (dd, 1H, J1 = 8.4 Hz, J2 = 2.2 Hz), 6.97 (dd, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 7.19 (td, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 7.28 (td, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 7.33 (s, 1H), 7.40 (d, 1H, J = 8.4 Hz), 8.27 (dd, 1H, J1 = 8.4 Hz, J2 = 2.2 Hz).

Compound **95**: 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-(2,3,5-trifluoro-benzyl)-1*H*-indole, structure **3** of scheme **I**, where R^1 = 2,3,5-difluorophenyl, R^2 = 2-nitrophenyl, $R^3 = R^4$ = H, R^5 = OMe. Cs_2CO_3 and NMP were used.	
	^{1}H-NMR ($CDCl_3$): δ 3.85 (s, 3H, OCH_3), 5.39 (s, 2H, NCH_2Ar), 6.42 (m, 1H), 6.82 (d, 1H, J = 2.7 Hz), 6.86 (dd, 1H, J1 = 7.6 Hz, J2 = 2.2 Hz), 6.90 (m, 1H), 6.96 (dd, 1H, J1 = 7.6 Hz, J2 = 2.2 Hz), 7.18 (td, 1H, J1 = 7.6 Hz, J2 = 1.5 Hz), 7.27 (td, 1H, J1 = 7.6 Hz, J2 = 1.5 Hz), 7.37 (s, 1H), 7.39 (d, 1H, J = 7.6 Hz), 8.27 (dd, 1H, J1 = 7.6 Hz, J2 = 1.5 Hz).

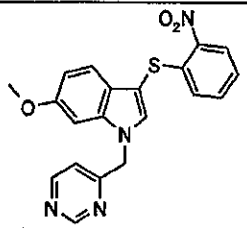
Compound **96**: 1-(6-Chloro-pyridin-3-ylmethyl)-6-methoxy-3-(2-nitro-phenylsulfanyl)-1*H*-indole, structure **3** of Scheme **I**, where R^1 = 4-chloro-3-pyridyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^5=OMe). Cs_2CO_3 and NMP were used.	
	^{1}H-NMR ($CDCl_3$): δ 3.82 (s, 3H, OCH_3), 5.37 (s, 2H, NCH_2Ar), 6.76 (d, 1H, J = 2.2 Hz), 6.84 (dd, 1H, J1 = 7.6 Hz, J2 = 2.2 Hz), 6.96 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 7.18 (td, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 7.27 (td, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 7.30-7.41 (m. 4H), 8.27 (dd, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 8.34 (d, 1H, J = 3.0 Hz).

Compound **115**: 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indole, structure **3** of Scheme **I**, where R^1 = 3,5-pyrimidyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^5=OMe. NaH and DMF were used. The synthesis of methanesulfonic acid pyrimidin-5-ylmethyl ester is described in example **23a**).



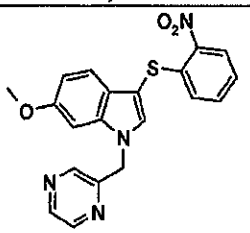
^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3H), 5.38 (s, 2H), 6.77 (d, 1H, J = 3.0 Hz), 6.86 (dd, 1H, J1 = 8.4 Hz, J2 = 3.0 Hz), 6.96 (dd, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 7.17-7.21 (m, 1H), 7.26-7.32 (m, 1H), 7.37 (s, 1H), 7.39 (d, 1H, J = 8.4 Hz), 8.27 (dd, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 8.61 (s, 2H), 9.20 (s, 1H).

Compound **116**: 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyrimidin-4-ylmethyl-1*H*-indole, structure **3** of Scheme **I**, where R^1 = 2,4-pyrimidyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^5=OMe. Cs_2CO_3 and NMP were used.



^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H), 5.44 (s, 2H), 6.74 (d, 1H, J = 2.2 Hz), 6.80 (dd, 1H, J1 = 4.6 Hz, J2 = 1.1 Hz), 6.86 (dd, 1H, J1 = 8.4 Hz, J2 = 3.0 Hz), 7.00 (dd, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 7.17-7.21 (m, 1H), 7.26-7.33 (m, 1H), 7.40 (d, 1H, J = 8.4 Hz), 7.42 (s, 1H), 8.27 (dd, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 8.66 (d, 1H, J = 4.6 Hz), 9.24 (d, 1H, J = 1.1 Hz).

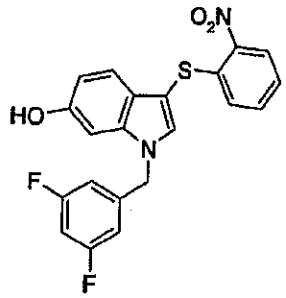
Compound **117**: 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyrazin-2-ylmethyl-1*H*-indole, structure **3** of Scheme **I**, where R^1 = 2,5-pyrazyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^5=OMe. Cs_2CO_3 and NMP were used.



^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3H), 5.49 (s, 2H), 6.82-6.86 (m, 2H), 6.99 (dd, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 7.16-7.20 (m, 1H), 7.25-7.29 (m, 1H), 7.38 (d, 1H, J = 8.4 Hz), 7.46 (s, 1H), 8.26 (dd, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 8.35 (d, 1H, J = 1.1 Hz), 8.55 (d, 1H, J = 3.0 Hz), 8.59-8.61 (m, 1H).

Example 21

Compound **61**: 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-ol, structure **25** of Scheme **VI**, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^5=OH.

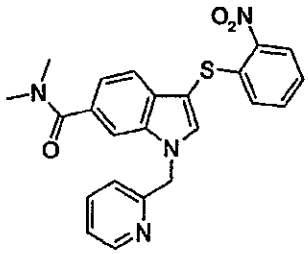


To a solution of compound **63** (240 mg, 0.56 mmol) in CH_2Cl_2 (10 mL) was added at 0 °C boron trifluoride-methyl sulfide complex (2.37 mL, 22.5 mmol). After stirring for 2 hrs at 0 °C the reaction mixture was allowed to warm to room temperature and stirring was continued for another 4 hrs. The reaction mixture was poored into ice water (20 mL) and after addition of ethyl acetate (10 mL) the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL) and dried over Na_2SO_4. Concentration gave the crude product which was purified using flash chromatography (heptane/ethylactate 3:2) to afford compound **61** as a yellow oil (87 mg, 0.21 mmol, 38%).

^{1}H NMR ($CDCl_3$) δ 4.75 (2, 1H), 5.29 (s, 2H), 4.66 (m, 1H), 6.72-6.79 (m, 3H), 6.98 (dd, 1H, J1 = 8.4 Hz, J2 = 1.5 Hz), 7.17-7.21 (m, 1H), 7.27-7.31 (m, 1H), 7.35-7.37 (m, 3H), 8.27 (dd, 1H, J1 = 8.4 Hz, J2 = 1.5 Hz).

Example 22

Compound **109**: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carboxylic acid dimethylamide, structure **15** of Scheme **IV**, where R^1 = 2-pyridyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^8=R^9=Me.



a) 1-Pyridin-2-ylmethyl-1*H*-indole-6-carboxylic acid methyl ester.

Under a nitrogen atmosphere: to a solution of 1*H*-indole-6-carboxylic acid methyl ester (for synthesis see example 2a), 2.47 g, 14.1 mmol) in NMP (140 mL) was added Cs_2CO_3 (10.1 mg, 31 mmol) at 0 °C. After stirring for 15 min 2-picolyl chloride hydrochloride (2.77 g, 16.9 mmol) was added and the mixture was stirred at room temperature for 18 h. Ethyl acetate (200 mL) was added and the mixture was washed with saturated aqueous ammonium chloride (3x150 mL) and brine (200 mL). The organic phase was dried (Na_2SO_4) and concentrated. The crude product was purified using column chromatography (ethyl acetate/heptane 1:3) to give the title compound as a colourless oil, which slowly crystallised on standing (2.72 g, 10.2 mmol, 72%).

b) 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carboxylic acid methyl ester, structure **13** of Scheme **IV**, where R^1 = 2-pyridyl, R^2 = 2-nitrophenyl, R^3=R^4=H.

To a solution of 1-pyridin-2-ylmethyl-1*H*-indole-6-carboxylic acid methyl ester (2.72 g, 10.2 mmol) in dichloromethane (75 mL) was added at room temperature a solution of 2-nitrobenzenesulfenyl chloride (1.93 g, 10.2 mmol) in dichloromethane (75 mL). The mixture was stirred at room temperature for 24 hrs. The reaction mixture was concentrated and the crude product was purified using column chromatography (ethyl acetate/heptane 1:5 to 1:2) to give the title compound as a yellow solid (3.21 g, 7.65 mmol, 75%).

c) 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carboxylic acid, structure **14** of Scheme **IV**, where R^1 = 2-pyridyl, R^2 = 2-nitrophenyl, R^3=R^4=H.

To a suspension of 3-(2-nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carboxylic acid methyl ester (3.0 g, 6.58 mmol) in dioxane (65 mL) was added a solution of $LiOH.H_2O$ (1.66 g, 39.6 mmol) in water (65 mL). The reaction mixture was stirred overnight at 60°C. The mixture was then acidified to pH 6 by addition of 15%

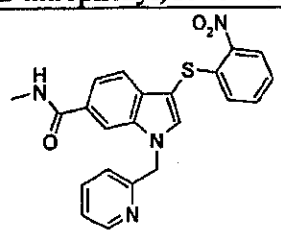
aqueous HCl and the mixture was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give a yellow powder. The product was recrystallised from heptane/ethyl acetate to give the title compound as yellow/orange crystals (2.47 g, 6.09 mmol, 93%)

General method 7: amidation of 6-carboxyl indoles of structure **14** to give 6-carboxamideindoles of structure **15** (Scheme **IV**).

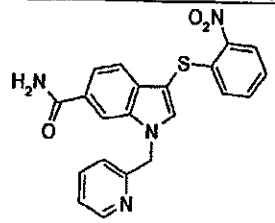
Under nitrogen atmosphere: to a solution of 3-(2-nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carboxylic acid (700 mg, 1.73mmol) in dry CH_2Cl_2 (70 mL) was added DIPEA (0.9 mL, 5.2 mmol), TBTU (840 mg, 2.6 mmol) and dimethylamine hydrochloride (420 mg, 5.1 mmol). The reaction mixture was stirred overnight at room temperature and then poured into saturated aqueous $NaHCO_3$ (100 mL). The organic layer was washed with brine (50 mL), dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (ethyl acetate/MeOH 95:5) to afford compound **109** (540 mg, 1.25 mmol, 72%, yellow solid).

^{1}H-NMR ($CDCl_3$): δ 2.97 (s, 3H), 3.11 (s, 3H), 5.53 (s, 2H), 6.90 (dd, 1H, J1 = 7.6 Hz, J2 = 1.5 Hz), 6.95 (d, 1H, J = 7.6 Hz), 7.17-7.28 (m, 4H), 7.51 (d, 1H, J = 7.6 Hz), 7.54 (s, 1H), 7.61-7.66 (m, 2H), 8.28 (dd, 1H, J1 = 8.4 Hz, J2 = 1.5 Hz), 8.61 (d, 1H, J = 4.6 Hz).

The following compounds were prepared using general procedure 7:

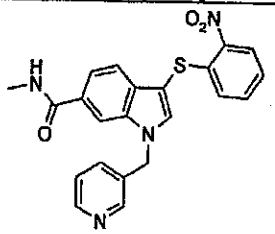
Compound **110**: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carboxylic acid methylamide, structure **15** of Scheme **IV**, where R^1 = 2-pyridyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^8=H, R^9=Me.	
	^{1}H-NMR (DMSO): δ 2.78 (d, 3H, J = 4.6 Hz), 5.70 (s, 2H), 6.88 (dd, 1H, J1 = 8.4 Hz, J2 = 1.5 Hz), 7.19 (d, 1H, J = 7.6 Hz), 7.30-7.37 (m, 2H), 7.41 (d, 1H, J = 8.4 Hz), 7.48-7.53 (m, 1H), 7.62 (dd, 1H, J1 = 7.6 Hz, J2 = 1.5 Hz), 7.79 (td, 1H, J1 = 7.6 Hz, J2 = 1.5 Hz), 8.13 (s, 1H), 8.20 (s, 1H), 8.28 (dd, 1H, J1 = 8.4 Hz, J2 = 1.5 Hz), 8.38 (q, 1H, J = 4.6 Hz), 8.55 (s, 1H, J = 4.6 Hz).

Compound **111**: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carboxylic acid amide, structure **15** of Scheme **IV**, where R^1 = 2-pyridyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^8=R^9=H.



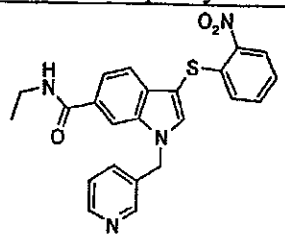
^{1}H-NMR (DMSO): δ 5.70 (s, 2H), 6.88 (dd, 1H, J1 = 8.4 Hz, J2 = 1.5 Hz), 7.21 (d, 1H, J = 7.6 Hz), 7.28-7.37 (m, 3H), 7.39 (d, 1H, J = 7.6 Hz), 7.48-7.53 (m, 1H), 7.66 (dd, 1H, J1 = 8.4 Hz, J2 = 1.5 Hz), 7.79 (td, 1H, J = 7.6 Hz, J2 = 1.5 Hz), 7.93 (s, 1H), 8.17 (s, 1H), 8.20 (s, 1H), 8.26 (dd, 1H, J1 = 7.6 Hz, J2 = 1.5 Hz), 8.55 (d, 1H, J = 4.6 Hz).

Compound **112**: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-3-ylmethyl-1*H*-indole-6-carboxylic acid methylamide, structure **15** of Scheme **IV**, where R^1 = 3-pyridyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^8=H, R^9=Me. 3-Picolyl chloride hydrochloride was used instead of 2-picolyl chloride hydrochloride.

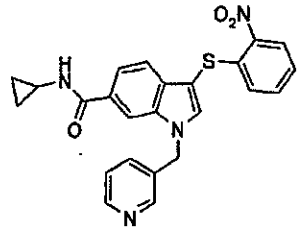


^{1}H-NMR (DMSO): δ 2.80 (d, 3H, J =4.6 Hz), 5.65 (s, 2H), 6.84 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 7.33-7.42 (m, 3H), 7.46-7.51 (m, 1H), 7.62 (dd, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 7.68 (dt, 1H, J1 = 7.6 Hz, J2 = 2.2 Hz), 8.19 (s, 1H), 8.26 (s, 1H), 8.28 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 8.41 (q, 1H, J = 4.6 Hz), 8.51 (dd, 1H, J1 = 4.6 Hz, J2 = 1.1 Hz), 8.64 (d, 1H, J = 3.0 Hz).

Compound **113**: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-3-ylmethyl-1*H*-indole-6-carboxylic acid ethylamide, structure **15** of Scheme **IV**, where R^1 = 3-pyridyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^8=H, R^9=Et. 3-Picolyl chloride hydrochloride was used instead of 2-picolyl chloride hydrochloride.

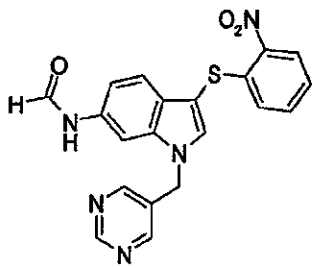


^{1}H-NMR (DMSO): δ 1.13 (t, 3H, J = 7.6 Hz), 3.30 (q, 2H, J = 7.6 Hz), 5.66 (s, 2H), 6.83 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 7.33-7.41 (m, 3H), 7.46-7.51 (m, 1H), 7.64 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 7.67 (dt, 1H, J1 = 7.6 Hz, J2 = 2.2 Hz), 8.19 (s, 1H), 8.26 (s, 1H), 8.27 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 8.45 (t, 1H, J = 5.7 Hz), 8.52 (dd, 1H, J1 = 4.6 Hz, J2 = 1.5 Hz), 8.64 (d, 1H, J = 3.0 Hz).

Compound **114**: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-3-ylmethyl-1*H*-indole-6-carboxylic acid cyclopropylamide, structure **15** of Scheme **IV**, where R^1 = 3-pyridyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^8=H, R^9=cyclopropyl. 3-Picolyl chloride hydrochloride was used instead of 2-picolyl chloride hydrochloride.	
	^{1}H-NMR (DMSO): δ 0.54-0.58 (m, 2H), 0.67-0.73 (m, 2H), 2.80-2.87 (m, 1H), 5.66 (s, 2H), 6.82 (d, 1H, J = 7.6 Hz), 7.33-7.41 (m, 3H), 7.46-7.50 (m, 1H), 7.61 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 7.67 (dt, 1H, J1 = 7.6 Hz, J2 = 1.5 Hz), 8.17 (s, 1H), 8.25 (s, 1H), 8.28 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 8.42 (t, 1H, J = 4.6 Hz), 8.52 (dd, 1H, J1 = 4.6 Hz, J2 = 1.5 Hz), 8.63 (d, 1H, J = 3.0 Hz).

Example 23

Compound **118**: *N*-[3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indol-6-yl]-formamide, structure **28** of Scheme **VII**, where R^1 = 3,5-pyrimidyl, R^2 = 2-nitrophenyl, R^3=R^4=H, Z = H



a) 6-Nitro-1-pyrimidin-5-ylmethyl-1*H*-indole

5-(Hydroxymethyl)pyrimidine (16.2 g, 147 mmol) was dissolved in 500 mL of CH_2Cl_2 and cooled to -40°C. MsCl (16.0 g, 140 mmol) was added at –40 °C. The mixture was stirred for 1 hour allowing to reach –20°C. The solution was used as such.

6-Nitroindole-1*H*-indole (35.6 g, 220 mmol) was dissolved in 750 mL of DMF and NaH (50%, 12 g, 250 mmol) was added in portions and the mixture was stirred for 1 hour. The mixture was cooled to -40°C and the solution of the mesylate was added dropwise. The mixture was allowed to reach room temperature overnight. The mixture was quenched with water and extracted with ethyl acetate (2x). The combined organic layers were washed with water (2x) and brine and dried over Na_2SO_4. After concentration *in*

vacuo the material was purified by means of column chromatography (silica, heptane/ethyl acetate (1:1)→(1:4)) affording compound the title compound as a yellow solid (14 g, 55 mmol, 39%).

b) 1-Pyrimidin-5-ylmethyl-1*H*-indol-6-ylamine.

6-Nitro-1-pyrimidin-5-ylmethyl-1*H*-indole (4.1 g, 16.1 mmol) was dissolved in 100 mL of THF and 100 mL of isopropanol. Pd/C (2 g) was added and the mixture was stirred under an H_2-atmosphere (balloon) for 2 hours. The mixture was filtered over Celite and washed with ethyl acetate affording the title compound after concentration (3.5 g, 15.6 mmol, 97 %).

c) 1-Pyrimidin-5-ylmethyl-1*H*-indol-6-yl)-carbamic acid tert-butyl ester

1-Pyrimidin-5-ylmethyl-1*H*-indol-6-ylamine (5.5 g, 24.6 mmol) was dissolved in 100 mL of NMP and triethylamine (3.5 g, 35 mmol) and di-*tert*-butyl dicarbonate (7.0 g, 32 mmol) were added. The mixture was stirred overnight, quenched with $NaHCO_3$-sat and extracted with toluene (3x). The combined organic layers were washed with water (4x) and brine and dried over Na_2SO_4. Concentration of the layers afforded the title compound (3.1 g, 39%).

d) [3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indol-6-yl]-carbamic acid tert-butyl ester

1-Pyrimidin-5-ylmethyl-1*H*-indol-6-yl)-carbamic acid tert-butyl ester (3.1 g, 9.6 mmol) was dissolved in 150 mL of CH_2Cl_2 and 2-nitrobenzene sulfenylchloride (1.86 g, 9.8 mmol) was added. The mixture was stirred for 18 hours and quenched with $NaHCO_3$-sat and extracted with ethyl acetate (2x). The combined organic layers were washed with brine and dried over Na_2SO_4. The product was purified by means of column chromatography (silica, heptane / ethyl acetate (1:1) which gave the title compound as a yellow solid (3.8 g, 83 %).

e) N-[3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indol-6-yl]-formamide

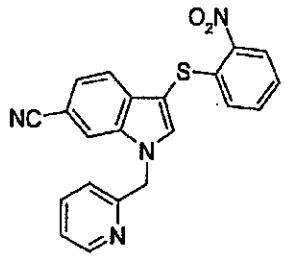
[3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indol-6-yl]-carbamic acid tert-butyl ester (3.8 g, 8.0 mmol) was dissolved in 150 mL of formic acid and stirred for 4 hours. The solution was concentrated *in vacuo*. $NaHCO_3$-sat was added and the mixture was extracted with CH_2Cl_2 (2x) The combined organic layers were washed with brine and dried over Na_2SO_4. The solution was allowed to stand overnight. The formed solid

was filtered affording a mixture of compound **118** and structure **23** of Scheme **VII**, where R^1 = 3,5-pyrimidyl, R^2 = 2-nitrophenyl, R^3=R^4=H (2.4 g).

Compound **118**: ^{1}H NMR ($CDCl_3$ + drop MeOD) δ 5.47 (s, 2H), 6.91 (dd, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 6.99 (dd, 1H, J1 = 8.4 Hz, J2 = 1.9 Hz), 7.19-7.23 (m, 1H), 7.27-7.31 (m, 1H), 7.33 (s, 1H), 7.42 (d, 1H, J = 8.4 Hz), 7.49 (s, 1H), 8.22 (d, 1H, J = 1.9 Hz), 8.27 (dd, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 8.66 (s, 2H), 9.16 (s, 1H).

Example 24

Compound **119**: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carbonitrile, structure **3** of scheme **I**, where R^1 = 2-pyridyl, R^2 = 2-nitrophenyl, R^3 = R^4 = H, R^5 = CN.



a) To a solution of 1*H*-indole-6-carbonitrile (1.00 g, 7.04 mmol) in diethyl ether (50 mL) was added at rt 2-nitrobenzenesulfenyl chloride (1.34 g, 7.04 mmol) and the reaction mixture was stirred for 18 hrs. The mixture was concentrated and the crude product was purified using column chromatography (ethyl acetate/heptane 1:4 → 4:1) to give 3-(2-Nitro-phenylsulfanyl)-1*H*-indole-6-carbonitrile (1.62 g, 5.49 mmol, 78%).

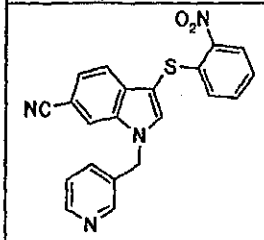
b) To a solution of 3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carbonitrile (200 mg, 0.68 mmol) in DMF (5 mL) was added at 0 °C Cs_2CO_3 (442 mg, 1.36 mmol) and the mixture was stirred for 20 min. Subsequently 2-picolylchloride hydrochloride (112 mg, 0.68 mmol) was added and the mixture was stirred for 18 hrs at room temperature. Aqueous saturated $NaHCO_3$ was added and the mixture was extracted with ethyl acetate (2x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The crude product was purified using column chromatography to afford compound **119** (223 mg, 0.58 mmol, 85%).

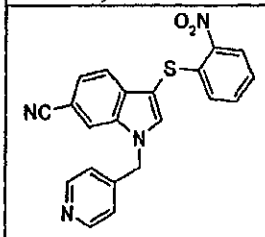
^{1}H NMR ($CDCl_3$) δ 5.54 (s, 2H), 6.86 (dd, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 7.04 (d, 1H, J = 8.4 Hz), 7.19-7.23 (m, 1H), 7.26-7.31 (m, 2H), 7.40 (dd, 1H, J1 = 8.4 Hz, J2 = 1.1

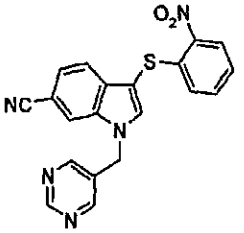
Hz), 7.59 (d, 1H, J = 8.4 Hz), 7.70 (td, 1H, J1 = 8.4 Hz, J2 = 1.9 Hz), 7.76 (s, 1H), 7.78 (s, 1H), 8.29 (dd, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 8.63 (d, 1H, J = 3.0 Hz).

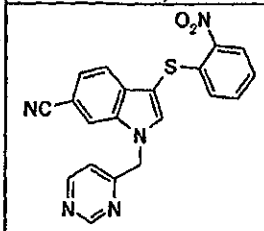
According to **general method 3** the following compounds were prepared:

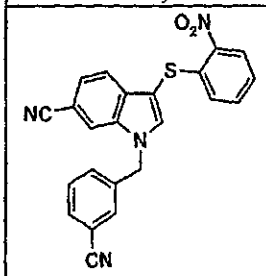
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Compound 121: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-3-ylmethyl-1*H*-indole-6-carbonitrile, structure **3** of scheme **I**, where R^1 = 3-pyridyl, R^2 = 2-nitrophenyl, R^3 = R^4 = H, R^5 = CN. Cs_2CO_3 and DMF were used.	
	^{1}H NMR ($CDCl_3$) δ 5.46 (s, 2H), 6.82 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 7.21-7.25 (m, 1H), 7.27-7.31 (m, 1H), 7.34 (dd, 1H, J1 = 8.4 Hz, J2 = 4.6 Hz), 7.43 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 7.49 (dt, 1H, J1 = 8.4 Hz, J2 = 1.9 Hz), 7.61 (d, 1H, J = 8.4 Hz), 7.66 (s, 1H), 7.71 (s, 1H), 8.29 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 8.55 (d, 1H, J = 3.0 Hz), 8.64 (dd, 1H, J1 = 8.4 Hz, J2 = 1.5 Hz).

Compound 122: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-4-ylmethyl-1*H*-indole-6-carbonitrile, structure **3** of scheme **I**, where R^1 = 4-pyridyl, R^2 = 2-nitrophenyl, R^3 = R^4 = H, R^5 = CN.	
	^{1}H NMR ($CDCl_3$) δ 5.46 (s, 2H), 6.84 (dd, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 7.04 (d, 2H, J = 6.1 Hz), 7.22-7.26 (m, 1H), 7.28-7.32 (m, 1H), 7.44 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 7.62 (d, 1H, J = 8.4 Hz), 7.64 (s, 1H), 7.68 (s, 1H), 8.30 (dd, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 8.63-8.65 (m, 2H). Cs_2CO_3 and DMF were used.

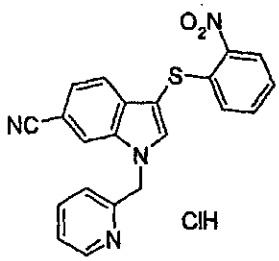
Compound 123: 3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indole-6-carbonitrile, structure **3** of scheme **I**, where R^1 = 3,5-pyrimidyl, R^2 = 2-nitrophenyl, R^3 = R^4 = H, R^5 = CN. NaH and DMF were used.	
	^{1}H NMR ($CDCl_3$) δ 5.48 (s, 2H), 6.81 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 7.22-7.32 (m, 2H), 7.46 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 7.63 (d, 1H, J = 8.4 Hz), 7.68 (s, 1H), 7.70 (s, 1H), 8.30 (dd, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 8.63 (s, 2H), 9.25 (s, 1H).

Compound **124**: 3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-4-ylmethyl-1*H*-indole-6-carbonitrile, structure **3** of scheme **I**, where R^1 = 2,4-pyrimidyl, R^2 = 2-nitrophenyl, $R^3 = R^4$ = H, R^5 = CN. Cs_2CO_3 and DMF were used.	
	^{1}H NMR ($CDCl_3$) δ 5.52 (s, 2H), 6.86 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 6.97 (dd, 1H, J1 = 4.6 Hz, J2 = 1.1 Hz), 7.22-7.32 (m, 2H), 7.44 (dd, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 7.62 (d, 1H, J = 8.4 Hz), 7.70 (s, 1H), 7.75 (s, 1H), 8.30 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 8.74 (d, 1H, J = 4.6 Hz), 9.24 (d, 1H, J = 1.1 Hz).

Compound **125**: 1-(3-Cyano-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carbonitrile, structure **3** of scheme **I**, where R^1 = 3-cyanophenyl, R^2 = 2-nitrophenyl, $R^3 = R^4$ = H, R^5 = CN. Cs_2CO_3 and DMF were used.	
	^{1}H NMR ($CDCl_3$) δ 5.48 (s, 2H), 6.83 (dd, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 7.21-7.26 (m, 1H), 7.30-7.35 (m, 1H), 7.38-7.42 (m, 3H), 7.45 (d, 1H, J = 8.4 Hz), 7.53 (d, 1H, J = 7.6 Hz), 7.64 (d, 1H, J = 6.1 Hz), 7.65 (d, 1H, J = 3.7 Hz), 7.66-7.69 (m, 1H), 8.30 (dd, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz).

Example 25

Compound **120**: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carbonitrile monohydrochloride



Concentrated hydrochloric acid (0.0225 ml) was added to a solution of compound **119** (0.093 g) in dioxane. The mixture was stirred for 20 min. and then concentrated under reduced pressure, to give compound **120** (0.096 g).

^{1}H NMR (MeOD) δ 6.01 (s, 2H), 6.98 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 7.28-7.32 (m, 1H), 7.36-7.41 (m, 1H), 7.48 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 7.53 (d, 1H, J = 8.4 Hz), 7.60 (d, 1H, J = 8.4 Hz), 7.93 (t, 1H, J = 6.1 Hz), 8.08 (s, 1H), 8.10 (s, 1H), 8.27 (dd, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 8.44 (td, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 8.85 (dd, 1H, J1 = 6.1 Hz, J2 = 1.9 Hz).

Compounds were tested for their Androgen Receptor activity in a transactivation assay and in a binding assay.

The (anti-)androgenic activity of test compounds (EC50 and intrinsic activity) was determined in an *in vitro* bioassay of Chinese hamster ovary (CHO) cells stably transfected with the human androgen receptor expression plasmid and a reporter plasmid in which the MMTV-promoter is linked to the luciferase reporter gene. The cell-line CHO-AR-pMMTV-LUC 1G12-A5-CA is described in Schoonen et al. (2000), Journal of Steroid Biochemistry and Molecular Biology 74(4):213-222. The antiandrogenic activity of a test compound was determined by the inhibition of the transactivation via the androgen receptor of the enzyme luciferase in the presence of 1 nM DHT (5α-dihydrotestosterone, 17β-hydroxy-5α-androstan-3-one). Intrinsic activity of antiandrogenic activity was determined in the presence of the reference antiandrogen 2-Hydroxy-2-methyl-*N*-(4-nitro-3-trifluoromethyl-phenyl)-propionamide (Hydroxyflutamide), and set at 100%. For androgenic activity, maximal intrinsic activity in the presence of 100 nM DHT was set at 100%. The results are presented in Table 4.

Table 4 Androgen receptor activity

Cpd. number	X	R^1	R^2	R^3	R^4	R^5	ago EC50	ago efficacy	ant EC50	ant efficacy
1	S	2,5-difluorophenyl	2-nitrophenyl	H	H	OMe	++	+	-	-
2	S	2,fluoro,3-methylphenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
3	S	2-chlorophenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
4	S	2-cyanophenyl	2-nitrophenyl	H	H	OMe	+	±	++	±
5	S	2-fluorophenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
6	S	2-methyl,3-nitrophenyl	2-nitrophenyl	H	H	OMe	+	+	-	-

Cpd. number	X	R^1	R^2	R^3	R^4	R^5	ago EC50	ago efficacy	ant EC50	ant efficacy
7	S	2-methylphenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
8	S	2-nitrophenyl	2-nitrophenyl	H	H	OMe	++	+	-	-
9	S	2-pyridyl	2-nitrophenyl	H	H	OMe	+++	+	+++	±
10	S	2-pyridyl HCl salt	2-nitrophenyl	H	H	OMe	++	+	-	-
11	S	2-tetrahydropyranyl	2-nitrophenyl	H	H	OMe	++	+	-	-
12	S	2-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
13	S	3-(5-methylisoxazolyl)	2-nitrophenyl	H	H	OMe	+	±	-	-
14	S	3,4-dichlorophenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
15	S	3,5-dichlorophenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
16	S	3,5-difluorophenyl	2-(hydroxymethylphenyl)	H	H	OMe	++	+	++	±
17	S	3,5-difluorophenyl	2-(N-methylbenzamide)	H	H	OMe	-	-	+	+
18	S	3,5-difluorophenyl	2-benzamide	H	H	OMe	++	+	++	±
19	S	3,5-difluorophenyl	2-benzoic acid methyl ester	H	H	OMe	+	+	-	-
20	S	3,5-difluorophenyl	2-cyanophenyl	H	H	OMe	++	++	-	-
21	S	3,5-difluorophenyl	2-methoxyphenyl	H	H	OMe	++			
22	S	3,5-difluorophenyl	2-nitrophenyl	H	H	Br	++	++	-	-
23	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CF3	+++	++	-	-
24	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CH2OH	++	++	-	-
25	S	3,5-difluorophenyl	2-nitrophenyl	H	H	Cl	+++	++	-	-
26	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CN	+++	++	-	-
27	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO(1-pyrrolidinyl)	++	+	-	-
28	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO(4-morpholinyl)	++	+	-	-
29	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO[1-(4-methylpiperazinyl)]	++	++	-	-
30	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO2H	+	+	-	-
31	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO2Me	+++	+	-	-
32	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONEt2	++	+	+	±
33	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONH2	+++	++	-	-
34	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2(2-furanyl)	++	+	-	-
35	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2(3-pyridyl)	++	±	-	-
36	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2CH2Nme2	++	+	-	-
37	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2CH2OH	+++	++	-	-
38	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2CH2OMe	+++	++	-	-

Cpd. number	X	R^1	R^2	R^3	R^4	R^5	ago EC50	ago efficacy	ant EC50	ant efficacy
39	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2CO2Me	++	++	-	-
40	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2CONMe2	++	+	-	-
41	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2cPr	+++	+	-	-
42	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2iPr	++	+	-	-
43	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2Ph	++	±	+	±
44	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHcPr	+++	+	-	-
45	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHEt	+++	++	-	-
46	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHiPr	++	+	++	±
47	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHMe	+++	+	-	-
48	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHnPr	++	+	+	±
49	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONMe2	+++	+	-	-
50	S	3,5-difluorophenyl	2-nitrophenyl	H	H	F	++	++	-	-
51	S	3,5-difluorophenyl	2-nitrophenyl	F	H	H	+++	++	-	-
52	S	3,5-difluorophenyl	2-nitrophenyl	H	H	H	++	++	-	-
53	S	3,5-difluorophenyl	2-nitrophenyl	H	F	H	++	++	-	-
54	S	3,5-difluorophenyl	2-nitrophenyl	Cl	H	H	++	++	-	-
55	S	3,5-difluorophenyl	2-nitrophenyl	Me	H	H	++	+	-	-
56	S	3,5-difluorophenyl	2-nitrophenyl	H	OH	H	+++			
57	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NH2	+	+	-	-
58	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHAc	+++	++	-	-
59	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHCOCF3	+++	+	-	-
60	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NO2	+++	++	-	-
61	S	3,5-difluorophenyl	2-nitrophenyl	H	H	OH	+++			
62	SO2	3,5-difluorophenyl	2-nitrophenyl	H	H	OMe	+++	++	-	-
63	S	3,5-difluorophenyl	2-nitrophenyl	H	H	OMe	+++	++	-	-
64	SO	3,5-difluorophenyl	2-nitrophenyl	H	H	OMe	-	±	+	+
65	S	3,5-difluorophenyl	2-pyridyl	H	H	OMe	++	++	-	-
66	S	3,5-difluorophenyl	2-pyridyl-N-oxide	H	H	OMe	+	+	++	±
67	S	3-chlorophenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
68	S	3-cyanophenyl	2-nitrophenyl	H	H	OMe	+++	++	-	-
69	S	3-fluoro,5-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
70	S	3-fluoro,6-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	++	+	-	-

Cpd. number	X	R^1	R^2	R^3	R^4	R^5	ago EC50	ago efficacy	ant EC50	ant efficacy
71	S	3-fluorophenyl	2-nitrophenyl	H	H	OMe	+++	++	-	-
72	S	3-methoxyphenyl	2-nitrophenyl	H	H	OMe	++	+	-	-
73	S	3-methylphenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
74	S	3-nitrophenyl	2-nitrophenyl	H	H	OMe	+++	++	-	-
75	S	3-pyridyl	2-nitrophenyl	H	H	OMe	+++	++	-	-
76	S	3-trifluoromethyl,4-chlorophenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
77	S	3-trifluoromethyloxyphenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
78	S	3-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
79	S	4-(2-methylthiazolyl)	2-nitrophenyl	H	H	OMe	++	+	-	-
80	S	4-(3,5-dimethylisoxazolyl)	2-nitrophenyl	H	H	OMe	+	±	+	±
81	S	4-chlorophenyl	2-nitrophenyl	H	H	OMe	+	+	+++	+
82	S	4-cyanophenyl	2-nitrophenyl	H	H	OMe	++	+	-	-
83	S	4-fluorophenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
84	S	4-methoxyphenyl	2-nitrophenyl	H	H	OMe	+	±	±	++
85	S	4-methylphenyl	2-nitrophenyl	H	H	OMe	+	+	-	±
86	S	4-morpholinyl	2-nitrophenyl	H	H	OMe	±	±	+	+
87	S	5-(2-chlorothiazolyl)	2-nitrophenyl	H	H	OMe	++	+	-	-
88	S	5-(2-chlorothiophenyl)	2-nitrophenyl	H	H	OMe	++	++	-	-
89	S	Cyclohexyl	2-nitrophenyl	H	H	OMe	++	+	+++	±
90	S	Phenyl	2-nitrophenyl	H	H	H	+	+	-	-
91	S	Phenyl	2-nitrophenyl	H	OMe	H	-	-	±	++
92	S	Phenyl	2-nitrophenyl	H	H	OMe	+++	++	-	-

note 1: EC50 scale: +++ <5 nM; ++ between 5 and 100 nM; + <1000 nM; ± between 1000 and 10000 nM; - >10000 nM

note 2: efficacy scale (maximal intrinsic activity, i.e. intrinsic activity observed in the presence of 100 nM DHT, was set at 1.00): ++ ≥0.80; + between 0.50 and 0.80; ± between 0.20 and 0.50; - <0.20

The androgenic activity (EC50, potency, and efficacy) of the compounds in Table 5 was determined in an *in vitro* bioassay of Chinese hamster ovary (CHO) cells stably transfected with the human androgen receptor expression plasmid and a reporter

plasmid in which the MMTV promotor is linked to the luciferase reporter gene. The cell line CHO-AR-pMMTV-LUC 1G12-A5-CA is described in Schoonen *et al.* (J. Steroid Biochem. Molec. Biol. 2002; 74: 213-222). The androgen receptor activity of compounds was determined in the presence of 0.1 µmol/l onapristone. The maximal efficacy in the presence of 100 nmol/l DHT was set as 100%. The potencies are expressed as percentage of DHT activity.

Table 5 Androgen receptor activity

Cpd. number	X	R^1	R^2	R^3	R^4	R^5	ago potency	ago efficacy
93	S	4-pyridyl	2-nitrophenyl	H	H	OMe	±	+
94	S	3,4,5-trifluorophenyl	2-nitrophenyl	H	H	OMe	+	++
95	S	2,3,5-trifluorophenyl	2-nitrophenyl	H	H	OMe	±	++
96	S	4-chloro-3-pyridyl	2-nitrophenyl	H	H	OMe	±	±
97	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHCOCH2F	+	++
98	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHCOCHF2	++	+
99	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHCOEt	±	+
100	S	2-pyridyl	2-nitrophenyl	H	H	NHCOCH2F	+	++
101	S	2-pyridyl	2-nitrophenyl	H	H	NHCOMe	+	+
102	S	2-pyridyl	2-nitrophenyl	H	H	NHCOEt	+	+
103	S	3-pyridyl	2-nitrophenyl	H	H	NHCOMe	+	+
104	S	3-pyridyl	2-nitrophenyl	H	H	NHCOCH2F	+	-
105	S	3-pyridyl	2-nitrophenyl	H	H	NHCOEt	+	±
106	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHSO2Me	+	++
107	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHSO2-(3-thiophene)	+	++
108	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHSO2-(1-Me-4-imidazolyl	+	++
109	S	2-pyridyl	2-nitrophenyl	H	H	CONMe2	+	++
110	S	2-pyridyl	2-nitrophenyl	H	H	CONHMe	+	+
111	S	2-pyridyl	2-nitrophenyl	H	H	CONH2	±	±
112	S	3-pyridyl	2-nitrophenyl	H	H	CONHMe	+	±
113	S	3-pyridyl	2-nitrophenyl	H	H	CONHEt	+	+
114	S	3-pyridyl	2-nitrophenyl	H	H	CONHcyclopropyl	+	++
115	S	3,5-pyrimidyl	2-nitrophenyl	H	H	OMe	++	+
116	S	2,4-pyrimidyl	2-nitrophenyl	H	H	OMe	+	+

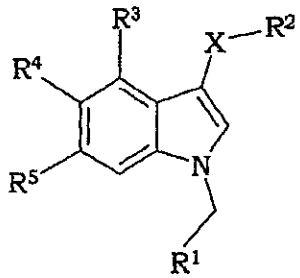
Cpd. number	X	R^1	R^2	R^3	R^4	R^5	ago potency	ago efficacy
117	S	2,5-pyrazyl	2-nitrophenyl	H	H	OMe	+	+
118	S	3,5-pyrimidyl	2-nitrophenyl	H	H	NHCHO	++	+
119	S	2-pyridyl	2-nitrophenyl	H	H	CN	++	++
120	S	2-pyridyl HCl salt	2-nitrophenyl	H	H	CN	++	++
121	S	3-pyridyl	2-nitrophenyl	H	H	CN	+	++
122	S	4-pyridyl	2-nitrophenyl	H	H	CN	+	+
123	S	3,5-pyrimidyl	2-nitrophenyl	H	H	CN	++	++
124	S	2,4-pyrimidyl	2-nitrophenyl	H	H	CN	++	++
125	S	3-cyanophenyl	2-nitrophenyl	H	H	CN	+	++

note 1: potency scale: ++ >5%; + between 1% and 5%; ± between 0.1% and 1%.
note 2: efficacy scale (maximal intrinsic activity, i.e. intrinsic activity observed in the presence of 100 nM DHT, was set at 1.00): ++ ≥0.80; + between 0.50 and 0.80; ± between 0.20 and 0.50; - <0.20.

Determination of competitive binding to cytoplasmic human androgen receptor from recombinant CHO cells is used to estimate the relative binding affinity (RBA) of a test compound for androgen receptors present in the cytosol prepared of the recombinant CHO cell-line, CHO-AR-pMMTV-LUC 1G12-A5-CA.
Compound 63 and compound 92 were tested in this binding assay and both compounds were found to have a relative binding affinity >1% relative to DHT.

Claims

1. A compound having the formula



wherein

X is S, SO or SO_2;

R^1 is a 5- or 6-membered monocyclic, hetero- or homocyclic, saturated or unsaturated ring structure optionally substituted with one or more substituents selected from the group consisting of halogen, CN, (1C-4C)fluoroalkyl, nitro, (1C-4C)alkyl, (1C-4C)alkoxy or (1C-4C)fluoroalkoxy;

R^2 is 2-nitrophenyl, 2-cyanophenyl, 2-hydroxymethyl-phenyl, pyridin-2-yl, pyridin-2-yl-N-oxide, 2-benzamide, 2-benzoic acid methyl ester or 2-methoxyphenyl;

R^3 is H, halogen or (1C-4C)alkyl;

R^4 is H, OH, (1C-4C)alkoxy, or halogen;

R^5 is H, OH, (1C-4C)alkoxy, NH_2, CN, halogen, (1C-4C)fluoroalkyl, NO_2, hydroxy(1C-4C)alkyl, CO_2H, CO_2(1C-6C)alkyl, or

R^5 is NHR^6, wherein R^6 is (1C-6C)acyl optionally substituted with one or more halogens, $S(O)_2$(1C-4C)alkyl, or $S(O)_2$aryl optionally substituted with (1C-4C)alkyl or one or more halogens, or

R^5 is $C(O)N(R^8,R^9)$, wherein R^8 and R^9 each independently are H, (3C-6C)cycloalkyl, or CH_2R^{10}, wherein R^{10} is H, (1C-5C)alkyl, (1C-5C)alkenyl, hydroxy(1C-3C)alkyl, (1C-4C)alkylester of carboxy(1C-4C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, (mono- or di(1C-4C)alkyl)aminomethyl, (mono- or di(1C-4C)alkyl)aminocarbonyl, or a 3-, 4-, 5- or 6-membered monocyclic, homo- or heterocyclic, aromatic or non-aromatic ring, or R^8 and R^9 form

together with the N a heterocyclic 5- or 6-membered saturated or unsaturated ring optionally substituted with (1C-4C)alkyl;

or a salt or hydrate form thereof.

2. A compound according to claim 1, characterised in that

R^1 is a 5- or 6-membered monocyclic, hetero- or homocyclic, saturated or unsaturated ring structure optionally substituted with one or more substituents selected from the group consisting of halogen, CN, CF_3, nitro, methoxy, trifluoromethoxy or methyl;

R^2 is 2-nitrophenyl, 2-cyanophenyl, 2-hydroxymethyl-phenyl, pyridin-2-yl, pyridin-2-yl-N-oxide, 2-benzamide, 2-benzoic acid methyl ester or 2-methoxyphenyl;

R^3 is H, halogen or (1C-2C)alkyl;

R^4 is H or F.

3. A compound according to claim 2, characterised in that

R^5 is H, OH, (1C-4C)alkoxy, CN, halogen, (1C-4C)fluoroalkyl, NO_2, hydroxy(1C-4C)alkyl, CO_2(1C-6C)alkyl, or

R^5 is NHR^6, wherein R^6 is (1C-6C)acyl optionally substituted with one or more halogens, $S(O)_2$(1C-4C)alkyl, or $S(O)_2$aryl optionally substituted with (1C-4C)alkyl or one or more halogens, or

R^5 is $C(O)N(R^8,R^9)$, wherein R^8 and R^9 each independently are H, (3C-6C)cycloalkyl, or CH_2R^{10}, wherein R^{10} is H, (1C-5C)alkyl, (1C-5C)alkenyl, hydroxy(1C-3C)alkyl, (1C-4C)alkylester of carboxy(1C-4C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, (mono- or di(1C-4C)alkyl)aminomethyl, (mono- or di(1C-4C)alkyl)-aminocarbonyl, or a 3-, 4-, 5- or 6-membered monocyclic, homo- or heterocyclic, aromatic or non-aromatic ring, or R^8 and R^9 form together with the N a heterocyclic 5- or 6-membered saturated or unsaturated ring optionally substituted with (1C-4C)alkyl.

4. A compound according to claim 3, characterised in that

R^3 is H or halogen;

R^4 is H;

R^5 is H, OH, (1C-4C)alkoxy, CN, F, Cl, CF_3, NO_2, hydroxy(1C-4C)alkyl, CO_2(1C-6C)alkyl, or

R^5 is NHR^6, wherein R^6 is (1C-3C)acyl optionally substituted with one or more halogens or

R^5 is $C(O)N(R^8,R^9)$, wherein R^8 and R^9 each independently are H, (3C-5C)cycloalkyl, or CH_2R^{10}, wherein R^{10} is H, (1C-5C)alkyl, (1C-5C)alkenyl, hydroxy(1C-3C)alkyl, (1C-2C)alkylester of carboxy(1C-2C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, (mono- or di(1C-4C)alkyl)aminomethyl, (mono- or di(1C-4C)alkyl)aminocarbonyl, (3C-5C)cycloalkyl, or a 5-membered heterocyclic ring.

5. A compound according to claim 4, characterised in that

X is S or SO_2;

R^2 is 2-nitrophenyl, 2-hydroxymethyl-phenyl, 2-benzamide, 2-methoxyphenyl, 2-cyanophenyl or pyridin-2-yl;

R^3 is H or F;

R^5 is H, OH, (1C-2C)alkoxy, CN, F, Cl, CF_3, NO_2, hydroxy(1C-4C)alkyl, CO_2(1C-4C)alkyl, or

R^5 is NHR^6, wherein R^6 is formyl, acetyl, fluoroacetyl, difluoroacetyl, or trifluoroacetyl, or

R^5 is $C(O)N(R^8,R^9)$, wherein R^8 is H, and R^9 is H, cyclopropyl or

R^9 is CH_2R^{10}, wherein R^{10} is H, (1C-2C)alkyl, hydroxy(1C-2C)alkyl, methoxy(1C-2C)alkyl, cyclopropyl.

6. A compound according to claim 5, characterised in that

X is S;

R^1 is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, pyrimidin-5-yl, pyrimidin-4-yl, pyrazin-2-yl, 3-fluorophenyl, 3-cyanophenyl, or 3-nitrophenyl;

R^2 is 2-nitrophenyl, 2-hydroxymethyl-phenyl, 2-methoxyphenyl, 2-cyanophenyl or pyridin-2-yl;

R^3 is H;

R^5 is OH, (1C-2C)alkoxy, CN, CF_3, NO_2, hydroxy(1C-4C)alkyl, CO_2(1C-4C)alkyl, or NHR^6, wherein R^6 is formyl, acetyl, fluoroacetyl, difluoroacetyl, or trifluoroacetyl.

7. A compound according to claim 6, characterised in that

R^1 is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, pyrimidin-5-yl, pyrimidin-4-yl, or pyrazin-2-yl;

R^2 is 2-nitrophenyl, or 2-hydroxymethyl-phenyl;

R^5 is OH, (1C-2C)alkoxy, CN, hydroxy(1C-4C)alkyl, or NHR^6, wherein R^6 is formyl, acetyl, fluoroacetyl, difluoroacetyl, or trifluoroacetyl.

8. A compound according to claim 7, characterised in that

R^1 is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, pyrimidin-5-yl, or pyrimidin-4-yl;

R^2 is 2-nitrophenyl;

R^5 is OH, (1C-2C)alkoxy, CN, or NHR^6, wherein R^6 is formyl, acetyl, fluoroacetyl, difluoroacetyl, or trifluoroacetyl.

9. A compound according to claim 8 selected from the group consisting of 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indole, 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carbonitrile, 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carbonitrile-hydrochloride, 3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indole-6-carbonitrile, 3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-4-ylmethyl-1*H*-indole-6-carbonitrile, *N*-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-2-fluoro-acetamide, and *N*-[3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indol-6-yl]-formamide.

10. A compound according to claim 5, characterised in that

X is S;

R^1 is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, 3-fluorophenyl, 3-cyanophenyl, or 3-nitrophenyl;

R^2 is 2-nitrophenyl, 2-hydroxymethyl-phenyl, 2-methoxyphenyl, 2-cyanophenyl or pyridin-2-yl;

R^3 is H;

R^5 is C(O)N(R^8,R^9), wherein R^8 is H, and R^9 is H, or CH_2R^{10}, wherein R^{10} is H, (1C-2C)alkyl, hydroxy(1C-2C)alkyl, or methoxy(1C-2C)alkyl.

11. A compound according to claim 10, characterised in that

R^1 is 3,5-difluorophenyl, pyridin-2-yl, or pyridin-3-yl;

R^2 is 2-nitrophenyl, or 2-hydroxymethyl-phenyl;

R^5 is C(O)N(R^8,R^9), wherein R^8 is H, and R^9 is CH_2R^{10}, wherein R^{10} is H, or (1C-2C)alkyl.

12. A compound according to claim 11 which is 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid methylamide.

13. A compound according to claim 4, characterised in that

X is S;

R^1 is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, 3-fluorophenyl, 3-cyanophenyl, or 3-nitrophenyl;

R^2 is 2-nitrophenyl, 2-hydroxymethyl-phenyl, 2-methoxyphenyl, 2-cyanophenyl or pyridin-2-yl;

R^3 is H;

R^5 is C(O)N(R^8,R^9), wherein R^8 and R^9 each independently are H, or CH_2R^{10}, wherein R^{10} is H, (1C-5C)alkyl, (1C-5C)alkenyl, hydroxy(1C-3C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, or (mono- or di(1C-4C)alkyl)aminomethyl.

14. A compound according to claim 13, characterised in that

R^1 is 3,5-difluorophenyl, pyridin-2-yl, or pyridin-3-yl;

R^2 is 2-nitrophenyl, or 2-hydroxymethyl-phenyl;

R^5 is C(O)N(R^8,R^9), wherein R^8 and R^9 each independently are H, or CH_2R^{10}, wherein R^{10} is H, (1C-5C)alkyl, hydroxy(1C-3C)alkyl, or (1C-3C)alkoxy(1C-3C)alkyl.

15. A compound according to claim 14 which is 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid dimethylamide.

16. The compound of any one of claims 1-15 for use in therapy.

17. A pharmaceutical composition comprising a compound according to any one of claims 1-15 and a pharmaceutically acceptable carrier.

18. A pharmaceutical composition according to claim 17 for the treatment of a disorder selected from the group consisting of an androgen-receptor related disorder, an androgen related disorder and androgen insufficiency.

19. A use of a compound according to any one of claims 1-15 for the manufacture of a medicament for the treatment of androgen-receptor related disorders, androgen related disorders and androgen insufficiency.