Title: 3-CYCLOPENTYLOXY-4-METHOXYPHENYL-ISOINDOLINONE DERIVATIVES AND THE USE THEREOF

Abstract: This invention relates to novel compounds of 3-cyclopentyl-4-methoxyphenyl-isoxindolinone derivatives having the activity to inhibit tumor necrosis factor-α (TNF-α) or cyclic AMP phosphodiesterase IV (PDE 4). In more detail, this invention is directed to the preparation processes of the novel compounds of formula [1], and a pharmaceutically acceptable salt thereof, and pharmaceutical compositions possessing important biological therapeutic effect on inflammatory and autoimmune diseases associated with a detrimental excess of TNF-α.
3-CYCLOPENTYLOXY-4-METHOXYPHENYL-ISOINDOLINONE
DERIVATIVES AND THE USE THEREOF

TECHNICAL FIELD

This invention relates to the novel compounds of formula [1] which are useful in inhibit Tumor necrosis factor-α (TNF-α) or cyclic AMP phosphodiesterase IV (PDE 4). These compounds may be useful in prevention or treatment of arthritis, bronchial asthma, bronchitis, chronic atretic airway, psoriasis, allergic rhinitis, dermatitis, AIDS, Crohn’s disease, septicemia, septic shock, other inflammatory diseases such as cachexia, graft versus host reaction, multiple sclerosis, systemic Lupus Erythematosus, etc. The invention is also directed to the preparation of these compounds, pharmaceutical compositions containing these compounds and methods for their pharmaceutical use.

BACKGROUND ART

TNF-α is a primary cytokine secreted by mononuclear phagocytes stimulated by several immune activators. These factors are known to induce acute infection, shock, inflammation, heat, hemolysis, coagulation and acute reaction in human or animal.

If TNF-α is excessed or not regulated well, many diseases like endotoxemia, toxic shock syndrome [Nature 330, 662-664(1987)] or cachexia [Lancet 335(1990), 662 (1990)] occur. It is predicted that inhibition of TNF-α production and action is a good therapy for inflammatory, infectious, and immune diseases. Inhibition of production and action of TNF-α can be deduced to treat the diseases like septic shock, sepsis, endotoxemia, septic syndrome, malaria mycobacterium infection, encephalomyelitis, psoriasis, cachexia, graft versus host reaction, asthma, cancer, autoimmune disease, rheumatoid arthritis, osteoarthritis, Crohn's disease, multiple sclerosis, systemic Lupus Erythematosus, etc.
Therefore, TNF-α inhibitor is now being studied extensively for therapeutics against the above diseases. Recently, a soluble receptor for TNF-α and an anti-TNF antibody were approved by FDA and demonstrated for the striking potency in human rheumatoid arthritis patients [Science 234. 470-474(1985), WO9211383, Clinical and Experimental Rheumatoid 5173-5175(1993), PNAS 9784-9788(1992), Annals of Rheumatoid Disease 480-486(1990)]. Xanthine compounds like pentoxifylline are known to inhibit TNF-α, but are weak in their potency [Circulatory Shock 44. 188-195 (1994)]. Although rolipram has CNS side effects like nausea and vomiting [Drugs of the Future 28. 793-803(1995)], it provides an active pharmacophore currently being studied as novel derivatives for inhibition of TNF-α [WO9212961, WO9503794, WO9402465, WO9505386, WO9509624, WO9620926].

Disease states associated with pathological conditions which are associated with secondary cellular messengers are modulated by inhibiting enzymes, such as PDE-4, are also treatable according to the invention which PDE 4 is an important enzyme that regulates cyclic AMP levels and in turn thereby regulates other important biological reactions. The ability to regulate PDEs, including PDE 4, therefore, has been implicated as being capable of treating associated biological conditions.

In particular, inhibitors of PDE 4 have been implicated as being bronchodilators, asthma-prophylactic agents, agents for inhibiting eosinophil accumulation, and for treating other diseases and conditions characterized by morbid eosinophil accumulation. Inhibitors of PDE 4 are also implicated in treating inflammatory diseases, proliferative diseases and conditions associated with cerebral metabolic inhibition.

United states patent application publication No. US 5,635,517 discloses that isoindolinone compounds of the formula

\[
\begin{array}{c}
\text{H}_2\text{N} \\
\text{X} \\
\text{Y} \\
\text{Z} \\
\text{O} \\
\end{array}
\]
wherein one of X and Y is C=O and the other of X and Y is C=O or CH₂, exhibit TNF-α-reducing activity. US 5,635,517 does not disclose or suggest compounds wherein the isoindolinone moiety is bonded phenyl moiety.

United states patent application publication No. US 6,020,358 discloses that isoindolinone compounds of the formula

\[
\begin{array}{c}
\text{R₁} \quad \text{R₂} \\
\text{R₃} \quad \text{R₄}
\end{array}
\]

wherein Y is C=O, CH₂, SO₂, or CH₂C=O exhibit TNF-α-reducing activity. US 5,635,517 does not disclose or suggest compounds wherein the isoindolinone moiety is bonded directly 3,4-dialkoxyphenyl moiety.

WO Patent Application No. 98/42666 that is our previous patent discloses that 3,4-dialkoxyphenyl derivatives are inhibitor of TNF-α release, but does not disclose or suggest that the compound inhibits PDE 4 and R₆ is a substituted isoindoilnone ring.

\[
\begin{array}{c}
\text{R₁} \quad \text{R₂} \\
\text{R₃} \quad \text{R₄} \quad \text{X} \quad \text{A=B} \quad \text{R₆}
\end{array}
\]

Therefore, it is expected that compounds with the inhibitory activity against PDE 4 or TNF-α will be pharmaceutically valuable and there is always a need to develop new compounds which inhibit PDE 4 and TNF-α.

The object of the present invention is directed to a compound that inhibits PDE 4 and TNF-α.
DISCLOSURE OF INVENTION

The inventors have studied extensively to settle the problems that the previous PDE 4 or TNF-α inhibitors possess. As a result, the novel 3-cyclopentyloxy-4-methoxyphenyl-isoindolinone derivatives depicted in formula [1] have shown selective and potent PDE 4 and TNF-α inhibitor. We elucidated that they had no side effect like nausea, or vomiting and also had long half-life in vivo. Hence we have achieved this invention.

The first aim of this invention presents the novel compounds with potent PDE 4 and TNF-α inhibition activity represented in formula [1].

The second aim of this invention presents the methods of synthesis of the novel 3-cyclopentyloxy-4-methoxyphenyl-isoindolinone derivatives and their salts in formula [1].

The third aim of this invention presents pharmaceutical compositions of PDE 4 and TNF-α inhibitor containing the novel 3-cyclopentyloxy-4-methoxyphenyl-isoindolinone derivatives and their salts in formula [1] as use of joint inflammation, rheumatoid arthritis, osteoarthritis, sepsis, septic shock, asthma, graft versus host reaction, psoriasis, allergic inflammation, and autoimmune diseases.

This invention provides the compound formula [1] of the novel 3-cyclopentyloxy-4-methoxyphenyl-isoindolinone derivatives and a pharmaceutically acceptable salt thereof.

\[
\text{[1]}
\]

where in
R1 is lower alkyl, cycloalkyl, hydroxycycloalkyl, arylalkyl, cycloalkylalkyl, bicycloalkyl;
R2 is hydrogen, hydroxy, oxo, halogen, lower alkyl, and amino;
R3 is hydrogen, hydroxy, oxo, halogen, lower alkyl, and amino;
R4 is hydrogen, halogen, hydroxy, methylhydroxy, lower alkyl, lower alkoxy, amino, lower alkylamino, cyano, aldehyde, aldehydoxime, -COR5;
R5 is hydroxy, -NHNH₂, lower alkyl;
X is oxygen or carbon, carbonyl, imine, amide;
A, B, C, and D are independently carbon, nitrogen or N-oxide;
or a pharmaceutically acceptable salt thereof.

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

**Definition**

"Halogen" means fluoro, chloro, or bromo. Preferred are fluoro and chloro.

"Lower alkyl" means aliphatic hydrocarbon group having 1 to 6 carbon atoms in the chain such as methyl, ethyl, propyl, butyl, pentyl and hexyl. Preferably, it means straight or branched hydrocarbon having 1 to 4 carbon atoms.

"Lower alkoxy" means alkyl oxy group that may be straight or branched having 1 to 4 carbon atoms in the chain such as methoxy, ethoxy, propoxy and butoxy.

"Cycloalkyl" means non-aromatic mono- or multicyclic ring system having 3 to 8 carbon atoms in the chain such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl and adamantyl. Preferably, it means hydrocarbon having 3 to 6 carbon atoms.

"Arylalkyl" means phenyl alkyl group having 3 to 10 carbon atoms in the chain such as phenylethyl, phenylpropyl, phenylbutyl and phenylpentyl. Preferably, it
means hydrocarbon having 3 to 8 carbon atoms.

"Cycloalkylalkyl" means cycloalkylalkyl group in which cycloalkyl is as previously defined, alkyl is methyl and ethyl. Preferably, cycloalkylalkyl is cyclopropylmethy1, cyclobutylmethyl, cyclopentylmethyl, and cyclopenty1ethyl.

"Bicycloalkyl" means indanyl group such as 1-indanyl and 2-indanyl.

"N-oxide" means a moiety of the following structure

\[
\begin{array}{c}
\text{N} \\
\ominus
\end{array}
\]

According to a compound aspect of the invention, preferred compounds described formula [1] is following:

Wherein

R1 is C1-C4 lower alkyl, C3-C6 cycloalkyl, hydroxy C3-C6 cycloalkyl, aryl C3-C8 alkyl, C3-C6 cycloalkyl C1-C2 alkyl, indanyl;

R2 is hydrogen, hydroxy, oxo, halogen, C1-C2 lower alkyl, and amino;

R3 is hydrogen, hydroxy, oxo, halogen, C1-C2 lower alkyl, and amino;

R4 is hydrogen, halogen, hydroxy, methylhydroxy, C1-C2 lower alkyl, C1-C2 lower alkoxy, amino, C1-C2 lower alkylamino, cyano, aldehyde, aldehydeoxime, -COR5;

R5 is hydroxy, -NHNH2, C1-C2 lower alkyl;

X is oxygen or carbon, carbonyl, imine, amide;

A, B, C, and D are independently carbon, nitrogen or N-oxide;

or a pharmaceutically acceptable salt thereof.

According to a compound aspect of the invention, more preferred compounds described formula [1] is following:

wherein
R1 is C₁-C₂ lower alkyl, C₃-C₆ cycloalkyl, hydroxy C₃-C₆ cycloalkyl, aryl C₃-C₆ alkyl, C₃-C₅ cycloalkyl C₁-C₂ alkyl, 1-indanyl or 2-indanyl;
R2 is hydrogen, hydroxy, oxo, halogen, C₁-C₂ lower alkyl, and amino;
R3 is hydrogen, hydroxy, oxo, halogen, C₁-C₂ lower alkyl, and amino;
R4 is hydrogen, halogen, hydroxy, methylhydroxy, methyl, methoxy, amino, methylamino, cyano, aldehyde, aldehydioxide, -COR₅;
R5 is hydroxy, -NHNH₂, C₁-C₂ lower alkyl;
X is oxygen or carbon, carbonyl, imine, amide;
A, B, C, and D are independently carbon, nitrogen or N-oxide;
or a pharmaceutically acceptable salt thereof.

Preferred compounds for use according to the invention are selected from the following:

2-(3-Cyclopentxyloxy-4-methoxyphenyl)-6-(1-oxo-2,3-dihydro-1H-2-
isoindolylmethyl)-1-isooindolinone
2-(3-Cyclopentxyloxy-4-methoxyphenyl)-6-(6-hydroxy-1-oxo-2,3-dihydro-
1H-2-isooindolylmethyl)-1-isooindolinone
6-[(6-Amino-1-oxo-2,3-dihydro-1H-2-isooindolyl)methyl]-2-[3-
(cyclopentxyloxy)-4-methoxyphenyl]-1-isooindolinone
2-[3-Cyclopentxyloxy-4-methoxyphenyl]-6-[(6-fluoro-1-oxo-2,3-dihydro-1H-
2-isooindolyl)methyl]-1-isooindolinone
2-(2-[3-(Cyclopentxyloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-
isooindolylmethyl)-3-oxo-5-isooindolinecarboxylic acid
2-(2-[3-(Cyclopentxyloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-
isooindolylmethyl)-3-oxo-5-isooindolinecarboximidamide
N₁-[2-(2-[3-(Cyclopentxyloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-
isooindolylmethyl)-3-oxo-2,3-dihydro-1H-5-isooindolyl]acetamide
N₁-[2-(2-[3-(Cyclopentxyloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-
isooindolylmethyl)-3-oxo-2,3-dihydro-1H-5-isooindolyl]ethanediamide
N1-[2-([3-(Cyclopentyloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-
isindolyl)methyl]-3-oxo-2,3-dihydro-1H-5-isindolyl]-2-aminoacetamide
2-[2-([3-(Cyclopentyloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-
isindolyl)methyl]-3-oxo-2,3-dihydro-1H-5-isindolyl]aminoacetamide
2-([3-(Cyclopentyloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-
isindolyl)methyl]-3-oxo-5-isoxindolinecarboxyhydrazide
2-([3-(Cyclopentyloxy)-4-methoxyphenyl]-6-[(6-hydroxymethyl)-1-oxo-2,3-
dihydro-1H-2-isoxindolyl]methyl)-1-isoxindolinone

2-([4-Methoxyphenyl]-3-(1-methyl-3-phenylpropoxy)phenyl]-6-(1-oxo-2,3-
dihydro-1H-2-isoxindolyl)methyl]-1-isoxindolinone
6-([6-Hydroxymethyl]-1-oxo-2,3-dihydro-1H-2-isoxindolyl)methyl]-2-([4-
methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-isoxindolinone
6-([6-Amino-1-oxo-2,3-dihydro-1H-2-isoxindolyl)methyl]-2-([4-
methoxyphenyl]-3-(1-methyl-3-phenylpropoxy)phenyl]-1-isoxindolinone
6-([6-Fluoro-1-oxo-2,3-dihydro-1H-2-isoxindolyl)methyl]-2-([4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-isoxindolinone
2-([2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-
dihydro-1H-5-isoxindolyl)methyl]-3-oxo-5-isoxindolinecarboxylic acid
2-([2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-
dihydro-1H-5-isoxindolyl)methyl]-3-oxo-5-isoxindolinecarboximidamide
N1-([2-([2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-
dihydro-1H-5-isoxindolyl)methyl]-3-oxo-2,3-dihydro-1H-5-isoxindolyl]acetamide
N1-([2-([2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-
dihydro-1H-5-isoxindolyl)methyl]-3-oxo-2,3-dihydro-1H-5-isoxindolyl]ethanediamide
N1-([2-([2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-
dihydro-1H-5-isoxindolyl)methyl]-3-oxo-2,3-dihydro-1H-5-isoxindolyl]2-
aminoacetamide
2-([2-([2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-
dihydro-1H-5-isoxindolyl)methyl]-3-oxo-2,3-dihydro-1H-5-
isoindolylaminoacetamide

2-\{(2-[4-Methoxy-3-\{1-methyl-3-phenylpropoxy\}phenyl]-3-oxo-2,3-dihydro-1H-5-isoindolyl]methyl\}-3-oxo-5-isoindolinecarboxyhydrazide

6-\{6-\{Hydroxymethyl\}-1-oxo-2,3-dihydro-1H-2-isoindolyl\}methyl\}-2-[4-methoxy-3-\{1-methyl-3-phenylpropoxy\}phenyl]-1-isoindolinone

2-(3-Cyclopentloxy-4-methoxyphenyl]-3-methyl-6-(1-oxo-2,3-dihydro-1H-2-isoindolylmethyl]-1-isoindolinone

2-(3-Cyclopentloxy-4-methoxyphenyl]-6-(6-hydroxy-1-oxo-2,3-dihydro-1H-2-isoindolylmethyl]-3-methyl-1-isoindolinone

6-\{6-Amino-1-oxo-2,3-dihydro-1H-2-isoindolyl\}methyl\}-2-[3-(cyclopentloxy)-4-methoxyphenyl]-3-methyl-1-isoindolinone

2-[3-Cyclopentloxy-4-methoxyphenyl]-3-methyl-oxo-2,3-dihydro-1H-2-isoindolylmethyl]-3-methyl-1-isoindolinone

2-\{(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolyl]methyl\}-3-oxo-5-isoindolinecarboxylic acid

2-\{(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl\}-3-oxo-5-isoindolinecarboximidamide

N1-[2-\{(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolyl]methyl\}-3-oxo-2,3-dihydro-1H-5-isoindolyl]acetamide

N1-[2-\{(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolyl]methyl\}-3-oxo-2,3-dihydro-1H-5-isoindolyl]ethanediamide

N1-[2-\{(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolyl]methyl\}-3-oxo-2,3-dihydro-1H-5-isoindolyl]2-aminoacetamide

2-\{(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolyl]methyl\}-3-oxo-2,3-dihydro-1H-5-isoindolylamino\}acetamide

2-\{(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolyl]methyl\}-3-oxo-5-isoindolinecarboxyhydrazide
2-[[3-(Cyclopentyloxy)-4-methoxyphenyl]-6-[[6-(hydroxymethyl)-1-oxo-2,3-dihydro-1H-2-isooindolyl]methyl]-3-methyl-1-isooindolone

2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-methyl-6-[(1-oxo-2,3-dihydro-1H-2-isooindolyl)methyl]-1-isooindolone

6-[(6-Hydroxy-1-oxo-2,3-dihydro-1H-2-isooindolyl)methyl]-2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-methyl-1-isooindolone

6-[(6-Amino-1-oxo-2,3-dihydro-1H-2-isooindolyl)methyl]-2-[4-methoxy-3-phenylpropoxy]phenyl]-3-methyl-1-isooindolone

6-[(6-Fluoro-1-oxo-2,3-dihydro-1H-2-isooindolyl)methyl]-2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-methyl-1-isooindolone

2-((2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isooindolyl)methyl)-3-oxo-5-isooindolinecarboxylic acid

2-((2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isooindolyl)methyl)-3-oxo-5-isooindolinecarboximidamide

N1-[[2-((2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isooindolyl)methyl]-3-oxo-2,3-dihydro-1H-5-isooindolyl]acetamide

N1-[[2-((2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isooindolyl)methyl]-3-oxo-2,3-dihydro-1H-5-isooindolyl]ethanediamide

N1-[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isooindolyl)methyl]-3-oxo-2,3-dihydro-1H-5-isooindolyl]aminoacetamide

2-[[2-((2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isooindolyl)methyl]-3-oxo-2,3-dihydro-1H-5-isooindolyl]amino] acetamide

2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isooindolyl)methyl]-3-oxo-5-isooindolinecarboxyhydrazide

6-[(6-(Hydroxymethyl)-1-oxo-2,3-dihydro-1H-2-isooindolyl)methyl]-2-[4-
methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-methyl-1-isooindolinone

2-[2-(3-Cyclopentylxoy-4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl]-1,3-isooindolinedione

5-Amino-2-((2-[3-(Cyclopentylxoy-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl)-5-hydroxy-1,3-isooindolinedione

2-((2-[3-(Cyclopentylxoy-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl)-5-fluoro-1,3-isooindolinedione

2-((2-[3-(Cyclopentylxoy-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl]-1,3-dioxo-5-isooindolinecarboxylic acid

2-((2-[3-(Cyclopentylxoy-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl]-1,3-dioxo-5-isooindolinecarboximidamide

\[N1\]-\[2-(2-[3-(Cyclopentylxoy-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl]-1,3-dioxo-2,3-dihydro-1H-5-isooindolyacetic acid

\[N1\]-\[((2-[3-(Cyclopentylxoy-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl]-1,3-dioxo-2,3-dihydro-1H-5-isooindolylethanediamide

\[N1\]-\[2-(2-[3-(Cyclopentylxoy-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl]-1,3-dioxo-2,3-dihydro-1H-5-isooindolyacetamide

2-((2-(2-[3-(Cyclopentylxoy-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl]-1,3-dioxo-2,3-dihydro-1H-5-isooindolylamino)acetamide

2-((2-[3-(Cyclopentylxoy-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl]-1,3-dioxo-5-isooindolinecarboxyhydrizide

2-((2-[3-(Cyclopentylxoy-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl)-5-(hydroxymethyl)-1,3-isooindolinedione

2-((2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl]-1,3-isooindolinedione

5-Hydroxy-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-
2,3-dihydro-1H-5-isooindolylmethyl)-1,3-isooindolinedione

5-Amino-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl)-1,3-isooindolinedione

5-Fluoro-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl)-1,3-isooindolinedione

2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl)-1,3-dioxo-5-isooindolinecarboxylic acid

2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl)-1,3-dioxo-5-isooindolinecarboximidamide

N1-[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-5-isooindolyl]acetamide

N1-[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-5-isooindolyl]ethanediame

2-[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-5-isooindolyl]aminocacetamide

2-[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl)-1,3-dioxo-5-isooindolinecarboxyhydrazide

5-(Hydroxymethyl)-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl)-1,3-isooindolinedione

2-(2-[3-(Cyclopentylxyloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl)-1,3-isooindolinedione

2-(2-[3-(Cyclopentylxyloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl)-5-hydroxy-1,3-isooindolinedione

5-Amino-2-(2-[3-(cyclopentylxyloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-
dihydro-1H-5-isoindolylmethyl)-1,3-isoindolinedione
2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-
1H-5-isoindolylmethyl)-5-fluoro-1,3-isoindolinedione
2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-
1H-5-isoindolylmethyl)-1,3-dioxo-5-isoindolinecarboxylic acid
2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-
1H-5-isoindolylmethyl)-1,3-dioxo-5-isoindolinecarboximidamide
N1-[2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-
dihydro-1H-5-isoindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-5-isoindolyl]acetamide
N1-[2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-
dihydro-1H-5-isoindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-5-isoindolyl]ethanedi amide
N1-[2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-
dihydro-1H-5-isoindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-5-isoindolyl]2-
aminoacetamide
2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-
dihydro-1H-5-isoindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-5-
isoindolylaminoacetamide
2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-
1H-5-isoindolylmethyl)-1,3-dioxo-5-isoindolinecarbohydrazide
2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-
1H-5-isoindolylmethyl)-5-(hydroxymethyl)-1,3-isoindolinedione
2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-
2,3-dihydro-1H-5-isoindolylmethyl)-1,3-isoindolinedione
5-Hydroxy-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-
methyl-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-1,3-isoindolinedione
5-Amino-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-
3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-1,3-isoindolinedione
5-Fluoro-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-
3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-1,3-isoindolinedione

2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-1,3-dioxo-5-isoindolinecarboxylic acid

2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-1,3-dioxo-5-isoindolinecarboximidamide

N1-[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-5-isoindolyl]acetamide

N1-[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-5-isoindolyl]ethanediamide

N1-[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-5-isoindolyl]aminoacetamide

5-(1-Hydrazinovinyl)-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-1,3-isoindolinedione

5-(Hydroxymethyl)-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-1,3-isoindolinedione

2-(2-[3-(Cyclopentoxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

2-(2-[3-(Cyclopentoxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-6-hydroxy-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

6-Amino-2-(2-[3-(cyclopentoxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

2-(2-[3-(Cyclopentoxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
isoindolylmethyl)-6-fluoro-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-3-oxo,2,3-dihydro-1H-5-isoindolylmethyl)-1-oxo,2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carboxylic acid
2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-3-oxo,2,3-dihydro-1H-5-isoindolylmethyl)-1-oxo,2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]acetamide
N1-[2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-3-oxo,2,3-dihydro-1H-5-isoindolylmethyl)-1-oxo,2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]ethanediame
N1-[2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-3-oxo,2,3-dihydro-1H-5-
isoindolylmethyl)-1-oxo,2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]-2-
aminoacetamide
2-[2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-3-oxo,2,3-dihydro-1H-5-
isoindolylmethyl)-1-oxo,2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]aminoacetamide
2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-3-oxo,2,3-dihydro-1H-5-
isoindolylmethyl)-1-oxo,2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carboxylic acid
2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-3-oxo,2,3-dihydro-1H-5-
isoindolylmethyl)-6-(hydroxymethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxo)phenyl]-3-oxo,2,3-dihydro-1H-5-isoindolylmethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
6-Hydroxy-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxo)phenyl]-3-oxo,2,3-dihydro-1H-5-isoindolylmethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
6-Amino-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxo)phenyl]-3-oxo,2,3-
dihydro-1H-5-isoindolylmethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
6-Fluoro-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxo)phenyl]-3-oxo,2,3-
dihydro-1H-5-isoindolylmethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxo)phenyl]-3-oxo,2,3-dihydro-1H-5-isoindolylmethyl)-1-oxo,2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carboxylic acid
2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-
1H-5-isindolylmethyl)-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-
carboximidamide

N1-[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-
dihydro-1H-5-isindolylmethyl)-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-
yl]acetamide

N1-[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-
dihydro-1H-5-isindolylmethyl)-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-
yl]ethanediamide

N1-[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-
dihydro-1H-5-isindolylmethyl)-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-
yl]2-aminoacetamide

2-[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-
dihydro-1H-5-isindolylmethyl)-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-
yl]aminoacetamide

2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-
1H-5-isindolylmethyl)-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-
carboxhydrazide

6-(Hydroxymethyl)-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-
3-oxo-2,3-dihydro-1H-5-isindolylmethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-
one

2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-
1H-5-isindolylmethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-
1H-5-isindolylmethyl)-6-hydroxy-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

6-Amino-2-(2-[3-(cyclopentloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-
dihydro-1H-5-isindolylmethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-
1H-5-isindolylmethyl)-6-fluoro-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
2-(2-[3-(Cyclopentyoxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carboxylic acid

2-(2-[3-(Cyclopentyoxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoiindolylmethyl)-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carboximidamide

N1-[2-(2-[3-(Cyclopentyoxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoiindolylmethyl)-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]acetamide

N1-[2-(2-[3-(Cyclopentyoxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoiindolylmethyl)-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]ethanediamide

N1-[2-(2-[3-(Cyclopentyoxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoiindolylmethyl)-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]2-aminoacetamide

2-[2-(2-[3-(Cyclopentyoxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoiindolylmethyl)-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]aminoacetamide

2-(2-[3-(Cyclopentyoxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoiindolylmethyl)-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carboxyrazide

2-(2-[3-(Cyclopentyoxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoiindolylmethyl)-6-(hydroxymethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoiindolylmethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

6-Hydroxy-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoiindolylmethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
6-Amino-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isopinocampheyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

6-Fluoro-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isopinocampheyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isopinocampheyl)-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carboxylic acid

2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isopinocampheyl)-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carboximidamide

N1-[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isopinocampheyl)-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]acetamide

N1-[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isopinocampheyl)-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]ethanedisamide

N1-[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isopinocampheyl)-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]-2-aminoacetamide

2-[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isopinocampheyl)-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]aminoacetamide

2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isopinocampheyl)-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carbohydrazide

6-(Hydroxymethyl)-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isopinocampheyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1\(H\)-5-isoinidolylmethyl)-2,3-dihydro-1\(H\)-pyrrolo[3,4-c]pyridine-1,3-dione

2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1\(H\)-5-isoinidolylmethyl)-6-hydroxy-2,3-dihydro-1\(H\)-pyrrolo[3,4-c]pyridine-1,3-dione

6-Amino-2-(2-[3-(cyclopentloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1\(H\)-5-isoinidolylmethyl)-2,3-dihydro-1\(H\)-pyrrolo[3,4-c]pyridine-1,3-dione

2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1\(H\)-5-isoinidolylmethyl)-6-fluoro-2,3-dihydro-1\(H\)-pyrrolo[3,4-c]pyridine-1,3-dione

2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1\(H\)-5-isoinidolylmethyl)-1,3-dioxo-2,3-dihydro-1\(H\)-pyrrolo[3,4-c]pyridine-6-carboxylic acid

2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1\(H\)-5-isoinidolylmethyl)-1,3-dioxo-2,3-dihydro-1\(H\)-pyrrolo[3,4-c]pyridine-6-carboximidamide

\(\text{N1}[-2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1\(H\)-5-isoinidolylmethyl)-1,3-dioxo-2,3-dihydro-1\(H\)-pyrrolo[3,4-c]pyridin-6-yl]ethanediamide\)

\(\text{N1}[-2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1\(H\)-5-isoinidolylmethyl)-1,3-dioxo-2,3-dihydro-1\(H\)-pyrrolo[3,4-c]pyridin-6-yl]aminoacetamide\)

2-[2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1\(H\)-5-isoinidolylmethyl)-1,3-dioxo-2,3-dihydro-1\(H\)-pyrrolo[3,4-c]pyridin-6-yl]aminoacetamide

2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1\(H\)-5-isoinidolylmethyl)-1,3-dioxo-2,3-dihydro-1\(H\)-pyrrolo[3,4-c]pyridine-6-carbohydrazide

2-(2-[3-(Cyclopentloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1\(H\)-5-
isoindolylmethyl)-6-(hydroxymethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-1,3-dione

2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-1,3-dione

6-Hydroxy-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-1,3-dione

6-Amino-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-1,3-dione

6-Fluoro-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-1,3-dione

2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carboxylic acid

2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carboximidamide

N1-[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]acetamide

N1-[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]ethanediamide

N1-[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]-2-aminoacetamide

2-[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]aminoacetamide
2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carbohydrazide
6-(Hydroxymethyl)-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-1,3-dione

2-(2-[3-Cycloptentlyloxy]-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-1,3-dione

2-(2-[3-(Cycloptentlyloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-6-hydroxy-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-1,3-dione
6-Amino-2-(2-[3-(cycloptentlyloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-1,3-dione
2-(2-[3-(Cycloptentlyloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-6-fluoro-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-1,3-dione
2-(2-[3-(Cycloptentlyloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carboxylic acid

2-(2-[3-(Cycloptentlyloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carboximidamide

N1-[2-(2-[3-(Cycloptentlyloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]acetamide
N1-[2-(2-[3-(Cycloptentlyloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]ethanediamide
N1-[2-(2-[3-(Cycloptentlyloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]-2-aminoacetamide
2-[2-(3-(Cyclopentylxoy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5 isoindolylmethyl]-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carboxylic acid

2-(2-[3-(Cyclopentylxoy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5 isoindolylmethyl]-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carboxylic acid

2-(2-[3-(Cyclopentylxoy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5 isoindolylmethyl]-6-(hydroxymethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-1,3-dione

2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5 isoindolylmethyl]-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-1,3-dione

6-Hydroxy-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5 isoindolylmethyl]-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-1,3-dione

6-Amino-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5 isoindolylmethyl]-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-1,3-dione

6-Fluoro-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5 isoindolylmethyl]-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-1,3-dione

2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5 isoindolylmethyl]-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carboxylic acid

2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5 isoindolylmethyl]-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carboximidamide

N1-[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5 isoindolylmethyl]-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carboximidamide
\[ \text{N1-[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]ethanamide} \]

\[ \text{N1-[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]-2-aminoacetamide} \]

\[ 2-[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]aminoacetamide \]

\[ 2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carboxyrazide \]

\[ 6-(Hydroxymethyl)-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-1,3-dione \]

\[ 2-[3-( Cyclopentoyloxy)-4-methoxyphenyl]-6-[(1-oxo-2,3-dihydro-1H-2-isooindolyl)carbonyl]-1-isooindolinone \]

\[ 2-(2-[3-( Cyclopentoyloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylcarbonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one \]

\[ 2-(2-[3-( Cyclopentoyloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylcarbonyl)-3-hydroxy-1-isooindolinone \]

\[ 2-(2-[3-( Cyclopentoyloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylcarbonyl)-3-hydroxy-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one \]

\[ 2-(2-[3-( Cyclopentoyloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylcarbonyl)-1,3-isooindolinedione \]

\[ 2-(2-[3-( Cyclopentoyloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylcarbonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-1,3-dione \]

\[ 2-[3-( Cyclopentoyloxy)-4-methoxyphenyl]-3-methyl-6-[(1-oxo-2,3-dihydro-}
$1H$-2-isoindolyl carbonyl]-1-isoindolinone
\[2-(2-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolyl carbonyl]-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one\]
\[2-[3-(Cyclopentyloxy)-4-methoxyphenyl]-6-[(1-hydroxy-3-oxo-2,3-dihydro-1H-2-isoindolyl carbonyl]-3-methyl-1-isoindolinone\]
\[2-(2-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolyl carbonyl]-3-hydroxy-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one\]
\[2-(2-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolyl carbonyl]-1,3-isoindolinedione\]
\[2-(2-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolyl carbonyl]-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-1,3-dione\]
\[2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-6-[(1-oxo-2,3-dihydro-1H-2-isoindolyl carbonyl]-1-isoindolinone\]
\[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isoindolyl carbonyl]-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one\]
\[3-Hydroxy-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isoindolyl carbonyl]-1-isoindolinone\]
\[3-Hydroxy-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isoindolyl carbonyl]-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one\]
\[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isoindolyl carbonyl]-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-1,3-dione\]
\[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-oxo-2,3-dihydro-1H-5-isoindolyl carbonyl]-1,3-isoindolinedione\]
\[2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-methyl-6-[(1-oxo-2,3-dihydro-1H-2-isoindolyl carbonyl]-1-isoindolinone\]
\[2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolyl carbonyl]-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one\]
\[6-[(1-Hydroxy-3-oxo-2,3-dihydro-1H-2-isoindolyl carbonyl]-2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-methyl-1-isoindolinone\]

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3-Hydroxy-2-(2-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolylcarbonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
2-(2-[4-Methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-5-isoindolylcarbonyl)-1,3-isoindolinedione
5

The compounds of the present invention are useful in the form of the acid, or N-oxide thereof or in the form of a pharmaceutically acceptable salt thereof. All forms are within the scope of the invention. Pharmaceutically acceptable salts within the scope of the invention are those derived from the following acids; mineral acids such as hydrochloric acid, sulfuric acid, phosphoric acid and sulfamic acid; organic acids such as acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid and p-toluenesulfonic acid, cyclohexylsulfamic acid, quinic acid, and the like.

This invention relates to the synthesis and preparation method of the novel 3-cyclopentloyloxy-4-methoxyphenyl-isoindolinone derivatives. According to this invention, the compound of formula [3] is prepared by reaction of formula [4] synthesized by WO Patent Application No. 98/42666 with [5] or [6]. Then the compound of formula [3] is reduced to afford the compound of formula [2]. The compound of formula [2] is dehydroxylated to produce the compound of formula [1], in which R3 is hydrogen, and one of C and D is nitrogen. By this way, the 3-cyclopentloyloxy-4-methoxyphenyl-isoindolinone derivatives can be prepared.
Wherein,

A, B, C, D, X, R1, R2, R3, R4, and R5 are as defined above.

The preparation for the compound of formula [1] in this invention can be described in the following reaction scheme 1.

[Scheme 1]
Wherein,

A, B, C, D, X, R1, R2, R3, R4, and R5 are as defined above.

In the following, the preparation of 3-cyclopentyloxy-4-methoxyphenyl-
isoindolinone derivatives of formula [1] is described in detail.

According to the prior WO Patent Application No. 98/42666, the compound
of formula [4] is prepared by reaction of 1-amino-3,4-dialkoxyphenyl derivatives
with isobenzofuran-1,3-dione derivatives or phthaloyl dichloride derivatives. The
reaction product, that is 2-(3,4-dimethoxy-phenyl)-isoindole-1,3-dione derivatives, a)
is reacted with Grignard reagent to produce 2-(3,4-dimethoxy-phenyl)-3-hydroxy-3-
methyl-2,3-dihydro-isoindol-1-one derivatives, or b) is reduced to give N-(3,4-
dimethoxy-phenyl)-2-hydroxymethyl-benzamide derivatives by using sodium
borohydride. Two types of the reduced product are obtained depending on the
amount of reducing reagents. This compound is cyclized by intramolecular
Mitsunobu reaction or dehydroxylated by using triethylsilane and trifluoroacetic acid.

The newly synthesized compound of formula [1] is prepared by the similar
procedure with the above-depicted method. In detail, the compound of formula [3] is
or [5] in the reaction A in different way. In case of amine compound, the reaction of
formula [4] with [6] is accomplished by refluxing with the acidic catalyst in
unreactive solvent. For this purpose either inorganic catalyst or organic catalyst is
used. The inorganic catalyst is hydrochloric acid, sulfuric acid, or nitric acid, and
organic catalyst is acetic acid or trifluoroacetic acid. Acetic acid is most preferably
used among these catalysts. Unreactive solvent such as chloroform, dichloromethane,
acetonitrile, tetrahydrofuran, benzene and toluene can desirably be used and
chloroform is most preferable among these solvents. The reaction is performed at the
temperature ranging 60-70°C for 4-48 hours. In another case, the hydroxy compound
more detail, compound of formula [4] is reacted with triphenylphosphine and
diethylazodicarboxylate in dichloromethane solvent. This reaction is generally
performed at the temperature between 0 and 100 °C, preferably at room temperature (rt) for 1-2h.

The compound of formula [3] is reduced to give compounds of formula [2] by using reaction B. The reducing agents used preferably in reaction B are sodium borohydride, lithium borohydride, or lithium aluminum hydride, and sodium borohydride is most preferable among these. Compound of formula [2] is obtained on using one equivalents of reducing reagent with one equivalent of compound of formula [3]. The reaction B is performed preferably in the alcohol solvent. The alcohol solvent such as methanol, ethanol, propanol, butanol, isopropyl alcohol can be desirable and ethanol, methanol is most preferable. In the reaction B, the compound of formula [2] is prepared at between -10-0 °C for 1-2h.

The Compound of formula [2] obtained from reaction B is dehydroxylated by the following reaction C to produce compound of formula [1], in which R3 is hydrogen and one or two of A, B, C and D is nitrogen. Using triethylsilane and trifluoroacetic acid can do dehydroxilation of reaction C in dichlorometane solvent at rt for 1-2h.

The 3-cyclopentyloxy-4-methoxyphenyl-isoindolinone compounds of formula [1] prepared from the above method can be separated and purified by general method such as column chromatography, or recrystallization.

The novel 3-cyclopentyloxy-4-methoxyphenyl-isoindolinone compounds of formula [1] in this invention can inhibit the action of detrimental excess of TNF-α and hence can prevent and treat various diseases such as joint inflammation, rheumatoid arthritis, osteoarthritis, sepsis, septic shock, asthma, graft versus host reaction, psoriasis, allergic inflammation and autoimmune disease. The representative compounds of this invention such as compound 12, 13 and 16 in Table 1 showed the oral median lethal dose of more than 3.5g per Kg of body weight in Table 4 which suggests that these compounds are acceptably non-toxic for pharmaceutical use. Therefore, in order to use compounds of formula [1] or pharmaceutically acceptable salt thereof for therapeutic purposes, it will normally be formulated into a pharmaceutical composition in accordance with standard
pharmaceutical practice. This invention, therefore, also relates to a pharmaceutical composition comprising an effective, non-toxic amount of a compound of formula [1] and a pharmaceutically acceptable carrier or diluent.

The composition in this invention can be mixed in general pharmaceutical method with pharmaceutically acceptable carrier to give variety of useful pharmaceutical formulations for oral administration such as tablet, capsule, granules, powders, aqueous solutions or suspensions; for injection such as injectable solutions, suspended solutions; for local administration such as suppositories, ointments, creams, gel, spray and patches.

The products according to the invention may be presented in forms permitting administration by the most suitable route and the invention also relates to pharmaceutical compositions containing at least one product according to the invention which are suitable for use in human or veterinary medicine. These compositions may be prepared according to the customary methods, using one or more pharmaceutically acceptable adjuvants or excipients. The adjuvants comprise, inter alia, diluents, sterile aqueous media and the various non-toxic organic solvents. The compositions may be presented in the form of tablets, pills, granules, powders, aqueous solutions or suspensions, injectable solutions, elixirs or syrups, and can contain one or more agents chosen from the group comprising sweeteners, flavorings, colorings, or stabilizers in order to obtain pharmaceutically acceptable preparations.

The choice of vehicle and the content of active substance in the vehicle are generally determined in accordance with the solubility and chemical properties of the product, the particular mode of administration and the provisions to be observed in pharmaceutical practice. For example, excipients such as lactose, sodium citrate, calcium carbonate, dicalcium phosphate and disintegrating agents such as starch, alginic acids and certain complex silicates combined with lubricants such as magnesium stearate, sodium lauryl sulfate and talc may be used for preparing tablets.

To prepare a capsule, it is advantageous to use lactose and high molecular weight polyethylene glycols. When aqueous suspensions are used they can contain emulsifying agents or agents which facilitate suspension. Diluents such as sucrose,
ethanol, polyethylene glycol, propylene glycol, glycerol and chloroform or mixtures thereof may also be used. For parenteral administration, emulsions, suspensions or solutions of the products according to the invention in vegetable oil, for example sesame oil, groundnut oil or olive oil, or aqueous-organic solutions such as water and propylene glycol, injectable organic esters such as ethyl oleate, as well as steril aqueous solutions of the pharmaceutically acceptable salts, are used. The solutions of the salts of the products according to the invention are especially useful for administration by intramuscular or subcutaneous injection. The aqueous solution, also comprising solutions of the salts in pure distilled water, may be used for intravenous administration with the proviso that their pH is suitably adjusted, that they are judiciously buffered and rendered isotonic with a sufficient quantity of glucose or sodium chloride and that they are sterilized by heating, irradiation or microfiltration. Suitable compositions containing the compounds of the invention may be prepared by conventional means. For example, compounds of the invention may be dissolved or suspended in a suitable carrier for use in a nebulizer or a suspension or solution aerosol, or may be absorbed or adsorbed onto a suitable solid carrier for use in a dry powder inhaler. Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one compound of formula [1]. The dose employed will be determined by the physician, and depends upon the desired therapeutic effect, the route of administration and the duration of the treatment, and the condition of the patient. In the adult, the doses are generally from 0.001 to 50, preferably 0.001 to 5mg/kg body weight per day by inhalation, from 0.01 to 100, preferably 0.1 to 70, more especially 0.5 to 10mg/kg body weight per day by oral administration, and from 0.001 to 10, preferably 0.01 to 1mg/kg body weight per day by intravenous administration. In each particular case, the doses will be determined in accordance with the factors distinctive to the subjects to be treated, such as age, weight, general state of health and other characteristics that can influence the efficacy of the medicinal product. The products according to the invention may be administered as frequency as necessary in order to obtain the desired therapeutic effect. It may be necessary to have long-
term treatments at the rate of 1 to 4 doses per day, in accordance with the physiological requirements of each particular patient. Generally, the active product may be administered orally 1 to 4 times per day.

The following examples represent this invention and this invention is not limited in only these examples.

EXAMPLES

Reference Example 1

3-Cyclopentyloxy-4-methoxynitrobenzene

To a solution of 2-methoxy-5-nitrophenol (3.0g, 17.74mmol) in DMF (30ml) were added cyclopentyl bromide (4.0g, 26.61 mmol) and potassium carbonate (5g, 35.48mmol). The reaction mixture was stirred at 60°C for 15h, cooled to rt, treated with distilled water (20ml), and extracted twice with ether. The ether layer was dried over MgSO₄, filtered, and concentrated in vacuo to give the title compound (4g, 95%) as a pale yellow solid.

^1H-NMR(CDCl₃, ppm) : δ 1.65-1.68(m, 2H), 1.86-2.02(m, 6H), 3.95(s, 3H), 4.87(m, 1H), 6.9(d, J=8.9Hz, 1H), 7.74(d, J=2.6Hz, 1H), 7.87-7.91(dd, J=2.6, 8.9 Hz, 1H).

Reference Example 2

3-Cyclopentyloxy-4-methoxyaniline

To a solution of 3-cyclopentyloxy-4-methoxynitrobenzene (4.2g, 17.73mmol) in methanol (30ml) were added ammonium formate (3.5g, 53.21 mmol) and 10% Pd-C (0.3g). The reaction mixture was refluxed for 2h, cooled to rt, filtered through Celite, and evaporated in vacuo to remove solvent. The residue was dissolved in ether, washed twice with distilled water, dried over MgSO₄, filtered, and
concentrated *in vacuo* to give the title compound (3g, 81%) as pale brown liquid.

\[ ^1H-NMR(CDCl_3, \text{ ppm}) : \delta 1.60-1.63(m, 2H), 1.85-1.95(m, 6H), 3.05(bs, 2H), 3.78(s, 3H), 4.73(m, 1H), 6.24(dd, J=2.6, 8.4Hz, 1H), 6.33(d, J=2.6Hz, 1H), 6.73(d, J=8.4Hz, 1H). \]

**Reference Example 3**

**N-(3-Cyclopentyloxy-4-methoxyphenyl)isoindolin-1,3-dione**

To a solution of 3-cyclopentyloxy-4-methoxyaniline (0.52g, 2.42mmol) in chloroform (10ml) was added phthalic anhydride (0.36g, 2.43mmol). The reaction mixture was stirred for 0.5h at rt, treated with acetic acid (10ml), refluxed for 4h, cooled to rt, and then concentrated *in vacuo* to remove chloroform and acetic acid. The residue was crystallized from methanol to afford the title compound (0.75g, 91%) as a white solid.

\[ ^1H-NMR(CDCl_3, \text{ ppm}) : \delta 1.60-1.64(m, 2H), 1.82-1.96(m, 6H), 3.90(s, 3H), 4.78(m, 1H), 6.96-7.00(m, 3H), 7.77-7.80(m, 2H), 7.93-7.96(m, 2H). \]

**Reference Example 4**

**3-Methyl-3-hydroxy-2-(3-cyclopentyloxy-4-methoxyphenyl)isoindolin-1-one**

To a solution of 2-(3-cyclopentyloxy-4-methoxyphenyl)isoindolin-1,3-dione (0.5g, 1.48mmol) in anhydrous THF (10ml) was slowly added 3.0M methylmagnesium bromide (0.2ml, 4.44mmol) at 0°C. The reaction mixture was warmed to rt, stirred for 20 minutes, quenched with saturated ammonium chloride solution, and diluted with ethyl acetate. The organic layer was washed with distilled water, dried over MgSO₄, filtered, and concentrated *in vacuo*. To the residue was added ether, stirred at rt, and filtered to give the title compound (0.35g, 67%) as a white solid.

\[ ^1H-NMR(CDCl_3, \text{ ppm}) : \delta 1.15-1.91(m, 8H), 1.56(s, 3H), 3.86(s, 3H), \]
4.43(s, 1H), 4.58(m, 1H), 6.75(d, J=8.7Hz, 1H), 6.90(dd, J=8.7, 2.4Hz, 1H), 6.99(d, J=2.4Hz, 1H), 7.28-7.56(m, 4H).

Reference Example 5

3-Methyl-2-(3-cyclopentloxy-4-methoxyphenyl)isoindolin-1-one

To a solution of 3-methyl-3-hydroxy-2-(3-cyclopentloxy-4-methoxyphenyl)isoindolin-1-one (0.52g, 1.48mmol) in dichloromethane (10ml) were added triethylsilane (1.29ml, 1.78mmol) and trifluoroacetic acid (0.14ml, 1.78mmol). The reaction mixture was stirred for 4h at rt, evaporated in vacuo, and then diluted with ethyl acetate. The organic layer was washed with distilled water, dried over MgSO₄, filtered, and concentrated in vacuo to give the title compound (0.46g, 92%) as a white solid.

¹H-NMR(CDCl₃, ppm) : δ 1.49(d, J=6.3Hz, 3H), 1.64-2.05(m, 8H), 3.92(s, 3H), 4.87(m, 1H), 5.15(q, J=6.3Hz, 1H), 6.97(s, 2H), 7.34(s, 1H), 7.56-7.62(m, 3H), 7.96(d, J=7.5Hz, 1H).

Reference Example 6

3-Hydroxy-2-(3-cyclopentloxy-4-methoxyphenyl)isoindolin-1-one

To a solution of 2-(3-cyclopentloxy-4-methoxyphenyl)isoindolin-1,3-dione (0.5g, 1.48mmol) in methanol (10ml) was added sodium borohydride (0.06g, 1.48mmol) at 0°C. The reaction mixture was treated with ice-water, extracted with ethyl acetate, dried over MgSO₄, filtered, and concentrated in vacuo to give the title compound (0.48g, 96%) as a white solid.

¹H-NMR(CDCl₃, ppm) : δ 1.60-2.00(m, 8H), 3.84(s, 3H), 4.76(m, 1H), 6.30(s, 1H), 6.87(d, J=8.5Hz, 1H), 7.43(d, J=2.1Hz, 1H), 7.50-7.80(m, 4H).

Reference Example 7

2-(3-Cyclopentloxy-4-methoxyphenyl)-2,3-dihydro-isoindolin-1-one
To a solution of 3-hydroxy-2-(3-cyclopentoxy-4-methoxyphenyl)-isoindolin-1-one (0.5g, 1.47mmol) in dichloromethane (10ml) was added triethylsilane (0.31ml, 1.48mmol) and trifluoroacetic acid (0.34ml, 4.42mmol) under nitrogen atmosphere. The reaction mixture was stirred at rt for 2h, quenched with saturated sodium bicarbonate solution, washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo to give the title compound (0.45g, 95%) as a white solid.

\(^1\)H-NMR(CDCl₃, ppm) : δ 1.60-2.01(m, 8H), 3.88(s, 3H), 4.83(s, 2H), 4.87(m, 1H), 6.97(s, 2H), 7.34(s, 1H), 7.52-7.62(m, 3H), 7.97(d, J=7.5Hz, 1H).

Reference Example 8

2-(3-Cyclopentoxy-4-methoxyphenyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1,3-dione

To a solution of pyridine-3,4-dicarboxylic acid (1.62g, 9.65mmol) in toluene (10ml) was added thionyl chloride (3.45g, 28.95mmol). The reaction mixture was refluxed for 4h, evaporated in vacuo to remove thionyl chloride. To the residue were added dichloromethane (10ml), 3-cyclopentoxy-4-methoxyaniline (2g, 9.65mmol) and triethylamine (2.44g, 25.13mmol), stirred for 6h at rt, and then concentrated in vacuo. The resultant mixture was treated with chloroform (10ml) and acetic acid (2ml), refluxed for 48h, cooled to rt, concentrated in vacuo to remove chloroform and acetic acid, added ethanol, and stirred at rt. The resultant solids were filtered to give the title compound (2.8g, 86%) as a yellow solid.

\(^1\)H-NMR(CDCl₃, ppm) : δ 1.60-2.05(m, 8H), 3.90(s, 3H), 4.75(m, 1H), 6.92(d, J=8.5Hz, 1H), 7.07(m, 2H), 7.44(dd, J=7.8, 4.8Hz, 1H), 8.10(dd, J=7.8, 1.5Hz, 1H), 8.72(dd, J=4.8, 1.5Hz, 1H).

Reference Example 9

N4-(3-Cyclopentoxy-4-methoxyphenyl)-3-(hydroxymethyl)
isonicotinamide

To a solution of 2-(3-cyclopentyloxy-4-methoxyphenyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1,3-dione (0.5g, 1.48mmol) in methanol (10ml) was slowly added sodium borohydride (0.28g, 7.41mmol) at rt. The reaction mixture was stirred for 1h at rt, evaporated *in vacuo*, added distilled water (10ml), and extracted twice with ethyl acetate. The organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica to afford the title compound (0.25g, 50%) as a white solid.

\[^1^H\text{-NMR(CDCl}_3\text{, ppm): } 6\ 1.60-2.05(m, 8H), 3.85(s, 3H), 4.52(s, 1H), 4.74(d, J=4.5Hz, 1H), 4.79(m, 1H), 6.84(d, J=8.5Hz, 1H), 7.07(dd, J=8.5, 2.1Hz, 1H), 7.38(m, 2H), 8.61(d, J=4.8Hz, 1H), 8.86(s, 2H).\]

**Reference Example 10**

2-(3-Cyclopentyloxy-4-methoxyphenyl)-2,3-dihydro-pyrrolo[3,4-c]pyridin-1-one

To a solution of N4-(3-cyclopentyloxy-4-methoxyphenyl)-3-(hydroxymethyl)-isonicotinamide (0.4g, 1.17mmol) in anhydrous THF (10ml) were added triphenylphosphine (0.37g, 1.41mmol) and diethylazodicarboxylate (0.25g, 1.41mmol) at rt. The reaction mixture was stirred for 1h at rt, evaporated *in vacuo*, treated with 6N HCl solution (10ml), and extracted with ethyl acetate. The aqueous layer was basified to pH 8-9 with 6N NaOH solution, and extracted with ethyl acetate. Then, the resultant organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo* to give the title compound (0.34g, 89%) as a white solid.

\[^1^H\text{-NMR(CDCl}_3\text{, ppm): } 6\ 1.60-2.05(m, 8H), 3.88(s, 3H), 4.85(m, 1H), 4.87(s, 2H), 6.91(d, J=8.5Hz, 1H), 7.02(dd, J=8.5, 2.1Hz, 1H), 7.51(d, J=5.1Hz, 1H), 7.82(d, J=2.1Hz, 1H), 8.82(d, J=5.1Hz, 1H).\]

**Reference Example 11**
2-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methylene-2,3-dihydro-1H-
pyrrolo[3,4-c]pyridin-1-one

To a solution of 2-(3-cyclopentyloxy-4-methoxyphenyl)-3-hydroxy-3-
methyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (0.52g, 1.48mmol) in benzene
(10ml) was added p-toluenesulfonic acid (0.28g, 1.48mmol). The reaction mixture
was stirred for 4h at rt, diluted with ethyl acetate. The organic layer was washed with
distilled water, dried over MgSO₄, filtered, and evaporated in vacuo to remove
solvent. The residue was purified by flash chromatography on silica to afford the title
compound (0.45g, 91%) as a white solid.

$^1$H-NMR(CDCl₃, ppm) : δ 1.60-2.05(m, 8H), 3.91(s, 3H), 4.85(m, 1H),
4.90(d, J=1.8Hz, 1H), 6.95(m, 2H), 7.25(s, 1H), 7.45(d, J=5.1Hz, 1H), 8.90(d,
J=5.1Hz, 1H), 9.20(s, 1H).

Reference Example 12

2-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-2,3-dihydro-
pyrrolo[3,4-c]pyridin-1-one

To a solution of 2-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylene-2,3-
dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (0.5g, 1.48mmol) in methanol (30ml) were
added ammonium formate (0.3g, 4.44mmol) and 10% Pd-C (0.1g). The reaction
mixture was stirred for 1h at rt, filtered through Celite, and evaporated in vacuo to
remove methanol. The residue was diluted with ethyl acetate, washed twice with
distilled water, dried over MgSO₄, filtered, and concentrated in vacuo to give the title
compound (0.36g, 94%) as a white solid.

$^1$H-NMR(CDCl₃, ppm) : δ 1.24(d, J=6.8Hz, 3H), 1.60-2.05(m, 8H), 3.90(s,
3H), 4.82(m, 1H), 5.14(q, J=6.8Hz, 1H), 6.91(m, 2H), 7.24(d, J=2.1Hz, 1H), 7.47(d,
J=5.1Hz, 1H), 8.84(d, J=5.1Hz, 1H), 9.19(s, 1H).

Reference Example 13
Ethyl 2-(3-cyclopent oxyloxy-4-methoxyphenyl)-3-oxo-5-isooindoline carboxylate

To a solution of 2-(3-cyclopent oxyloxy-4-methoxyphenyl)-1,3-dio xo-5-isooindoline carboxylic acid (0.92g, 2.42mmol), prepared following the procedure described in reference example 3, in anhydrous aceton (10ml) was added slowly triethylamine (1ml, 7.26mmol). The reaction mixture was stirred at rt for 10min, treated with iodoethan (1.13g, 7.26mmol), refluxed for 10h, cooled to rt, evaporated in vacuo, and added methanol. The resultant solid was filtered to afford ethyl 2-(3-cyclopent oxyloxy-4-methoxyphenyl)-1,3-dioxo-5-isooindoline carboxylate (0.94g, 95%) as a pale yellow solid. The title compound was prepared as following described in reference example 6 and 7 as a white solid (0.36g, 40%).

$^1$H-NMR(CDCl$_3$, ppm) : δ 1.45(t, J=7.1Hz, 3H), 1.62-1.66(m, 2H), 1.83-2.07(m, 6H), 3.89(s, 3H), 4.43(q, J=7.1Hz, 2H), 4.86-4.89(m, 1H), 4.90(s, 2H), 6.92(d, J=8.7Hz, 1H), 7.05(dd, J=8.7, 2.5Hz, 1H), 7.88(d, J=2.5Hz, 1H), 7.97(d, J=8.3Hz, 1H), 8.21(m, 2H).

Reference Example 14
2-(3-Cyclopent oxyloxy-4-methoxyphenyl)-6-hydroxymethyl-1-
isoindolinone

To a solution of ethyl-2-(3-cyclopent oxyloxy-4-methoxyphenyl)-3-oxo-5-isooindoline carboxylate (0.96g, 2.42mmol) in anhydrous THF (10ml) was added lithium borohydride (0.08g, 3.63mmol). The reaction mixture was stirred for 1h at rt, evaporated in vacuo, diluted with ethyl acetate, and washed twice with distilled water. The organic layer was dried over MgSO$_4$, filtered, and concentrated in vacuo to give the title compound (0.83g, 97%) as a white solid.

$^1$H-NMR(CDCl$_3$, ppm) : δ 1.61-1.68(m, 2H), 1.84-2.08(m, 6H), 3.89(s, 3H), 4.83-4.91(m, 5H), 5.10(bs, 1H), 6.90(d, J=8.8Hz, 1H), 7.06(dd, J=8.9, 2.6Hz, 1H), 7.52(d, J=7.8Hz, 1H), 7.65(d, J=7.8Hz, 1H), 7.88-7.91(m, 2H).
Reference Example 15

6-(Aminomethyl)-2-(3-cyclopentoxy-4-methoxyphenyl)-1-isoindolinone

To a solution of 2-(3-cyclopentoxy-4-methoxyphenyl)-6-hydroxymethyl-1-iso-indolinone (0.86g, 2.42mmol) in dichloromethane (10ml) were slowly added methane sulfonylchloride (0.33g, 2.90mmol) and triethylamine (0.37g, 3.63mmol) at 0°C. The reaction mixture was stirred for 0.5h at rt, washed twice with distilled water, dried over MgSO₄, filtered, and concentrated in vacuo to give [2-(3-cyclopentoxy-4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-5-isoindolyl]methyl ethanesulfonate (0.96g, 96%) as a white solid.

1H-NMR(CDCl₃, ppm): δ 1.61-1.66(m, 2H), 1.83-2.06(m, 6H), 3.02(s, 3H), 3.88(s, 3H), 4.87(s, 2H), 4.86-4.89(m, 1H), 5.36(s, 2H), 6.91(d, J=8.7Hz, 1H), 7.04(dd, J=8.7, 2.5Hz, 1H), 7.58(d, J=7.8Hz, 1H), 7.68(dd, J=7.8, 1.5Hz, 1H), 7.85(d, J=2.5Hz, 1H), 7.96(s, 1H).

To a solution of [2-(3-cyclopentoxy-4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-5-isoindolyl]methyl methanesulfonate (1g, 2.42mmol) in DMF (10ml) was added sodium azide (0.47g, 7.26mmol). The reaction mixture was stirred for 2h at 60°C, cooled to rt, added ethyl acetate, washed three times with distilled water, dried over MgSO₄, filtered, and concentrated in vacuo to give 6-(azidomethyl)-2-(3-cyclopentoxy-4-methoxyphenyl)-1-isoindolinone (0.9g, 97%) as a white solid.

1H-NMR(CDCl₃, ppm): δ 1.61-1.66(m, 2H), 1.86-2.07(m, 6H), 3.89(s, 3H), 4.48(s, 2H), 4.85(s, 2H), 4.86-4.90(m, 1H), 6.91(d, J=8.7Hz, 1H), 7.04(dd, J=8.7, 2.5Hz, 1H), 7.56(m, 2H), 7.86(m, 2H).

To a solution of 6-(azidomethyl)-2-(3-cyclopentoxy-4-methoxyphenyl)-1-iso-indolinone (0.92g, 2.42mmol) in THF (10ml) was added triphenylphosphine (0.7g, 2.66mmol). The reaction mixture was stirred for 20min., added distilled water (1ml), stirred for 8h at rt, added 1N HCl solution, and extracted with ethyl acetate. The aqueous layer was basified to pH 8-9 with 2N NaOH solution, and extracted with ethyl acetate. The organic layer was dried over MgSO₄, filtered, and
concentrated in vacuo to give the title compound (0.79g, 92%) as a white solid.

\[ ^1H\text{-NMR(CDCl}_3, \text{ ppm}) : \delta 1.56-1.66(m, 2H), 1.85-2.07(m, 6H), 3.88(s, 3H),
4.01(s, 2H), 4.83(s, 2H), 4.82-4.89(m, 1H), 6.90(d, J=8.7Hz, 1H), 7.05(dd, J=8.7,
2.5Hz, 1H), 7.48(m, 1H), 7.58(d, J=7.7Hz, 1H), 7.87(m, 2H). \]

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Example 1

1-Methoxy-2-(1-methyl-3-phenyl-propoxy)-4-nitrobenzene

The title compound was prepared following the procedures described in
reference example 1 with 4-phenyl-butan-2-ol (0.89g, 5.92mmol) as a pale yellow
solid (1.64g, 92%).

\[ ^1H\text{-NMR(CDCl}_3, \text{ ppm}) : \delta 1.39(d, J=6.1Hz, 3H), 1.94-2.13(m, 2H), 2.83(m,
2H), 3.90(s, 3H), 4.40(m, 1H), 6.92(d, J=8.8Hz, 1H), 7.17-7.28(m, 5H), 7.48(d,
J=5.1 Hz, 1H), 7.72(d, J=2.6Hz, 1H). \]

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Example 2

4-Methoxy-3-(1-methyl-3-phenyl-propoxy)aniline

The title compound was prepared following the procedures described in
reference example 2 with 1-methoxy-2-(1-methyl-3-phenyl-propoxy)-4-nitrobenzene
(1.5g, 4.98mmol) as a pale yellow solid (1.09g, 81%).

\[ ^1H\text{-NMR(CDCl}_3, \text{ ppm}) : \delta 1.39(d, J=6.1Hz, 3H), 1.93-2.12(m, 2H), 2.81(m,
2H), 3.87 (b, 2H), 3.88(s, 3H), 4.41(m, 1H), 6.91(d, J=8.8Hz, 1H), 7.15-7.24(m, 5H),
7.46(d, J=5.1 Hz, 1H), 7.70(d, J=2.6Hz, 1H). \]

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Example 3

2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-isoindole-1,3-
dione

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The title compound was prepared following the procedures described in
reference example 3 with 4-methoxy-3-(1-methyl-3-phenyl-propoxy)aniline (1.0g, 3.69mmol) as a white solid (1.30g, 91%).

$^1$H-NMR(CDCl₃, ppm) : δ 1.38(d, J=6.1Hz, 3H), 1.92-2.14(m, 2H), 2.83(m, 2H), 3.87(s, 3H), 4.42(m, 1H), 6.91(d, J=8.8Hz, 1H), 7.15-7.24(m, 5H), 7.46(d, J=5.1 Hz, 1H), 7.70(d, J=2.6Hz, 1H), 7.78(m, 2H), 7.95(m, 2H).

**Example 4**

2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-3-methyl-2,3-dihydro-isooindol-1-one

The title compound was prepared following the procedures described in reference example 4, 5, and example 3 with 2-[4-methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-isooindole-1,3-dione (1.0g, 2.58mmol) as a white solid (1.0g, 62%).

$^1$H-NMR(CDCl₃, ppm) : δ 1.39(d, J=6.1Hz, 3H), 1.57(d, J=8.3Hz, 3H), 1.92-2.14(m, 2H), 2.82(m, 2H), 3.87(s, 3H), 4.43(m, 1H), 5.05(q, J=6.8Hz, 1H), 6.87(d, J=8.8Hz, 1H), 7.17-7.25(m, 5H), 7.43(d, J=5.1 Hz, 1H), 7.68(d, J=2.6Hz, 1H), 7.72(m, 2H), 7.94(m, 2H).

**Example 5**

2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-2,3-dihydro-isooindol-1-one

The title compound was prepared following the procedures described in reference example 7 with 2-[4-methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-isooindole-1,3-dione (1.0g, 2.58mmol) as a white solid (0.83g, 86%).

$^1$H-NMR(CDCl₃, ppm) : δ 1.38(d, J=6.1Hz, 3H), 1.93-2.11(m, 2H), 2.82(m, 2H), 3.87(s, 3H), 4.43(m, 1H), 4.85(s, 2H), 6.89(d, J=8.7Hz, 1H), 7.15-7.23(m, 5H), 7.42(d, J=5.1 Hz, 1H), 7.67(d, J=2.6Hz, 1H), 7.72(m, 2H), 7.93(m, 2H).

**Example 6**
2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-pyrrolo[3,4-c]pyridine-1,3-dione

The title compound was prepared following the procedures described in reference example 8 with 4-methoxy-3-(1-methyl-3-phenyl-propoxy)aniline (2.48g, 9.65mmol) and pyridine-3,4-dicarboxylic acid (1.62g, 9.65mmol) as a white solid (3.18g, 85%).

$^1$H-NMR(CDCl$_3$, ppm) :  $\delta$ 1.38(d, J=6.1Hz, 3H), 1.92-2.14(m, 2H), 2.83(m, 2H), 3.90 (s, 3H), 4.42(m, 1H), 6.91(d, J=8.8Hz, 1H), 7.15-7.23(m, 5H), 7.45(d, J=5.0 Hz, 1H), 8.11(dd, J=7.8, 1.5Hz, 1H), 8.72(dd, J=4.8, 1.5Hz, 1H).

Example 7

2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-3-methyl-2,3-dihydro-pyrrolo[3,4-c]pyridin-1-one

The title compound was prepared following the procedures described in reference example 11 and 12 with 2-[4-methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-pyrrolo[3,4-c]pyridine-1,3-dione (1.0g, 2.58mmol) as a white solid (0.47g, 87%).

$^1$H-NMR(CDCl$_3$, ppm) :  $\delta$ 1.39(d, J=6.1Hz, 3H), 1.56(d, J=8.3Hz, 3H), 1.92-2.14(m, 2H), 2.82(m, 2H), 3.87(s, 3H), 4.43(m, 1H), 5.06(q, J=6.8Hz, 1H) 6.98-7.07(m, 3H), 7.17-7.25(m, 5H), 7.48(d, J=5.1 Hz, 1H), 8.85(d, J=5.1Hz, 1H), 9.19(s, 1H).

Example 8

2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-2,3-dihydro-pyrrolo[3,4-c]pyridin-1-one

The title compound was prepared following the procedures described in reference example 8 and 9 with 2-[4-methoxy-3-(1-methyl-3-phenyl-propoxy)-
phenyl]-pyrrolo[3,4-c]pyridine-1,3-dione (1.0g, 2.58mmol) as a white solid (0.83g, 86%).

$^1$H-NMR(CDCl$_3$, ppm) : $\delta$ 1.38(d, J=6.1Hz, 3H), 1.93-2.11(m, 2H), 2.82(m, 2H), 3.87(s, 3H), 4.43(m, 1H), 4.85(s, 2H), 6.97-7.07(m, 3H), 7.157.25(m, 5H), 7.48(d, J=5.1 Hz, 1H), 8.83d, J=5.1Hz, 1H), 9.18s, 1H).

**Example 9**

6-Hydroxymethyl-2-[4-methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-2,3-dihydro-isooindol-1-one

The title compound was prepared following the procedures described in reference example 14 with 2-[4-methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-3-oxo-2,3-dihydro-1H-isooindole-5-carboxylic acid ethyl ester (1.0g, 2.18mmol) as a white solid (0.77g, 85%).

$^1$H-NMR(CDCl$_3$, ppm) : $\delta$ 1.32(d, J=6.1Hz, 3H), 1.91-2.09(m, 2H), 2.82(m, 2H), 3.87(s, 3H), 4.42(m, 1H), 4.84(s, 2H), 6.88(d, J=8.7Hz, 1H), 7.13-7.23(m, 5H), 7.41(d, J=5.1 Hz, 1H), 7.65(d, J=2.6Hz, 1H), 7.72(m, 1), 7.93(m, 2H).

**Example 10**

6-Aminomethyl-2-[4-methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-2,3-dihydro-isooindol-1-one

The title compound was prepared following the procedures described in reference example 15 with 6-azidomethyl-2-[4-methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-2,3-dihydro-isooindol-1-one (1.0g, 2.26mmol) as a white solid (0.86g, 91%).

$^1$H-NMR(CDCl$_3$, ppm) : $\delta$ 1.33(d, J=6.1Hz, 3H), 1.93-2.09(m, 2H), 2.81(m, 2H), 3.88(s, 3H), 4.44(m, 1H), 4.83(s, 2H), 6.90(d, J=8.7Hz, 1H), 7.15-7.23(m, 5H), 7.43(d, J=5.1 Hz, 1H), 7.67(d, J=2.6Hz, 1H), 7.71(m, 1), 7.92(m, 2H).
Example 11

2-[2-(3-Cyclopentyl-oxy-4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl]-1,3-isooindolinedione

To a solution of 2-[3-(cyclopentyl-oxy-4-methoxyphenyl)]-6-(hydroxymethyl)-1-isooindolinone (0.5g, 1.41mmol) and phthalamide (0.21g, 1.41mmol) in anhydrous THF (10ml) were added triphenylphosphine (0.56g, 2.12mmol) and diethylazodicarboxylate (0.38g, 2.12mmol) at rt. The reaction mixture was stirred for 40min at rt. The reaction mixture was evaporated in vacuo, and recrystalized with methanol to give the title compound (0.57g, 85%) as a white solid.

$^1$H-NMR(CDCl$_3$, ppm) : δ 1.61-2.06(m, 8H), 3.87(s, 3H), 4.82(s, 2H), 4.87(m, 1H), 4.92(s, 2H), 6.92(d, J=2.5Hz, 1H), 7.00(dd, J=2.5, 6.2Hz, 1H), 7.42-7.57(m, 5H), 7.81-7.92(m, 3H).

Example 12

2-(2-[3-(Cyclopentyl-oxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl)-3-hydroxy-1-isooindolinone

The title compound was prepared following the procedures described in reference example 6 with 2-[2-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-5-isooindolylmethyl]-1,3-isooindolinedione (0.5g, 1.04mmol) as a white solid (0.46g, 92%).

$^1$H-NMR(CDCl$_3$, ppm) : δ 1.60-2.05(m, 8H), 3.87(s, 3H), 4.63(d, J=15.2Hz, 1H), 4.75(s, 2H), 4.85(m, 1H), 5.08(d, J=15.2Hz, 1H), 5.75(d, J=9.9Hz, 1H), 6.45(b, 1H), 6.97(d, J=2.5Hz, 1H), 6.99(dd, J=2.5, 6.2Hz, 1H), 7.43-7.63(m, 5H), 7.72-7.79(m, 3H).

Example 13

2-[3-(Cyclopentyl-oxy)-4-methoxyphenyl]-6-[(1-oxo-2,3-dihydro-1H-2-
isoindolyl)methyl]-1-isoindolinone

The title compound was prepared following the procedures described in reference example 7 with 2-(2-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-3-hydroxy-1-isoindolinone (0.3 g, 0.62 mmol) as a white solid (0.25 g, 85%).

\(^1\)H-NMR (CDCl\(_3\), ppm) : \(\delta\) 1.60-2.06 (m, 8H), 3.88 (s, 3H), 4.32 (s, 2H), 4.83 (s, 2H), 4.86 (m, 1H), 4.93 (s, 2H), 6.91 (d, \(J=2.5\)Hz, 1H), 7.01 (dd, \(J=2.5, 6.2\)Hz, 1H), 7.43-7.59 (m, 5H), 7.83-7.91 (m, 3H).

**Example 14**

2-(2-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-1,3-dione

The title compound was prepared following the procedures described in example 11 with 2-[3-(cyclopentyloxy-4-methoxyphenyl)]-6-(hydroxymethyl)-1-isoindolinone (0.5 g, 1.41 mmol) and phthalimide (0.21 g, 1.41 mmol) and pyrrolo[3,4-c]pyridine-1,3-dione (0.22 g, 1.49 mmol) as a yellow solid (0.55 g, 80%).

\(^1\)H-NMR (CDCl\(_3\), ppm) : \(\delta\) 1.61-2.05 (m, 8H), 3.87 (s, 3H), 4.81 (s, 2H), 4.85 (m, 1H), 5.00 (s, 2H), 6.89 (d, \(J=2.5\)Hz, 1H), 6.99 (dd, \(J=2.5, 6.2\)Hz, 1H), 7.50 (d, \(J=7.7\)Hz, 1H), 7.67 (dd, \(J=1.6, 6.2\)Hz, 1H), 7.79 (dd, \(J=1.0, 3.8\)Hz, 1H), 7.85 (d, \(J=2.5\)Hz, 1H), 7.90 (s, 1H), 9.10 (d, \(J=4.8\)Hz, 1H), 9.18 (d, \(J=0.9\)Hz, 1H).

**Example 15**

2-(2-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-3-hydroxy-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

The title compound was prepared following the procedures described in reference example 6 with 2-(2-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-1,3-dione.
(0.5 g, 1.03 mmol) as a white solid (0.45 g, 90%).

$^1$H-NMR (CDCl$_3$, ppm): $\delta$ 1.63-2.01 (m, 8H), 3.86 (s, 3H), 4.70-4.79 (m, 5H), 6.48 (b, 1H), 6.84 (d, J=2.5 Hz, 1H), 6.99 (dd, J=2.5, 6.2 Hz, 1H), 7.46-7.72 (m, 5H), 7.72-7.79 (m, 3H), 8.63 (d, J=4.8 Hz, 1H), 8.84 (d, J=0.9 Hz, 1H).

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**Example 16**

2-[(2-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-oxo-2,3-dihydro-1H-isoindol-5-ylmethyl]-2,3-dihydro-pyrrolo[3,4-c]pyridin-1-one

The title compound was prepared following the procedures described in reference example 7 with 2-(2-[(3-cyclopentyloxy)-4-methoxyphenyl]-3-oxo-2,3-dihydro-1H-5-isoindolylmethyl)-3-hydroxy-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (0.3 g, 0.62 mmol) as a white solid (0.23 g, 78%).

$^1$H-NMR (CDCl$_3$, ppm): $\delta$ 1.60-2.06 (m, 8H), 3.87 (s, 3H), 4.39 (s, 2H), 4.83 (s, 2H), 4.86 (m, 1H), 4.93 (s, 2H), 6.91 (d, J=2.5 Hz, 1H), 7.01 (dd, J=2.5, 6.2 Hz, 1H), 7.39-7.59 (m, 3H), 7.83 (m, 2H), 8.79 (m, 1H), 9.16 (s, 1H).

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**Example 17**

2-[(2-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-oxo-2,3-dihydro-1H-isoindol-5-ylmethyl]-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid

The title compound was prepared following the procedures described in reference example 3 with 6-aminomethyl-2-(3-cyclopentyloxy-4-methoxy-phenyl)-2,3-dihydro-isoindol-1-one (0.5 g, 1.42 mmol) and 1,2,4-benzenetricarboxylic anhydride (0.27 g, 1.42 mmol) as a brown solid (0.74 g, 95%).

$^1$H-NMR (CDCl$_3$, ppm): $\delta$ 1.62-2.01 (m, 8H), 3.88 (s, 3H), 4.79 (s, 2H), 4.85 (m, 1H), 5.01 (s, 2H), 6.89 (d, J=8.8 Hz, 1H), 7.01 (dd, J=2.5, 6.2 Hz, 1H), 7.50 (d, J=7.9 Hz, 1H), 7.68 (d, J=7.7 Hz, 1H), 7.88 (d, J=2.5 Hz, 1H), 7.91 (s, 1H), 7.96 (d, J=7.7 Hz, 1H), 8.25 (d, J=6.5 Hz, 1H), 8.50 (s, 1H).
Example 18

2-(3-Cyclopentylxyloxy-4-methoxy-phenyl)-3-oxo-2,3-dihydro-1H-isoinole-5-carboxylic acid (1,3-dioxo-1,3-dihydro-isindol-2-yl)-amide

To a solution of ethyl-2-(3-cyclopentylxyloxy-4-methoxyphenyl)-3-oxo-5-isoindoline carboxylate (0.96g, 2.42mmol) in ethanol (10ml) was added excess hydrazine solution. The reaction mixture was stirred for 24h at room temperature, evaporated in vacuo, and added distilled water. The resultant solid was filtered to afford 2-(3-cyclopentylxyloxy-4-methoxyphenyl)-3-oxo-5-isoindolinecarbo hydrazide (0.48g, 48%) as a white solid.

$^1$H-NMR(CDCl$_3$, ppm) : δ 1.60-1.67(m, 2H), 1.84-2.06(m, 6H), 3.89(s, 3H), 4.43(bs, 2H), 4.87-4.89(m, 1H), 4.90(s, 2H), 6.90(d, J=8.8Hz, 1H), 7.06(dd, J=8.8, 2.5Hz, 1H), 7.56(bs, 1H), 7.64(d, J=7.7Hz, 1H), 7.80(d, J=2.5Hz, 1H), 8.13(dd, J=7.7, 1.5Hz, 1H), 8.20(d, J=1.5Hz, 1H).

The title compound was prepared following the procedures described in reference example 3 with 2-(3-cyclopentylxyloxy-4-methoxy-phenyl)-3-oxo-2,3-dihydro-1H-isoinole-5-carboxylic acid hydrazide (0.5g, 1.31mmol) as a white solid (0.42g, 62%).

$^1$H-NMR(DMSO-d$_6$, ppm) : δ 1.62-2.03(m, 8H), 3.78(s, 3H), 4.82(m, 1H), 4.93(s, 2H), 6.87(d, J=8.8Hz, 1H), 7.03(dd, J=2.5, 8.7Hz, 1H), 7.43-7.62(m,6H), 8.19(d, J=7.9Hz, 1H), 8.45(s, 1H), 10.95(s, 1H).

Example 19

2-[[2-(3-Cyclopentylxyloxy-4-methoxy-phenyl)-3-oxo-2,3-dihydro-1H-isoinole-5-ylmethylen]-amino]-isoindole-1,3-dione

To a solution of 2-(3-cyclopentylxyloxy-4-methoxy-phenyl)-3-oxo-2,3-dihydro-1H-isoinole-5-carbaldehyde (0.5g, 1.42mmol) in CH$_2$Cl$_2$ (5ml), methanol (8ml) and water (2ml) was added pyrrolo[3,4-c]pyridine-1,3-dione (0.25g, 1.42mmol). The reaction mixture was stirred for 3 days at rt, and then concentrated in vacuo. The title
compound was prepared by flash chromatography on silica as a yellow solid (0.57g, 82%).

\[^{1}\text{H-NMR(DMSO-d6, ppm)}: \delta \ 1.62-2.02(m, 8H), \ 3.89(s, 3H), \ 4.77(m, 1H), 4.89(s, 2H), \ 6.92(d, J=8.8Hz, 1H), \ 7.04(dd, J=2.5, 8.7Hz, 1H), \ 7.64(d, J=7.7Hz, 1H), 7.81-7.85(m, 3H), \ 7.97(m, 2H), \ 8.30(m, 2H), \ 9.59(s, 1H).\]

**Example 20**

2-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3-methyl-6-[(1-oxo-2,3-dihydro-1H-2-isindolyl)methyl]-1-isooindolinone

The title compound was prepared following the procedures described in example 10, 6 and 7 with 2-[3-(cyclopentyloxy-4-methoxyphenyl)]-6-(hydroxymethyl)-1-isooindolinone (0.5g, 1.41mmol) as a white solid (0.43g, 64%).

\[^{1}\text{H-NMR(CDCl3, ppm)}: \delta \ 1.48(d, J=6.3Hz, 3H), \ 1.64-2.06(m, 8H), \ 3.87(s, 3H), \ 4.32(s, 2H), \ 4.86(m, 1H), \ 4.91(s, 2H), \ 5.15(q, J=6.3Hz, 1H), \ 6.91(d, J=2.5Hz, 1H), \ 7.01(dd, J=2.5, 6.2Hz, 1H), \ 7.43-7.59(m, 5H), \ 7.83-7.91(m, 3H).\]

**Example 21**

2-[2-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-methyl-3-oxo-2,3-dihydro-1H-isooindol-5-ylmethyl]-2,3-dihydro-pyrrolo[3,4-c]pyridin-1-one

The title compound was prepared following the procedures described in reference example 11, 12 and 13 with 2-(3-cyclopentyloxy-4-methoxyphenyl)-6-hydroxymethyl-3-methyl-2,3-dihydro-isooindol-1-one (0.5g, 1.36mmol) as a white solid (0.36g, 55%).

\[^{1}\text{H-NMR(CDCl3, ppm)}: \delta \ 1.49(d, J=6.3Hz, 3H), \ 1.60-2.06(m, 8H), \ 3.87(s, 3H), \ 4.39(s, 2H), \ 4.86(m, 1H), \ 4.93(s, 2H), \ 5.14(q, J=6.3Hz, 1H), \ 6.91(d, J=2.5Hz, 1H), 7.01(dd, J=2.5, 6.2Hz, 1H), \ 7.39-7.59(m, 3H), \ 7.83(m, 2H), \ 8.79(m, 1H), \ 9.16(s, 1H).\]
Example 22

2-(3-Cyclopentyloxy-4-methoxy-phenyl)-6-(1-oxo-1,3-dihydro-isooindol-2-ylmethyl)-2,3-dihydro-pyrrolo[3,4-c]pyridin-1-one

The title compound was prepared following the procedures described in example 20 with 6-aminomethyl-2-(3-cyclopentyloxy-4-hydroxy-phenyl)-2,3-dihydro-pyrrolo[3,4-c]pyridin-1-one (0.5g, 1.36mmol) as a white solid (0.35g, 54%).

$^1$H-NMR(CDCl$_3$, ppm) : $\delta$ 1.61-2.06(m, 8H), 3.89(s, 3H), 4.38(s, 2H), 4.85(s, 2H), 4.86(m, 1H), 4.91(s, 2H), 6.92(d, $J$=2.5Hz, 1H), 7.00(dd, $J$=2.5, 6.2Hz, 1H), 7.37-7.89(m, 4H), 7.82(m, 2H), 9.05(s, 1H).

Example 23

2-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-methyl-6-(1-oxo-1,3-dihydro-isooindol-2-ylmethyl)-2,3-dihydro-pyrrolo[3,4-c]pyridin-1-one

The title compound was prepared following the procedures described in example 20 with 6-aminomethyl-2-(3-cyclopentyloxy-4-methoxy-phenyl)-3-methyl-2,3-dihydro-pyrrolo[3,4-c]pyridin-1-one (0.5g, 1.36mmol) as a white solid (0.36g, 51%).

$^1$H-NMR(CDCl$_3$, ppm) : $\delta$ 1.49(d, $J$=6.3Hz, 3H), 1.61-2.05(m, 8H), 3.87(s, 3H), 4.37(s, 2H), 4.85(s, 2H), 4.87(m, 1H), 5.14(q, $J$=6.3Hz, 1H), 6.92(d, $J$=2.5Hz, 1H), 7.00(dd, $J$=2.5, 6.2Hz, 1H), 7.37-7.89(m, 3H), 8.79(m, 1H), 9.16(s, 1H).

Example 24

2-[3-(Cyclopentyloxy)-4-methoxyphenyl]-6-[(1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-2-yl)methyl]-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

The title compound was prepared following the procedures described in example 21 with 6-aminomethyl-2-(4-methoxy-3-propoxy-phenyl)-2,3-dihydro-pyrrolo[3,4-c]pyridin-1-one (0.5g, 1.41mmol) as a yellow solid (0.34g, 51%).
$^1$H-NMR(CDCl$_3$, ppm) : δ 1.62-2.06(m, 8H), 3.87(s, 3H), 4.38(s, 2H), 4.85(s, 2H), 4.87(m, 1H), 4.93(s, 2H), 6.91(d, J=2.5Hz, 1H), 7.01(dd, J=2.5, 6.2Hz, 1H), 7.37-7.89(m, 3H), 8.79(m, 1H), 9.02(s, 1H), 9.15(s, 1H).

Example 25

2-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3-methyl-6-[1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-2-yl)methyl]-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

The title compound was prepared following the procedures described in example 21 with 6-aminomethyl-2-(3-cyclopentyloxy-4-methoxy-phenyl)-3-methyl-2,3-dihydro-pyrrolo[3,4-c]pyridin-1-one (0.5g, 1.36mmol) as a yellow solid (0.32g, 48%).

$^1$H-NMR(CDCl$_3$, ppm) : δ 1.48(d, J=6.3Hz, 3H), 1.60-2.06(m, 8H), 3.89(s, 3H), 4.37(s, 2H), 4.85(s, 2H), 4.88(m, 1H), 5.13(q, J=6.3Hz, 1H), 6.94(d, J=2.5Hz, 1H), 7.02(dd, J=2.5, 6.2Hz, 1H), 7.35-7.89(m, 3H), 8.75(m, 1H), 9.04(s, 1H), 9.18(s, 1H).

Example 26

2-[2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-3-oxo-2,3-dihydro-1H-isooindol-5-ylmethyl]-isooindole-1,3-dione

The title compound was prepared following the procedures described in example 11 with 6-hydroxymethyl-2-[4-methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-2,3-dihydro-isooindol-1-one (0.5g, 1.20mmol) as a white solid (0.52g, 80%).

$^1$H-NMR(CDCl$_3$, ppm) : δ 1.31(d, J=6.1Hz, 3H), 1.93-2.09(m, 2H), 2.83(m, 2H), 3.89(s, 3H), 4.42(m, 1H), 4.83(s, 2H), 6.89(d, J=8.7Hz, 1H), 7.02(dd, J=2.5, 6.2Hz, 1H), 7.11-7.23(m, 5H), 7.42-7.56(m, 4H), 7.72-7.93(m, 4H).

Example 27
2-{2-[4-Methoxy-3-(1-methyl-3-phenyl-propox)-phenyl]-1-methyl-3-oxo-2,3-dihydro-1H-isouindol-5-ylmethyl}-isoindole-1,3-dione

The title compound was prepared following the procedures described in example 11 with 6-hydroxymethyl-2-[4-methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-3-methyl-2,3-dihydro-isoindol-1-one (0.5g, 1.16mmol) as a white solid (0.51g, 78%).

$^1$H-NMR(CDCl$_3$, ppm) : δ 1.32(d, J=6.1Hz, 3H), 1.47(d, J=6.3Hz, 3H), 1.89-2.09(m, 2H), 2.82(m, 2H), 3.87(s, 3H), 4.41(m, 1H), 5.11(q, J=6.3Hz, 1H), 6.88(d, J=8.7Hz, 1H), 7.02(dd, J=2.5, 6.2Hz, 1H), 7.09-7.22(m, 5H), 7.41-7.56(m, 4H), 7.75-7.93(m, 4H).

Example 28
2-{2-[4-Methoxy-3-(1-methyl-3-phenyl-propox)-phenyl]-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-ylmethyl}-isoindole-1,3-dione

The title compound was prepared following the procedures described in example 11 with 6-aminomethyl-2-[4-methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-2,3-dihydro-pyrrolo[3,4-c]pyridin-1-one (0.59g, 1.41mmol) as a white solid (0.61g, 79%).

$^1$H-NMR(CDCl$_3$, ppm) : δ 1.33(d, J=6.1Hz, 3H), 1.91-2.09(m, 2H), 2.83(m, 2H), 3.87(s, 3H), 4.42 (m, 1H), 4.83(s, 2H), 6.90(d, J=8.7Hz, 1H), 7.02(dd, J=2.5, 6.2Hz, 1H), 7.11-7.22(m, 5H), 7.39-7.56(m, 2H), 7.83-7.92(m, 4H), 9.17(s, 1H).

Example 29
2-{2-[4-Methoxy-3-(1-methyl-3-phenyl-propox)-phenyl]-3-methyl-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-ylmethyl}-isoindole-1,3-dione

The title compound was prepared following the procedures described in example 11 with 6-aminomethyl-2-[4-methoxy-3-(1-methyl-3-phenyl-propoxy)-
phenyl]-3-methyl-2,3-dihydro-pyrrolo[3,4-c]pyridin-1-one (0.5g, 1.16mmol) as a white solid (0.50g, 77%).

$^1$H-NMR (CDCl$_3$, ppm): $\delta$ 1.31(d, $J$=6.1Hz, 3H), 1.48(d, $J$=6.3Hz, 3H), 1.87-2.09(m, 2H), 2.81(m, 2H), 3.88(s, 3H), 4.42(m, 1H), 5.10(q, $J$=6.3Hz, 1H), 6.87(d, $J$=8.7Hz, 1H), 7.02(dd, $J$=2.5, 6.2Hz, 1H), 7.09-7.22(m, 5H), 7.41-7.56(m, 2H), 7.83-7.93(m, 4H), 9.17(s, 1H).

The following composition examples illustrate pharmaceutical compositions according to the present invention.

**Composition Example 1**

2-[2-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-oxo-2,3-dihydro-1H-isooindol-5-ylmethyl]-2,3-dihydro-pyrrolo[3,4-c]pyridin-1-one (1g) (mean particle size 3.5 microns) and lactose (99g) (mean particle size 72 microns) are blended together for 30 minutes in a mechanical shaker/mixer. The resultant blend is filled, to a fill weight of 25mg, into No. 3 hard gelatine capsules, to give a product suitable for use, for example, with a dry powder inhaler.

**Composition Example 2**

No. 2 size gelatine capsules each containing:

2-[2-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-oxo-2,3-dihydro-1H-isooindol-5-ylmethyl]-2,3-dihydro-pyrrolo[3,4-c]pyridin-1-one 20mg
Lactose 100mg
Starch 60mg
Dextrin 40mg
Magnesium stearate 1mg
are prepared in accordance with the usual procedure.

Compositions similar to those above are prepared from other compounds of formula [1].

**Experimental Example 1**

TNF-α *in vitro* assay (reference; Taffet S.M. et al., Cellular Immunology (1989) 120, 291-300);

After cancer cell line of mouse macrophage (RAW264.7) is diluted with RPMI1640 medium (containing 5% FCS), then plated out in 24 well plates at 1x10⁶ cells/ml. Then, the culture is incubated for 18 hours at 5% CO₂ and 37°C. 1μM of compound and 1μg/ml of lipopolysaccharide (LPS) are added to the plate and the culture is incubated for 6 hours at 37°C. After incubated, the culture is centrifuged and supernatants are collected. The supernatants are stored at -20°C till measurement. The measurement of TNF-α in the media is performed with a mouse TNF-α kit (Amersham, UK). And the procedure is in accordance with the guidance provided by Amersham. Inhibition percentage of each compound is calculated by comparison of amount of TNF-α, released in the well treated with compound, with that in the well without any treatment. Inhibitory activities of compounds on *in vitro* TNF-α synthesis are listed in Table 1. And IC₅₀ of the compounds of formula [1] is between 1 and 1000nM.

<table>
<thead>
<tr>
<th>Example No.</th>
<th>% Inhibition</th>
<th>Example No.</th>
<th>% Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>54.2</td>
<td>19</td>
<td>49.8</td>
</tr>
<tr>
<td>4</td>
<td>72.6</td>
<td>20</td>
<td>65.8</td>
</tr>
<tr>
<td>5</td>
<td>68.9</td>
<td>21</td>
<td>72.2</td>
</tr>
<tr>
<td>7</td>
<td>83.6</td>
<td>22</td>
<td>70.9</td>
</tr>
<tr>
<td>8</td>
<td>79.2</td>
<td>23</td>
<td>75.6</td>
</tr>
</tbody>
</table>
Experimental Example 2

TNF-\(\alpha\) in vivo assay (reference; Novogrodsky A. et al., Science (1994) 264, 319-322)

After compound is suspended in 5% sodium carboxymethyl cellulose (CMC), starved mouse (C57BL/6, 6-week old, male) is administered orally at the volume of 0.1ml per 10g of body weight. Lipopolysaccharide (LPS) is injected intraperitoneally at the concentration of 1.5mg/mouse for 2 hours after compound administration. The control is administered orally with 5% Na CMC at the volume of 0.1ml per 10g of body weight. After one and half hours, mice are anaesthetized with ether, blood is collected from vena cava and serum is collected from blood after 5-minute centrifugation at 12,000 rpm. The serum collected is stored at -20°C till TNF-\(\alpha\) ELISA assay. The amount of TNF-\(\alpha\) in serum is measured with a mouse TNF-\(\alpha\) kit (Amersham, UK). And the procedure is in accordance with the guidance provided by Amersham. Inhibitory activities of compounds on in vivo TNF-\(\alpha\) synthesis are listed in Table 2.

Table 2

<table>
<thead>
<tr>
<th>Example No.</th>
<th>Control (TNF-(\alpha): 1750 pg/ml)</th>
<th>12</th>
<th>13</th>
<th>16</th>
<th>25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amount (mg/kg)</td>
<td></td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Inhibitory Activity (%)</td>
<td></td>
<td>79.3</td>
<td>87</td>
<td>92.2</td>
<td>82.5</td>
</tr>
</tbody>
</table>
According to Table 1 and Table 2, compounds invented by us, show high inhibitory effect on *in vitro* and *in vivo* TNF-α synthesis.

Experimental Example 3

Assay for PDE 4 inhibitory activity

PDE 4 activity was determined by using partially purified PDE 4 from human monocyte (U937) and [³H]-cAMP (1µM) as the substrate. Human monocyte PDE 4 was isolated as described by Torphy et al. (J. Pharmacol. Exp. Ther., 263, 1195-1205, 1992). Synthetic compounds and rolipram were tested at seven concentrations from 10⁻⁹ to 10⁻³ M in duplicate. The test compounds and the substrate with U937 cells was incubated at 37 °C for 30 min. The product of reaction ([³H] 5′AMP) was separated from the substrate by elution on cation-exchange columns and radioactivity was determined with a liquid scintillation counter (LS 1701, Beckman) using a liquid scintillation cocktail. IC₅₀ values were determined by non-linear regression analysis of the competition curves. Inhibitory activities of compounds on *in vitro* PDE 4 are listed in Table 3.

<table>
<thead>
<tr>
<th>Example No.</th>
<th>IC₅₀ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>0.25</td>
</tr>
<tr>
<td>13</td>
<td>0.046</td>
</tr>
<tr>
<td>16</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Experimental Example 4

Acute Toxicity Test (LD₅₀)

The compounds in Table 3 are administered orally at various dose with SPF ICR mice (body weight 20±1g). The animal number of each group is 5. The number of
the dead is checked for 24 hours after administration. And animal condition and the number of the dead have been observed for 7 days. The lethal dose of 50% (LD$_{50}$) is calculated in accordance with Litchfield-Wilcoxon) method. The result is listed in Table 4.

Table 4

<table>
<thead>
<tr>
<th>No. of compound</th>
<th>Route of Administration</th>
<th>LD$_{50}$ (g/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>PO*</td>
<td>&gt; 3.5</td>
</tr>
<tr>
<td>13</td>
<td>PO</td>
<td>&gt; 3.5</td>
</tr>
<tr>
<td>16</td>
<td>PO</td>
<td>&gt; 3.5</td>
</tr>
</tbody>
</table>

* indicates post oral.
WHAT IS CLAIMED IS:

1. A compound of formula 1 wherein,

   ![Chemical Structure](image)

   R1 is lower alkyl, cycloalkyl, hydroxycycloalkyl, arylalkyl, cycloalkylalkyl, bicycloalkyl;

   R2 is hydrogen, hydroxy, oxo, halogen, lower alkyl, and amino;

   R3 is hydrogen, hydroxy, oxo, halogen, lower alkyl, and amino;

   R4 is hydrogen, halogen, hydroxy, methylhydroxy, lower alkyl, lower alkoxy, amino, lower alkylamino, cyano, aldehyde, aldehydoxime, -COR5;

   R5 is hydroxy, -NHNH₂, lower alkyl;

   X is oxygen or carbon, carbonyl, imine, amide;

   A, B, C, and D are independently carbon, nitrogen or N-oxide;

   or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 wherein,

   R1 is C₁-C₄ lower alkyl, C₃-C₆ cycloalkyl, hydroxy-C₃-C₆ cycloalkyl, aryl-C₃-C₆ alkyl, C₃-C₅ cycloalkyl-C₁-C₂ alkyl, 1-indanyl or 2-indanyle;

   R2 is hydrogen, hydroxy, oxo, halogen, methyl, ethyl, and amino;

   R3 is hydrogen, hydroxy, oxo, halogen, methyl, ethyl, and amino;

   R4 is hydrogen, halogen, hydroxy, methylhydroxy, C₁-C₄ lower alkyl, C₁-C₄ lower alkoxy, amino, C₁-C₄ lower alkylamino, cyano, aldehyde, aldehydoxime, -COR₅;
R5 is hydroxy, -NHNH₂, C₁-C₄ lower alkyl;
X is oxygen or carbon, carbonyl, imine, amide;
A, B, C, and D are independently carbon, nitrogen or N-oxide;
or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 2 wherein,

R1 is methyl, ethyl, propyl, C₃-C₆ cycloalkyl, hydroxy-C₃-C₆ cycloalkyl, aryl-C₃-C₆ alkyl, C₃-C₅ cycloalkyl-C₁-C₂ alkyl, 1-indanyl or 2-indanyl;
R2 is hydrogen, hydroxy, oxo, halogen, methyl, ethyl, and amino;
R3 is hydrogen, hydroxy, oxo, halogen, methyl, ethyl, and amino;
R4 is hydrogen, halogen, hydroxy, methylhydroxy, methyl, methoxy, amino, methylamino, cyano, aldehyde, aldehydeoxime, -COR₅;
R5 is hydroxy, -NHNH₂, methyl, ethyl;
X is carbon, carbonyl, imine, and amide;
A, B, C, and D are independently carbon, nitrogen or N-oxide;
or a pharmaceutically acceptable salt thereof.

4. A process for preparing 3-cyclopentyloxy-4-methoxyphenyl-isoindolinone derivatives having the formula [1], which comprises the following procedures. The compound of formula [3] is prepared by reacting the formula [4] with the formula [5] or [6]. Then the formula [3] is reduced to afford the compound of formula [2]. The compound of formula [2] is dehydroxylated to produce the compound of formula [1], in which R₃ is hydrogen, and one of C and D is nitrogen.
wherein,

R1 is methyl, ethyl, propyl, C3-C6 cycloalkyl, hydroxy-C3-C6 cycloalkyl, aryl-C3-C6 alkyl, C3-C5 cycloalkyl-C1-C2 alkyl, 1-indanyl or 2-indanyl;

R2 is hydrogen, hydroxy, oxo, halogen, methyl, ethyl, and amino;

R3 is hydrogen, hydroxy, oxo, halogen, methyl, ethyl, and amino;

R4 is hydrogen, halogen, hydroxy, methylhydroxy, methyl, methoxy, amino, methylamino, cyano, aldehyde, aldehydeoxime, -COR5;

R5 is hydroxy, -NHNH2, methyl, ethyl;

X is carbon, carbonyl, imine, and amide;

A, B, C, and D are independently carbon, nitrogen or N-oxide;

5. A method for treating a disease state capable of being modulated by inhibiting TNF comprising administering to a patient suffering from said disease state an effective amount of the compound of claim 1.
6. The method of claim 5, wherein said disease state is an inflammatory disease or autoimmune disease.

7. The method of claim 5, wherein said disease state is selected from the group consisting of joint inflammation, rheumatoid arthritis, osteoarthritis, sepsis, septic shock, asthma, graft versus host reaction, psoriasis, Crohn’s disease, ulcerative colitis, systemic lupus erythematosus, multiple sclerosis, type I diabetes mellitus, chronic glomerulonephritis, and inflammatory bowel disease.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 209/46
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)
IPC7: C07D 209/46, C07D 471/04, A61K 31/40, A61K 31/435

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean Patents and application for inventions since 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MEDLINE, NPS, PAI, STN on line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>WO 9842666 A (DAEWOONG PHARMACEUTICAL CO., LTD.) 01 OCT 1998 claims 1-14</td>
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Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
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"&" document member of the same patent family

Date of the actual completion of the international search
28 DECEMBER 2001 (28.12.2001)

Date of mailing of the international search report
28 DECEMBER 2001 (28.12.2001)

Name and mailing address of the ISA/KR
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Facsimile No. 82-42-472-3556

Authorized officer
BAIK, Kyong Up
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