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(54) Title: CARBOXYL SUBSTITUTED INDOLES FOR USE AS PPAR ALPHA MODULATORS

(57) Abstract: There is provided according to the invention novel compounds of formula (I) or pharmaceutically acceptable salts or solvates thereof wherein one of R1 and R2 is H and the other is COOH. The compounds are useful as PPAR modulators.
CARBOXYL SUBSTITUTED INDOLES FOR USE AS PPAR ALPHA MODULATORS

Field of the Invention
The present invention relates to indole derivatives, compositions and medicaments containing said indole derivatives and processes for their preparation. The invention also relates to the use of said indole derivatives, compositions and medicaments, for example as activators of the alpha subtype of the human peroxisome proliferator activated receptor (hPPAR) and/or for the treatment of disorders mediated by hPPAR alpha.

Background to the Invention
Several independent risk factors have been associated with cardiovascular disease. These include hypertension, increased fibrinogen levels, high levels of triglycerides, elevated LDL cholesterol, elevated total cholesterol, and low levels of HDL cholesterol. HMG CoA reductase inhibitors ("statins") are useful for treating conditions characterized by high LDL-c levels. It has been shown that lowering LDL-c is not sufficient for reducing the risk of cardiovascular disease in some patients, particularly those with normal LDL-c levels. This population pool is identified by the independent risk factor of low HDL-c. The increased risk of cardiovascular disease associated with low HDL-c levels has not yet been successfully addressed by drug therapy (i.e., currently there are no drugs on the market that are useful for raising HDL-c >40%). (Bisgaier, C. L.; Pape, M. E. Curr. Pharm. Des. 1998, 4, 53-70).

Syndrome X (including metabolic syndrome) is loosely defined as a collection of abnormalities including hyperinsulinemia, obesity, elevated levels of triglycerides, uric acid, fibrinogen, small dense LDL-c particles, and plasminogen activator inhibitor 1 (PAI-1), and decreased levels of HDL-c.

NIDDM is described as insulin resistance which in turn causes anomalous glucose output and a decrease in glucose uptake by skeletal muscle. These factors eventually lead to impaired glucose tolerance (IGT) and hyperinsulinemia.

Three mammalian Peroxisome Proliferator-Activated Receptors have been isolated and termed PPAR-alpha, PPAR-gamma, and PPAR-delta (also known as NUC1 or PPAR-beta). These PPARs regulate expression of target genes by binding to DNA sequence elements, termed PPAR response elements (PPRE). To date, PPRE's have been identified in the enhancers of a number of genes encoding proteins that regulate lipid metabolism suggesting that PPARs play a pivotal role in the adipogenic signaling cascade and lipid homeostasis (H. Keller and W. Wahli, *Trends Endocrin. Met* 291-296, 4 (1993)).

Certain compounds that activate or otherwise interact with one or more of the PPARs have been implicated in the regulation of triglyceride and cholesterol levels in animal models. See, for example, WO 01/40207, WO 01/00603, WO 97/31907, WO 02/46174 (Glaxo Group Ltd et al).

**Summary of the Invention**

In one aspect of the invention there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof:

![Chemical Structure](image)

wherein:

one of $R^1$ and $R^2$ is H, the other is COOH;

$R^3$ is H or $-\text{CH}_2\text{N(CH}_3\text{)}_2$;

$Z$ is C$_3$-7 cycloalkyl, phenyl (optionally substituted by $-\text{C}_1\text{,}_3\text{alkoxy, -OH, -C}_1\text{,}_3\text{alkyl}$), a 5 or 6 membered monocyclic heteroaryl (optionally substituted by $-\text{C}_1\text{,}_3\text{alkyl}$), benzo thiophenyl or benzofuranyl;

$X$ is a linker group of 6 or 7 above in shortest length between N and Y.

$Y$ is
(a) phenyl (substituted by one, two or three substituents, each independently selected from -OH, -Cr₃alkyl, -Cr₃alkoxy, -Ci₃haloalkyl, halogen, -C₅₋₆cycloalkyl, a 5 or 6 membered monocyclic heteroaryl, -NRᵃRᵇ (wherein Rᵃ and Rᵇ are independently selected from H or -Ci₃alkyl); 
(b) phenyl fused to a 5 or 6 membered heterocyclic ring containing one or two oxygen atoms (said phenyl and heterocyclic ring each being optionally substituted by -Ci₃alkyl); 
(c) phenyl fused to a 5 or 6 membered cycloalkyl (said phenyl being optionally substituted by -OH); 
(d) a 5 or 6 membered monocyclic heteroaryl (optionally substituted by one or more substituents independently selected from -C₁₋₃alkyl, -CF₃, halogen).

or X-Y is

```
        O
       /|
      / \
     R²  R¹
       |  |
       |  N
       |  |
       |  N
       |  |
       |  R³
       |  \
       |  N
       |  |
       |  R⁴
       |  \
       |  N
       |  |
       |  R⁵
       |  \
       |  N
       |  |
       |  R⁶
       |  \
       |  N
       |  |
       |  R⁷
       |  |
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R⁷ is H or -Cr₃alkyl; 
R⁸ is H or -Cr₃alkyl.

In a further aspect of the present invention, there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof for use in therapy.

In a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and one or more of pharmaceutically acceptable carriers, diluents and excipients.

In a further aspect of the present invention, there is provided a method of treating hPPAR mediated disorders in a subject comprising administering a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In an further aspect of the present invention, there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof in the preparation of a medicament for use in the treatment of hPPAR mediated disorders.
In a sixth aspect of the invention there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of hPPAR mediated disorders.

5 Detailed Description of the Invention

As used herein, the term "alkyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms. For example, C\textsubscript{1-6} alkyl means a straight or branched alkyl chain containing at least 1, and at most 6 carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, t-butyl, n-pentyl.

As used herein, the term "cycloalkyl" refers to a non-aromatic hydrocarbon ring containing the specified number of carbon atoms. For example C\textsubscript{3-7} cycloalkyl means a non-aromatic ring containing at least three, and at most seven, ring carbon atoms. Examples of "cycloalkyl" as used herein include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

As used herein the term "halogen" refers to fluorine (F), chlorine (Cl), bromine (Br) or iodine (I), and the radicals, thereof, fluoro (-F), chloro (-Cl), bromo (-Br) and iodo (-I).

As used herein, the term "C\textsubscript{1-6} haloalkyl" refers to an alkyl group as defined above containing at least 1, and at most 6, carbon atoms substituted with at least one halo group, halo being as defined herein. Examples of branched or straight chained "C\textsubscript{1-6} haloalkyl" groups useful in the present invention include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl and n-butyl substituted independently with one or more halos, e.g., fluoro, chloro, bromo and iodo.

As used herein, the term "alkoxy" refers to the group R\textsubscript{a}O-, where R\textsubscript{a} is alkyl as defined above and the term "C\textsubscript{1-6} alkoxy" refers to an alkoxy group as defined herein wherein the alkyl moiety contains at least 1, and at most 6, carbon atoms. Exemplary C\textsubscript{1-6} alkoxy groups useful in the present invention include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, and t-butoxy.
As used herein, the term "heterocyclic" or the term "heterocyclyl" refers to a non-aromatic three to seven-membered (unless otherwise specified) heterocyclic ring being saturated or having one or more degrees of unsaturation containing one or more oxygen atoms.

As used herein, the term "heteroaryl" refers to a monocyclic aromatic ring having the specified number of carbon atoms, and which contains one or more nitrogen, sulphur, and/or oxygen heteroatoms, where N-oxides and sulphur oxides and dioxides are permissible heteroatom substitutions. Examples of "heteroaryl" groups used herein include furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, isothiazolyl, pyridyl, pyridazyl, pyrazinyl, pyrimidyl.

The term hPPAR activator is used to mean a compound which binds to and activates hPPAR, for example in the binding and transfection assays described below.

The term "hPPAR mediated disorders" is used to mean any disorder mediated or modulated by hPPAR, including dyslipidemia (including associated diabetic dyslipidemia and mixed dyslipidemia), obesity, syndrome X (as defined in this application this embraces metabolic syndrome), heart failure, hypercholesteremia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidemia, inflammation, Alzheimers disease or other cognitive disorders, epithelial hyperproliferative diseases including eczema and psoriasis and conditions associated with the lining and gut, regulation of appetite and food intake in subjects suffering from disorders such as obesity, bulimia, and anorexia nervosa, Alzheimers disease, multiple sclerosis and other cognitive disorders.

Included within the scope of "compounds of the invention" are all solvates, complexes, polymorphs of compounds of formula (I) and pharmaceutically acceptable salts thereof.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also
includes within its scope amounts effective to enhance normal physiological function.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I), or a salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, acetone, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid. Most preferably the solvent is water.

The compounds of formula (I) may have the ability to crystallize in more than one form, a characteristic, which is known as polymorphism, and it is understood that such polymorphic forms ("polymorphs") are within the scope of formula (I). Polymorphism generally can occur as a response to changes in temperature or pressure or both and can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics known in the art such as x-ray diffraction patterns, solubility and melting point.

Certain of the compounds described herein may contain one or more chiral atoms, or may otherwise be capable of existing as two enantiomers. Accordingly, the compounds of this invention include mixtures of enantiomers as well as purified enantiomers or enantiomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds represented by formula (I) above as well as any wholly or partially equilibrated mixtures thereof. The present invention also covers the individual isomers of the compounds represented by the formulas above as mixtures with isomers thereof in which one or more chiral centres are inverted.

It is also noted that the compounds of the invention may form tautomers. It is understood that all tautomers and mixtures of tautomers of the compounds of the present invention are included within the scope of the compounds of the present invention.

In one aspect, R² is H and R¹ is COOH,

In one aspect, R³ is H.
In one aspect, $Z$ represents phenyl (optionally substituted by OH or -OCH$_3$), cyclohexyl, a monocyclic 5 or 6 membered heteroaryl (optionally substituted by CH$_3$), a benzothiophenyl or benzofuranyl.

In a further aspect, $Z$ represents phenyl, furanyl, benzofuranyl, benzothiophenyl, pyridinyl, thiophenyl (substituted by -CH$_3$), phenyl (substituted by OH), phenyl (substituted by -CH$_3$), cyclohexyl.

In a further aspect $Z$ represents phenyl.

In one aspect, $X$ represents a linker group selected from

-$(CH_2)_4 NR^C(O)$ - ,
-$(CH_2)_4 C(O)NH$ - ,
-$(CH_2)_2 O CH_2 C(O)NH$ - ,

$\text{-CH}_2 C(O)-N\text{-}$ ,

$\text{-CH}_2\text{-}$ ,

-$(CH_2)_2 NR^d CH_2 C(O)NH$ - .
R^c = H, C1-3 alkyl,
R^d = H, C1-3 alkyl,

In one aspect X represents -(CH\_2\(^\text{NHCO}^-\)) or -(CH\_2\text{OCH}_2\text{CONH}^-),

5

In one aspect X-Y together represent

\[\text{\begin{diagram}
\text{CH}_3 & \text{N} & \text{O} \\
\text{C} & \text{O} & \text{N}
\end{diagram}}\]

10 In one aspect, Y is phenyl (optionally substituted by one or more substituents independently selected from d-3 alkyl, OH, d-3 haloalkyl, -halogen, d-3 alkoxy, C\text{5-6 cycloalkyl}), a 5 or 6 membered heteroaryl, NR\text{xR}^y (wherein R\text{x} and R\text{y} are independently H or C\text{r}_3 alkyl), phenyl fused to a 5 membered heterocyclic ring containing one O atom, phenyl fused to a 6 membered heterocyclic ring containing two O atoms.

15 In one aspect, Y is

\[\text{\begin{diagram}
\text{X}_n \\
\text{phenyl}
\end{diagram}}\]

20 (n is 1, 2 or 3 and each X is independently selected from C\text{1-3 alkyl}, C\text{1-3 alkoxy}, OH, cycloalkyl, NR\text{xR}^y (R\text{x} and R\text{y} are independently C\text{r}_3 alkyl), chloro, C\text{F}_3, pyridyl),
\[ \text{in a further aspect } Y \text{ is } \]
\[ \begin{array}{c}
\text{Cl} \\
\text{N} \\
\text{CH}_3 \\
\end{array} \]
\[ (X)_n \]

(where \( n \) is 1, 2 or 3 and each \( X \) is independently selected from \( \text{C}_r \text{ alkyl, C}_r \text{ alkoxy, COH, cycloalkyl, NR}_x \text{R}_y (R^x \text{ and } R^y \text{ are independently C}_r \text{ alkyl}), \text{ chloro, CF}_3, \text{ pyridyl}). \]

In one aspect \( Z \) is phenyl, \( X \) is \(-\text{(CH}_2)_2\text{OCH}_2\text{CONH-}\) and \( Y \) is phenyl, (substituted by \(-\text{C}_r \text{ alkyl}). \]

While aspects for each variable have generally been listed above separately for each variable this invention includes those compounds in which several or each aspect in formula (I) is selected from each of the aspects listed above. Therefore, this invention is intended to include all combinations of aspects for each variable.

Specific Examples of compounds of the prevent invention include the following:

Example 1
1-\{2-[(2-\{4-(1-methylethyl)phenylamino\}-2-oxoethyl)oxyethyl]-3-phenyl-1/-/-indole-6-carboxylic acid;

Example 2
1-\{2-[(2-(1-methylethyl)phenylamino]-2-oxoethyl)oxyethyl]-3-phenyl-1/-/-indole-6-carboxylic acid;
Example 3
1-[2-((2-oxo-2-[2,4,6-trimethylphenyl]amino)ethyl]oxy)ethyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 4
1-[2-((2-[[3-hydroxy-5,6,7,8-tetrahydro-2-naphthalenyl]amino]-2-oxoethyl]oxy)ethyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 5
1-[2-[[2-[(3-(methyloxy)phenyl]amino]-2-oxoethyl]oxy]ethyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 6
1-[2-[[2-[[1-(methylethyl)phenyl]amino]-2-oxoethyl]oxy]ethyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 7
1-[2-((2-hydroxy-4-methylphenyl]amino]-2-oxoethyl]oxy)ethyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 8
1-(2-[(2-[2,3-dihydro-1,4-benzodioxin-6-ylamino]-2-oxoethyl]oxy)ethyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 9
1-[2-[[2-(2,3-dihydro-1H-inden-5-ylamino)-2-oxoethyl]oxy]ethyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 10
1-[2-[(4-cyclohexylphenyl]amino]-2-oxoethyl]oxy)ethyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 11
1-[2-[(2-[4-(1,1-dimethylethyl)phenyl]amino]-2-oxoethyl]oxy]ethyl]-3-phenyl-1H-indole-6-carboxylic acid;
Example 12
1-[2-({2-[(4-methylphenyl)amino]-2-oxoethyl}oxy)ethyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 13
1-[2-({2-[(4-ethylphenyl)amino]-2-oxoethyl}oxy)ethyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 14
1-[4-({[4-(1-methylethyl)phenyl]carbonyl}amino)butyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 15
1-[4-({[4-(dimethylamino)phenyl]carbonyl}amino)butyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 16
1-(4-{{[4-(chlorophenyl)carbonyl]amino}butyl}-3-phenyl-1H-indole-6-carboxylic acid;

Example 17
1-[4-({2-(ethyloxy)phenyl]carbonyl]amino)butyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 18
1-[4-({[4-(methyloxy)phenyl]carbonyl]amino)butyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 19
1-[4-({[4-(1,1-dimethylethyl)phenyl]carbonyl]amino)butyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 20
3-phenyl-1-[4-({[4-(trifluoromethyl)phenyl]carbonyl]amino)butyl]-1H-indole-6-carboxylic acid;

Example 21
1-(4-{{[4-(methylphenyl)carbonyl]amino}butyl}-3-phenyl-1H-indole-6-carboxylic acid;


Example 22
3-phenyl-1-[4-({[4-(2-pyridinyl)phenyl]carbonyl}amino)butyl]-1 H-indole-6-carboxylic acid;

Example 23
1-[4-({[2-hydroxy-3-(1-methylethyl)phenyl]carbonyl}amino)butyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 24
1-[(4-([3-hydroxyphenyl]carbonyl)amino)butyl]-3-phenyl-1 H-indole-6-carboxylic acid;

Example 25
1-[(4-[((2-methyl-3,4-dihydro-2H-chromen-8-yl)carbonyl]amino)butyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 26
1-[(4-([2,4-bis(methyloxy)phenyl]carbonyl)amino)butyl]-3-phenyl-1 H-indole-6-carboxylic acid;

Example 27
1-[(4-([methyl(propyl)amino]phenyl)carbonyl)amino]butyl]-3-phenyl-1 H-indole-6-carboxylic acid;

Example 28
1-[(4-([dimethylamino]-2-hydroxyphenyl]carbonyl]amino)butyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 29
3-phenyl-1-[4-({[2-(propyloxy)phenyl]carbonyl}amino)butyl]-1 H-indole-6-carboxylic acid;

Example 30
1-[(4-([1,3-benzodioxol-5-yl]carbonyl)amino]butyl]-3-phenyl-1 H-indole-6-carboxylic acid;

Example 31
3-phenyl-1-[4-({[2-(1H-pyrrol-1-yl)phenyl]carbonyl}amino)butyl]-1 H-indole-6-carboxylic acid;
Example 32
1-[4-(((4-(dimethylamino)-3-methylphenyl)carbonyl)amino)butyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 33
1-(4-((2,3-dihydro-1-benzofuran-5-yl)carbonyl)amino)butyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 34
1-(4-(2-methyl-4-oxo-3(4H)-quinazolinyl)butyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 35
3-phenyl-1-(4-(((6-(trifluoromethyl)-3-pyridinyl)carbonyl)amino)butyl]-1H-indole-6-carboxylic acid;

Example 36
1-(4-(((3-methyl-2-furanyl)carbonyl)amino)butyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 37
1-(4-(((5-methyl-2-thienyl)carbonyl)amino)butyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 38
1-(4-(((2-chloro-6-methyl-3-pyridinyl)carbonyl)amino)butyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 39
1-(4-(((1-methyl-1H-pyrrol-2-yl)carbonyl)amino)butyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 40
1-(4-(((2-hydroxy-4-methylphenyl)carbonyl)amino)butyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 42
1-(4-((2,3-dihydro-1,4-benzodioxin-6-yl)carbonyl)amino)butyl]-3-phenyl-1H-indole-6-carboxylic acid;
Example 43
1-\(\{4-([1-(1,1\text{-dimethylethyl})\text{-}1/-/-\text{imidazol-5-yl}]\text{carbonyl}][\text{amino}]\text{butyl}\}\)-3-phenyl-1/-/-indole-6-carboxylic acid;

Example 44
1-\(\{4-([4-(1\text{-methylethyl})\text{phenyl}]\text{carbonyl})(\text{propyl})\text{amino}]\text{butyl}\}\)-3-phenyl-1H-indole-6-carboxylic acid;

Example 45
1-\(\{4-([4-(1\text{-methylethyl})\text{phenyl}]\text{carbonyl}][\text{amino}]\text{butyl}\}\)-3-phenyl-1H-indole-6-carboxylic acid;

Example 46
1-(2-\(\{4-([4-(1\text{-methylethyl})\text{phenyl}]\text{-}1\text{-piperazinyl}]\text{-}2\text{-oxoethyl}\}\)-3-phenyl-1H-indole-6-carboxylic acid;

Example 47
3-(3-furanyl)-1-\(\{4-([4-(1\text{-methylethyl})\text{phenyl}]\text{carbonyl}][\text{amino}]\text{butyl}\}\)-1H-indole-6-carboxylic acid;

Example 48
3-cyclohexyl-1-\(\{4-([4-(1\text{-methylethyl})\text{phenyl}]\text{carbonyl}][\text{amino}]\text{butyl}\}\)-1H-indole-6-carboxylic acid;

Example 49
1-\(\{4-([4-(1\text{-methylethyl})\text{phenyl}]\text{carbonyl}][\text{amino}]\text{butyl}\}\)-3-[3-(methyloxy)\text{phenyl}]-1H-indole-6-carboxylic acid;

Example 50
1-\(\{4-([4-(1\text{-methylethyl})\text{phenyl}]\text{carbonyl}][\text{amino}]\text{butyl}\}\)-3-(5-methyl-2-thienyl)-1H-indole-6-carboxylic acid;

Example 51
3-(1-benzothien-2-yl)-1-\(\{4-([4-(1\text{-methylethyl})\text{phenyl}]\text{carbonyl}][\text{amino}]\text{butyl}\}\)-1H-indole-6-carboxylic acid;
Example 52
3-(1-benzofuran-2-yl)-1-[4-([4-(1-methylethyl)phenyl]carbonyl)amino]butyl]-1/-/-indole-6-carboxylic acid;

Example 53
3-(2-hydroxyphenyl)-1-[4-([4-(1-methylethyl)phenyl]carbonyl)amino]butyl]-1 H-indole-6-carboxylic acid;

Example 54
1-[4-([4-(1-methylethyl)phenyl]carbonyl)amino]butyl]-3-(2-pyridinyl)-1 H-indole-6-carboxylic acid;

Example 55
1-[4-([4-cyclohexylphenyl]carbonyl)amino]phenyl)methyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 56
1-[4-((4-(dimethylamino)-2-hydroxyphenyl]carbonyl)amino]butyl]-3-(3-furanyl)-1H-indole-6-carboxylic acid;

Example 57
1-[4-([4-(1-methylethyl)phenyl]carbonyl)amino]phenyl)methyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 58
1-((5-([4-(1-methylethyl)phenyl]amino)-5-oxopentyl)-3-phenyl-1H-indole-6-carboxylic acid;

Example 59
1-[2-((2-[4-(1-methylethyl)phenyl]amino)-2-oxoethyl]amino]ethyl]-3-phenyl-1H-indole-6-carboxylic acid (non-preferred name);

Example 60
1-[2-[methyl(2-[[4-(1-methylethyl)phenyl]amino]-2-oxoethyl]amino]ethyl]-3-phenyl-1H-indole-6-carboxylic acid (non-preferred name);
Example 6.1
2-[(dimethylamino)methyl]-1-[4-((4-(1-methylethyl)phenyl)carbonyl)amino]butyl]-3-phenyl-1H-indole-6-carboxylic acid;

Example 6.2
1-2-[2-[[4-(1-methylethyl)phenyl]amino]-2-oxoethyl]oxyethyl]-3-(2-pyridinyl)-1H-indole-6-carboxylic acid;

Example 6.3
3-(1-benzothen-2-yl)-1-[2-[(2-[4-(1-methylethyl)phenyl]amino)-2-oxoethyl]oxyethyl]-1H-indole-6-carboxylic acid;

and pharmaceutically acceptable salts thereof.

The compounds of the invention are modulators of human PPARs, particularly PPAR alpha and PPAR gamma. In one aspect they are agonists or partial agonists. The hPPAR agonists of formula (I) may be agonists of only one hPPAR ("selective agonists"), agonists for two hPPAR subtypes ("dual agonists"), or agonists for all three hPPAR subtypes ("pan agonists").

As used herein, by "agonist", or "activating compound", or "activator", or the like, is meant those compounds which have a pKi of at least 6.0 preferably at least 7.0 to the relevant PPAR, for example hPPAR alpha in the binding assay described below, and which achieve at least 50% activation of the relevant PPAR relative to the appropriate indicated positive control in the transfection assay described below at concentrations of 10^{-5} M or less. EC_{50} is defined in the transfection assay described below and is the concentration at which a compound achieves 50% of its maximum activity.

Partial agonists can be defined as compounds that transactivate the relevant PPAR, for example PPAR alpha in CV1 cells with less than 50% fold activation compared to the reference PPAR alpha full agonist in the transfection assays of the type described below. Suitably the compounds of formula (1) are hPPAR alpha agonists.

The compounds of Formula (I) may be in the form of a salt.
Typically, the salts of the present invention are pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. For a review on suitable salts see Berge et al, J. Pharm. Sci. 1977, 66, 1-19.

Suitable pharmaceutically acceptable salts can include acid addition salts.

A pharmaceutically acceptable acid addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic acid (such as hydrobromic, hydrochloric, sulfuric, nitric, phosphoric, p-toluenesulfonic, benzenesulfonic, methanesulfonic, ethanesulfonic, naphthalenesulfonic such as 2-naphthalenesulfonic), optionally in a suitable solvent such as an organic solvent, to give the salt which is usually isolated for example by crystallisation and filtration. A pharmaceutically acceptable acid addition salt of a compound of formula (I) can comprise or be for example a hydrobromide, hydrochloride, sulfate, nitrate, phosphate, p-toluenesulfonate, benzenesulfonate, methanesulfonate, ethanesulfonate, naphthalenesulfonate (e.g. 2-naphthalenesulfonate) salt.

Other non-pharmaceutically acceptable salts, e.g. trifluoroacetates, may be used, for example in the isolation of compounds of the invention, and are included within the scope of this invention.

The invention includes within its scope all possible stoichiometric and non-stoichiometric forms of the compounds of formula (I).

In particular the compounds of the invention are believed to be activators of hPPAR alpha, and thus be potentially useful in the treatment of hPPAR mediated disorders.

The invention thus provides a compound of formula (I) or a pharmaceutically acceptable salts thereof for use in therapy, and particularly in the treatment of hPPAR mediated disorders.

In a further aspect of the present invention, there is provided a method of treating hPPAR mediated disorders comprising administering to a subject a compound of formula (I) or a pharmaceutically acceptable salt thereof. The subject is a mammal, particularly a human.
In a further aspect of the present invention, there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof in the preparation of a medicament for use in the treatment of hPPAR mediated disorders.

In further aspect of the invention there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of hPPAR mediated disorders.

hPPAR mediated diseases or conditions include dyslipidemia (including associated diabetic dyslipidemia and mixed dyslipidemia), syndrome X (as defined in this application this embraces metabolic syndrome), heart failure, hypercholesterolemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridemia, type II diabetes mellitus, type 1 diabetes, insulin resistance, hyperlipidemia, obesity, inflammation, epithelial hyperproliferative diseases including eczema and psoriasis and conditions associated with the lung and gut and regulation of appetite and food intake in subjects suffering from disorders such as obesity, anorexia bulimia, and anorexia nervosa, cancer, Alzheimers disease, multiple sclerosis or other cognitive disorders. In particular, the compounds of this invention are useful in the treatment and prevention of diabetes and cardiovascular diseases and conditions including atherosclerosis, arteriosclerosis, hypertriglyceridemia, and dyslipidaemia.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the invention further provides pharmaceutical compositions comprising a compound of the formula (I) or a pharmaceutically acceptable salts thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The carrier(s), diluent(s) or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipient thereof. In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical composition including admixing a compound of the formula (I), or pharmaceutically acceptable salts thereof, with one or more pharmaceutically acceptable carriers, diluents or excipients. The pharmaceutical composition can be for use in the treatment and/or prophylaxis of any of the conditions described herein.
Since the compounds of the invention are intended for use in pharmaceutical compositions it will be readily understood that they are each preferably provided in substantially pure form, for example, at least 60% pure, more suitably at least 75% pure and preferably at least 85% pure, especially at least 98% pure (% in a weight for weight basis).

Pharmaceutical compositions may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Preferred unit dosage compositions are those containing a daily dose or sub-dose, or an appropriate fraction thereof, of an active ingredient. Such unit doses may therefore be administered once or more than once a day. Such pharmaceutical compositions may be prepared by any of the methods well known in the pharmacy art.

Pharmaceutical compositions may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, inhaled, intranasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such compositions may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical compositions adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by reducing the compound to a suitable fine size and mixing with a similarly prepared pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium
carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, glidants, lubricants, sweetening agents, flavours, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an alginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcoho
preservatives, flavor additive such as peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit compositions for oral administration can be microencapsulated. The composition can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

The compounds of the invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Pharmaceutical compositions adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time.

Pharmaceutical compositions adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the compositions are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical compositions adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical compositions adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical compositions adapted for rectal administration may be presented as suppositories or as enemas.
Dosage forms for nasal or inhaled administration may conveniently be formulated as aerosols, solutions, suspensions, drops, gels or dry powders.

For compositions suitable and/or adapted for inhaled administration, it is preferred that the compound or salt of formula (I) is in a particle-size-reduced form, and more preferably the size-reduced form is obtained or obtainable by micronisation. The preferable particle size of the size-reduced (e.g. micronised) compound or salt or solvate is defined by a D50 value of about 0.5 to about 10 microns (for example as measured using laser diffraction).

Compositions adapted for administration by inhalation include the particle dusts or mists. Suitable compositions wherein the carrier is a liquid for administration as a nasal spray or drops include aqueous or oil solutions/suspensions of the active ingredient which may be generated by means of various types of metered dose pressurised aerosols, nebulizers or insufflators.

Aerosol formulations, e.g. for inhaled administration, can comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-aqueous solvent. Aerosol formulations can be presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device or inhaler. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve (metered dose inhaler) which is intended for disposal once the contents of the container have been exhausted.

Where the dosage form comprises an aerosol dispenser, it preferably contains a suitable propellant under pressure such as compressed air, carbon dioxide or an organic propellant such as a hydrofluorocarbon (HFC). Suitable HFC propellants include 1,1,1,2,3,3-heptfluoropropane and 1,1,1,2-tetrafluoroethane. The aerosol dosage forms can also take the form of a pump-atomiser. The pressurised aerosol may contain a solution or a suspension of the active compound. This may require the incorporation of additional excipients e.g. co-solvents and/or surfactants to improve the dispersion characteristics and homogeneity of suspension formulations. Solution formulations may also require the addition of co-solvents such as ethanol. Other excipient modifiers may also be incorporated to improve, for example, the stability and/or taste and/or fine particle mass characteristics (amount and/or profile) of the formulation.
For pharmaceutical compositions suitable and/or adapted for inhaled administration, the pharmaceutical composition may be a dry powder inhalable composition. Such a composition can comprise a powder base such as lactose, glucose, trehalose, mannitol or starch, the compound of formula (I) or salt or solvate thereof (preferably in particle-size-reduced form, e.g. in micronised form), and optionally a performance modifier such as L-leucine or another amino acid, cellobiose octaacetate and/or metals salts of stearic acid such as magnesium or calcium stearate.

Aerosol formulations are preferably arranged so that each metered dose or "puff" of aerosol contains a particular amount of a compound of the invention. Administration may be once daily or several times daily, for example 2, 3 4 or 8 times, giving for example 1, 2 or 3 doses each time. The overall daily dose and the metered dose delivered by capsules and cartridges in an inhaler or insufflator will generally be double those with aerosol formulations.

Pharmaceutical compositions adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical compositions adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the composition isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

It should be understood that in addition to the ingredients particularly mentioned above, the compositions may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

A therapeutically effective amount of a compound of the present invention will depend upon a number of factors including, for example, the age and weight of the subject, the
precise condition requiring treatment and its severity, the nature of the formulation, and
the route of administration, and will ultimately be at the discretion of the attendant
physician or veterinarian. In particular, the subject to be treated is a mammal, particularly
a human.

The pharmaceutically acceptable compounds or salts of the invention may be
administered in a daily dose (for an adult patient) of, for example, an oral or parenteral
dose of 0.01 mg to 100 mg/kg per day body weight. This amount may be given in a single
dose per day or more usually in a number (such as two, three, four, five or six) of sub-
doses per day such that the total daily dose is the same. An effective amount of a salt or
solvate, thereof, may be determined as a proportion of the effective amount of the
compound of formula (I) per se. Thus, for a 70kg adult mammal, the actual amount per
day would usually be from 70 to 700 mg and this amount may be given in a single dose
per day or more usually in a number (such as two, three, four, five or six) of sub-doses per
day such that the total daily dose is the same. An effective amount of a salt or solvate, or
physiologically functional derivative thereof, may be determined as a proportion of the
effective amount of active ingredient.

The compounds of the present invention may be employed alone or in combination with
other therapeutic agents.

Thus in a further aspect, the invention provides a combination comprising at least one
compound of formula (I) or a pharmaceutically acceptable salt thereof, and at least one
other pharmaceutically active agent. Thus, combination therapies according to the
present invention comprise the administration of at least one compound of formula (I) or a
pharmaceutically acceptable salt thereof, and at least one other pharmaceutically active
agent. The compound(s) of formula (I) and the other pharmaceutically active agent(s)
may be administered together in a single pharmaceutical composition or separately and,
when administered separately this may occur simultaneously or sequentially in any order.

When administered separately, they may be at different times of the day. Thus, the
amounts of the compound(s) of formula (I) and the other pharmaceutically active agent(s)
and the relative timings of administration will be selected in order to achieve the desired
combined therapeutic effect.

The compound and pharmaceutical compositions according to the invention may be used
in combination with or include one or more other therapeutic agents, for example selected
from statins (HMG CoA reductase inhibitors) and/or other lipid lowering drugs for example
MTP inhibitors and LDLR upregulators. The compounds of the invention may also be
used in combination with antidiabetic agents, e.g. metformin, sulfonylureas and/or PPAR
activators (for example thiazolidinediones such as e.g. pioglitazone and rosiglitazone).

The compounds may also be used in combination with antihypertensive agents such as
angiotensin antagonists calcium channel antagonists and ACE inhibitors. The invention
thus provides in a further aspect the use of a combination comprising a compound of
formula (I) with a further therapeutic agent in the treatment of a hPPAR mediated
disorders.

It will be clear to a person skilled in the art that, where appropriate, the other therapeutic
ingredient(s) may be used in the form of salts, for example as alkali metal or amine salts
or as acid addition salts, or prodrugs, or as esters, for example lower alkyl esters, or as
solvates, for example hydrates, to optimise the activity and/or stability and/or physical
characteristics, such as solubility, of the therapeutic ingredient. It will be clear also that,
where appropriate, the therapeutic ingredients may be used in optically pure form.

When a compound of formula (I) is used in combination with other therapeutic agents, the
compounds may be administered either sequentially or simultaneously by any convenient
route.

The combinations referred to above may conveniently be presented for use in the form of
a pharmaceutical composition and thus pharmaceutical compositions comprising a
combination as defined above optimally together with a pharmaceutically acceptable
carrier or excipient comprise a further aspect of the invention. The individual components
of such combinations may be administered either sequentially or simultaneously in
separate or combined pharmaceutical compositions.

When combined in the same composition it will be appreciated that the two compounds
must be stable and compatible with each other and the other components of the
composition and may be formulated for administration. When formulated separately they
may be provided in any convenient composition, conveniently in such a manner as are
known for such compounds in the art.

When the compound of formula (I) is used in combination with a second therapeutic agent
active against the same hPPAR mediated disorder, the dose of each compound may differ
from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

Compounds of general formula (I) may be prepared by methods known in the art of organic synthesis as set forth in the schemes below and/or the specific Examples described below. In all of the methods, it is well understood that protecting groups for sensitive or reactive groups may be employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Green and P. G. M. Wuts (1999) Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection of processes as well as the reaction conditions and order of their execution shall be consistent with the preparation of compounds of Formula (I).

Compounds of the invention may be prepared by one or more of the following general schemes, and the routes described in the specific Examples section below.

In all the following schemes R¹ is depicted as H and R² as COOH. The schemes are equally applicable to those compounds of formula (I) wherein R¹ is COOH and R² is H.

**Scheme 1**

P, P and P* are independently C₁₋₆ alkyl or another suitable protecting group. Compounds wherein X is -(CH₂)₂OCH₂C(O)NH- may be prepared by this route.
Scheme 2

Compounds wherein

\[ X = -(CH_2)_4NHC \]

may be prepared by the following scheme
Z can be introduced in the molecule either before or after the -XY group.
Scheme 3

Compounds where the linker is

\[-\text{CH}_2\text{O})\text{N}N\text{--}\]

may be prepared by the following scheme:
Scheme 4

Compounds where the linker is

\[ \text{CH}_2 - \text{NHC(O)} - \]

may be prepared by this route

\( \text{Z} \)

\( \text{OOC} \)

\( \text{CH}_2 \)

\( \text{NO}_2 \)

\( \text{NH}_2 \)

\( \text{CH}_2 \)

\( \text{Y} \)

\( \text{OOC} \)

\( \text{CH}_2 \)

\( \text{NH}_2 \)

\( \text{OOC} \)

\( \text{CH}_2 \)

\( \text{NH}_2 \)

\( \text{OOC} \)

\( \text{CH}_2 \)

\( \text{NH}_2 \)
Compounds where the linker is \((\text{CH}_2)_2\text{N(R^d)}\text{CH}_2\text{C(O)NH-}\) may be prepared by this route:

\[(\text{V})\]  
\[(\text{I})\]

\[(\text{e})\]  
\[(\text{s})\]
Compounds wherein R³ is CH₂N(CH₃)₂ can be prepared for example as in Scheme 6.

Scheme 7

Compounds where the linker is (CH₂)₄N(Rᵈ)CO⁻ may be prepared by this route.
Scheme 8

Compounds where the linker is \((\text{CH}_2)_4\text{C(O)NH-}\) may be prepared by this route.

\[
\begin{align*}
\text{(g)} & \quad \xrightarrow{\text{P-OOC}} \quad \text{(w)} \\
\text{(l)} & \quad \xrightarrow{\text{P-OOC}} \quad \text{(x)} \\
\text{(i)} & \quad \xrightarrow{\text{P-OOC}} \quad \text{(j)} \\
\end{align*}
\]
EXAMPLES

Various aspects of the invention will now be described by reference to the following examples. These examples are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

Abbreviations

<table>
<thead>
<tr>
<th></th>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>APCI MS</td>
<td>Atmospheric Pressure Chemical Ionization quadrupole Mass Spectrometer</td>
</tr>
<tr>
<td>11</td>
<td>AcOH</td>
<td>Acetic acid</td>
</tr>
<tr>
<td>12</td>
<td>APTS</td>
<td>Acid para-toluene sulfonic</td>
</tr>
<tr>
<td>13</td>
<td>CH2Cl2</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>15</td>
<td>CDC13</td>
<td>deuterated chloroform</td>
</tr>
<tr>
<td>16</td>
<td>DMAP</td>
<td>dimethylaminopyridine</td>
</tr>
<tr>
<td>17</td>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>18</td>
<td>DMSO d6</td>
<td>deuterated dimethylsulfoxide</td>
</tr>
<tr>
<td>19</td>
<td>EDCI</td>
<td>1-ethyl-3-(3-dimethylaminopropyl)carbodiimide</td>
</tr>
<tr>
<td>20</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N</td>
<td>triethylamine</td>
</tr>
<tr>
<td>21</td>
<td>EtOH</td>
<td>ethanol</td>
</tr>
<tr>
<td>22</td>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>23</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>24</td>
<td>HCl</td>
<td>hydrochloric acid</td>
</tr>
<tr>
<td>25</td>
<td>HOBT</td>
<td>1-hydroxybenzotriazole</td>
</tr>
<tr>
<td>26</td>
<td>HATU</td>
<td>O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate</td>
</tr>
<tr>
<td>27</td>
<td>iPr&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>diisopropyl ether</td>
</tr>
<tr>
<td>28</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>potassium carbonate</td>
</tr>
<tr>
<td>30</td>
<td>KOH</td>
<td>potassium hydroxide</td>
</tr>
<tr>
<td>31</td>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>32</td>
<td>MgSO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>magnesium sulfate</td>
</tr>
<tr>
<td>33</td>
<td>NaOH</td>
<td>sodium hydroxide</td>
</tr>
<tr>
<td>34</td>
<td>NaBH(OAc)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>sodium triacetoxyborohydrure</td>
</tr>
<tr>
<td>35</td>
<td>Na&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>sodium carbonate</td>
</tr>
</tbody>
</table>
DME - Dimethoxyethane
TBAF - Tetrabutylammonium fluoride
DiBaIH - Diisobutylaluminum hydride
NaHCO₃ - sodium hydrogen carbonate
Na₂SO₄ - sodium sulphate
NBS - N-bromo succinimide
Pd/C - palladium on carbon
Pd(PPh₃)₄ - tetrakis(triphenylphosphine)palladium(0)
POCl₃ - phosphorus oxychloride
TFA - trifluoro acetic acid
THF - tetrahydrofuran

**Intermediate 1**

**Methyl 3-bromo-1 H-indole-6-carboxylate**

To a solution of 17.5 g of methyl 1H-indole-6-carboxylate dissolved in 200 ml of DMF, cooled at -60°C, was added dropwise a solution of 19.6g of NBS in 150 ml of DMF. The reaction mixture was stirred until room temperature was reached, then poured into 2L of an ice/water mixture. The precipitate was filtered then solubilised with 2L of ethyl acetate and washed twice with brine. The solution was dried with Na₂SO₄ then concentrated "in vacuum."

23.5g of brown solid was obtained and re-crystallized using chloroform to give 18.5g of pink crystals of methyl 3-bromo-1 H-indole-6-carboxylate (72.8%). [APCI-MS] m/z: 256.12 (M+H)⁺, Rt= 3.00 min.

**Intermediate 2**

1-(1,1-dimethylethyl) 6-methyl 3-bromo-1 H-indole-1,6-dicarboxylate
To a solution of 5.5g of methyl 3-bromo-1H-indole-6-carboxylate (Intermediate 1) in 50 ml of THF, was added 5.2g of DMAP, 5.68g of BOC₂O then the reaction mixture was stirred for 16h at room temperature. The reaction mixture was concentrated and solubilised by adding CH₂Cl₂ then washed using HCl 0.5N and dried with Na₂SO₄. Flash chromatography CH₂Cl₂/Cyclohexane gave 6.5g of 1-(1,1-dimethylethyl) 6-methyl 3-bromo-1 H-indole-1,6-dicarboxylate (85%).

[APCI-MS] m/z: 355.95 (M+H)⁺, Rt= 4.01 min.

**Intermediate 3**

1-(1,1-dimethylethyl) 6-methyl 3-phenyl-1 H-indole-1,6-dicarboxylate

To a solution of 8.2g of 1-(1,1-dimethylethyl) 6-methyl 3-bromo-1 H-indole-1,6-dicarboxylate (Intermediate 2) in 100ml of DME was added 4.25g of phenyl boronic acid, 30 mg of Pd tetrakis, 6.8 ml of a 2.5M water solution of cesium carbonate, then the reaction mixture was heated to reflux for 18 hours, then an additional 2 mg of Pd tetrakis was added and the reaction mixture was heated again 4 hours. After cooling the mixture was concentrated under vacuum, 200ml of ethyl acetate was added and the solution was washed respectively with HCl 1N and brine. After concentration the brown solid obtained was triturated into pentane, the filtration gives of 1-(1,1-dimethylethyl) 6-methyl 3-phenyl-1 H-indole-1,6-dicarboxylate as a white solid (4g, 100%).

[APCI-MS] m/z: 352 (M+H)⁺, Rt= 4.45 min.

**Intermediate 4**

Methyl 3-phenyl H-indole-6-carboxylate
A solution of 49.8 g of 1-(1,1-dimethylethyl) 6-methyl 3-phenyl-1H-indole-1,6-dicarboxylate (Intermediate 3) in 500 ml of ACOEt was saturated with HCl gas then stirred overnight, saturated again with HCl gas and stirred two days. The solution was degassed using a stream of nitrogen, the precipitate filtered and washed with ethyl acetate. The white solid was solubilised into a mixture 50/50 ethyl acetate/Sat. NaHCO₃, then the organic layer was washed with brine and dried with Na₂SO₄. After concentration, methyl 3-phenyl-1H-indole-6-carboxylate was obtained as a beige solid (12.45g, 47%).

**[APCI-MS] m/z:** 252 (M+H)⁺, Rt= 3.46 min.

**Intermediate 5**

**Methyl 1-r2-(f2-r(1,1-dimethylethyl)oxy1-2-oxoethyl)oxy)ethvn-3-phenyl-1H-indole-6-carboxylate**

To a solution of 12.45g of methyl 3-phenyl-1H-indole-6-carboxylate (Intermediate 4) in 150 ml of DMF, was added 31.95g of CS₂CO₃ and 19.35g of 1,1-dimethylethyl [(2-chloroethyl)oxy]acetate, the reaction mixture was heated at 70°C for 16 hours, then filtered and washed with DMF, after concentration in vacuum the crude mixture was dissolved in dichloromethane, washed with brine and dried with Na₂SO₄. 200 ml of heptane are added to the solution and the mixture was put under vacuum until dichloromethane was completely removed.

A beige precipitate appears, the solution was cooled using an ice bath, the precipitate was filtered and washed with heptane to give methyl 1-[2-[(2-[(1,1-dimethylethyl)oxy]-2-oxoethyl)oxy]ethyl]-3-phenyl-1H-indole-6-carboxylate (18.13g, 90%).
Intermediate 6

\[ r(2\text{-}6\text{-}(\text{methyl oxy})\text{carbonyl}\text{-}3\text{-}phenyl\text{-}1\text{-}H\text{-}indol\text{-}1\text{-}yl)\text{ethyl}oxy\text{acetic acid} \]

To a solution of 18.13g of \((\text{methyl }1\text{-}[2\text{-}[(1\text{-}\text{dimethyl ethyl)}\text{oxy}]-2\text{-}\text{oxoethyl}oxy)\text{ethyl}]-3\text{-}phenyl\text{-}1\text{-}H\text{-}indole\text{-}6\text{-}carboxylate)\) (Intermediate 5) in 150 ml of dichloromethane was added 33 ml of TFA, then the reaction mixture was stirred at room temperature for 16 hours. 20 ml of TFA was added followed by an additional stirring at room temperature for 24 hours. The reaction mixture was washed twice with brine, then dried using Na\textsubscript{2}SO\textsubscript{4} and concentrated under vacuum. \([2\text{-}[6\text{-}(\text{methyl oxy})\text{carbonyl}\text{-}3\text{-}phenyl\text{-}1\text{-}H\text{-}indol\text{-}1\text{-}yl)\text{ethyl}oxy]\text{acetic acid} \) was obtained as a white solid (14.9g, 95%). [APCI-MS] m/z: 354.17 (M+H)\textsuperscript{+}, Rt= 2.58 min.

Intermediate 7

\[ \text{Methyl }1\text{-}[2\text{-}[4\text{-}(1\text{-methyl ethyl)}\text{phenylamino}]-2\text{-}\text{oxoethyl}oxy)\text{ethyl}]-3\text{-}phenyl\text{-}1\text{-}H\text{-}indole\text{-}6\text{-}carboxylate \]

To a solution of 13.97g of \([2\text{-}[6\text{-}(\text{methyl oxy})\text{carbonyl}\text{-}3\text{-}phenyl\text{-}1\text{-}H\text{-}indol\text{-}1\text{-}yl)\text{ethyl}oxy]acetic acid \) (Intermediate 6) in 150 ml of DMF was added, 6.4g of HOBT, 9.1g of EDCI, 6.5 ml of p-isopropyl aniline, and 11 ml of triethylamine, then the reaction mixture was stirred for 16 hours at room temperature.
The reaction was completed by concentration at 60°C under vacuum. The mixture was dissolved in ethyl acetate, washed with brine and dried with Na₂SO₄. After concentration under vacuum the minimum quantities of dichloromethane were added to get a solution, and heptane was added until precipitation of beige solid appeared. Dichloromethane was evaporated under vacuum and after filtration, methyl 1-{2-[[4-(1-methylethyl)phenyl]amino]-2-oxoethyl}oxyethyl]-3-phenyl-1H-indole-6-carboxylate was obtained as a beige solid (19.36g, 100%). [APCI-MS] m/z: 471.23 (M+H)⁺, Rt= 3.98 min.

**Example 1**

1-(2-r(2-f(4-(1-methylethyl)phenyllamino)-2-oxoethyl)oxylethyl)-3-phenyl-1H-indole-6-carboxylic acid

To a solution of 4.7g of methyl 1-{2-[[4-(1-methylethyl)phenyl]amino]-2-oxoethyl}oxyethyl]-3-phenyl-1H-indole-6-carboxylate (Intermediate 7) in 50ml of THF was added 50ml of methanol, and 50ml of LiOH 1M, the reaction mixture was heated at 70°C for 45 min , then 60 ml of HCl 1N was added immediately, after cooling at room temperature, ethyl acetate was added and reaction mixture was washed with brine then dried with Na₂SO₄. After concentration under vacuum 4.32g of crude material was obtained and purified on SiO₂ to yield 3.53g of 1-{2-[[4-(1-methylethyl)phenyl]amino]-2-oxoethyl}oxyethyl]-3-phenyl-1H-indole-6-carboxylic acid. Example 1 was re-crystallized in acetonitrile : yield of the re-crystallisation (80%)

<table>
<thead>
<tr>
<th>Intermediates</th>
<th>structures</th>
<th>NMR¹H NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The following Intermediates were prepared in an analogous manner to the preparation of Methyl 1-{2-[[4-(1-methylethyl)phenyl]amino]-2-oxoethyl}oxyethyl]-3-phenyl-1H-indole-6-carboxylate (Intermediate 7):
<table>
<thead>
<tr>
<th>Intermediate 8</th>
<th>(300 MHz)/LC-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Intermediate 8" /></td>
<td>CDCl₃, δ: 8.12 (s, 1H), 7.83 (m, 2H), 7.47 (d, 2H), 7.33 (d, 1H), 7.09 (m, 4H), 6.95 (td, 1H), 6.71 (t, 1H), 6.61 (d, 1H), 4.46 (t, 2H), 4.05 (s, 2H), 3.98 (d, 2H), 3.81 (s, 3H), 2.57 (m, 1H), 0.94 (d, 6H).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intermediate 9</th>
<th>APCI-MS m/z: 471.2 (M+H)+, Rt= 3.73 min.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image2" alt="Intermediate 9" /></td>
<td>CDCl₃, δ: 8.19 (s, 1H), 7.95 (s, 2H), 7.89 (s, 1H), 7.82 (m, 2H), 7.52 (m, 2H), 7.42 (s, 1H), 7.36 (t, 2H), 4.48 (t, 2H), 4.03 (s, 2H), 3.94 (t, 2H), 3.81 (s, 3H), 2.56 (m, 4H), 1.62 (m, 4H).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intermediate 10</th>
<th>APCI-MS m/z: 459.10 (M+H)+, Rt= 3.53 min.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image3" alt="Intermediate 10" /></td>
<td>CDCl₃, δ: 8.19 (s, 1H), 7.95 (s, 2H), 7.89 (s, 1H), 7.82 (m, 2H), 7.52 (m, 2H), 7.42 (s, 1H), 7.36 (t, 2H), 4.48 (t, 2H), 4.03 (s, 2H), 3.94 (t, 2H), 3.81 (s, 3H), 2.56 (m, 4H), 1.62 (m, 4H).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intermediate 11</th>
<th>APCI-MS m/z: 471.09 (M+H)+, Rt= 4.19 min.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image4" alt="Intermediate 11" /></td>
<td>CDCl₃, δ: 8.19 (s, 1H), 7.95 (s, 2H), 7.89 (s, 1H), 7.82 (m, 2H), 7.52 (m, 2H), 7.42 (s, 1H), 7.36 (t, 2H), 4.48 (t, 2H), 4.03 (s, 2H), 3.94 (t, 2H), 3.81 (s, 3H), 2.56 (m, 4H), 1.62 (m, 4H).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intermediate 12</th>
<th>APCI-MS m/z: 433.06 (M+H)+, Rt= 2.89 min.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image5" alt="Intermediate 12" /></td>
<td>CDCl₃, δ: 8.19 (s, 1H), 7.95 (s, 2H), 7.89 (s, 1H), 7.82 (m, 2H), 7.52 (m, 2H), 7.42 (s, 1H), 7.36 (t, 2H), 4.48 (t, 2H), 4.03 (s, 2H), 3.94 (t, 2H), 3.81 (s, 3H), 2.56 (m, 4H), 1.62 (m, 4H).</td>
</tr>
</tbody>
</table>
The following examples were prepared in an analogous manner to the preparation of 1-{2-[(2-[[4-(1-methylethyl)phenyl]amino]-2-oxoethyl)oxy]ethyl}-3-phenyl-1H-indole-6-carboxylic acid (Example 1), from compounds having the structures depicted in the numbered Intermediates above and e.g. prepared as described above.
<table>
<thead>
<tr>
<th>Example</th>
<th>Intermediate</th>
<th>Target Mass for C28H28N2O4:</th>
<th>455.1971 (M-H)+, Found: 455.1942</th>
<th>Rt: 2.53 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 2</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Example 3</th>
<th>Intermediate 9</th>
<th>Target Mass for C28H28NO4:</th>
<th>455.1971 (M-H)+, Found: 455.1945</th>
<th>Rt: 2.44 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 4</td>
<td>Intermediate 10</td>
<td>Target Mass for C29H28N2O5:</td>
<td>483.1920 (M-H)+, Found: 483.1900</td>
<td>Rt: 2.54 min</td>
</tr>
<tr>
<td>Example 5</td>
<td>Intermediate 11</td>
<td>CDCl3, δ: 8.23 (s, 1H), 7.91 (q, 2H), 7.58 (m, 3H), 7.49 (s, 1H), 7.39 (t, 2H), 7.26 (m, 2H), 7.00 (s, 1H), 6.93 (t, 1H), 6.49 (dd, 1H), 6.35 (d, 1H), 4.49 (m, 2H), 3.99 (s, 2H), 3.93 (m, 2H), 3.61 (s, 3H).</td>
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</tr>
<tr>
<td>Example</td>
<td>Intermediate</td>
<td>Target Mass for C26H24N2O5: 443.1607 (M-H)+, Found: 443.1577, Rt: 2.32 min</td>
<td></td>
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<tr>
<td>-----------</td>
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<td>------------------------------------------------------------------</td>
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<td></td>
</tr>
<tr>
<td>Example 8</td>
<td>Intermediate 14</td>
<td>Target Mass for C27H24N2O6: 473.1712 (M-H)+, Found: 473.1750, Rt: 2.31 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Example 10</td>
<td>Intermediate 16</td>
<td>Target Mass for C31H32N2O4: 497.2440 (M-H)+, Found: 497.2477, Rt: 2.97 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Example 11</td>
<td>Intermediate 17</td>
<td>Target Mass for C29H30N2O4: 471.2284 (M-H)+, Found: 471.2276, Rt: 2.74 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Example 12</td>
<td>Intermediate 18</td>
<td>Target Mass for C26H24N2O4: 427.1658 (M-H)+, Found:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Intermediate 20
Methyl 1-[4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)butyl]-3-phenyl-1H-indole-6-carboxylate

To a solution of methyl 3-phenyl-1H-indole-6-carboxylate (Intermediate 4) (3.2g, 12.75mmol) in CH₂CN (100mL) were added Cs₂CO₃ (12.47g, 38.3mmol) and 5.39g (19.13 mM) of 2-(4-bromobutyl)-1H-isoindole-1,3(2H)-dione, the mixture was stirred to reflux for 2 hours. After cooling, the reaction mixture was solubilised into 300 mL of CH₂Cl₂+100mL of ethyl acetate and washed with brine. The organic phase was dried over Na₂SO₄, filtered off, the solvent was removed under reduced pressure and the crude product yellow powder was triturated into hot acetonitrile (50-60°C), after cooling the white precipitate was filtered to give methyl 1-[4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)butyl]-3-phenyl-1H-indole-6-carboxylate (4.75g, 80%).

NMR ¹H NMR (300 MHz), CDCl₃ δ: 8.05 (s, 1H), 7.85 (d, 1H), 7.76 (m, 3H), 7.63 (m, 2H), 7.56 (m, 2H), 7.38 (m, 3H), 7.23 (m, 1H), 4.22 (t, 2H), 3.89 (s, 3H), 3.67 (t, 2H), 1.89 (m, 2H), 1.69 (m, 2H).

Intermediate 21
Methyl 1-(4-aminobutyl)-3-phenyl-1H-indole-6-carboxylate
A solution of methyl 1-[4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)butyl]-3-phenyl-1H-indole-6-carboxylate (Intermediate 20), (4.65 g, 10.28 mmol) in MeOH (50 ml.) was treated with hydrazine monohydrate (1 ml, 20.6 mmol). The resulting mixture was stirred at 75°C for 16 hours. After cooling to room temperature, evaporation in vacuo, the residue was taken up in CH₂Cb. Filtration and evaporation of filtrate gave methyl 1-(4-aminobutyl)-3-phenyl-1H-indole-6-carboxylate as yellow oil (3.2 g, 96%).

[APCI-MS] m/z: 323 (M+H)⁺, Rt = 2.73 min.

**Intermediate 22**

Methyl 1-[4-(1-methylethyl)phenylcarbonyl]amino)butyl-3-phenyl-1H-indole-6-carboxylate

To a solution of 4-(1-methylethyl)benzoic acid (763 mg, 4.65 mM) in 30 ml of toluene was added 1.7 ml of thionyl chloride (23.25 mM), the reaction mixture was stirred 4 h under reflux. Toluene was evaporated under vacuum, 50 ml of toluene are added to the mixture and evaporated under vacuum. The crude oil was solubilized in 30 ml of CH₂Cl₂, and that solution was added drop wise to solution of methyl 1-(4-aminobutyl)-3-phenyl-1H-indole-6-carboxylate (Intermediate 21) (1g, 3.1 mM) in 100 ml of CH₂Cl₂ + 622 µl of triethylamine.
The reaction mixture was stirred for V A hours at room temperature, washed with brine dried on Na₂SO₄, after evaporation the crude solid was purified on SiO₂ to give methyl 1-[4-([4-(1-methylethyl)phenyl]carbonyl)amino]butyl]-3-phenyl-1H-indole-6-carboxylate (1.1g, 76%).

[APCI-MS] m/z: 469.12 (M+H)+, Rt= 3.87 min.

Alternatively Intermediates 22 and analogues can be prepared by the following protocol:

To a solution of methyl 1-(4-aminobutyl)-3-phenyl-1H-indole-6-carboxylate (Intermediate 21) (205 mg, 0.63 mM) in a mixture THF/DMF (20 ml/3ml), was added 290 mg of HATU, 125 mg of 4-(1-methylethyl)benzoic acid. The reaction mixture was stirred at room temperature for 24 hours.

50 ml of EtAc was added and the reaction mixture was washed with HCl 1N, NaOH 1N, brine and dried on Na₂SO₄, after concentration under vacuum the crude material was purified on SiO₂ to give methyl 1-[4-([4-(1-methylethyl)phenyl]carbonyl)amino]butyl]-3-phenyl-1H-indole-6-carboxylate (125mg, 42%).

NMR ¹H NMR (300 MHz), CDCl₃ δ: 8.06 (s, 1H), 7.86 (d, 1H), 7.78 (dd, 1H), 7.56 (m, 4H), 7.36 (m, 3H), 7.23 (m, 1H), 7.18 (m, 2H), 4.19 (t, 2H), 3.87 (s, 3H), 3.38 (q, 2H), 2.85 (m, 1H), 1.89 (m, 2H), 1.55 (m, 2H), 1.16 (d, 6H).

Example 14

1-14-(114-(1-methylethyl)phenyllcarbonyl)amino]butyl]-3-phenyl-1H-indole-6-carboxylic acid
To a solution of methyl 1-[4-([(4-(1-methylethyl)phenyl)carbonyl]amino)butyl]-3-phenyl-1H-indole-6-carboxylate (Intermediate 22) (1.1g) in THF/MeOH 100ml/10ml was added 23.5 ml of NaOH (1 N solution) and the reaction mixture was heated to reflux for 3 hours.

After evaporation of organic solvent under vacuum, 100 ml of water was added and the mixture was acidified until pH=1. A pale yellow precipitate appears which was filtered and dried to give 1-[4-([(4-(1-methylethyl)phenyl)carbonyl]amino)butyl]-3-phenyl-1H-indole-6-carboxylic acid (995 mg, 93%).

NMR \( ^1H \) NMR (300 MHz), CDCl3 \( \delta \): 8.01 (bs, 1H), 7.72 (bs, 1H), 7.52 (m, 3H), 7.34 (m, 2H), 7.21 (m, 2H), 7.10 (m, 2H), 6.97 (d, 2H), 3.75 (bs, 2H), 3.06 (bs, 2H), 2.70 (m, 1H), 1.52 (m, 2H), 1.23 (m, 2H), 1.04 (d, 6H).

The following intermediates were prepared in an analogous manner to methyl 1-[4-([(4-(1-methylethyl)phenyl)carbonyl]amino)butyl]-3-phenyl-1H-indole-6-carboxylate (Intermediate 22) from intermediate compounds having the structures depicted above and e.g. prepared as above:

<table>
<thead>
<tr>
<th>Intermediate</th>
<th>( R )</th>
<th>From</th>
<th>NMR ( ^1H ) NMR (300 MHz)/LC-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate 23</td>
<td><img src="image" alt="Structure" /></td>
<td>Intermediate 21</td>
<td>NMR ( ^1H ) NMR (300 MHz), CDCl3, ( \delta ): 8.14 (s, 1H), 7.94 (d, 1H), 7.84 (dd, 1H), 7.62 (m, 4H), 7.45 (m, 3H), 7.28</td>
</tr>
<tr>
<td>----------------</td>
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<td>----------------</td>
<td>----------------</td>
</tr>
<tr>
<td><img src="image" alt="Intermediate 24" /></td>
<td><img src="image" alt="Intermediate 25" /></td>
<td><img src="image" alt="Intermediate 26" /></td>
<td><img src="image" alt="Intermediate 27" /></td>
</tr>
<tr>
<td>NMR&lt;sup&gt;1&lt;/sup&gt;H NMR (300 MHz), DMSO, δ: 8.20 (s, 1H), 7.96 (m, 2H), 7.82 (d, 2H), 7.70 (m, 3H), 7.48 (m, 4H), 7.27 (m, 1H), 4.36 (m, 2H), 3.88 (s, 3H), 3.25 (m, 2H), 1.86 (m, 2H).</td>
<td>[APCI-MS] m/z: 472 (M+H)&lt;sup&gt;+&lt;/sup&gt;, Rt= 10.43 min.</td>
<td>NMR&lt;sup&gt;1&lt;/sup&gt;H NMR (300 MHz), DMSO, δ: 8.32 (m, 1H), 8.21 (s, 1H), 8.02 (s, 1H), 7.95 (d, 1H), 7.76 (m, 5H), 7.46 (t, 2H), 7.27 (t, 1H), 6.96 (d, 2H), 4.37 (t, 2H), 3.88 (s, 3H), 3.79 (s, 3H), 3.25 (m, 2H), 1.88 (m, 2H), 1.52 (m, 2H).</td>
<td>[APCI-MS] m/z: 481.22 (M+H)&lt;sup&gt;+&lt;/sup&gt;, Rt= 4.05 min.</td>
</tr>
<tr>
<td>Intermediate 29</td>
<td>Intermediate 21</td>
<td>[APCI-MS] m/z: 439.27 (M+H)⁺, Rt = 3.69 min.</td>
<td></td>
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<tr>
<td>----------------</td>
<td>----------------</td>
<td>---------------------------------</td>
<td></td>
</tr>
<tr>
<td>Intermediate 30</td>
<td>Intermediate 21</td>
<td>NMR¹H NMR (300 MHz), DMSO, δ : 8.70 (d, 1H), 8.57 (m, 1H), 8.17 (s, d, 3H), 7.97 (m, 6H), 7.72 (m, 3H), 7.43 (m, 3H), 7.27 (t, 1H), 4.39 (t, 2H), 3.88 (s, 3H), 3.31 (m, 2H), 1.89 (m, 2H), 1.59 (m, 2H).</td>
<td></td>
</tr>
<tr>
<td>Intermediate 31</td>
<td>Intermediate 21</td>
<td>NMR¹H NMR (300 MHz), DMSO, δ : 8.88 (m, 1H), 8.21 (s, 1H), 8.01 (s, 1H), 7.96 (d, 1H), 7.67 (m, 5H), 7.29 (m, 4H), 4.37 (t, 2H), 3.87 (s, 3H), 3.29 (m, 2H), 2.5 (m, 1H), 7.88 (m, 2H), 1.56 (m, 2H), 1.18 (d, 6H).</td>
<td></td>
</tr>
<tr>
<td>Intermediate 32</td>
<td>Intermediate 21</td>
<td>[APCI-MS] m/z: 486 (M+H)⁺, Rt = 9.44 min.</td>
<td></td>
</tr>
<tr>
<td>Intermediate 33</td>
<td>Intermediate 21</td>
<td>NMR¹H NMR (300 MHz), DMSO, δ : 8.21 (m, 1H), 8.02 (m, 3H), 7.70 (m, 3H), 7.43 (m, 3H), 7.24 (m, 2H), 6.85 (m, 1H), 4.38 (t, 2H), 4.17 (m, 1H), 3.86 (s, 3H), 2.79 (m, 3H), 1.92 (m, 3H), 1.55 (m, 3H), 1.20 (d, 3H).</td>
<td></td>
</tr>
</tbody>
</table>
| Intermediate 34 | Intermediate 21 | NMR \(^1\)H NMR (300 MHz),
DMSO, \(\delta: 8.21\) (s, 1H), 8.02
(m, 3H), 7.72 (m, 4H), 7.45
t (2H), 7.27 (t, 1H), 6.59 (m,
2H), 4.37 (t, 2H), 3.88 (s,
3H), 3.81 (d, 6H), 3.33 (m,
2H), 1.87 (m, 2H), 1.53 (m,
2H). |
| Intermediate 35 |
| Intermediate 21 | [APCI-MS] m/z: 499.1 (M+H)^+, 
Rt= 9.85 min. |
| Intermediate 36 | Intermediate 21 | NMR \(^1\)H NMR (300 MHz),
DMSO, \(\delta: 8.41\) (m, 1H), 8.21
(s, 1H), 8.01 (s, 1H), 1.95
(d, 1H), 7.70 (m, 3H), 7.57
d (1H), 7.44 (t, 2H),
7.26 (m, 1H), 6.20 (dd, 1H), 6.00
d (1H), 4.36 (t, 2H), 3.88
(s, 3H), 3.33 (m, 2H),
2.92 (s, 6H), 1.85 (m, 2H),
1.55 (m, 2H). |
| Intermediate 37 | Intermediate 21 | NMR \(^1\)H NMR (300 MHz),
DMSO, \(\delta: 8.21\) (s, 1H), 8.07
(m, 1H), 8.01 (s, 1H), 7.97
d (1H), 7.70 (m, 4H), 7.42
(m, 3H), 7.28 (m, 1H), 7.07
d (1H), 6.98 (t, 1H), 4.37 (t,
2H), 3.95 (t, 2H), 3.87 (s,
3H), 3.29==30 (m, 2H), 1.88
(m, 2H), 1.59 (m, 4H), 0.85
(t, 3H). |
<table>
<thead>
<tr>
<th>Intermediate</th>
<th>Structure</th>
<th>Intermediate 21</th>
<th>Spectral Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td><img src="image1" alt="Intermediate 38" /></td>
<td><img src="image2" alt="Intermediate 21" /></td>
<td>NMR$^1$H NMR (300 MHz), DMSO, $\delta$ : 8.31 (m, 1H), 8.20 (s, 1H), 8.00 (s, 1H), 7.95 (d, 1H), 7.70 (m, 3H), 7.30 (m, 5H), 6.94 (d, 1H), 6.06 (s, 2H), 4.35 (t, 2H), 3.87 (s, 3H), 3.25 (m, 2H), 1.86 (m, 2H), 1.50 (m, 2H).</td>
</tr>
<tr>
<td>39</td>
<td><img src="image3" alt="Intermediate 39" /></td>
<td><img src="image2" alt="Intermediate 21" /></td>
<td>[APCI-MS] m/z: 493 (M+H)$^+$, Rt= 10.10 min.</td>
</tr>
<tr>
<td>40</td>
<td><img src="image4" alt="Intermediate 40" /></td>
<td><img src="image2" alt="Intermediate 21" /></td>
<td>[APCI-MS] m/z: 485 (M+H)$^+$, Rt= 8.12 min.</td>
</tr>
<tr>
<td>41</td>
<td><img src="image5" alt="Intermediate 41" /></td>
<td><img src="image2" alt="Intermediate 21" /></td>
<td>NMR$^1$H NMR (300 MHz), DMSO, $\delta$ : 8.28 (m, 1H), 8.21 (s, 1H), 8.01 (s, 1H), 7.96 (d, 1H), 7.68 (m, 5H), 7.45 (t, 2H), 7.28 (m, 1H), 6.76 (d, 1H), 4.57 (t, 2H), 4.37 (t, 2H), 3.87 (s, 3H), 3.30 (m, 2H), 3.18 (t, 2H), 1.85 (m, 2H), 1.51 (m, 2H).</td>
</tr>
<tr>
<td>42</td>
<td><img src="image6" alt="Intermediate 42" /></td>
<td><img src="image2" alt="Intermediate 21" /></td>
<td>[APCI-MS] m/z: 466.9(M+H)$^+$, Rt= 9.03min.</td>
</tr>
<tr>
<td>43</td>
<td><img src="image7" alt="Intermediate 43" /></td>
<td><img src="image2" alt="Intermediate 21" /></td>
<td>NMR$^1$H NMR (300 MHz), CDCl$_3$, $\delta$ : 8.99 (s, 1H), 8.20 (dd, 1H), 8.14 (s, 1H), 7.94 (d, 1H), 7.83 (dd, 1H), 7.72 (d, 1H), 7.63 (m, 2H), 7.44 (m, 3H), 7.30 (m, 1H),</td>
</tr>
<tr>
<td><strong>Intermediate 44</strong></td>
<td>6.26 (m, 1H), 4.31 (t, 2H), 3.95 (s, 3H), 3.51 (q, 2H), 2.02 (m, 2H), 1.68 (m, 2H).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intermediate 45</strong></td>
<td>NMR $^1$H NMR (300 MHz), CDCl3 $\delta$ : 8.06 (s, 1H), 7.88 (d, 1H), 7.78 (dd, 1H), 7.57 (d, 2H), 7.38 (m, 3H), 1.23 (d, 1H), 1.18 (m, 2H), 4.22 (t, 2H), 3.89 (s, 3H), 3.36 (q, 2H), 2.32 (s, 3H), 1.92 (m, 2H), 1.54 (m, 2H).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intermediate 46</strong></td>
<td>NMR $^1$H NMR (300 MHz), CDCl3 $\delta$ : 8.06 (s, 1H), 7.88 (t, 2H), 7.76 (dd, 1H), 7.56 (d, 2H), 7.37 (m, 3H), 7.22 (t, 1H), 7.07 (d, 1H), 6.49 (m, 1H), 4.23 (t, 2H), 3.88 (s, 3H), 3.42 (q, 2H), 2.47 (s, 3H), 1.95 (m, 2H), 1.61 (m, 2H).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intermediate 47</strong></td>
<td>[APCI-MS] m/z: 444.90 (M-H)$^+$, Rt= 3.56 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intermediate 48</strong></td>
<td>[APCI-MS] m/z: 429.05(M+H)$^+$, Rt=3.51min.</td>
<td></td>
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</tbody>
</table>
The following examples were prepared in an analogous manner to 1-[[4-([4-(1-
5 methylethyl)phenyl]carbonyl)amino]butyl]-3-phenyl-1H-indole-6-carboxylic acid
(Example 14), from intermediate compounds having the structures depicted above and
e.g. prepared as described above.
<table>
<thead>
<tr>
<th>Example</th>
<th>R</th>
<th>From</th>
<th>NMR$^1$H / TOF MS ES+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 15</td>
<td></td>
<td>Intermediate 23</td>
<td>DMSO, $\delta$: 8.19 (s, 1H), 8.13-8.10 (m, 1H), 7.98-7.92 (m, 2H), 7.74-7.67 (m, 5H), 7.47-7.42 (m, 2H), 7.29-7.24 (m, 1H), 6.68-6.65 (d, 2H), 4.37-4.33 (m, 2H), 3.33-3.28 (m, 2H), 2.95 (s, 6H), 1.89-1.84 (m, 2H), 1.52-1.47 (m, 2H).</td>
</tr>
</tbody>
</table>
| Example 16|    | Intermediate 24 | DMSO, $\delta$: 8.57-8.54 (m, 1H), 8.19 (s, 1H), 7.97-7.93 (m, 2H), 7.84-7.67 (m, 4H), 7.52-7.43 (m, 4H), 7.29-7.24 (m, 1H), 4.38-4.33 (m, 2H), 3.33 (m, 2H), 1.90-1.86 (m, 2H), 1.58-1.52 (m, 2H).  
M.p. : 96°C |
| Example 17|    | Intermediate 25 | DMSO, $\delta$: 8.19 (s, 1H), 8.11-8.08 (m, 1H), 7.99-7.93 (m, 2H), 7.75-7.65 (m, 4H), 7.47-7.38 (m, 3H), 7.29-7.24 (m, 1H), 7.08-7.05 (d, 1H), 6.99-6.96 (m, 2H), 4.39-4.35 (m, 2H), 4.10-4.03 (q, 2H), 3.33 (m, 2H), 1.92-1.88 (m, 2H), 1.56-1.51 (m, 2H), 1.27-1.22(t, 3H).  
M.p. : 133-134°C |
| Example 18 | Intermediate 26 | DMSO, δ : 8.34-8.30 (m, 1H), 8.19 (s, 1H), 7.99-7.93 (m, 2H), 7.81-7.67 (m, 5H), 7.48-7.43 (m, 2H), 7.29-7.24 (m, 1H), 6.98-6.95 (m, 2H), 4.38-4.34 (m, 2H), 3.79 (s, 3H), 3.33 (m, 2H), 1.90-1.85 (m, 2H), 1.55-1.50 (m, 2H).  
Mp : 102°C |
| Example 19 | Intermediate 27 | DMSO, δ : 8.50 (m, 1H), 8.25 (s, 1H), 8.01-7.96 (m, 2H), 7.86-7.83 (m, 3H), 7.79-7.77 (m, 2H), 7.56-7.51 (m, 4H), 7.34 (m, 1H), 4.42 (m, 2H), 3.40 (m, 2H), 1.97 (m, 2H), 1.64 (m, 2H), 1.37 (s, 9H). |
| Example 20 | Intermediate 28 | DMSO, δ : 8.49 (m, 1H), 7.91 (s, 1H), 7.78-7.75 (d, J= 8.1 Hz, 2H), 7.66 (s, 1H), 7.64-7.61 (d, J= 8.4 Hz, 1H), 7.58-7.56 (d, J= 8.3 Hz, 2H), 7.50-7.47 (dd, J= 8.3-1.2 Hz, 1H), 7.45-7.42 (dd, J= 8.3-1.1 Hz, 2H), 7.22-7.17 (m, 2H), 7.03-6.98 (m, 1H), 4.11-4.07 (m, 2H), 3.12-3.05 (m, 2H), 1.70-1.60 (m, 2H), 1.36-1.27 (m, 2H). |
| Example 21 | Intermediate 29 | CDCl₃, δ : 8.17 (s, 1H), 7.93-7.85 (m, 2H), 7.59-7.54 (m, 4H), 7.41 (s, 2H), 7.39-7.37 (m, 1H), 7.26-7.24 (m, 1H), 7.15-7.12 (m, 2H), 6.07 (m, 1H), 4.27-4.23 (m, 2H), 3.47-3.40 (m, 2H), 2.30 (s, 3H), 1.99-1.90 (m, 2H), 1.65-1.55 (m, 2H).  
Mp : 189-190°C |
| Example 22 | Intermediate 30 | DMSO, δ : 8.72-8.70 (d, 1H), 8.60 (m, 1H), 8.21-7.93 (m, 9H), 7.75-7.68 (m, 3H), 7.48-7.41 (m, 3H), 7.29-7.24 |
| Example 23          | Intermediate 31 | DMSO, δ : 8.91-8.89 (m, 1H), 8.19 (s, 1H), 7.98-7.92 (m, 2H), 7.74-7.65 (m, 4H), 7.47-7.42 (m, 2H), 7.34-7.26 (m, 2H), 6.84-6.81 (m, 1H), 4.36 (m, 2H), 3.33 (m,2H), 1.91-1.86 (m, 2H), 1.59-1.56 (m, 2H), 1.24 (m, 1H), 1.17-1.16 (d, 6H). Mp : 130.8°C |
| Example 24          | Intermediate 32 | DMSO, δ : 12.67 (brs, 1H), 8.84-8.83 (m, 1H), 8.20 (s, 1H), 7.99-7.93 (m, 2H), 7.78-7.67 (m, 4H), 7.48-7.24 (m, 4H), 6.89-6.84 (m, 2H), 4.39-4.34 (m, 2H), 3.38-3.34 (m,2H), 1.91-1.86 (m, 2H), 1.59-1.55 (m, 2H). Mp : 130.8°C |
| Example 25          | Intermediate 33 | DMSO, δ : 12.66 (brs, 1H), 8.19 (s, 1H), 8.08-8.07 (m, 1H), 8.05-7.96 (m, 2H), 7.75-7.67 (m, 3H), 7.53-7.42 (m, 3H), 7.29-7.15 (m, 2H), 6.88-6.83 (m, 1H), 4.39-4.35 (m, 2H), 4.21-4.16 (m, 1H),4.16 (m, 2H), 3.33-2.88 (m,2H), 2.0-1.92 (m, 2H), 1.82-1.76(m, 2H), 1.13-1.11 (d, 3H). Mp : 92.1°C |
| Example 26          | Intermediate 34 | DMSO, δ : 12.69 (brs, 1H), 8.19 (s, 1H), 7.99-7.92 (m, 3H), 7.74-7.67 (m, 4H), 7.44 (m, 2H), 7.26 (m, 1H), 6.60 (m, 2H), 4.38-4.33 (m, 2H), 3.82 (s,
<table>
<thead>
<tr>
<th>Example</th>
<th>Intermediate</th>
<th>Spectral Data</th>
<th>Physical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>35</td>
<td>DMSO, δ: 8.18 (s, 1H), 8.02 (m, 3H), 7.73 (m, 3H), 7.57 (d, 1H), 7.45 (t, 2H), 7.27 (m, 1H), 6.51 (d, 1H), 6.07 (m, 1H), 4.36 (m, 2H), 3.33 (m, 4H), 3.02 (m, 2H), 2.50 (s, 3H), 1.88 (m, 2H), 1.52 (m, 2H), 0.9 (m, 3H).</td>
<td>Mp: 93.3°C</td>
</tr>
<tr>
<td>28</td>
<td>36</td>
<td>DMSO, δ: 8.48 (m, 1H), 8.17 (s, 1H), 7.94-7.89 (m, 2H), 7.74-7.58 (m, 4H), 7.46-7.41 (m, 2H), 7.28-7.25 (m, 1H), 6.22-6.21 (dd, 1H), 6.05-6.04 (d, 1H), 4.36-4.32 (m, 2H), 2.92 (s, 6H), 1.89-1.85 (m, 2H), 1.61-1.50 (m, 2H).</td>
<td>Mp: 115°C (decomposed)</td>
</tr>
<tr>
<td>29</td>
<td>37</td>
<td>DMSO, δ: 12.70 (brs, 1H), 8.19 (s, 1H), 8.07 (m, 1H), 7.98-7.93 (m, 2H), 7.74-7.67 (m, 4H), 7.47-7.38 (m, 3H), 7.29-7.26 (m, 1H), 7.08-6.98 (m, 2H), 4.36-4.34 (m, 2H), 3.98-3.94 (m, 2H), 3.34 (m, 2H), 1.89-1.87 (m, 2H), 1.64-1.53 (m, 4H), 0.92 (t, 3H).</td>
<td>Mp: 80°C (decomposed)</td>
</tr>
<tr>
<td>30</td>
<td>38</td>
<td>DMSO, δ: 12.73 (brs, 1H), 8.32 (m, 1H), 8.18 (s, 1H), 7.98-7.92 (m, 2H), 7.74-7.67 (m, 3H), 7.47-7.27 (m, 5H), 6.96-6.93 (d, 1H), 6.07 (s, 2H), 4.37-4.32 (m, 2H), 3.28-3.20 (m, 2H), 1.89-1.81 (m, 2H), 1.54-1.49 (m, 2H).</td>
<td>Mp &lt; 100°C (decomposed)</td>
</tr>
<tr>
<td>Example 31</td>
<td>Intermediate 39</td>
<td>DMSO, δ: 8.21 (m, 1H), 8.17 (s, 1H), 7.96-7.94 (m, 2H), 7.76-7.69 (m, 3H), 7.54-7.44 (m, 3H), 7.38-7.25 (m, 4H), 6.90-6.89 (m, 2H), 6.08-6.07 (m, 2H), 4.30-4.25 (m, 2H), 3.15-3.09 (m, 2H), 1.75-1.69 (m, 2H), 1.41-1.39 (m, 2H). Mp &lt; 229°C (decomposed)</td>
<td></td>
</tr>
<tr>
<td>Example 32</td>
<td>Intermediate 40</td>
<td>DMSO, δ: 8.38 (m, 1H), 8.19 (s, 1H), 7.96 (m, 2H), 7.70 (m, 3H), 7.39 (m, 3H), 7.18 (m, 2H), 4.36 (m, 2H), 3.30 (m, 2H), 2.63 (s, 6H), 2.27 (s, 3H), 1.88 (m, 2H), 1.55 (m, 2H). Mp: 127°C</td>
<td></td>
</tr>
<tr>
<td>Example 33</td>
<td>Intermediate 41</td>
<td>NMR$^1$H (300 MHz), DMSO, δ: 8.27 (m, 1H), 8.19 (s, 1H), 7.99 (s, 1H), 7.95 (d, 1H), 7.70 (m, 4H), 7.92 (d, 1H), 7.45 (t, 2H), 7.27 (t, 1H), 6.78 (d, 1H), 4.58 (t, 2H), 4.35 (m, 2H), 3.28 (m, 2H), 3.18 (t, 2H), 1.87 (m, 2H), 1.52 (m, 2H).</td>
<td></td>
</tr>
<tr>
<td>Example 34</td>
<td>Intermediate 42</td>
<td>NMR$^1$H NMR (300 MHz), DMSO, δ: 8.22 (s, 1H), 8.09 (d, 1H), 8.02 (s, 1H), 7.94 (d, 1H), 7.74 (m, 4H), 7.57 (d, 1H), 7.48 (m, 3H), 7.27 (m, 1H), 4.39 (m, 2H), 4.11 (m, 2H), 2.60 (s, 3H), 1.92 (m, 2H), 1.71 (m, 2H).</td>
<td></td>
</tr>
<tr>
<td>Example 35</td>
<td>Intermediate 43</td>
<td>DMSO, δ: 9.11 (s, 1H), 8.88 (m, 1H), 8.40 (d, 1H), 8.19 (s, 1H), 7.95 (m, 3H), 7.71 (m, 3H), 7.45 (t, 2H), 7.26 (t, 1H), 4.36 (m, 2H), 3.34 (m, 4H), 1.58 (m, 2H).</td>
<td></td>
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<tr>
<td>Example</td>
<td>Intermediate</td>
<td>Chemical Data</td>
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</tr>
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<td></td>
</tr>
</tbody>
</table>
| 36      | 44           | DMSO, δ : 7.98 (s, 1H), 7.71-7.60 (m, 2H), 7.39-7.36 (d, J=7.3Hz, 2H), 7.24-7.13 (m, 4H), 6.97 (s,1H), 6.21 (brs, 1H), 6.06 (s,1H), 3.83 (m, 2H), 3.06 (m, 2H), 2.17 (s, 3H), 1.58 (m, 2H), 1.26 (m, 2H).  
Target Mass for C_{25}H_{24}N_{2}O_{4}+: 417.1814(M+H)+.  
Found: 417.1797; Rt: 2.30min |
| 37      | 45           | CDCl₃, δ : 8.16 (s, 1H), 7.92-7.84 (m, 2H), 7.58-7.56 (d, J=7.4Hz, 2H), 7.41-7.36 (m, 3H), 7.23-7.21 (m,1H), 6.63-6.62 (m,1H), 5.89 (brs, 1H), 4.22 (m, 2H), 3.39 (m, 2H), 2.40 (s, 3H), 1.92 (m, 2H), 1.56 (m, 2H).  
Target Mass for C_{26}H_{24}N_{2}O_{3}S: 433.1586(M+H)+.  
Found: 433.1568; Rt: 2.34min |
| 38      | 46           | CDCl₃, δ : 8.14 (s, 1H), 7.91-7.81 (m, 3H), 7.57-7.54 (d, J=7.7Hz, 2H), 7.40-7.35 (m, 3H), 7.25-7.23 (m,1H), 7.07-7.05 (m,1H), 6.50 (brs, 1H), 4.22 (m, 2H), 3.42 (m, 2H), 3.40 (s, 3H), 1.97 (m, 2H), 1.60 (m, 2H). |
| 39      | 47           | CDCl₃, δ : 8.16 (s, 1H), 7.92-7.84 (m, 2H), 7.59-7.56 (d, J=7.1Hz, 2H), 7.42-7.36 (m, 3H), 7.26-7.23 (m,1H), 6.63 (m,1H), 6.41 (m,1H), 5.98 (m,1H), 5.81 (brs, 1H), 4.27-4.22 (m, 2H), 3.86 (s, 3H), 3.39-3.32 (m, 2H), 1.98-1.88 (m, 2H), 1.59-1.54 (m, 2H).  
Target Mass for C_{26}H_{25}N_{3}O_{3}+: |
<table>
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<th>Example</th>
<th>Intermediate</th>
<th>Spectral Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>48</td>
<td>DMSO, $\delta$: 8.75 (m, 1H), 8.20 (s, 1H), 7.93 (m, 2H), 7.71 (m, 4H), 7.43 (t, 2H), 7.28 (m, 1H), 6.67 (m, 2H), 4.36 (m, 2H), 3.34 (m, 2H), 2.26 (s, 3H), 1.90 (m, 2H), 1.60 (m, 2H).</td>
</tr>
<tr>
<td>42</td>
<td>50</td>
<td>DMSO, $\delta$: 8.33 (m, 1H), 8.18 (m, 1H), 7.98 (m, 2H), 7.70 (m, 3H), 7.45 (t, 2H), 7.32 (m, 2H), 6.88 (m, 1H), 4.34 (m, 2H), 4.24 (s, 4H), 3.27 (m, 2H), 1.86 (m, 2H), 1.53 (m, 2H).</td>
</tr>
<tr>
<td>43</td>
<td>51</td>
<td>$^1$H NMR (300 MHz), MeOD, $\delta$: 8.20 (s, 1H), 8.04 (m, 1H), 7.91 (d, 1H), 7.86 (s, 1H), 7.83 (dd, 1H), 7.68 (s, d, 3H), 7.42 (t, 2H), 7.25 (t, 1H), 4.36 (t, 2H), 3.41 (t, 2H), 1.97 (m, 2H), 1.65 (m, 2H), 1.60 (s, 9H).</td>
</tr>
<tr>
<td>44</td>
<td>52</td>
<td>Target Mass for C$<em>{32}$H$</em>{36}$N$_2$O$_3$: 495.2648 (M-H)+. Found: 495.2598; Rt: 2.92 min</td>
</tr>
<tr>
<td>45</td>
<td>53</td>
<td>DMSO, $\delta$: 8.29 (sd, 1H), 8.18 (t, 1H), 7.66 (s, 1H), 7.60 (dd, 1H), 7.53 (d, 2H), 7.45 (m, 3H), 7.27 (t, 2H), 7.09 (d, 2H), 4.10 (t, 2H), 3.08 (t, 2H), 2.71 (m, 1H), 1.66 (m, 2H), 1.32 (m, 2H), 0.99 (d, 6H).</td>
</tr>
</tbody>
</table>
Intermediate 54

**Methyl 3-phenyl-1-r4-(propylamino)butyl1-1H-indole-6-carboxylate**

To a solution of methyl 1-(4-aminobutyl)-3-phenyl-1 H-indole-6-carboxylate (Intermediate 21) (0.4 g, 1.24 mmol) in methanol/THF (50ml/50ml) was added propanal (90 µl, 1.24 mmol). The mixture was stirred at room temperature for 30 min and then were added acetic acid (300 µl) and sodium cyanoborohydride (0.526 mg, 2.48 mmol). The reaction mixture was stirred at room temperature for 24 hours. The solvent was evaporated. The residue was diluted with dichloromethane, washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude was purified on SiO₂ eluting with dichloromethane/methanol (95/5) to give the title compound (100 mg, 22%).

**[APCI-MS] m/z: 365.1 (M+H)+, Rt= 3.40 min.**

Intermediate 55

**Methyl 1-{2-r(1,1-dimethylethyl)oxy1-2-oxoethyl)-3-phenyl1H-indole-6-carboxylate**
To a solution of methyl 3-phenyl-1H-indole-6-carboxylate (Intermediate 4) (700 mg, 2.79mM) in 80 mL of acetonitrile was added cesium carbonate (2.72, 8.35 mM), 0.613 mL of 1,1-dimethylethyl bromoacetate, the reaction mixture was heated for 1 hour at 90°C. The reaction mixture was cooled at room temperature, 50 mL of water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried on MgSO₄, filtered and concentrated under vacuum to give methyl 1-[2-[(1,1-dimethylethyl)oxy]-2-oxoethyl]-3-phenyl-1H-indole-6-carboxylate as a yellow solid (1.08g, qqt).

NMR ¹H NMR (300 MHz), CDCl₃ δ: 8.07 (m, 1H), 7.94 (dd, 1H), 7.87 (dd, 1H), 7.65 (m, 2H), 7.46 (m, 3H), 7.30 (m, 1H), 4.85 (s, 2H), 3.75 (s, 3H), 1.48 (s, 9H).

Intermediate 56

fe-rdVlethyloxy^arbonvn-S-phenyl-IH-indol-i-vDacetic acid (FIDE/U1218/116/1)

To a solution of methyl 1-[(1,1-dimethylethyl)oxy]-2-oxoethyl]-3-phenyl-1H-indole-6-carboxylate (intermediate 55) (1.02g, 2.79 mM) in 10 mL of CH₂Cl₂ was added 10 mL of TFA, the reaction mixture was stirred under argon atmosphere for 65 h, after evaporation of the solvent, 1.14 g of crude [6-[(methyloxy)carbonyl]-3-phenyl-1H-indol-1-yl]acetic acid was recovered (99%).

NMR ¹H NMR (300 MHz), DMSO δ: 8.11 (s, 1H), 7.95 (m, 2H), 7.76 (dd, 1H), 7.67 (d, 2H), 7.47 (t, 2H), 7.29 (m, 1H), 5.16 (s, 2H), 3.87 (s, 3H).

Intermediate 57

Methyl 1-(2-(4-[(I-methylethyl)phenyli-piperaziny])-2-oxoethyl)-3-phenyl-1H-indole-6-carboxylate
To a solution of \{6-[(methyloxy)carbonyl]-3-phenyl-1H-indol-1-yl\}acetic acid Intermediate 56 (14g, 3.69 mM) in 16 ml of CH₂Cl₂ was added 753 mg (3.69 mM) of 1-[4-(1-methylethyl)phenyl]piperazine, EDCI (777 mg, 4.05 mM), 135 mg of DMAP (3.69 mM), the reaction mixture was refluxed for 7 hours, then 5ml of DMF was added and the mixture was heated to reflux at room temperature for 15 hours.

After cooling to room temperature, 10 ml of water and 10 ml of EtOAc was added to the reaction mixture, the organic layer was dried on MgSO₄, after filtration and concentration under vacuum, the crude material was purified on SiO₂ to give methyl 1-(2-{4-[4-(1-methylethyl)phenyl]-1-piperazinyl}-2-oxoethyl)-3-phenyl-1H-indole-6-carboxylate as a white solid yield (950 mg, 52%).

NMR: H NMR (300 MHz), CDCl₃ δ: 7.30 (d, 2H), 6.87 (d, 2H), 4.49 (s, 2H), 4.18 (q, 2H), 4.13 (t, 3H), 1.46 (s, 6H), 1.28 (t, 3H).

Example 46

1-(2-[4-(1-Methylethyl)phenyl-1-piperazinyl]-2-oxoethyl)-3-phenyl-1H-indole-6-carboxylic acid
Example 46 was prepared in an analogous manner to Example 1 from Methyl 1-(2-[4-[4-(1-methylethyl)phenyl]-1-piperazinyl]-2-oxoethyl)-3-phenyl-1H-indole-6-carboxylate (Intermediate 57) to afford the title compound as a white solid.

NMR $^1$H NMR (300 MHz), DMSO $\delta$: 8.08 (s, 1H), 7.90 (d, 1H), 7.77 (m, 2H), 7.73 (d, 2H), 7.46 (t, 2H), 7.27 (t, 1H), 7.12 (d, 2H), 6.92 (d, 2H), 5.41 (s, 2H), 3.77 (m, 2H), 3.63 (m, 2H), 3.25 (m, 2H), 3.10 (m, 2H), 2.79 (m, 1H), 1.17 (d, 6H).

Intermediate 58

1,1-dimethylethyl 1H-indole-6-carboxylate

A solution of methyl 1H-indole-6-carboxylate (2.5 g, 15.51 mmol) in toluene (27 ml) was heated to reflux. N,N-dimethylformamide di-tert-butyl acetal (16.5 ml, 62 mmol) was added drop by drop. The mixture was heated for 5h45 and N,N-dimethylformamide di-tert-butyl acetal (4.12 ml) was added after 2% hours of heat. The mixture was cooled to room temperature and ethyl acetate was added. The mixture was washed with water, a saturated solution of NaHCO$_3$, water and brine. The organic phase was dried over MgSO$_4$, filtered and evaporated. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 80:20) to give the title compound as light yellow solid (2.38 g, 70%).

NMR $^1$H NMR (300 MHz), CDCl$_3$ $\delta$: 8.13 (m, 1H), 7.77 (d, 1H), 7.64 (d, 1H), 7.35 (t, 1H), 6.59 (m, 1H), 1.63 (s, 9H).

Intermediate 59

1,1-dimethylethyl 3-bromo-1-[1,1-dimethylethyl](dimethyl)silyl 1H-indole-6-carboxylate

15
To a solution of 1,1-dimethylethyl 1H-indole-6-carboxylate (Intermediate 58) (2.38 g, 10.95 mmol) in THF (45 ml) under nitrogen was added at -78°C a solution of n-BuLi in hexane 2.5 mol/l (4.82 ml, 12 mmol) drop by drop. The temperature was adjusted to -10°C and the mixture was stirred for 20 min. The temperature was cooled to -50°C and a solution of tBDMSCI (1.816 g, 12 mmol) in THF (9.5 ml) was added drop by drop. The mixture was stirred at 0°C for 3 hours and the temperature was cooled to -78°C. NBS (1.95 g, 10.95 mmol) was added. The mixture was stirred at room temperature for 15/2 hours. Cyclohexane (32 ml) and pyridine (0.32 ml) were added. The suspension was filtered on celite and washed with THF. The filtrate was evaporated and the residue was purified by flash chromatography on silica gel (dichloromethane/cyclohexane 90:10) to give a product. This product was purified by flash chromatography on silica gel (dichloromethane/cyclohexane 30:70) to give the title compound as light yellow solid (1.56 g, 77%).

NMR ¹H NMR (300 MHz), CDCl₃ δ: 8.22 (s, 1 H), 7.83 (d, 1 H), 7.54 (d, 1 H), 7.28 (d, 1 H), 1.62 (s, 9 H), 0.94 (s, 9 H), 0.63 (s, 6 H).

**Intermediate 60**

3-(1-cyclohexen-1-yl)-1H-indole-6-carboxylic acid

KOH (6.4 g, 0.11 mol) was dissolved in water (10 ml) and methanol (10 ml) was added. Methyl indole-6-carboxylate (2 g, 11.4 mmol) was added and the reaction mixture was stirred at 75°C for 18 hours. Methanol was evaporated and the residue was diluted with water (100 ml), pH was neutralized to pH=6 with acetic acid. The precipitate was filtered, washed with water and dried. The solid was triturated in isopropyl ether, filtered and washed with isopropyl ether to give the title compound (2.2 g, 80%).

NMR ¹H NMR (300 MHz), δ : 8.16 (sdd, 1 H), 8.00 (d, 1 H), 7.78 (dd, 1 H), 7.72 (d, 1 H), 6.36 (m, 1 H), 2.58 (m, 2 H), 2.39 (m, 2 H), 1.90 (m, 2 H), 1.81 (m, 2 H).

**Intermediate 61**
3-cyclohexyl-1H-indole-6-carboxylic acid

To a solution of 3-(1-cyclohexen-1-yl)-1H-indole-6-carboxylic acid (Intermediate 60) (1 g, 4.1 mmol) in ethanol was added Pd/C 10% (catalytic quantity) and ammonium formiate (2.6 g, 41 mmol). The mixture was stirred at 50°C for 4 hours. A precipitate was formed, HCl 1N was added until the precipitate was dissolved. The mixture was filtered on celite, the filtrate was evaporated. The residue was diluted with diethyl ether, washed with water. The organic phase was dried over Na₂SO₄, filtered and evaporated to give the title compound as beige solid (900 mg, 90%).

NMR

1H NMR (300 MHz), δ : 7.96 (s, 1H), 7.57 (q, 2H), 7.28 (s, 1H), 2.77 (m, 1H), 1.96 (m, 1H), 1.77 (m, 3H), 1.43 (m, 4H), 1.26 (m, 1H).

Intermediate 62

1.1-dimethylethyl-1-FM-1-dimethylethylHdimethyl)silyll-3-(2-pyridinyl)-1H-indole-6-carboxylate

To a solution of 1,1-dimethylethyl 3-bromo-1-[(1,1-dimethylethyl)(dimethyl)silyl]-1H-indole-6-carboxylate (Intermediate 59) (250 mg, 0.61 mmol) in THF (1 ml) was added at -78°C under argon tBuLi (0.8 ml, 1.22 mmol). The mixture was stirred for 10 min and ZnCl₂ (1.35 ml, 0.67 mmol) was added and the reaction mixture was stirred at room temperature for 30 min. Separately, 2-bromopyridine (40 μl, 0.43 mmol) was added to PdCl₂(PPh₃)₂ (9 mg, 0.012 mmol) and DibalH (24 μl, 0.024 mmol) in THF (1 ml). This mixture was added on the first mixture. The mixture was stirred at reflux for 4 hours. The reaction mixture was poured into a saturated solution of Na₂CO₃ and extracted with diethyl ether. The organic
phase was dried over MgSO₄, filtered and evaporated. The residue was purified by flash chromatography on silica gel (toluene to toluene/ethyl acetate 80:20) to give the title compound (67 mg, 27%).

LC/MS: m/z 4409.10 (M+H)+, Rt: 9.23 min

**Intermediate 63**

**Methyl 3-(5-methyl-2-thienyl)-1 H-indole-6-carboxylate**

To a solution of the 1-(1,1-dimethylethyl) 6-methyl 3-bromo-1H-indole-1,6-dicarboxylate (intermediate 2) (0.2g, 0.56mmol) in DME (7ml) was added PdCbdppf.dichloromethane (23 mg, 0.03mmol), (5-Methyl-2-thienyl)boronic acid (0.180 g, 1.2mmol) and K₃PO₄ (0.26g, 1.2mmol). The resulting mixture was irradiation under microwave activation for 25 min at 120 watts and 120°C. After cooling to room temperature, the remaining mixture was filtrated and dissolved in ethyl acetate. The organic phase was washed with water, drying over Na₂SO₄ and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel (Cyclohexane/ethyl acetate 70:30) to give the title compound as a yellow solid (75mg, 50%).

NMR: ¹H NMR (300 MHz), CDCl₃, δ: 8.09 (s, 1H), 7.89 (d, 1H), 7.80 (dd, 1H), 7.43 (d, 1H), 6.99 (d, 1H), 6.70 (m, 1H), 3.88 (s, 3H), 2.46 (s, 3H).

**Intermediate 64**

**Methyl 3-cyclohexyl H-indole-6-carboxylate**

To a solution of S-cyclohexyl-1H-indole-6-carboxylic acid Intermediate 61 (900 mg, 3.7 mmol) in methanol was added HCl gas. The mixture was stirred at 75°C for 18 hours. The solvent was evaporated and the residue was diluted with water and NaOH and extracted
with diethyl ether. The organic phase was dried over Na$_2$SO$_4$, filtered and evaporated to give the title compound as orange beige solid (650 mg, 68%).

NMR $^1$H NMR (300 MHz), $\delta$: 8.03 (s, 1H), 7.71 (dd, 1H), 7.59 (d, 1H), 7.04 (s, 1H), 3.86 (s, 3H), 2.77 (m, 1H), 2.02 (m, 2H), 1.77 (m, 3H), 1.40 (m, 5H).

**Intermediate 65**

1,1-dimethylethyl 3-(2-pyridinyl)-1H-indole-6-carboxylate

A mixture of 1,1-dimethylethyl 1-[(1,1-dimethylethyl)(dimethyl)silyl]-3-(2-pyridinyl)-1H-indole-6-carboxylate Intermediate 62 (67 mg, 0.163 mmol) and TBAF (409 µl, 0.409 mmol) in THF (4 ml) was stirred at room temperature for 2Vx hours. The mixture was quenched with water (10 ml) and extracted with diethyl ether (2x10 ml). The organic phase was dried over Na$_2$SO$_4$, filtered and evaporated. The residue was purified by flash chromatography on silica gel to give the title compound (25.7 mg, 45%).

LC/MS: m/z 295 (M+H)$^+$, Rt: 6.08 min

**Intermediate 66**

Methyl 3-(3-furanyl)-1H-indole-6-carboxylate

A solution of 1-(1,1-dimethylethyl) 6-methyl 3-bromo-1H-indole-1,6-dicarboxylate (Intermediate 2) (350 mg, 1 mmol), Pd(PPh$_3$)$_4$ (12 mg, 0.01 mol), 3-furanboronic acid (168 mg, 1.5 mmol) and Cs$_2$CO$_3$ (490 mg, 1.5 mmol) in a mix of toluene (3 ml), ethanol (3 ml) and water (0.5 ml) was microwaved at 110$^\circ$C and 110 watts during 25 min. The reaction was not complete, 3-furanboronic acid (50 mg) and a catalytic quantity of catalyst were added and the mixture was re-microwaved at 110$^\circ$C and 110 watts during 25 min. The
mixture was diluted with ethyl acetate, filtered and washed with HCl (0.5 N), a saturated solution of NaHCO₃ and brine. The organic phase was dried over Na₂SO₄, filtered and evaporated. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 70:30) to give the title compound (80 mg, 23%).

RMN: CDCl₃ δ: 8.11 (s, 1H), 7.81 (d, 1H), 7.74 (s, 1H), 7.71 (d, 1H), 7.46 (s, 1H), 7.40 (m, 1H), 6.63 (s, 1H), 3.88 (s, 3H).

Intermediate 67

Methyl 3-bromo-1-[4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)butyl]-1H-indole-6-carboxylate

To a solution of methyl 3-bromo-1H-indole-6-carboxylate (intermediate 1) (8.7 g, 34 mmol) in acetonitrile was added K₂CO₃ crushed (9.5 g, 68 mmol). The mixture was stirred at 80°C. After 15 min, N-(4-bromobutyl)phthalimide (10.6g, 37.4 mmol) was added, and the mixture was stirred at 80°C during 90 hours. The solvent was evaporated and the residue was diluted with water. The precipitate was filtered, washed with water and dry to give the title compound as beige solid (15 g, quantitative yield).

NMR: H NMR (300 MHz), δ: 8.00 (s, 1H), 7.76 (m, 3H), 7.63 (m, 2H), 7.48 (d, 1H), 7.20 (m, 1H), 4.15 (t, 2H), 3.88 (s, 3H), 3.65 (t, 2H), 1.83 (m, 2H), 1.64 (m, 2H).

The following Intermediates were prepared in an analogous manner to Methyl 3-bromo-1-[4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)butyl]-1H-indole-6-carboxylate (Intermediate 67), from compounds having the intermediate structures depicted above and e.g. prepared as described above.
**Intermediate 70**

**1,1-dimethylethyl r(2-chloroethyl)oxy1acetate**

To a solution of t-butyl bromoacetate (27.84, 0.14 mol) in DMF (40 ml) was added a solution of chloroethanol (11.49 ml, 0.17 mol) in DMF (10 ml). The mixture was cooled at 0°C and pellets of NaOH (6.84 g, 0.17 mmol) were added. The reaction mixture was stirred at 0°C for 2 hours and at room temperature overnight. Water (50 ml) and heptane (150 ml) were added. The mixture was stirred vigorously and extracted 2 times. The organic phases were washed with water (50 ml), dried over Na₂SO₄, filtered and evaporated to give the title compound as colourless liquid (22.06g, 79%)

NMR ¹H NMR (300 MHz), CDCl₃ δ: 4.06 (s, 2H), 3.84 (t, 2H), 3.69 (t, 2H), 1.50 (s, 9H).

<table>
<thead>
<tr>
<th>Intermediate</th>
<th>R</th>
<th>From</th>
<th>NMR ¹H NMR (300 MHz)/ LC-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate 68</td>
<td></td>
<td>Intermediate 64</td>
<td>NMR ¹H NMR (300 MHz), DMSO δ: 8.02 (sd, 1H), 7.95 (m, 1H), 7.74 (m, 1H), 7.69 (dd, 1H), 7.62 (m, 2H), 7.60 (d, 1H), 7.55 (d, 1H), 3.84 (s, 3H), 3.62 (m, 4H), 2.72 (m, 1H), 1.99 (m, 4H), 1.75 (m, 10H).</td>
</tr>
<tr>
<td>Intermediate 69</td>
<td></td>
<td>Intermediate 63</td>
<td>NMR ¹H NMR (300 MHz), CDCl₃ δ: 8.00 (s, 1H), 7.84 (d, 1H), 7.75 (m, 3H), 7.62 (d, 1H), 7.60 (d, 1H), 7.32 (s, 1H), 6.94 (d, 1H), 6.66 (m, 1H), 4.15 (t, 2H), 3.87 (s, 3H), 3.65 (t, 2H), 2.43 (s, 3H), 1.84 (m, 2H), 1.64 (m, 2H)</td>
</tr>
</tbody>
</table>

5

10

70
**Intermediate 71**

1,1-dimethyl ethyl 1-[4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)butyl]-3-(2-pyridinyl)-1H-indole-6-carboxylate

A mixture of 1,1-dimethyl ethyl 3-(2-pyridinyl)-1H-indole-6-carboxylate (Intermediate 65) (318.5 mg, 1.08 mmol), Cs$_2$CO$_3$ (1.41 g, 4.32 mmol) and N-(4-bromobutyl)phtalimide (458 mg, 1.62 mmol) in acetonitrile (10 ml) was stirred at reflux for 5 hours. Water and ethyl acetate were added, aqueous phase was extracted with ethyl acetate. The organic phases were washed with brine, dried over Na$_2$SO$_4$, filtered and evaporated. The residue was purified by flash chromatography on silica gel (toluene/ethyl acetate 95:5) to give the title compound (31.1 mg, 58%).

LC/MS : m/z 496.10 (M+H)$^+$, Rt: 7.51 min

**Intermediate 72**

methyl 1-(4-aminobutyl)-3-(3-furanyl)-1H-indole-6-carboxylate

A solution of intermediate 66 (157 mg, 0.65 mmol), 2-(4-bromobutyl)-1H-isoindole-1,3(2H)-dione (220 mg, 0.78 mmol) and Cs$_2$C$_6$H$_3$ (423 mg, 1.3 mmol) in acetonitrile was heated at 80°C for 2 Oh. The resulting mixture was evaporated, diluted in ethyl acetate and water, separated and purified by chromatography (cyclohexane/ethyl acetate 70:30) to give a pale oil. (170 mg, 60%).
$^1$H NMR (300 MHz), CDCl₃ δ: 8.03 (s, 1H), 7.77 (d, 1H), 7.75 (d, 1H), 7.64 (d, 1H), 7.63 (d, 1H), 7.44 (t, 1H), 6.63 (s, 1H), 4.18 (t, 2H), 3.89 (s, 3H), 3.66 (t, 2H), 1.87 (m, 2H), 1.66 (m, 2H).

Intermediate 73
methyl 1-(4-nitrophenyl)methyn-3-phenyl-1 H-indole-6-carboxylate

To a solution of Methyl 3-phenyl-1 H-indole-6-carboxylate (intermediate 4) 1.5g, 5.98mmol) in acetonitrile was added Cs₂CO₃ (3.9g, 11.96mmol) and 1-(bromomethyl)-4-nitrobenzene (1.55g, 7.18mmol). The suspension was heated at 80°C overnight, filtered and evaporated. The residue was diluted in water and dichloromethane, extracted, dried over Na₂SO₄, filtered, evaporated and purified by chromatography (dichloromethane/cyclohexane 70:30) to give a yellow solid. (1.12g, 49%)

$^1$H NMR (300 MHz), CDCl₃ δ: 8.20 (d, 2H), 8.03 (m, 2H), 7.93 (td, 1H), 7.68 (m, 2H), 7.49 (m, 4H), 7.37 (m, 2H), 5.57 (s, 2H), 3.95 (s, 3H).

Intermediate 74
methyl 1-(5-oxo-5-(phenylmethyl)oxypentyl)-3-phenyl-1 H-indole-6-carboxylate

To a suspension of Methyl 3-phenyl-1 H-indole-6-carboxylate (intermediate 4) (100mg, 0.39mmol) and Cs₂CO₃ (388mg, 1.1mmol) in acetonitrile, was added phenylmethyl 5-chloropentanoate (180mg, 0.79mmol) and it was stirred at reflux for 16h. The mixture was evaporated, diluted in dichloromethane, washed with brine, dried over Na₂SO₄, filtered, evaporated and purified by chromatography (cyclohexane/ ethyl acetate 80:20) to give a colourless oil. (110mg, 63%)
LC/MS: m/z 442 (M+H)+, Rt: 4.03 min

Intermediate 75
methyl 1-r2-((r(1,1-dimethylethyl)oxy1carbonyl)amino)ethyn-3-phenyl-1H-indole-6-carboxylate

To a solution of Methyl 3-phenyl-1H-indole-6-carboxylate (intermediate 4) (500mg, 2 mmol) in acetonitrile was added Cs2CO3 (2g, 6 mmol) and 1,1-dimethylethyl (2-bromoethyl)carbamate (672mg, 3mmol) and it was stirred for 16h at room temperature. Then Cs2CO3 (2g, 6mmol) and 1,1-dimethylethyl (2-bromoethyl)carbamate (1.344g, 6mmol) were added. The mixture was stirred further, filtered and the filtrate was evaporated. The residue was diluted in ethyl acetate, washed with brine, dried over Na2SO4, concentrated and purified by chromatography (dichloromethane/ethyl acetate 95:5) to give the title compound. (470mg, 60%)

LC/MS: m/z 396.10 (M+H)+, Rt: 3.65 min

Intermediate 76
methyl 3-bromo-1-r2-((2-r(1,1-dimethylethyl)oxy1-2-oxoethyl)oxy)ethyn 1H-indole-6-carboxylate

To a solution of Methyl 3-bromo-1H-indole-6-carboxylate (intermediate 1) (10.16g, 40mmol) in DMF was added Cs2CO3 (26.1g, 80mmol) and 1,1-dimethylethyl [(2-chloroethyl)oxy]acetate (Intermediate 70) (11.7g, 60mmol). The mixture was stirred at room temperature for 2h, heated at 70°C for 5h then at room temperature for 2 days. Then 1,1-dimethylethyl [(2-chloroethyl)oxy]acetate (Intermediate 70) (5g, 25mmol) was added and it was stirred at 70°C for 3h. The mixture was filtrated, concentrated, diluted in ethyl acetate, washed with brine and dried over Na2SO4 to give a brown oil. (20g, quantitative)
Intermediate 77

Methyl 1-(4-aminobutyl)-3-bromo-1H-indole-6-carboxylate

\[
\text{Methyl} \quad 3\text{-bromo-1-[4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)butyl]-1H-indole-6-carboxylate}\]

(Intermediate 67) (15 g, 34 mmol) was diluted in ethanol and hydrazine (10 ml, 0.2 mmol) was added. The reaction mixture was stirred at 80°C for 18 hours. 80% of the solvent was evaporated, the residue was diluted with water, the precipitate was filtered and washed with water. The expected product and phthalylhydrazide are insoluble; they aren't separated for next step.

NMR

\[
\begin{align*}
1^\text{H} \text{ NMR (300 MHz), CDCl}_3 \delta: & \ 8.19 (s, 1H), 8.08 (d, 1H), 8.05 (d, 1H), 7.88 (s, 1H), \\
& \ 7.81 (d, 1H), 7.79 (s, 1H), 7.75 (dd, 1H), 7.52 (d, 1H), 4.29 (t, 2H), 3.88 (s, 3H), 2.61 (t, 2H), 1.81 (m, 2H), 1.37 (m, 2H).
\end{align*}
\]

The following Intermediates were prepared in an analogous manner to methyl 1-(4-aminobutyl)-3-bromo-1H-indole-6-carboxylate (Intermediate 77), from intermediate compounds having the structures depicted above and e.g. prepared as described above.

<table>
<thead>
<tr>
<th>Intermediate</th>
<th>R</th>
<th>From</th>
<th>NMR (^1\text{H} \text{ NMR (300 MHz)}/\text{LC-MS} )</th>
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<tr>
<td>Intermediate 78</td>
<td><img src="image" alt="Image" /></td>
<td>Intermediate 68</td>
<td>LC/MS : m/z 239 (M+H)(^+), Rt: 3.04 min.</td>
</tr>
</tbody>
</table>
Intermediate 82

**Methyl 1-(4-aminophenyl)methyl1-3-phenyl-1 H-indole-6-carboxylate**

To a solution of a compound of structure Intermediate 73 and e.g. prepared as above (1.12 g, 2.9 mmol) in methanol (30 ml) under nitrogen was added Pd/C 10% (110 mg) and ammonium formate (1.83 g, 29 mmol). The reaction mixture was stirred at reflux for 4 hours. The suspension was filtered on paper. The filtrate was concentrated and the residue was diluted with dichloromethane and a saturated solution of NaHCO₃. The organic phase was extracted, dried over Na₂SO₄, filtered and evaporated. The residue was purified by flash chromatography on silica gel (DICHLOOROMETHANE) and the solid obtained was triturated with isopropyl ether, filtered and washed with pentane to give after drying the title compound as white solid (650 mg, 63%).
NMR $^1$H NMR (300 MHz), CDCI$_3$ δ: 8.18 (s, 1H), 7.97 (d, 1H), 7.87 (dd, 1H), 7.64 (d, 2H), 7.47 (d, 1H), 7.42 (d, 2H), 7.31 (d, 1H), 7.07 (d, 2H), 6.76 (d, 2H), 5.33 (s, 2H), 3.96 (s, 3H).

Intermediate 83

Methyl 1-(2-aminoethyl)-3-phenyl-1H-indole-6-carboxylate hydrochloride

To a solution of intermediate 75 and e.g. prepared as above (470 mg, 1.2 mmol) in methanol was added concentrated HCl (24 mmol) and the mixture was stirred at room temperature for 4 hours. The reaction was not complete, 20 equivalent of concentrated HCl were added and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated and ethanol was added to co-evaporated water (2 times). The white solid obtained was triturated with diethyl ether, filtered and dried to give the title compound (210 mg, 53%).

NMR $^1$H NMR (300 MHz), DMSO δ: 8.20 (s, 1H), 7.96 (s, 1H), 7.89 (d, 1H), 7.69 (dd, 1H), 7.60 (d, 2H), 7.39 (t, 2H), 7.20 (t, 1H), 4.50 (t, 2H), 3.80 (s, 3H), 3.21 (t, 2H).

Intermediate 84

2-bromo- $N$-r4-(1-methylethyl)phenynacetamide

To a solution of 4-isopropylaniline (6.76 g, 50 mmol) in dichloromethane was added triethylamine (7.61 ml, 55 mmol) and drop by drop at 0°C a solution of bromoacetyl bromide (4.8 ml, 55 mmol) in dichloromethane. The mixture was stirred at room temperature for 2 hours. The solution was quenched with brine and extracted. The organic
phase was washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated. The obtained solid was recrystallised with n-heptane to give the title compound as beige solid (10.41 g, 81%).

NMR $^1$H NMR (300 MHz), CDCl$_3$ $\delta$: 7.54 (d, 2H), 7.32 (d, 2H), 4.12 (s, 2H), 3.00 (m, 1H), 1.34 (d, 6H).

**Intermediate 85**

5-f6-r(methyloxy)carbonyln-3-phenyl-1H-indol-1-vDpentanoic acid

![Intermediate 85 structure]

To a solution of a compound of structure Intermediate 74 and e.g. prepared as above (210 mg, 0.47 mmol) in ethanol (15 ml) was added Pd/C 10% (40 mg). The mixture was hydrogenated under 2 bars at room temperature overnight. The catalyst was filtered and the filtrate was evaporated. The residue was purified by flash chromatography on silica gel (dichloromethane/methanol 95:5) to give the title compound as yellow solid (120 mg, 72%).

LC/MS: m/z 350 (M+H)+, Rt: 2.73 min

**Intermediate 86**

r(2$l^1$3-bromo-6-r(methyloxy)carbonyln-1H-indol-1-yl)ethyl)oxylacetic acid

![Intermediate 86 structure]

To a solution of a compound of structure Intermediate 76 and e.g. prepared as above (20 g brut, 40 mmol) in dichloromethane (100 ml) was added TFA (20 ml, 0.27 mol). The reaction mixture was stirred at room temperature overnight. The reaction was not complete, 10 ml of TFA were added. The mixture was stirred at room temperature 1 hour.
The reaction mixture was washed with brine (2 times). A precipitate was formed in organic phase, heptane was added and the suspension was filtrate. The precipitate was washed with heptane and dried to give the title compound as pink solid (10.58 g, 74%).

LC/MS: m/z 357.98 (M+H)+, Rt: 2.28 min

### Intermediate 87

**Methyl 3-bromo-1-[4-((4-(1-methylethyl)phenylcarbonyl)amino)butyl]-1H-indole-6-carboxylate**

![Chemical Structure](image)

4-(1-methylethyl)benzoic acid (6.7 g, 41 mmol) was diluted in toluene and SOCl₂ (15 ml, 0.2 mmol) was added. The mixture was stirred at 80°C for 18 hours and evaporated to dryness. The acid chloride obtained was diluted in toluene (20 ml), Methyl 1-(4-aminobutyl)-3-bromo-1H-indole-6-carboxylate (Intermediate 77) and triethylamine (10 ml, 82 mmol) were added. The mixture was stirred at room temperature for 1 hour. The solvent was evaporated, the crude was diluted in diethyl ether, washed with water and brine. The organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography on silica gel (dichloromethane and dichloromethane/methanol 99:1) to give the title compound (11.6 g, 72%).

NMR: ¹H NMR (300 MHz), δ: 8.29 (s, 1H), 8.06 (dd, 1H), 7.86 (d, 2H), 7.77 (d, 1H), 7.45 (s, 1H; d, 2H), 6.52 (m, 1H), 4.39 (t, 2H), 4.14 (s, 3H), 3.64 (q, 2H), 3.13 (m, 1H), 2.10 (m, 2H), 1.79 (m, 2H), 1.45 (d, 6H).

### Intermediate 88

**Methyl 1-[4-((4-(1-methylethyl)phenylcarbonyl)amino)butyl]-3-r2-(methoxy)phenyl-1H-indole-6-carboxylate**
A solution of methyl 3-bromo-1-[4-[[4-(1-methylethyl)phenyl]carbonyl]amino]butyl]-1H-indole-6-carboxylate (Intermediate 87) (0.5 g, 1.06 mmol), 2-methoxyphenylboronic acid (486 mg, 3.2 mmol), PdCl$_2$·dpf·dichloromethane (43 mg, 0.05 mmol) and K$_3$PO$_4$ (680 mg, 3.2 mmol) in DME (7 ml) was micro waved at 120°C, 120 watts and 15 bars during 25 min. The mixture was diluted with ethyl acetate, filtered, washed with HCl 1N, a saturated solution of NaHCO$_3$ and brine. The organic phase was dried over Na$_2$SO$_4$, filtered and concentrated. The crude was purified by flash chromatography on silica gel to give the title compound as colourless oil (406 mg, 77%).

LC/MS: m/z 499 (M+H)$^+$, Rt: 3.82 min

**Intermediate 89**

**Methyl 3-(2-hydroxyphenyl)-1-[4-[[4-(1-methylethyl)phenyl]carbonyl]amino]butyl]-1H-indole-6-carboxylate**

To a solution of methyl 1-[4-[[4-(1-methylethyl)phenyl]carbonyl]amino]butyl]-3-[2-(methoxy)phenyl]-1H-indole-6-carboxylate (Intermediate 88) (350 mg, 0.70 mmol) in dichloromethane (30 ml) at 0°C under argon was added drop by drop a solution of BBr$_3$ in dichloromethane 1M (8.4 ml, 8.4 mmol). The reaction mixture was stirred for 5 hours from 0°C to room temperature. The mixture was quenched at 0°C with methanol (5 ml) drop by drop and water. The mixture was diluted with dichloromethane and the organic phase was washed with water, a saturated solution of NaHCO$_3$ and HCl 1N. The organic phase was dried over Na$_2$SO$_4$, filtered and evaporated. The crude was purified by flash chromatography on silica gel (Cyclohexane/ethyl acetate 50:50) to give the title compound as yellow oil (36 mg, 11%).
NMR $^1$H NMR (300 MHz), CDCl$_3$ $\delta$: 8.08 (s, 1H), 7.73 (dd, 1H), 7.53 (m, 3H), 7.37 (s, 1H), 7.30 (dd, 1H), 7.16 (m, 3H), 6.94 (m, 2H), 4.20 (t, 2H), 3.87 (s, 3H), 3.36 (q, 2H), 2.85 (m, 1H), 1.91 (m, 2H), 1.58 (m, 2H), 1.17 (d, 6H).

5 **Intermediate 90**

1,1-dimethylethyl 1-r4-(U4-(1-methylethyl)phenv π carbonyl)amino)butyl-3-(2-pyridinyl)-1H-indole-6-carboxylate

A mixture of 4-isopropyl benzoic acid (73 mg, 0.45 mmol), EDCI (94 mg, 0.49 mmol), DMAP (94 mg, 0.49 mmol), Intermediate 80 (165 mg, 0.45 mmol) in dichloromethane (4 ml) was stirred at reflux for 4 hours. The reaction wasn't complete, 4-isopropyl benzoic acid (0.1 eq) and EDCI (0.1 eq) were added. The mixture was heated at reflux 1 hour. The mixture was washed with brine. The organic phase was dried over Na$_2$SO$_4$, filtered and evaporated. The residue was purified by flash chromatography on silica gel (toluene/ethyl acetate 5/5 to 1/9). The obtained product was purified by semi preparative HPLC to give the title compound as yellow oil (96 mg, 42%).

LC/MS : m/z 512.09 (M+H)+, Rt: 8.191 min

5 **Intermediate 91**

Methyl 1-r4-(fr4-(1-methylethyl)phenv π carbonyl)amino)butv π 3-(5-methyl-2-thienyl)-1H-indole-6-carboxylate

80
To a solution of Intermediate 79 (80 mg, 0.23 mmol) and triethylamine (100 µl, 0.70 mmol) in anhydrous dichloromethane (20 ml) was added 4-isopropyl-benzoyl chloride (64 mg, 0.35 mmol) and the mixture was stirred at room temperature for 5 hours. The reaction mixture was diluted with ethyl acetate (50 ml) and washed with a saturated solution of NaHCO₃, HCl 1N and brine. The organic phase was dried over Na₂SO₄, filtered and evaporated. The residue was by flash chromatography on silica gel (Cyclohexane/ ethyl acetate 70:30) to give the title compound as pale yellow oil (40 mg, 35%).

NMR ¹H NMR (300 MHz), CDCl₃ δ: 8.04 (s, 1H), 7.87 (d, 1H), 7.78 (d, 1H), 7.57 (d, 2H), 7.34 (s, 1H), 7.19 (d, 2H), 6.96 (d, 1H), 6.68 (m, 1H), 6.00 (m, 1H), 4.18 (t, 2H), 3.87 (s, 3H), 3.40 (q, 2H), 2.86 (m, 1H), 1.90 (m, 2H), 1.55 (m, 2H), 1.17 (d, 6H).

The following Intermediates were prepared in an analogous manner to methyl 1-[4-[[4-(1-methylethyl)phenyl]carbonyl]amino]butyl]-3-(5-methyl-2-thienyl)-1H-indole-6-carboxylate (Intermediate 91) from intermediate compounds having the structure depicted above and e.g. prepared as above:

<table>
<thead>
<tr>
<th>Intermediate</th>
<th>R</th>
<th>From</th>
<th>NMR ¹H NMR (300 MHz)/ LC-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate 92</td>
<td>![Intermediate 92 structure]</td>
<td>Intermediate 78</td>
<td>NMR ¹H NMR (300 MHz), CDCl₃ δ: 7.97 (s, 1H), 7.67 (d, 1H), 7.57 (m, 3H), 7.17 (d, 2H), 6.93 (s, 1H), 6.17 (m, 1H), 4.08 (t, 2H), 3.84 (s, 3H), 3.35 (q, 2H), 2.85 (m, 1H), 2.73 (m, 1H), 1.99 (m, 2H), 1.80 (m, 6H), 1.51 (m, 2H), 1.36 (m, 2H), 1.16 (d, 6H).</td>
</tr>
</tbody>
</table>
Intermediate 94

Methyl 1-(4-(cyclohexylphenylamino)cyclohexylphenyl)-3-phenyl-1H-indole-6-carboxylate

A solution of methyl 1-[(4-aminophenyl)methyl]-3-phenyl-1H-indole-6-carboxylate (Intermediate 82) (100 mg, 0.28 mmol), 4-cyclohexylbenzoic acid (70 mg, 0.34 mmol), HOBT (45 mg, 0.34 mmol), EDCI (65 mg, 0.34 mmol) and triethylamine (80 µl, 0.56 mmol) in DMF (5 ml) was stirred at room temperature for 30 hours. The solvent was evaporated and the residue was diluted with dichloromethane and a saturated solution of NaHCO₃. The organic phase was extracted, dried over Na₂SO₄, filtered and evaporated. The residue was purified by flash chromatography on silica gel (gradient: cyclohexane 100% to cyclohexane/ethyl acetate 80:20 to ethyl acetate 100%) to give the title compound as white solid (110 mg, 72%).

LC/MS: m/z 543 (M+H)+, Rt: 4.35 min

Intermediate 95

Methyl 1-(5-{4-(1-methylethyl)phenylamino}-5-oxopentyl)-3-phenyl-1H-indole-6-carboxylate

Intermediate 82

LC/MS: m/z 503.04 (M+H)+, Rt: 4.07 min
A solution of 5-{6-[(methyloxy)carbonyl]-3-phenyl-1H-indol-1-yl}pentanoic acid (intermediate 85) (120mg, 0.34mmol), 4-isopropylaniline (60mg, 0.44mmol), HOBT (60mg, 0.44mmol), EDCI (85mg, 0.44mmol) and Et₃N (45mg, 0.44mmol) in dichloromethane was stirred at room temperature for 5 days. The reaction mixture was washed twice with HCl (1N), once with NaOH (1N) and brine, dried over Na₂SO₄, filtered, evaporated and purified by chromatography (dichloromethane/methanol 99:1) to give an orange oil. (120mg, 75%)

**Intermediate 96**

methyl 3-bromo-1-(2-(2-[(4-(4-methylethyl)phenyllamino}-2-oxoethyl)oxylethyl)-1 H-indole-6-carboxylate

![Intermediate 96](image)

To a solution of [(2-3-bromo-6-[(methyloxy)carbonyl]-1H-indol-1-yl)ethyl]oxy]acetic acid (intermediate 86) (5g, 14mmol) in DMF was added HOBT (2.27g, 16.8mmol), EDCI (3.23g, 16.8mmol), 4-isopropyl aniline (2.27g, 16.8mmol) and Et₃N (3.9mL, 28mmol) and it was stirred at room temperature for 4h. The mixture was poured into water, extracted with ethyl acetate, dried over sodium sulphate, evaporated and purified by chromatography (dichloromethane/ ethyl acetate 95:5 ) to give the title compound. (4.46g, 67%)

**Intermediate 97**

Methyl 3-(3-furanyl)-1-[4-((4-(4-(4-methylethynphenyllcarbonyl) amino)butyl)-1H-indole-6-carboxylate

![Intermediate 97](image)
A solution of methyl 3-bromo-1-[[4-[[4-(1-methylethyl)phenyl]carbonyl]amino]butyl]-1H-indole-6-carboxylate Intermediate 87 (133 mg, 0.28 mmol), 3-furanylboronic acid (47 mg, 0.42 mmol), Pd$_2$dba$_3$ (13 mg, 0.014 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (12 mg, 0.028 mmol), K$_3$PO$_4$ (120 mg in 0.5 ml of water, 0.56 mmol) in DME (5 ml) was micro waved at 120°C, 120 watts during 20 min. The reaction was not complete, catalyst was added and the mixture was micro waved at 120°C, 120 watts during 20 min. The mixture was diluted with ethyl acetate, washed with a saturated solution of NaHCO$_3$ and brine. The organic phase was decanted, dried over Na$_2$SO$_4$, filtered and evaporated. The crude was purified by flash chromatography on silica gel (Cyclohexane/ ethyl acetate 70:30 to 50:50) to give the title compound as white powder (55 mg, 43%).

LC/MS : m/z 459 (M+H$^+$), Rt: 3.63 min

The following Intermediates were prepared in an analogous manner to Methyl 3-(3-furanyl)-1-[[4-[[4-(1-methylethyl)phenyl]carbonyl]amino]butyl]-1H-indole-6-carboxylate (Intermediate 97) from intermediate compounds having the structures depicted above and e.g. prepared as described above.

<table>
<thead>
<tr>
<th>Intermediate</th>
<th>R</th>
<th>From</th>
<th>NMR$^1$H NMR (300 MHz)/ LC-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intermediate 98</strong></td>
<td></td>
<td>Intermediate 87</td>
<td>LC/MS : m/z 499 (M+H$^+$), Rt: 3.82 min</td>
</tr>
<tr>
<td><strong>Intermediate 99</strong></td>
<td></td>
<td>Intermediate 87</td>
<td>LC/MS : m/z 525.22 (M+H$^+$), Rt: 3.83 min</td>
</tr>
</tbody>
</table>
Example 47

5 3-(3-furanyl)-1-[4-([4-(1-methylethyl)phenyl]carbonyl)amino]butyl-1H-indole-6-carboxylic acid

To a solution of methyl 3-(3-furanyl)-1-[4-([4-(1-methylethyl)phenyl]carbonyl)amino]butyl-1H-indole-6-carboxylate (Intermediate 97) (55 mg, 0.1 mol) in ethanol was added NaOH 1N (1 ml, 1 mmol) and the reaction mixture was stirred at 80°C for 6 hours with and addition of NaOH 1N (1 ml) after 3 hours. The solvent was evaporated and the residue was diluted with water, acidified with HCl 1N. The precipitate formed was filtered, rinse with water and dried to give the title compound as an off-white solid (44 mg, 99%).

NMR 1H NMR (300 MHz), CDCl3 δ: 8.03 (s, 1H), 7.75 (d, 1H), 7.62 (d, 2H), 7.47 (d, 2H), 7.33 (s, 1H), 7.24 (s, 1H), 7.08 (d, 2H), 6.51 (s, 1H), 5.94 (m, 1H), 4.10 (m, 2H), 3.31 (m, 2H), 2.74 (m, 1H), 1.80 (m, 2H), 1.46 (m, 2H), 1.05 (d, 6H).

TOF MS ES+ exact mass calculated for C27H28N2O4: 445.2135 (M+H)+ Found: 445.2127 (M+H)+; RT = 2.42 min.

The following examples were prepared in an analogous manner to 3-(3-furanyl)-1-[4-([4-(1-methylethyl)phenyl]carbonyl)amino]butyl-1H-indole-6-carboxylic acid (Example 47), from intermediate compounds having the structures depicted and e.g. prepared as described above.
<table>
<thead>
<tr>
<th>EXAMPLE</th>
<th>R</th>
<th>From</th>
<th>NMR $^1$H NMR (300 MHz)/ LC-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 48</td>
<td><img src="image1.png" alt="Image" /></td>
<td>Intermediate 92</td>
<td>Target Mass for C29H30N2O3: 461.2804 (M-H)$^+$, Found: 461.2794; Rt: 3.01 min</td>
</tr>
<tr>
<td>Example 49</td>
<td><img src="image2.png" alt="Image" /></td>
<td>Intermediate 98</td>
<td>Target Mass for C30H32N2O4: 485.2440 (M-H)$^+$, Found: 485.2436; Rt: 2.60 min</td>
</tr>
<tr>
<td>Example 50</td>
<td><img src="image3.png" alt="Image" /></td>
<td>Intermediate 94</td>
<td>Target Mass for C28H30N2O3S: 475.2055 (M-H)$^+$, Found: 475.2090; Rt: 2.67 min</td>
</tr>
<tr>
<td>Example 51</td>
<td><img src="image4.png" alt="Image" /></td>
<td>Intermediate 99</td>
<td>Target Mass for C31H30N2O3S: 511.2055 (M-H)$^+$, Found: 511.2077; Rt: 2.80 min</td>
</tr>
<tr>
<td>Example 52</td>
<td><img src="image5.png" alt="Image" /></td>
<td>Intermediate 100</td>
<td>Target Mass for C31H30N2O4: 495.2284 (M-H)$^+$, Found: 495.2263; Rt: 2.77 min</td>
</tr>
<tr>
<td>Example 53</td>
<td><img src="image6.png" alt="Image" /></td>
<td>Intermediate 89</td>
<td>Target Mass for C29H30N2O4: 471.2284 (M-H)$^+$, Found: 471.2302;</td>
</tr>
</tbody>
</table>
Intermediate 101
Methyl 1-f4-((f4-(dimethylamino)-2-hydroxyphenylcarbonyl)amino)butyl-3-(3-furanyl)-1H-indole-6-carboxylate

A mixture of a compound of structure Intermediate 81 and e.g. prepared as above (118 mg, 0.37 mmol), 4-(dimethylamino)-2-hydroxybenzoic acid (82 mg, 0.45 mmol), HATU (211 mg, 0.55 mmol) and iPr2NEt (130 µl, 0.74 mmol) in DMF (5 ml) was stirred at room temperature for 24 hours. The mixture was dilute with ethyl acetate (50 ml) and washed with a saturated solution of NaHCO₃ (1 time) and brine (1 time). The organic phase was dried over Na₂SO₄, filtered and evaporated. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 70:30) to give the title compound as yellow oil (45 mg, 27%).

LC/MS: m/z 476 (M+H)+, Rt: 3.54 min.

Intermediate 102
Methyl 1-{2-r(2-{F4-(1-methylethyl)phenyllamino}-2-oxoethyl)aminol ethyl)-3-phenyl-1H-indole-6-carboxylate
To a solution of methyl 1-(2-aminoethyl)-3-phenyl-1H-indole-6-carboxylate hydrochloride (Intermediate 83) (110 mg, 0.332 mmol) in THF was added triethylamine (140 µl, 1 mmol) and 2-bromo-4′-[4-(1-methylethyl)phenyl]acetamide (Intermediate 84) (85 mg, 0.332 mmol). The mixture was stirred at room temperature for 24 hours. The reaction was not complete, one equivalent of 2-bromo-4′-[4-(1-methylethyl)phenyl]acetamide Intermediate 84 was added. The mixture was stirred at 60°C during 24 hours. The mixture was cooled to room temperature, brine was added and the solution was extracted with ethyl acetate. The organic phase was dried over Na₂SO₄, filtered and evaporated. The residue was purified by flash chromatography on silica gel (dichloromethane/methanol 98:2) to give the title compound (50 mg, 32%).

LC/MS : m/z 470.12 (M+H)+, Rt: 3.86 min.

Intermediate 103
Methyl 2-bromo-1-4-lf4-[4-(1-methylethyl)phenyl]carbonvDamino) butyl1-3-phenyl-1 H-indole-6-carboxylate

To a solution of methyl 1-[4-([4-(1-methylethyl)phenyl]carbonyl)amino]butyl]-3-phenyl-1H-indole-6-carboxylate (Intermediate 22) (1.78 g, 3.8 mmol) in THF was added NBS (880 mg, 4.94 mmol). The reaction mixture was stirred at 70°C for 3 hours. After cooling, brine was added and the mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried over Na₂SO₄, filtered and evaporated. The residue was purified by flash chromatography on silica gel (dichloromethane/ethyl acetate 93:7) to give the title compound as a white solid (1.92 g, 92%).

LC/MS : m/z 549 (M+H)+, Rt: 4.18 min.

Intermediate 104
Methyl 2-ethenyl-1-F4-(fr4-f1 -methylethylhphenyllcarbonvDamino) butyll-3-phenyl-1H-indole-6-carboxylate
To a solution of methyl 2-bromo-1-[4-({4-(1-methylethyl)phenyl}carbonyl)amino]butyl]-3-phenyl-1H-indole-6-carboxylate (Intermediate 103) (1.92 mg, 3.5 mmol) in DMF (17.5 ml) was added vinyltributyltin (1.55 ml, 5.25 mmol) and Pd(PPh3)2Cl2 (125 mg, 0.175 mmol). The reaction mixture was micro waved at 120°C and 150 watts during 22 min. The reaction mixture was filtered on Whatman paper. The filtrate was concentrated and the residue was diluted with ethyl acetate. This solution was washed with a saturated solution of NaHCO3 and a saturated solution of NH4Cl. The organic phase was dried over Na2SO4, filtered and evaporated. The residue was purified by flash chromatography on silica gel (dichloromethane/ethyl acetate 95:5) to give the title compound as a yellow solid (1.39 g, 80%).

LC/MS: m/z 495.1 (M+H)+, Rt: 4.1 min.

Intermediate 105
methyl 2-formyl-1-[4-({4-(1-methylethyl)phenyl}carbonyl)amino]butyl]-3-phenyl-1H-indole-6-carboxylate

To a solution of methyl 2-ethenyl-1-[4-({4-(1-methylethyl)phenyl}carbonyl)amino]butyl]-3-phenyl-1H-indole-6-carboxylate (Intermediate 104) (1.39 g, 2.81 mmol) in dioxane (50 ml) was added water (5 ml) and OsO4 2.5% in tBuOH (1.5 ml). The mixture was stirred 2 minutes and NaIO4 (1.26 g, 5.9 mmol) was added. The reaction mixture was stirred at room temperature for 48 hours. The reaction mixture was poured into water and NaHCO3 was added until pH=7. The mixture was extracted with ethyl acetate. The organic phase was dried over Na2SO4, filtered and evaporated. The residue was purified by flash
chromatography on silica gel (DICHROMETHANE/ethyl acetate 9:1) to give the title compound as a yellow solid (680 mg, 49%).

LC/MS: m/z 497.09 (M+H)+, Rt: 3.95 min.

**Intermediate 106**

Methyl 2-(methylamino)methyn-1-(4-(1-methylethyl)phenylcarbonyl)amino)butyn-3-phenyl-1H-indole-6-carboxylate

To a hot solution of methyl 2-formyl-1-[4-[[4-(1-methylethyl)phenyl]carbonyl]amino]butyl]-3-phenyl-1H-indole-6-carboxylate (Intermediate 105) (300 mg, 0.605 mmol) in methanol was added via a syringe, methylamine (3 ml, 6.05 mmol). The mixture was stirred at room temperature for 24 hours. The reaction was not complete, the precipitate formed was dissolved by heating and 3 ml of methylamine were added. The mixture was stirred at room temperature for 6 hours. The reaction mixture was concentrated and the white solid obtained was dissolved in ethanol and concentrated. The solid was dissolved with a mix of THF (10 ml) and methanol (50 ml) and NaBH₄ (115 mg, 3 mmol) was added. The mixture was stirred at room temperature for 2 hours. Brine was added and the mixture was extracted with ethyl acetate (2 times). The organic phase was washed with brine, dried over Na₂SO₄, filtered and evaporated to give the title compound as orange amorphous solid (300 mg, quantitative yield).

LC/MS: m/z 512.1 1 (M+H)+, Rt: 3.62 min.

**Intermediate 107**

Methyl 1-(2-rmethyl(2-{r4-(1-methylethyl)phenylamino}2-oxoethyl)aminoethyl)-3-phenyl-1H-indole-6-carboxylate
To a solution of methyl 1-{2-[(2-[4-(1-methylethyl)phenyl]amino)-2-oxoethyl]amino}-3-phenyl-1H-indole-6-carboxylate (Intermediate 102) (42 mg, 0.09 mmol) in THF was added formaldehyde (35 µl, 0.45 mmol) and NaBH(OAc)_3 (96 mg, 0.45 mmol). The mixture was stirred at room temperature for 16 hours. Brine was added, and the mixture was extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography on silica gel (dichloromethane/ethyl acetate 98:2) to give the title compound (31 mg, 71%).

Intermediate 108

Methyl 1-{2-[(2-[4-(1-methylethyl)phenyl]amino)-2-oxoethyl]oxylethyl}-3-(2-pyridinyl)-1H-indole-6-carboxylate

To a solution of Methyl 2-[(methylamino)methyl]-1-[[4-(1-methylbutyl)phenyl]carbonyl]amino]butyl]-3-phenyl-1H-indole-6-carboxylate (Intermediate 106) (300 mg, 0.59 mmol) in THF was added formaldehyde (220 µl, 2.95 mmol) and NaBH(OAc)_3 (625 mg, 2.95 mmol). The mixture was stirred at room temperature for 1.5 hours. Brine was added, and the mixture was extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography on silica gel (dichloromethane/MeOH 97:2) to give the title compound (280 mg, 90%).

Intermediate 109
**Methyl 1-\{2-(2-U4-(1-methylethyl)phenyllamino)-2-oxoethyl\}oxylethyl\} -3-(2-pyridinyl)-1H-indole-6-carboxylate**

A solution of a compound of structure Intermediate 96 e.g. prepared as described above (473 mg, 1 mmol), trimethyl(2-pyridyl)tin (520 µl, 3 mmol), Pd$_2$dba$_3$ (183 mg, 0.2 mmol) and tri-o-tolylphosphine (61 mg, 0.2 mmol) in DME (2 ml) was microwaved at 120°C and 120 watts during 62 min. The reaction mixture was filtered and washed with ethyl acetate. The filtrate was washed with brine, dried over Na$_2$SO$_4$, filtered and evaporated. The residue was purified by flash chromatography on silica gel (dichloromethane/ethyl acetate 9:1) to give the title compound (55 mg, 11%).

LC/MS: m/z 472.1 (M+H)$^+$, Rt: 3.57 min.

**Intermediate 110**

**Methyl 3-(1-benzothien-2-yl)-1-\{2-K2-I F4-M-methylethyl\}phenyllamino\}2-oxoethyl\}oxy1ethyl\}1H-indole-6-carboxylate**

A solution of a compound of structure Intermediate 96 e.g. prepared as described above (473 mg, 1 mmol), thianaphtene-2-boronic acid (356 mg, 2 mmol), Pd$_2$dba$_3$ (46 mg, 0.05 mmol) and K$_3$PO$_4$ (424 mg, 2 mmol) in DME (3 ml). The reaction mixture was microwaved with stirring and cooling at 120°C, 120 watts and 15 bars during 22 min. The reaction mixture was filtered on Whatman paper. The filtrate was extracted with ethyl acetate, washed with brine, dried over Na$_2$SO$_4$, filtered and evaporated. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 5:5) to give the title compound (280 mg, 53%).

LC/MS: m/z 527.2 (M+H)$^+$, Rt: 4.32 min.

**Example 54**
To a solution of 1,1-dimethylethyl 1-[[4-[[4-(1-methylethyl)phenyl]carbonyl]amino]phenyl]methyl]-3-phenyl-1H-indole-6-carboxylate (Intermediate 94) (110 mg, 0.2 mmol) in ethanol (10 ml) was added NaOH 1N (2ml, 2mmol). The mixture was stirred at 80°C overnight. HCl 1N (2ml) was added. The precipitate was filtered, washed with water, ethanol and rinse with pentane to give the title compound as white solid (75 mg, 70%).
TOF MS ES+ exact mass calculated for C35H32N2O3: 529.2491 (M+H)+ Found: 529.2528 (M+H)+; RT = 3.19 min.

The following examples were prepared in an analogous manner to 1-[(4-[[4-cyclohexylphenyl]carbonyl]amino]phenyl)methyl]-3-phenyl-1H-indole-6-carboxylic acid (Example 55), from intermediate compounds having the structures depicted above and e.g. prepared as described above.

<table>
<thead>
<tr>
<th>EXAMPLE</th>
<th>R</th>
<th>FROM</th>
<th>NMR $^1$H NMR (300 MHz) / LC-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 56</td>
<td><img src="Example56.png" alt="Image" /></td>
<td>Intermediate 101</td>
<td>Target Mass for C26H27N3O5: 462.2029 (M-H)+, Found: 462.1986; Rt: 2.34 min</td>
</tr>
<tr>
<td>Example 57</td>
<td><img src="Example57.png" alt="Image" /></td>
<td>Intermediate 93</td>
<td>Target Mass for C32H28N2O3: 489.2178 (M-H)+, Found: 489.2238; Rt: 9.40 min</td>
</tr>
<tr>
<td>Example 58</td>
<td><img src="Example58.png" alt="Image" /></td>
<td>Intermediate 95</td>
<td>Target Mass for C29H30N2O3: 455.2335 (M-H)+, Found: 455.2350; Rt: 2.70 min</td>
</tr>
<tr>
<td>Example 59</td>
<td><img src="Example59.png" alt="Image" /></td>
<td>Intermediate 102</td>
<td>Target Mass for C28H29N3O3: 456.2287 (M-H)+, Found: 456.2283; Rt: 2.49 min</td>
</tr>
</tbody>
</table>
Example 62
1-{2-r(2-{r4-(1-methylethyl)phenylamino)-2-oxoethyl)oxy1ethyl)-3-(2-pyridinyl)-1H-indole-6-carboxylic acid

To a solution of 1-[(4-[(4-cyclohexylphenyl)carbonyl]amino[phenyl)methyl]-3-phenyl-1H-indole-6-carboxylic acid (Intermediate 109) (47 mg, 0.1 mmol) in THF (500 µl) was added methanol (250 µl) and LiOH 1N (200 µl, 0.2 mmol). The mixture was stirred at room temperature for 24 hours. The reaction was not complete and 200 µl of LiOH 1N was added, the mixture was stirred at room temperature for 24 hours. The mixture was neutralised with HCl 1N and extracted with ethyl acetate. The organic phase was washed with brine, dried over Na₂SO₄, filtered and evaporated. The residue was purified by flash chromatography on silica gel (dichloromethane/methanol 95:5). The obtained product was recrystallised in isopropanol, washed with water and dry to give the title compound (30 mg, 66%).

TOF MS ES+ exact mass calculated for C₂₇H₂₇N₃O₄: 458.2119 (M+H)+ Found: 458.2180 (M+H)+ ; RT = 2.31 min.
The following example was prepared in an analogous manner to example 62, from intermediate compounds having the structures depicted above and e.g. prepared as described above

<table>
<thead>
<tr>
<th>EXAMPLE</th>
<th>R</th>
<th>From</th>
<th>NMR(^1)H NMR (300 MHz)/ LC-MS</th>
</tr>
</thead>
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<tr>
<td>Example 63</td>
<td><a href="#">Structure</a></td>
<td>Intermediate 110</td>
<td>Target Mass for C30H28N2O4S: 511.1692 (M-H)+, Found: 511.1719; Rt: 2.87 min</td>
</tr>
</tbody>
</table>

**Biological Assays**

**Binding Assay:**

Compounds were tested for their ability to bind to hPPAR gamma hPPARalpha or PPARdelta using a Scintillation Proximity Assay (SPA). The PPAR ligand binding domain (LBD) was expressed in E. coli as polyHis tagged fusion proteins and purified. The LBD was then labelled with biotin and immobilised on streptavidin-modified scintillation proximity beads. The beads were then incubated with a constant amount of the appropriate radioligand (5-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-benzyl}-thiazolidine-2,4-dione \(\text{J.Med.Chem.}\ 1994,\ 37(23),\ 3977\), for PPARgamma), and labelled GW 2433 (see Brown, P. J et al. *Chem. Biol.*, 4, 909-918 (1997), for the structure and synthesis of this ligand) for PPAR alpha and PPAR delta) and variable concentrations of test compound, and after equilibration the radioactivity bound to the beads was measured by a scintillation counter. The amount of nonspecific binding, as assessed by control wells containing 50 μM of the corresponding unlabeled ligand, was subtracted from each data point. For each compound tested, plots of ligand concentration vs. CPM of radioligand bound were constructed and apparent \(K_I\) values were estimated from nonlinear least squares fit of the data assuming simple competitive binding. The details of this assay have been reported elsewhere (see, Blanchard, S. G. et. al. Development of a Scintillation Proximity Assay for Peroxisome Proliferator-Activated Receptor gamma Ligand Binding Domain. *Anal. Biochem.*, 257, 112-119 (1998)).
Transfection assay:
Compounds were screened for functional potency in transient transfection assays in CV-1 cells for their ability to activate the PPAR subtypes (transactivation assay). A previously established chimeric receptor system was utilized to allow comparison of the relative transcriptional activity of the receptor subtypes on the same target gene and to prevent endogenous receptor activation from complicating the interpretation of results. See, for example, Lehmann, J. M.; Moore, L. B.; Smith-Oliver, T. A.; Wilkison, W. O.; Willson, T. M.; Kliwer, S. A., An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPARgamma), J. Biol. Chem., 270, 12953-6 (1995). The ligand binding domains for murine and human PPAR alpha, PPAR gamma, and PPAR delta were each fused to the yeast transcription factor GAL4 DNA binding domain. CV-1 cells were transiently transfected with expression vectors for the respective PPAR chimera along with a reporter construct containing five copies of the GAL4 DNA binding site driving expression of secreted placental alkaline phosphatase (SPAP) and beta-galactosidase. After 16 h, the medium was exchanged to DME medium supplemented with 10% delipidated fetal calf serum and the test compound at the appropriate concentration. After an additional 24 h, cell extracts were prepared and assayed for alkaline phosphatase and β-galactosidase activity. Alkaline phosphatase activity was corrected for transfection efficiency using the beta-galactosidase activity as an internal standard (see, for example, Kliwer, S. A., et. al. Cell 83, 813-819 (1995)).

Rosiglitazone (BRL 49653) was used as a positive control in the hPPAR gamma assay. The positive control in the hPPAR alpha assays was 2-4-[2-(3-[4-fluorophenyl]-1-heptylureido)ethyl]-phenoxy-(2-methyl propionic acid (WO 97/36579). The positive control for PPAR delta assays was 2-{2-methyl-4-[(4-methyl-2-{trifluoromethyl)phenyl]-1 ,3-thiazol-5-yl]methyl}sulfanyl]phenoxy)acetic acid (WO 01/00603). The positive control was (5-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-benzyl}-thiazolidine-2,4-dione (J. Med. Chem. 1994, 37(23), 3977), for PPAR gamma.

Activities in three hPPAR subtypes determined by assays as described or similar to those above, are reported in the table and are expressed in micromolar.

<table>
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<tr>
<th>Example</th>
<th>EC50 μM HPPARα</th>
<th>EC50 μM HPPARδ</th>
<th>EC50 μM HPPARγ</th>
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<td>Example</td>
<td>Value 1</td>
<td>Value 2</td>
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<td>-----------</td>
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<tr>
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<td>&gt;25</td>
<td>&gt;25</td>
</tr>
</tbody>
</table>
CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:

   \[
   \begin{array}{c}
   \text{X} \\
   \text{Y} \\
   Z \\
   \end{array}
   \]

   (I)

   wherein:-
   - one of \( R_1 \) and \( R_2 \) is H, the other is COOH;
   - \( R_3 \) is H or \(-\text{CH}_2\text{N(CHa)}_2\);
   - \( Z \) is \( C_{3-7} \) cycloalkyl, phenyl (optionally substituted by \(-\text{C}_1\text{-C}_3 \) alkoxy, \(-\text{OH}, -\text{C}_1\text{-C}_3 \) alkyl), a 5 or 6 membered monocyclic heteroaryl (optionally substituted by \(-\text{C}_1\text{-C}_3 \) alkyl), benzothiophenyl or benzofuranyl;
   - \( X \) is a linker group of 6 or 7 above in shortest length between \( N \) and \( Y \).
   - \( Y \) is
     - (a) phenyl (substituted by one, two or three substituents, each independently selected from \(-\text{OH}, -\text{Cr}_3\text{alkyl}, -\text{Cr}_3\text{alkoxy}, -\text{C}_1\text{-C}_3 \) haloalkyl, halogen, -\(\text{Cs-ecycloalkyl}, -\text{CF}_3\), -halogen);
     - (b) phenyl fused to a 5 or 6 membered heterocyclic ring containing one or two oxygen atoms (said phenyl and heterocyclic ring each being optionally substituted by \( \text{C}_1\text{-C}_3 \) alkyl);
     - (c) phenyl fused to a 5 or 6 membered cycloalkyl (said phenyl being optionally substituted by \(-\text{OH})
     - (d) a 5 or 6 membered monocyclic heteroaryl (optionally substituted by one or more substituents independently selected from \(-\text{C}_1\text{-C}_3 \) alkyl, \(-\text{CF}_3\), -halogen).

2. A compound or salt according to claim 1 wherein \( R_2 \) is H and \( R_1 \) is COOH,

3. A compound or salt according to claims 1 - 2 wherein \( R_3 \) is H.

4. A compound or salt according to claims 1 - 3 wherein \( Z \) represents phenyl (optionally substituted by OH or \(-\text{OCH}_3\)), cyclohexyl, a monocyclic 5 or 6 membered heteroaryl (optionally substituted by \( \text{CH}_3\)), a benzothiophenyl or benzofuranyl.
5. A compound or salt according to claim 4 wherein Z represents phenyl, furanyl, benzofuranyl, benzo thiophenyl, pyridinyl, thiophenyl (substituted by -CH\textsubscript{3}), phenyl (substituted by OH), phenyl (substituted by -CH\textsubscript{3}), cyclohexyl.

6. A compound or salt according to claim 5 wherein Z represents phenyl, furanyl, benzofuranyl, benzo thiophenyl, pyridinyl, thiophenyl (substituted by -CH\textsubscript{3}), phenyl (substituted by OH), phenyl (substituted by -CH\textsubscript{3}), cyclohexyl.

7. A compound or salt according to claim 6 wherein Z represents phenyl.

8. A compound or salt according to claims 1 - 7 wherein X represents a linker group selected from -(CH\textsubscript{2})\textsubscript{4} NR\textsuperscript{C}(O) -, -(CH\textsubscript{2})\textsubscript{4} C(O)NH -, -(CH\textsubscript{2})\textsubscript{2} O CH\textsubscript{2}C(O)NH - , -CH\textsubscript{2}C(O) - , -CH\textsubscript{2}C(O)NH - , -CH\textsubscript{2}N - , -CH\textsubscript{2}NHC(O) - , -(CH\textsubscript{2})\textsubscript{2} NR\textsuperscript{d} CH\textsubscript{2}C(O)NH - , R\textsuperscript{c} = H, C\textsubscript{r}\textsuperscript{3} alkyl, R\textsuperscript{d} = H, C\textsubscript{i}\textsuperscript{3} alkyl,
9. A compound or salt according to claim 8 wherein X represents -(CH\textsubscript{2})\textsuperscript{4}NHCO-, or -(CH\textsubscript{2})\textsubscript{2}OCH\textsubscript{2}CONH-.

10. A compound or salt according to claims 1 - 7 wherein X-Y together represent

![Chemical Structure]

11. A compound or salt according to claims 1 - 9 wherein Y is phenyl (optionally substituted by one or more substituents independently selected from d\textsubscript{-3} alkyl, OH, d\textsubscript{-3} haloalkyl, -halogen, d\textsubscript{-3} alkoxy, C\textsubscript{5-6} cycloalkyl), a 5 or 6 membered heteroaryl, NR\textsuperscript{x}R\textsuperscript{y} (wherein R\textsuperscript{x} and R\textsuperscript{y} are independently H or C\textsubscript{r}\textsubscript{3} alkyl), phenyl fused to a 5 membered heterocyclic ring containing one O atom, phenyl fused to a 6 membered heterocyclic ring containing two O atoms.

12. A compound or salt according to claim 11 wherein Y is

![Chemical Structure]

(n is 1, 2 or 3 and each X is independently selected from C\textsubscript{1-3} alkyl, C\textsubscript{1-3} alkoxy, OH, cycloalkyl, NR\textsuperscript{x}R\textsuperscript{y} (R\textsuperscript{x} and R\textsuperscript{y} are independently C\textsubscript{r}\textsubscript{3} alkyl), chloro, C\textsubscript{F}\textsubscript{3}, pyridyl),
in a further aspect \( Y \) is 

\[
\begin{align*}
&\text{(where } n \text{ is 1, 2 or 3 and each } X \text{ is independently selected from } \text{Cr}_3 \text{ alkyl, Cr}_3 \text{ alkoxy, COH, cycloalkyl, NR}_xR_y \text{(} R_x \text{ and } R_y \text{ are independently } \text{Cr}_3 \text{ alkyl)}, \text{ chloro, CF}_3, \text{ pyridyl).}
\end{align*}
\]

13. A compound or salt according to claim 1 wherein \( Z \) is phenyl, \( X \) is \(-\text{(CH}_2)_2\text{OCH}_2\text{CONH-} \) and \( Y \) is phenyl, (substituted by \(-\text{C}_x\text{alkyl}).

14. A compound according to claim 1 selected from the group consisting of:

1-\{2-\{2-\{(4-\text{(1-methylethyl)phenyl}amino)-2-\text{oxoethyl}oxy\}ethyl\}-3-phenyl-1H-indole-6-carboxylic acid;

15 1-\{2-\{2-\{(1-methylethyl)phenyl}amino)-2-\text{oxoethyl}oxy\}ethyl\}-3-phenyl-1H-indole-6-carboxylic acid;

1-\{2-\{(2,4,6-\text{trimethylphenyl}amino)\text{ethyl}oxy\}ethyl\}-3-phenyl-1H-indole-6-carboxylic acid;

1-\{2-\{(3-hydroxy-5,6,7,8-\text{tetrahydro-2-naphthalenyl}amino)\text{-2-oxoethyl}oxy\}ethyl\}-3-phenyl-1H-indole-6-carboxylic acid;

1-\{2-\{2-\{(3-\text{(1-methylethyl)phenyl}amino)-2-\text{oxoethyl}oxy\}ethyl\}-3-phenyl-1H-indole-6-carboxylic acid;

1-\{2-\{2-\{(3-methyloxy)phenyl}amino)-2-\text{oxoethyl}oxy\}ethyl\}-3-phenyl-1H-indole-6-carboxylic acid;
1-[2-({2-[2-hydroxy-4-methylphenyl]amino]-2-oxoethyl}oxy)ethyl]-3-phenyl-1H-indole-6-carboxylic acid;
1-(2-{[2-(2,3-dihydro-1,4-benzodioxin-6-ylamino)-2-oxoethyl]oxy}ethyl)-3-phenyl-1H-indole-6-carboxylic acid;
1-(2-{[2-(2,3-dihydro-1/-/-inden-5-ylamino)-2-oxoethyl]oxy}ethyl)-3-phenyl-1/-/-indole-6-carboxylic acid;
1-[2-{2-{[4-cyclohexylphenyl]amino]}-2-oxoethyl]oxy]ethyl]-3-phenyl-1H-indole-6-carboxylic acid;
1-[2-{2-{[4-(1,1-dimethylethyl)phenyl]amino]-2-oxoethyl]oxy]ethyl]-3-phenyl-1H-indole-6-carboxylic acid;
1-[2-{[2-{[4-methylphenyl]amino]-2-oxoethyl}oxy}ethyl]-3-phenyl-1H-indole-6-carboxylic acid;
1-[2-{[2-{[4-ethylphenyl]amino]-2-oxoethyl}oxy}ethyl]-3-phenyl-1H-indole-6-carboxylic acid;
1-[4-{[4-(1-methylethyl)phenyl]carbonyl}amino]butyl]-3-phenyl-1H-indole-6-carboxylic acid;
1-{2-{[4-(1,1-dimethylethyl)phenyl]amino]-2-oxoethyl]oxy}ethyl]-3-phenyl-1H-indole-6-carboxylic acid;
1-[2-{2-{[4-(1-methylethyl)phenyl]carbonyl|amino]butyl]-3-phenyl-1H-indole-6-carboxylic acid;
3-phenyl-1-[4-{[4-(trifluoromethyl)phenyl]carbonyl|amino]butyl]-1H-indole-6-carboxylic acid;
1-(4-{[2-hydroxy-3-(1-methylethyl)phenyl]carbonyl|amino]butyl]-3-phenyl-1H-indole-6-carboxylic acid;
1-[4-{[2,4-bis(methyloxy)phenyl]carbonyl|amino]butyl]-3-phenyl-1 H-indole-6-carboxylic acid;
1-[4-{[2-hydroxy-3-(1-methylethyl)phenyl]carbonyl|amino]butyl]-3-phenyl-1H-indole-6-carboxylic acid;
1-[2,4-bis(methyloxy)phenyl]carbonyl|amino]butyl]-3-phenyl-1 H-indole-6-carboxylic acid;
1-[4-({[4-(dimethylamino)-2-hydroxyphenyl]carbonyl}amino)butyl]-3-phenyl-1H-indole-6-carboxylic acid;
3-phenyl-1-[4-({[2-(propyloxy)phenyl]carbonyl}amino)butyl]-1H-indole-6-carboxylic acid;
1-[4-[[1,3-benzodioxol-5-ylcarbonyl]amino]butyl]-3-phenyl-1H-indole-6-carboxylic acid;
3-phenyl-1-[4-({[2-(1H-pyrrol-1-yl)phenyl]carbonyl}amino)butyl]-1H-indole-6-carboxylic acid;
1-{4-[[4-(dimethylamino)-3-methylphenyl]carbonyl]amino}butyl]-3-phenyl-1H-indole-6-carboxylic acid;
1-{4-[(2,3-dihydro-1-benzofuran-5-ylcarbonyl)amino]butyl}-3-phenyl-1H-indole-6-carboxylic acid;
1-(4-{{[1,3-benzodioxol-5-ylcarbonyl]amino}butyl}-1H-indole-6-carboxylic acid;
1-{4-[[4-(1-methyl-1H-pyrrol-2-yl)carbonyl]amino]butyl}-3-phenyl-1H-indole-6-carboxylic acid;
1-{4-[[2,3-dihydro-1,4-benzodioxin-6-ylcarbonyl]amino]butyl}-3-phenyl-1H-indole-6-carboxylic acid;
1-{4-[[1-methyl-1H-imidazol-5-yl]carbonyl]amino}butyl]-S-phenyl-1H-indole-6-carboxylic acid;
1-{4-{[4-(1-methylethyl)phenyl]carbonyl}(propyl)amino}butyl]-3-phenyl-1H-indole-6-carboxylic acid;
1-{4-[(2,3-dihydro-1,4-benzodioxin-6-ylcarbonyl)amino]butyl}-3-phenyl-1H-indole-6-carboxylic acid;
1-[4-{{[4-(1-methyl-1H-imidazol-5-yl)carbonyl]amino}butyl}-3-phenyl-1H-indole-6-carboxylic acid;
1-[(2-4-[4-(1-Methylthyl)phenyl]-1-piperazinyl]-2-oxoethyl]-3-phenyl-1H-indole-6-carboxylic acid;
3-(3-furanyl)-1-[4-{{[4-(1-methylthethyl)phenyl]carbonyl} amino]butyl]-1H-indole-6-carboxylic acid;
3-cyclohexyl-1-[4-{{[4-(1-methylthethyl)phenyl]carbonyl]amino}butyl]-1H-indole-6-carboxylic acid;
1-\{(4-(5-methyl-2-thienyl)-1H-indole-6-carboxylic acid; 1-[4-\{(4-(1-methylethyl)phenyl[carbonyl]amino)butyl]-3-(5-methyl-2-thienyl)-1H-indole-6-carboxylic acid; 3-(1-benzothien-2-yl)-1-[4-\{(4-(1-methylethyl)phenyl[carbonyl]amino)butyl]-1H-indole-6-carboxylic acid; 3-(1-benzofuran-2-yl)-1-[4-\{(4-(1-methylethyl)phenyl[carbonyl]amino)butyl]-1H-indole-6-carboxylic acid; 3-(2-hydroxyphenyl)-1-[4-\{(4-(1-methylethyl)phenyl[carbonyl]amino)butyl]-1H-indole-6-carboxylic acid; 1-[4-\{(4-(1-methylethyl)phenyl[carbonyl]amino)butyl]-3-(2-pyridinyl)-1H-indole-6-carboxylic acid; 1-[4-\{(4-cyclohexyl[phenyl][carbonyl]amino)[phenyl]methyl]-3-phenyl-1H-indole-6-carboxylic acid; 1-\{(4-(1-methylethyl)phenyl)[carbonyl]amino)phenyl)methyl]-3-phenyl-1H-indole-6-carboxylic acid; 1-(5-\{(4-(1-methylethyl)phenyl[amino]-5-oxopentyl)-3-phenyl-1H-indole-6-carboxylic acid; 1-[2-[\{2-(\{4-(1-methylethyl)phenyl)[amino]-2-oxoethyl]amino\}ethyl]-3-phenyl-1H-indole-6-carboxylic acid (non-preferred name); 1-[2-[methyl(\{2-(\{4-(1-methylethyl)phenyl)[amino]-2-oxoethyl]amino\}ethyl]-3-phenyl-1H-indole-6-carboxylic acid (non-preferred name); 2-[\{dimethylamino\}methyl]-1-[4-\{(4-(1-methylethyl)phenyl[carbonyl]amino)butyl]-3-phenyl-1H-indole-6-carboxylic acid; 1-[2-[\{2-(\{4-(1-methylethyl)phenyl)[amino]-2-oxoethyl]oxy\}ethyl]-3-(2-pyridinyl)-1H-indole-6-carboxylic acid; 3-(1-benzothien-2-yl)-1-[2-[\{2-(\{4-(1-methylethyl)phenyl)[amino]-2-oxoethyl]oxy\}ethyl]-1H-indole-6-carboxylic acid; or a pharmaceutically acceptable salt thereof.

15. A compound according to claim 1 which is
1-{2-[2-[4-(1-methylethyl)phenyl]amino]-2-oxoethyl]oxy}ethyl]-3-phenyl-1H-indole-6-carboxylic acid

or a pharmaceutically acceptable salt thereof.

16. A method of treatment to a human of a hPPAR mediated disease or a condition, which comprises administration of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to any of claims 1 to 15.

17. A compound or a pharmaceutically acceptable salt thereof, according to claims 1 to 15 for use in therapy.

18. A compound or a pharmaceutically acceptable salt or solvate thereof, according to claims 1 to 15 for use in the treatment of a hPPAR mediated disease or condition.

19. The use of a compound according to claims 1 to 15, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a hPPAR mediated disease or condition.

20. A pharmaceutical composition which comprises a compound according to claims 1 to 14 or a pharmaceutically acceptable salt thereof optionally with a pharmaceutically acceptable carrier or excipient.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/08 C07D401/04 C07D401/12 C07D403/12 C07D405/04
C07D405/12 C07D409/04 C07D409/12 A61K31/404 A61P3/10

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

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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D. Further documents are listed in the continuation of Box C

X See patent family annex

Date of the actual completion of the international search
14 July 2009

Date of mailing of the international search report
18/08/2009

Authorized officer
Johnson, Claire

Form PCT/ISA/210 (second sheet) (April 2005)
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