Abstract: This invention relates to compounds for the treatment of disease induced, caused or dependent on activation of the Sonic hedgehog pathway, wherein the compound is a thyromimetic lacking inner-ring iodines. Preferably the compound is of formula (I) or a pharmaceutically acceptable ester, amide, solvate or salt thereof, including a salt of such an ester or amide, and a solvate of such an ester, amide or salt, formula (I), wherein G is a group selected from: formula (II) (III) (IV) (V) and the remaining groups/substituents are as defined herein.
This invention relates to a novel use of thyromimetic compounds.

Thyromimetic compounds are known from WO 99/00353, WO 00/39077, WO 01/60784, WO 01/98256, WO 03/018515, WO 03/084915, WO04/007430, WO04/067482, WO05/092316, WO05/092317, WO07/003419, WO 07/10226, WO 07/128492, and WO 07/134864.

The present application provides a novel use of the compounds described in the above applications.

The hedgehog signaling pathway, which takes its name from an intercellular signaling molecule called hedgehog (Hh), is important in growth and cell differentiation during embryogenesis and for the proper functioning of many adult tissues. The pathway has been recognized to have a central role in vertebrate growth and morphogenesis.

The Hh-protein binds to the cell-membrane receptor proteins Patched (PTCH1 and PTCH2 in humans). In their non-bound state PTCH1 and PTCH2 inhibit the transmembrane protein Smoothened (SMOH); however, when bound to Hh the inhibition is relieved. SMOH triggers downstream intracellular targets to induce gene expression.

The Gli proteins (Gli-I, Gli-2 and Gli-3) are the downstream effectors of hedgehog signaling that enter the nucleus and initiate gene transcription.

The Sonic Hedgehog pathway (SHh) in mammals is of particular interest due to its involvement in the growth and survival of cells and tissues and because its deregulation is thought to be important in the pathogenesis of many forms of cancer. SHh signaling has a major role in controlling cell-cycle fates during cell proliferation. Inhibition of the SHh pathway has been proven to cause G1 and G2 cell-cycle blockade. Studies of epithelial cell proliferation showed that cells expressing SHh
oppose epithelial cell-cycle arrest by keeping the cell in S and G2/M phases by induction of Cyclin D and E.

Thus, SHh signaling can enable cells to evade apoptosis and cell cycle arrest which suggests that deregulation in SHh signaling could contribute to multistep carcinogenesis in multiple tumor types. Recent studies have demonstrated that the SHh pathway is deregulated in colon, breast, esophagus, lung, stomach and pancreatic neoplasms as well as in basal cell carcinoma. Interestingly, SHh is known to play an important role in the normal development of most of these organs lending credence to the idea that these malignancies arise from aberrant signaling of normal developmental pathways (The sonic hedgehog signaling network in development and neoplasia; Chari NS, McDonnell TJ. *Adv Anat Pathol* 2007 Sep;14(5):344-52).

Organs dependent on SHh signaling for normal development frequently exhibit deregulation of the SHh pathway in carcinomas arising from these organs. A set of these carcinomas are listed below and since many of these malignancies are characterized by high mortality rates due to an insufficient therapeutic arsenal, novel effective therapies are desired:


In some tumors SHH-Smo independent activation of Gli-signaling occurs and molecules that directly blocks Gli transcriptional activity (through blocking Gli DNA-binding) has been showed to block cell growth in an in vivo xenograft model using human prostate cancer cells harboring downstream activation of the Hh pathway (Inhibition of GLI-mediated transcription and tumor cell growth by small-molecule antagonists; Lauth M, Bergstrom A, Shimokawa T, Toftgard R; *Proc Natl Acad Sci U SA*. 2007 May 15;104(20):8455-60).
Activation of SHh is seen in most gastric cell lines and in primary tumors and is correlated with more aggressive forms of cancer (Frequent activation of the hedgehog pathway in advanced gastric adenocarcinomas; Ma X, Chen K, Huang S, Zhang X, Adegboyega PA, Evers BM, Zhang H, Xie J. Carcinogenesis. 2005 Oct;26(10):1698-705).

Pancreatic cancer, the fourth leading cause of cancer-related deaths in the United States: Elevated levels components of the SHh pathway are observed in pancreatic ductal adenocarcinoma precursor lesions, and these levels increase further as lesions progress to more advanced stages. It has been demonstrated that SHh expression enhances tumor initiation and growth and reduces tumor cell death after therapeutic intervention (Sonic hedgehog acts at multiple stages during pancreatic tumorigenesis; Morton JP, Mongeau ME, Klimstra DS, Morris JP, Lee YC, Kawaguchi Y, Wright CV, Hebrok M, Lewis BC and Proc Natl Acad Sci USA. 2007 Mar 20;104(12):5103-8 SHh signaling and pancreatic cancer: implications for therapy? Morton JP, Lewis BC; Cell Cycle. 2007 Jul 1;6(13):1553-7).

GLII, a transcription factor induced by SHh activation was expressed in most small cell lung cancer (SCLC) tumors studied. Surprisingly, only in 3 of 20 SCLC cell lines SHh activation expression was detected. Thus it appears like SCLC cells can circumvent the apparent in vivo requirement of SHh signaling when they are grown in culture (Hedgehog signaling in small-cell lung cancer: frequent in vivo but a rare event in vitro Vestergaard J, Pedersen MW, Pedersen N, Ensinger C, Turner Z, Tommerup N, Poulsen HS, Larsen LA.; Lung Cancer. 2006 Jun;52(3):281-90).

Basal Cell Carcinoma (BCC) is the most common cancer in the western world, with well over 750,000 new cases annually in the United States alone. A potent small molecule Hh inhibitor (CUR61414) arrested proliferation of basal cells within BCC-like lesions in mice lesions and induced them to undergo apoptosis leading to complete regression of the lesions, without affecting neighboring skin cells Identification of a small molecule inhibitor of the hedgehog signaling pathway: effects on basal cell carcinoma-like lesions; Williams JA, Guicherit OM, Zaharian BI, Xu Y, Chai L, Wichterle H, Kon C, Gatchalian C, Porter JA, Rubin LL, Wang FY. Proc Natl Acad Sci USA. 2003 Apr 15;100(8):4616-21).
PTCH (the receptor of SHh) is mutated in sporadic as well as hereditary BCCs, and inactivation of this gene is probably a necessary if not sufficient step for tumorigenesis. Correlations between the Sonic Hedgehog Pathway and basal cell carcinoma; Lupi O *J Dermatol* 2007 Nov;46(1):1 113-7).

An increased expression of SHh mRNA in human colonic adenocarcinomas SHh was demonstrated. In a colorectal cell line, exogenous SHh promoted cell proliferation, while inhibition of SHh expression decreased proliferation (Sonic Hedgehog-dependent proliferation in a series of patients with colorectal cancer; Douard R, Moutereau S, Pernet P, Chimingqi M, Allory Y, Manivet P, Conti M, Vaubourdolle M, Cugnenc PH, Loric *Surgery* 2006 May;139(5):665-70).

The theory of an association between tumor cells and stem cells has been discussed for decades. The theory postulates that cancer is a stem cell disease caused by mutations in stem cell signaling pathways which trigger cell growth and proliferation. Chemo radiotherapy constitutes the primary clinical treatment for cancer but frequently tumors become resistant to such therapies during treatment. However, since SHH-signaling is known to be involved in many forms of cancer; the relationship between SHH-signaling and resistance to chemotherapeutic agents has been studied. It was found that Cyclopamine (in inhibitor of SHH-signaling) in itself only had minor effects in a set of cancer cell-lines from a range of different tumors. But it was also found that Cyclopamine in combinations with chemotherapeutic agents greatly enhanced death of tumor cells. Thus agents targeting the SHH pathway
could have a clinical role to overcome resistance to chemotherapy (Targeting hedgehog in cancer stem cells: how a paradigm shift can improve treatment response; Tung DC, Chao KS. *Future Oncol* 2007 Oct;3 (5):569-74).

Inhibition of SHh signaling pathway for therapeutic effects towards various cancer forms is receiving widespread attention. The first known inhibitor of the SHh pathway was the teratogenic alkaloid cyclopamine which binds and inhibits the signaling intermediate SMO (The sonic hedgehog signaling network in development and neoplasia; Chari NS, McDonnell TJ. *Adv Anat Pathol.* 2007 Sep;14(5):344-52).

![Cyclopamine](image)

Other inhibitors are the molecules CUR61414 (mentioned above) and "HhAntag"; a small molecule inhibitor of the SHh pathway which blocked the function of Smoothened in mice with medulloblastoma which resulted in suppression of several genes highly expressed in medulloblastoma, inhibition of cell proliferation, and increase in cell death and, at the highest dose, complete eradication of tumors. Long-term treatment with HhAntag prolonged medulloblastoma-free survival (Suppression of the SHh pathway using a small molecule inhibitor eliminates medulloblastoma in Ptcl(+/-)p53(-/-) mice; Romer JT, Kimura H, Magdaleno S, Sasai K, Fuller C, Baines H5 Connelly M, Stewart CF, Gould S, Rubin LL, Curran T.; *Cancer Cell* 2004 Sep;6(3):229-40).

Small-molecule antagonists of GLI-mediated transcription acting in the nucleus to block GLI function interfering with GLII DNA binding in living cells. The compounds inhibited in vitro tumor cell proliferation and blocked cell growth in an in vivo xenograft model using human prostate cancer cells (Inhibition of GLI-mediated transcription and tumor cell growth by small-molecule antagonists; Lauth M,


In many cells and tissues, intracellular thyroid hormone activity is regulated by the activity of two enzymes denoted deiodinases. Type 2 deiodinase (D2) activates the prohormone thyroxine (T4) by converting it to thyroid hormone (T3), whereas D3, by inactivating T3, terminates thyroid hormone action by reducing intracellular T3. Together with transmembrane transporters, that control import and export of T4 and T3, D2 and D3 controls intracellular T3-homeostasis because the Dio3 gene is transcriptionally stimulated by T3, whereas D2 is inhibited by two thyroid hormone-mediated effects, a transcriptional down regulation of Dio2 as well as protein inactivation by ubiquitination. During development, pre-programmed changes in D2 and D3 expression are thought to regulate intracellular T3 concentrations essential to the normal development of the central nervous system, including the retina and the inner ear. However, the signals governing the changes in D2 and D3 expression during these complex processes has until now been essentially unknown.

Both the prohormone T4 and the active hormone T3 are substrates for the inactivating enzyme D3. The enzyme cleaves off one iodine-atom in the inner ring (3 or 5 position). Thus D3 converts T4 to the transcriptionally inactive substance reverse T3 (revT3) and it converts T3 to the transcriptionally inactive substance 3,3’-T2. Induction of D3 in a cell will decrease the intracellular levels of the transcriptionally active hormone T3 thus inducing "cellular hypothyroidism" (Activation and inactivation of thyroid hormone by deiodinases: Local action with general consequences; Gereben B, Zeöld A, Dentice M, Salvatore D, Bianco AC Cell Mol Life Sci. 2007 Nov 9).
Moreover, Dentice et al also demonstrated that the activating enzyme D2 (which converts T4 to T3) is down regulated by SHh-signalling.

It has also been shown that activation of SHh increase MDRI-activity (Sonic Hedgehog promotes multiple drug resistance by regulation of drug transport; Sims-Mourtada J, Izzo JG, Ajani J, Chao KS. Oncogene. 2007 Aug 16;26(38):5674-9) and since it is known that T3 is a substrate for MDRI (Thyroid hormone export in rat FRTL-5 thyroid cells and mouse NIH-3T3 cells is carrier-mediated, verapamil-sensitive, and stereospecific; Cavalieri RR, Simeoni LA, Park SW, Baxter JD, Scharschmidt BF, Ribeiro RC, Lomri N; Endocrinology. 1999 Nov;140(11):4948-54) this should also contribute to lowered intracellular levels of T3.

In contrast to steroid hormone receptors that are transcriptionally inactive in the absence of ligand, unliganded Thyroid hormone Receptors (apo-TRs) binds to regulatory promotor-sequences and modulate transcription of target genes. Several genes has been showed to be under negative transcriptional control of T3, best known example is the control of TSHβ-gene expression in pituitary where expression is induced by apo-TRβ and conversely reduced by T3-bound TRβ (holo-TR).

In rodents, D3 is expressed in the pregnant uterus and placenta and in most fetal tissues, including the CNS. After birth, the expression of D3 is more restricted and in rats occurs primarily in the skin and CNS (Activation and inactivation of thyroid hormone by deiodinases: Local action with general consequences; Gereben B, Zeold A, Dentice M, Salvatore D, Bianco AC Cell Mol Life Sci. 2007 Nov 9). However, recent studies have suggested that D3 is induced in adult cells and tissues during abnormal/pathological conditions (Induction of type 3 deiodinase activity in inflammatory cells of mice with chronic local inflammation; Boelen A, Kwakkel J, Alkemade A, Renckens R, Kaptein E, Kuiper G, Wiersinga WM, Visser TJ; Endocrinology. 2005 Dec;146(12):5128-34 and Thyroid function disturbance and type 3 iodothyronine deodinase induction after myocardial infarction in rats a time course study; Olivares EL, Marassi MP, Fortunato RS, da Silva AC, Costa-e-Sousa RH, Araújo IG, Mattos EC, Masuda MO, Mulcahey MA, Huang SA, Bianco AC, Carvalho DP; Endocrinology. 2007 Oct;148(10):4786-92).
The pattern of D3 expression suggests that in the developing fetus it plays a role in limiting tissue exposure to thyroid hormone. This is critical since serum thyroid hormone levels in the fetal rat are much lower than those present in the mother.

It is known that D3 overexpression in vascular tumors results in consumptive hypothyroidism. A conserved Gli-2 binding site has been demonstrated in the D3-promotor. D3 knockout mice display high growth retardation and neonatal mortality, which may result from exposure to excessive levels of maternal thyroid hormone. D3-protein forms dimers and has a long half-life (~12 h) and there is no evidence of regulation of dio3 expression at the post-transcriptional level (Activation and inactivation of thyroid hormone by deiodinases: Local action with general consequences; Gereben B, Zeδld A, Dentice M, Salvatore D, Bianco AC Cell Mol Life ScL 2007 Nov 9).

Therefore the work conducted by Dentice et Al, who through a set of experiments clearly demonstrates that SHh-signalling promotes D2 degradation in normal and malignant keratinocytes and increase D3 expression in the same cells, is important since it provides an improved understanding of how SHh activation and inactivation regulates cell-proliferation and differentiation and also suggest the use of exogenous T3 as antineoplastic agent (see figure 1).

Proposed pathway (figure published by Dentice et Al) for how SHh (which by binding to PTCH release SMO) can influence the balance between cell proliferation and differentiation in the tissue microenvironment by inactivating T3 as well as blocking its production. Importantly, the SHH-mediated effects can occur in vivo in a time- and tissue-specific fashion independently from the constant serum levels of circulating thyroid hormone. Blocking D3 synthesis by RNAi or opposing its action by excess T3 resulted in a dramatic impairment of proliferation in normal and malignant keratinocytes. These findings suggest that not only is D3 up-regulated in BCC but its action, i.e., induction of hypothyroidism at a cellular level, is required for proliferation. Dentice et Al further speculate that since D3 is expressed in many different neoplastic cells as well as in placenta and human fetal epithelium the resulting reduced intracellular T3 provides a metabolic advantage for these rapidly
proliferating cells. Reversing this T3 deficiency may be a reasonable therapeutic approach for Basal Cell Carcinoma and perhaps other D3-expressing tumors.

There are a few published studies that denotes T3 a potential therapeutic efficacy for treatment of carcinomas. Ledda-Columbano et Al showed that T3 (given in food) reduced the incidence of diethylnitrosamine-induced Hepatocellular Carcinoma in rats and totally inhibited metastases in the lungs (3,3',5-Triiodo-L-thyronine inhibits ductal pancreatic adenocarcinoma proliferation improving the cytotoxic effect of chemotherapy; Michienzi S, Bucci B, Verga Falzacappa C, Patriarca V, Stigliano A, Panacchia L, Brunetti E, Toscano V, Misiti S. J Endocrinol. 2007 May;193(2):209-23). A synthetic T3-analogue has also been shown to have similar anticancerous activity as T3 (Effects in the early and late phase of treatment with KAT-681, a liver selective thyromimetic, on rat hepatocarcinogenesis induced by 2-acetylaminofluorene and partial hepatectomy after diethylnitrosamine initiation; Hayashi M, Tamura T, Kuroda J, Ohnota H, Shibata N, Akahane M, Kashida Y, Mitsumori K Toxicol Set 2005 84:22-28).

Michienzi et Al showed that T3 reduced proliferation of two cell lines of human pancreatic carcinoma and also that concomitant T3-treatment potentiated the cytotoxic action of the chemotherapeutic drugs Gemcitabin and Cisplatin. Both major TR-subtypes (TRalfal and TRbetal) where expressed in the cell-lines (Cell proliferation induced by triiodothyronine in rat liver is associated with nodule regression and reduction of hepatocellular carcinomas; Ledda-Columbano GM, Perra A, Loi R, Shinozuka H, Columbano A. Cancer Res. 2000 Feb 1;60(3):603-9).

Recently, a set of studies have published suggesting that induction and maintenance of a lowered intracellular T3-concentration increase the ability of a cancer cell to proliferate also in some types of tumours which are suspected to be dependent on other signaling pathways than SHh/Patch/Gli.

For example, Turowska et Al, investigated tumors from patients suffering from clear cell renal cell carcinoma and found that the tumor tissue contained higher numbers of TR-alpha and TR-beta than control tissue. (Over expression of E2F1 in Clear Cell Renal Cell Carcinoma: A Potential Impact of Erroneous Regulation by Thyroid Hormone Nuclear Receptors”; Olga Turowska, Alicja Nauman, Maciej Pietrzak, Piotr
Poplawski, Adam Master, Maria Nygard, Maria Bondesson, Zbigniew Tanski, Monika Puzianowska-Kuznicka. Thyroid 2007 Vol. 17(1): 1037-48

Turowska et Al also demonstrated that the transcription factor E2F1 was over expressed in the tumor tissue as well and could demonstrate, in cell-based in-vitro systems, that transcription of E2F1 was up-regulated by TR in the absence of T3 but that addition of T3 to the cell-medium reduced transcription of E2F1. It has been demonstrated that T3-TR repress (and that apo-TR activates) transcription of the E2F1-gene through a negative TRE (Thyroid hormone Response Element) which has been identified in the E2F1-promoter (Hormone-dependent repression of the E2F-1 gene by thyroid hormone receptors. Nygard M, Wahlstrom GM, Gustafsson MV, Tokumoto YM, Bondesson M 2003 Mol Endocrinol 17:79-92.).

It is likely that in a normally functioning cell, TR binds to the negative TRE in the E2F1 promoter, and when T3 is bound to the TR transcription of this gene is inhibited. As a result, a lower amount of E2F1 mRNA and protein is produced. In a cancer cell the control of this series of events is disturbed. Transition from Gl-phase to S-phase in the cell-cycle is controlled by the Retinoblastoma (Rb) family of proteins via an intricate set of intracellular events. In brief: 1) when Rb becomes phosphorylated by cyclin D-dependent kinases, the E2F/DP/Rb repressor complex is replaced by E2F/DP activator complex leading to activation of a number of genes that are essential for executing the DNA-synthesis during the S-phase.

It is clear that most cancers include genetic aberrations affecting Rb/E2F regulation and it has been speculated that every single solid tumor may have a mutation affecting this pathway which will favor proliferation of the tumor.

Thus, in Clear Cell Renal Cell Carcinoma an increased E2F1-expression transfers into an increased mitosis and eventually to increase number of tumor cells. Since E2F1 expression is positively controlled by apo-TR and negatively controlled by T3-TR this suggest an additional mechanism for how T3 or synthetic T3-analouges (i.e. NIOTA) could be used to reduce proliferation of cancer cells.

Another example regards the Wnt/β-catenin-pathway. Activation of the Wnt/β-catenin pathway has been implied to drive progression of many cancers (i.e. melanoma and colon carcinoma), this activation is achieved by stabilization of β-catenin by protecting this protein for ubiquitination and resultant degradation via the proteosomal pathway proteases. (Regulation of beta-catenin by a novel nongenomic action of

Guigon et al uncovered a novel action of TRβ to cross talk with Wnt/β-catenin signaling via regulating the cellular level of β-catenin. They could demonstrate that T3-bound TRβ facilitated the degradation of β-catenin through a physical interaction of TR with β-catenin. Moreover, they demonstrated that β-catenin is protected from proteosomal degradation when associated with unliganded TRβ. Furthermore they showed that c-Myc, one of the downstream target genes of Wnt/β-catenin signaling, was repressed in the presence of T3 both at the mRNA levels and protein levels.

Another signalling pathway that has been found to be aberrantly regulated in many tumours is the PI3K-pathway. It has recently been demonstrated by Furuya et al that apo-TRbeta, act via direct protein-protein interaction to mediate critical oncogenic actions via that pathway. (Nongenomic activation of phosphatidyl inositol 3-kinase signaling by thyroid hormone receptors.Furuya F, Lu C, Guigon CJ, Cheng SY. Steroids. 2008 Oct 30.) Authors could demonstrate that apo-TRbeta physically interacts with the regulatory subunit of phosphatidylinositol 3-kinase (PI3K) to activate the downstream mammalian target of rapamycin (mTOR) and p70s6β and PI3K-integrin-linked kinas matrix metalloproteinase-2 signaling pathways. The apo-TRbeta mediated PI3K activation results in increased cell proliferation, motility, migration, and metastasis.

Taken together, it has been demonstrated that apo-TR have a clear role in driving growth of tumor cells (i.e. proliferation, motility, migration, and metastasis) in four of the control mechanisms or signaling pathways most well recognized to be aberrantly activated in cancer cells namely Sonic Hedgehog-, Wnt-B-catenin-, E2F/Rb- and PDKYPTEN-pathways. (Chapter 8. Signaling pathways in Cancer. By Daniel Kalderon in Principles of Molecular Oncology 3rd Edition, Humana Press Inc. 2008)

It has also been demonstrated that T3-bound TR have an opposite action to apo-TR and that an increased ratio of T3-TR/apo-TR inside the cancer-cell will slow down or arrest growth (proliferation, motility, migration, and metastasis) of the cell. Thus the ability of a tumor cell to create an intracellular milieu with a decreased ratio of T3-TR/apo-TR may be conditional for the growth of that cell.
It has been demonstrated that induction of the intracellular T3-degrading enzyme Deiodinase 3 is a requisite for growth of a Sonic Hedgehog activated tumor (BCC, supra) but so far it is not known whether Deiodinase 3 also is up regulated in Wnt-B-catenin-, E2F/Rb- and PI3K/PTEN-pathways. However, there are additional mechanisms that a cancer-cell can possibly utilize to reduce intracellular T3-levels such as inducing MDRI which increase efflux of T3 (see reference Cavalieri-Endocrinology. 1999 Nov;140(U):4948-54) above.

If intracellular levels of T3 can be increased to reach a restored ratio of T3-TR/apo-TR to what is normal in a senescent cell the cancer cell should lose its ability to proliferate.

Based on the examples described above it is anticipated that the cancer cell, in order to increase its capacity to proliferate, actively reduce its pool of intracellular T3 in order to achieve an increased ratio of apo-TR/T3-TR. It is likely that the cancer-cell can achieve this by activating intracellular pathways such as 1) induction of an increased degradation of T3 via induction of Deiodinase type-3, 2) a reduced production of T3 by down-regulation of Deiodinase type-2, 3) an increased efflux of T3 via MDRI and 4) an decreased uptake of T3 by down-regulation of cellular membrane transport mechanisms (ie OATPC and MCT8) which facilitate diffusion of T3 into the cell.

It is well known that cancer-cells share functional similarities with fetal cells and that reactivation of genes that are dormant in a senescent or mature cell occurs. It is also well known that fetal cells, as well as fetuses, have active mechanisms (ie Deiodinase type-3 activity) operating to achieve low intracellular T3-levels. The lowered intracellular level will increase the ratio of apo-TR/T3-TR and thereby stimulate proliferation of the fetal cell.

It is therefore likely that the cancer-cell can reduce its intracellular T3-levels by utilizing the same mechanisms as the fetal cell and since these pathways have evolved to specifically handle T3 and T4 it is very likely that a NIOTA will be a poor substrate for these mechanisms.

It is likely that progression of several common malignancies is driven by an increased intracellular ratio of apo-TRs/holo-TRs and that a normalization of that ratio with exogenous T3 (to increase the number of holo-TRs) stops proliferation and induce
differentiation of the cancer cells. It has been demonstrated that T3 (in relatively high doses) have anti proliferative effects in cancer cell-lines and that T3 can protect rats from hepatocarcinoma. Dentice et Al propose the use of topical T3 as a potential treatment of Basal Cell Carcinoma T3.

However, the low intracellular levels of T3 inside the cell are caused by the presence of the enzyme Deiodinase 3. This enzyme has high specificity and high catalytic activity (Km <10 nM) for T3 and T4 and thus, a substantial amount of the exogenous T3 that enters the cell will be consumed by D3 rather than binding to TRs. Thus, the amounts of exogenous T3 that can be given to a patient, considering the narrow therapeutic window to deleterious cardiac effects of T3 (tachycardia, atrial fibrillation etc), are most likely to low to allow for robust antitumor effect.

Several non-iodinated T3-analogues (NIOTA) have been synthesized. These T3-analogues have been demonstrated to bind to TRs and to induce same/similar structural changes in the TR-molecules as is induced by T3. It is thus likely that these NIOTA could be used to normalize/reduce the apo-TRs/holo-TRs ratio in tumor cells and thus have anti proliferative effects in cancer forms driven by the Sonic Hedgehog pathway. Several of these NIOTA has been showed more potent anti proliferative activity than T3 in cancer cell lines. Several of these NIOTA has also showed to reduce invasive growth of tumor cells with higher potency than T3 in cancer cell lines. Several of these NIOTA has also been showed to inhibit SHh induced proliferation in different in-vitro systems. A representative set of these NIOTA has also been showed to inhibit SHh-driven growth of tumor xenografts in nude mice. One NIOTA reduced/reversed progress of Basal Cell Carcinoma in patients.

Thus, this invention encompass the use of NIOTA with high affinity (Kd<30 nM) or lower to any or both subtypes of TR (alpha and beta) for all types of malignancies dependent/driven by the Sonic Hedgehog pathway including factors downstream the pathway (Gli1&2 transcriptional activation of Deiodinase 3). These malignancies include prostate cancer, gastric cancer, pancreas cancer, liver cancer, colon cancer, lung cancer, basal cell carcinomas of the skin. The invention also encompasses treatment of Gorlin's syndrome.
Furthermore, the invention also encompass the use of NIOTA with high affinity (Kd<30 nM) or lower to any or both subtypes of TR (alpha and beta) for all types of malignancies where pathway either of the three following signaling pathways Wnt-B-catenin-, E2F/Rb- or PI3K/PTEN-pathways are dysregulated.

According to the invention, the applicant also provides a compound for the treatment of disease induced, caused or dependent on activation of the Sonic hedgehog pathway, wherein the compound is a thyromimetic lacking inner-ring iodines.

According to the invention, the applicant also provides A compound of formula (I) or a pharmaceutically acceptable ester, amide, solvate or salt thereof, including a salt of such an ester or amide, and a solvate of such an ester, amide or salt,

![Chemical Structure](image)

wherein:

G is a group selected from:

![Chemical Structure](image)

in group IV, N is a sp² nitrogen with a non-bonded electron pair in a sp² orbital;

in group V, Z is selected from C or N with the proviso that when Z is N than R⁸ is an electron pair;

n is an integer from 0 to 2;

R⁴ and R⁵ are independently selected from hydrogen, halogen, C₄ alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, C₄ alkoxy, fluoromethoxy,
difluoromethoxy and trifluoromethoxy with the proviso that only one of $R^4$ and $R^5$ can simultaneously be hydrogen;

$R^6$ is selected from hydrogen, halogen, trifluoromethyl, $C_i$-$a$ alkyl, where the alkyl can be linked through the available atoms to position $W$ to from a saturated $C_5$ cycloalkyl as in the structure below:

$R^9$ is selected from hydrogen and halogen;

$W$ is selected from $C_{0-4}$ alkenylene, $C_{0-2}$ alkenylene $C(O)$, $C_{2-4}$ alkenylene, $N(R^a)$-$C_i$-$3$ alkenylene, $C(O)$-$C_{0-2}$ alkenylene, $S(0)$-$C_{0-3}$ alkenylene, where $p$ is an integer from 0 to 2, $O$-$C_i$-$3$ alkenylene, $C_{0-3}$ alkenylene-$O$-$C_{1-3}$ alkenylene, $C(O)N(R^d)$-$R^3$ alkenylene, $N(R^a)(C(O))$-$C_{0-3}$ alkenylene, $C_{0-3}$ alkenylene-$NR^a$-$SO_2$-$R^a$, $C_{0-3}$ alkenylene $C(O)$-$NR^a$-$SO_2$-$R^a$ and $C_{1-3}$ alkenylene$C(O)$-$N(R^d)$-$C_i$-$3$ alkenylene, said alkenylene or alkenylene groups or portions of groups optionally being substituted with 1 or 2 groups selected from $R^b$, said substitution can also be connected to $R^a$, to form a 5 or 6 membered ring as in the structure represented below:

$Y$ is O or $CH_2$;

$Q$ is selected from O or NH;

$R^7$ is selected from $-CO_2R^a$, $-PO(OR^a)_2$, $-SO_2OR^a$, $-C(O)CO_2R^a$, $C(O)NR^aOR^a$, $-SO_2N(R^a)_2$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)NR^aSO_2R^3$, $C_{3-7}$ heterocyclyl, $N(R^%$ -
CN, -OH, and each R^a can be the same or different and can optionally be substituted with 1, 2 or 3 groups independently selected R^b;

R^8 is selected from a non bonded electron pair and C_{1,3} alkyl;

R^1 is independently selected from hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{3-6} cycloalkyl-C_{3-3} alkyl, phenyl, benzyl and C_{3-7} heterocyclcyl, -(CH_2)_m-SO_2-R^a, -(CH_2)_m-C(O)R^a, -(CH_2)_m-CSN(R^a)_2, -(CH_2)_m-CO-NR^a_2, -(CH_2)_m-S-R^a, -(CH_2)_m-NR^a-SO_2-R^a, -(CH_2)_m-SO_2-NH-R^a, -(CH_2)_m-NR^a-CO-R^a, said alkyl, cycloalkyl, aryl, heterocyclyl groups or portions of groups optionally being substituted with 1, 2 or 3 groups each independently selected from R^b, each R^a is independently selected and optionally substituted with 1, 2 or 3 groups independently selected from R^b;

m is an integer from 0 to 3;

R^2 is selected from hydrogen, halogen, cyano, -NO_2, C_6-H aryl, C_{1-6} alkyl, C_{9} heteroaryl, C_{3-8} cycloalkyl, C_{2-4} alkenyl said alkyl, cycloalkyl, aryl, heteroaryl and alkenyl optionally substituted with 1, 2 or 3 groups each independently selected from R^b;

R^3 is selected from hydrogen, halogen, C_{1-4} alkyl, cyano, C_{1-4} alkoxy, and N(R^a)_2. Said alkyl and alkoxy optionally substituted with 1, 2 or 3 groups selected from R^b;

each R^a is independently selected from hydrogen, C^a alkyl, C_{2-4} alkenyl, benzyl, heterocyclyl and C_{2-10} aryl, said alkyl, alkenyl, or aryl groups or portions of groups optionally being substituted with 1, 2 or 3 groups independently selected R^b; and

each R^b is independently selected from the group consisting of hydroxy, mercapto, amino, halogen, -CO_2-R^a, -C(O)H, C_{1-4} alkylthio, Arylthio, -N(R^a)_2, C_{1-10} alkyl, C_{3-8} cycloalkyl, C_{2-6} alkenyl, C_{2-4} alkylnyl, C_{1-4} alkoxy, C_{6-11} aryl ,C_9 heterocyclyl, haloC_{4} alkyl, dihaloC_{1-4} alkyl, trihaloC_{4} alkyl, haloC_{1-4} alkoxy, dihaloC_{1-4} alkoxy, and trihaloC_{1-4} alkoxy, said alkyl, cycloalkyl, alkenyl, alkylnyl, aryl, heteroaryl and heterocyclyl optionally substituted with 1, 2 or 3 groups selected from R^b.
for the treatment of disease induced, caused or dependent on activation of the Sonic hedgehog pathway.

In a preferred embodiment, the applicant also provides a compound of formula (I) or a pharmaceutically acceptable ester, amide, solvate or salt thereof, including a salt of such an ester or amide, and a solvate of such an ester, amide or salt,

\[
\begin{align*}
&\text{G} - \text{Y} \\
&\text{R}^4, \text{R}^5, \text{R}^6, \text{R}^7
\end{align*}
\]

wherein

G is a group selected from:

\[
\begin{align*}
(H) & \quad (HI) & \quad (IV) & \quad (V)
\end{align*}
\]

in group IV, N is a sp\(^2\) nitrogen with a non-bonded electron pair in a sp\(^2\) orbital;

in group V, Z is selected from C or N with the proviso that when Z is N than \(R^8\) is an electron pair;

n is an integer from 0 to 2;

\(R^4\) and \(R^5\) are independently selected from halogen, \(C_{1-4}\) alkyl, trifluoromethyl;

\(R^6\) is selected from hydrogen, halogen, \(C_{2}\) alkyl, where the alkyl can be linked through the available atoms to position W to from a saturated \(C_5\) cycloalkyl as in the structure below:
**R** is selected from hydrogen and halogen:

W is selected from C_0-4 alkylene, N(R^a)-C, -3 alkylene, O-C_i-3 alkylene, C(O)N(R^a)-Ci-2 alkylene, N(R^a)(CO)-Co-2 alkylene, said alkylene groups or portions of groups optionally being substituted with 1 or 2 groups selected from R^b, said substitution can also be connected to R^a, to form a 5 or 6 membered ring as in the structure represented below:

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{H}
\end{array}
\]

Y is O;

Q is selected from O or NH;

**R** is selected from -CO_2R^a, -PO(OR^a)_2, each R^a can be the same or different and can optionally be substituted with 1, 2 or 3 groups independently selected from R^b;

**R** is selected from a non bonded electron pair and C_i-3 alkyl;

**R** is independently selected from hydrogen, C_i-0 alkyl, C_3-7cycloalkyl, C_3-6 cycloalkyl-C_i-3 alkyl, phenyl, benzyl and C_3-7 heterocycl, -(CH_2)_m-VC(O)R^a, and -(CH_2)_m-CO-NR^a)_2, said alkyl, cycloalkyl, aryl, heterocycl groups or portions of groups optionally being substituted with 1, 2 or 3 groups each independently selected from R^b, each R^b is independently selected and optionally substituted with 1, 2 or 3 groups independently selected from R^b;

m is an integer from 0 to 3;

**R** is selected from hydrogen, halogen, C_6-1 i aryl, C_i-10 alkyl, C_i-9 heteroaryl, C_3-8 cycloalkyl, said alkyl, cycloalkyl, aryl and heteroaryl, optionally substituted with 1, 2 or 3 groups each independently selected from R^b;
R³ is selected from hydrogen, halogen, C₁₋₄ alkyl, said alkyl optionally substituted with 1, 2 or 3 groups selected from Rᵇ;

each Rᵃ is independently selected from hydrogen and C₁₋₄ alkyl, said alkyl groups or portions of groups optionally being substituted with 1, 2 or 3 groups independently selected Rᵇ;

each Rᵇ is independently selected from halogen, -CO₂Rᵃ, Ct-io alkyl, C₃₋₅ cycloalkyl, Cl₋₄ alkoxy and C₆-H ary1, said alkyl, cycloalkyl, alkylenyl, alkynyl, aryl and heterocyclyl optionally substituted with 1, 2 or 3 groups selected from Rᵇ, for the treatment of disease induced, caused or dependent on activation of the Sonic hedgehog pathway.

Depending upon the substituents present in compounds of the formula I, the compounds may form esters, amides and/or salts. Salts and solvates of compounds of formula (I) which are suitable for use in medicine are those wherein a counter ion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counter ions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of the compounds of formula (I) and their pharmaceutically acceptable salts, solvates and physiologically functional derivatives. By the term "physiologically functional derivative" is meant a chemical derivative of a compound of formula (I) having the same physiological function as the free compound of formula (I), for example, by being convertible in the body thereto. Esters and amides are examples of physiologically functional derivatives.

Suitable salts according to the invention include those formed with organic or inorganic acids or bases. In particular, suitable salts formed with acids according to the invention include those formed with mineral acids, strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted, for example, by halogen, such as saturated or unsaturated dicarboxylic acids, such as hydroxycarboxylic acids, such as amino acids, or with organic sulfonic acids.
acids, such as (C,-C₄)-alkyl- or aryl-sulfonic acids which are unsubstituted or substituted, for example by halogen. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulphuric, nitric, citric, tartaric, acetic, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, succinic, perchloric, fumaric, maleic, glycolic, lactic, salicylic, oxaloacetic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic, benzenesulfonic, isethionic, ascorbic, malic, phthalic, aspartic, and glutamic acids, lysine and arginine. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful as intermediates in obtaining the compounds of the invention and their pharmaceutical acceptable acid addition salts.

Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts, for example those of potassium and sodium, alkaline earth metal salts, for example those of calcium and magnesium, and salts with organic bases, for example dicyclohexylamine, N-methy3-D-glucamine, morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, for example ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethyl-propylamine, or a mono-, di- or trihydroxy lower alkylamine, for example mono-, di- or triethanolamine. Corresponding internal salts may furthermore be formed.

Compounds of formula (I) may have an appropriate group converted to an ester or an amide. Thus typical ester and amide groups formed from an acid group in the compound of the formula I include -COORᵃ, -CONRᵃ₂, -SO₂O摅³, or -SO₂NRᵃ₂, while typical ester and amide groups formed from an -OH or -NHRᵃ group in the compound of the formula I include -O.CO.Rᵃ, -NRᵃ.CO.Rᵃ, -O.SO₂Rᵃ, and -NRᵃ.SO₂Rᵃ, where Rᵈ has one of the meanings given above.

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate".
A compound which, upon administration to the recipient, is capable of being converted into a compound of formula (I) as described above, or an active metabolite or residue thereof, is known as a "prodrug". A prodrug may, for example, be converted within the body, e.g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutical acceptable prodrugs are described in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A. C. S. Symposium Series (1976); "Design of Prodrugs" ed. H. Bundgaard, Elsevier, 1985; and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, which are incorporated herein by reference.

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

As used herein, the term "alkyl" means both straight and branched chain saturated hydrocarbon groups. Examples of alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, t-butyl, i-butyl, sec-butyl, pentyl and hexyl groups. Among unbranched alkyl groups, there are preferred methyl, ethyl, n-propyl, iso-propyl, n-butyl groups. Among branched alkyl groups, there may be mentioned t-butyl, i-butyl, 1-ethylpropyl and 1-ethylbutyl groups.

As used herein, the term "alkoxy" means the group O-alkyl, where "alkyl" is used as described above. Examples of alkoxy groups include methoxy and ethoxy groups. Other examples include propoxy and butoxy.

As used herein, the term "alkenyl" means both straight and branched chain unsaturated hydrocarbon groups with at least one carbon carbon double bond. Examples of alkenyl groups include ethenyl, propenyl, butenyl, pentenyl and hexenyl. Preferred alkenyl groups include ethenyl, 1-propenyl and 2-propenyl.

As used herein, the term "alkynyl" means both straight and branched chain unsaturated hydrocarbon groups with at least one carbon carbon triple bond. Examples of alkynyl groups include ethynyl, propynyl, butynyl, pentynyl and hexynyl. Preferred alkynyl groups include ethynyl 1-propynyl and 2-propynyl.
As used herein, the term "cycloalkyl" means a saturated group in a ring system. A cycloalkyl group can be monocyclic or bicyclic. A bicyclic group may, for example, be fused or bridged. Examples of monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl and cyclopentyl. Other examples of monocyclic cycloalkyl groups are cyclohexyl, cycloheptyl and cyclooctyl. Examples of bicyclic cycloalkyl groups include bicyclo [2.2.1]hept-2-yl. Preferably, the cycloalkyl group is monocyclic.

As used herein, the term "aryl" means a monocyclic or bicyclic aromatic carbocyclic group. Examples of aryl groups include phenyl and naphthyl. A naphthyl group may be attached through the 1 or the 2 position. In a bicyclic aromatic group, one of the rings may, for example, be partially saturated. Examples of such groups include indanyl and tetrahydronaphthyl. Specifically, the term C_{5,10} aryl is used herein to mean a group comprising from 5 to 10 carbon atoms in a monocyclic or bicyclic aromatic group. A particularly preferred C_{5,10} aryl group is phenyl.

As used herein, the term "halogen" means fluorine, chlorine, bromine or iodine. Fluorine, chlorine and bromine are particularly preferred.

As used herein, the term "haloalkyl" means an alkyl group having a halogen substituent, the terms "alkyl" and "halogen" being understood to have the meanings outlined above. Similarly, the term "dihaloalkyl" means an alkyl group having two halogen substituents and the term "trihaloalkyl" means an alkyl group having three halogen substituents. Examples of haloalkyl groups include fluoromethyl, chloromethyl, bromomethyl, fluoromethyl, fluoropropyl and fluorobutyl groups; examples of dihaloalkyl groups include difluoromethyl and difluoroethyl groups; examples of trihaloalkyl groups include trifluoromethyl and trifluoroethyl groups.

As used herein, the term "heterocyclyl" means an aromatic or a non-aromatic cyclic group of carbon atoms wherein from one to three of the carbon atoms is/are replaced by one or more heteroatoms independently selected from nitrogen, oxygen or sulfur. A heterocyclyl group may, for example, be monocyclic or bicyclic. In a bicyclic heterocyclyl group there may be one or more heteroatoms in each ring, or only in one of the rings. A heteroatom is preferably O or N. Heterocyclyl groups containing a
suitable nitrogen atom include the corresponding N-oxides. Examples of monocyclic heterocycloalkyl rings include aziridinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl and azepanyl.

Examples of bicyclic heterocyclic rings in which one of the rings is non-aromatic include dihydrobenzofuranyl, indanyl, indolinyl, isoindolmyl, tetrahydroisoquinolinyl, tetrahydroquinolyl and benzoazepanyl.

Examples of monocyclic heteroaryl groups include furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl, pyrazolyl and pyrimidinyl; examples of bicyclic heteroaryl groups include quinoxaliny1, quinazolinyl, pyridopyrazinyl, benzoxazolyl, benzothiophenyl, benzimidazolyl, naphththiridinyl, quinolyl, benzofuranyl, indolyl, benzothiazolyl, oxazolyl[4,5-b]pyridiyl, pyridopyrimidinyl, isoquinolinyl and benzodroxazole.

Examples of preferred heterocyclyl groups include piperidinyl, tetrahydrofuranyl, tetrahydropyranyl, pyridyl, pyrimidyl and indolyl. Preferred heterocyclyl groups also include thiophenyl, thiazoyl, furanyl, pyrazolyl, pyrrolyl and imidazolyl.

As used herein the term "cycloalkylalkyl" means a group cycloalkyl-alkyl- attached through the alkyl group, "cycloalkyl" and "alkyl" being understood to have the meanings outlined above.

As mentioned as above, the applicant also provides a compound for the treatment of disease induced, caused or dependent on activation of the Sonic hedgehog pathway, wherein the compound is selected from:
3-[[3,5-dibromo-4-[4-hydroxy-3-(1-methylemyl)-phenoxy]-phenyl]-amino]-3-oxopropanoic acid).
3-(3,5-dibromo-4-{{3-(methylamino)benzyl}oxy}phenyl)propanoic acid.
4-[(3-aminobenzyl)oxy]-3,5-dibromobenzoic acid
3-(4-{{3-amino-5-( trifluoromethyl)benzyl}oxy}-3,5-dibromophenyl)propanoic acid.
3-(3,5-dibromo-4-{[3-(methylamino)-5-trifluoromethyl]benzyl oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[2-methyl-3-(methylamino)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-(ethy lamino)-5-(trifluoromethyl)benzyl]oxy}phenyl)propanoic acid
3-{4-[3-(amino-5-chlorobenzyl)oxy]-3,5-dibromophenyl} propanoic acid
3-(3,5-dibromo-4-{[3-chloro-5-(ethylamino)benzyl]oxy}phenyl)propanoic acid
3-{4-{[3-amino-4-methylbenzyl]oxy}-3,5-dibromophenyl} propanoic acid
3-(3,5-dibromo-4-{[3-(ethylamino)-2-methylbenzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-(ethylamino)-5-methylbenzyl]oxy}phenyl)propanoic acid
3-{4-{[3-amino-5-trifluoromethyl]benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-(ethylamino)-4-methylbenzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-(isopropylamino)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-(isopropylamino)-5-(trifluoromethyl)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-(butylamino)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-(butylamino)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-(4-(2-ethyl)butyl)amino]benzyl}oxy)phenyl)propanoic acid
3-{4-{[3-amino-3-(methylamino)benzyl]oxy}-3,5-dichlorophenyl} propanoic acid
3-(3,5-dichloro-4-{[3-(methylamino)benzyl]oxy}phenyl)propanoic acid
S-fS^-dichloro^-IP-tethylamino^enzyljoxyjphenyOpropanoic acid
3-(3,5-dichloro-4-{[3-(ethylamino)-S-(trifluoromethyl)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{[3-(propylamino)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{[3-(isopropylamino)benzyl]oxy}phenyl)propanoic acid
3-(4-{[3-(sec-butylamino)benzyl]oxy}-3,5-dichlorophenyl)propanoic acid
3-[3,5-dichloro-4-{[3-(isopropylamino)benzyl]oxy}phenyl]propanoic acid

N-{4-{[3-aminobenzyl]oxy}-3,5-dibromobenzoyl} glycine
N-(3,5-dibromo-4-{[3-(ethylamino)benzyl]oxy}benzoyl)glycine
N-(3,5-dibromo-4-{[3-(methylamino)benzyl]oxy}benzoyl)glycine
N-(3,5-dibromo-4-{[3-(propylamino)benzyl]oxy}benzoyl)glycine
N-(3,5-dibromo-4-{[3-(isopropyiamino)benzyl]oxy}benzoyl)glycine
N-(3,5-dibromo-4-{[3-(cyclobutylamino)benzyl]oxy}benzoyl)glycine
N-(3,5-dibromo-4-{[3-(sec-butyIamino)benzyl]oxy}benzoyl)glycine
N-(3,5-dibromo-4-{[3-(ethylamino)-5-(trifluoromethyl)benzyl]oxy}benzoyl)glycine
N-(3,5-dibromo-4-{[3-chloro-5-(ethylamino)benzyl]oxy}benzoyl)glycine
N-(3,5-dibromo-4-{[3-(ethylamino)-5-methylbenzyl]oxy}benzoyl)glycine
N-(3,5-dibromo-4-{[3-(cyano-5-(ethylamino)benzyl)oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{[3-chloro-5-(ethylamino)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{[2-chloro-3-(ethylamino)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{[3-chloro-5-(ethylamino)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{[3-chloro-5-(ethylamino)-5-methylbenzyl]oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{[3-chloro-5-(ethylamino)-5-methylbenzyl]oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{[3-chloro-5-(ethylamino)-5-methylbenzyl]oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{[3-chloro-5-(ethylamino)-5-methylbenzyl]oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{[3-chloro-5-(ethylamino)-5-methylbenzyl]oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{[3-chloro-5-(ethylamino)-5-methylbenzyl]oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{[3-(cyclobutylamino)-5-methylbenzyl]oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{[3-(cyclobutylamino)-5-methylbenzyl]oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{[3-chloro-5-(cyclobutylamino)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{[3-chloro-5-(cyclobutylamino)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{[3-chloro-5-(cyclobutylamino)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{[3-chloro-5-(cyclobutylamino)benzyl]oxy}phenyl)propanoic acid

(3,5-dichloro-4-{[3-(ethylamino)-5-methylbenzyl]oxy}phenyl)acetic acid
(3,5-dichloro-4-{[3-(ethylamino)benzyl]oxy}phenyl)acetic acid
3-(3,5-dibromo-4-{[3-(cyano-5-(ethylamino)benzyl)oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-(ethylamino)-2-fluorobenzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[2-chloro-3-(ethylamino)benzyl]oxy}phenyl)propanoic acid
N-(3,5-dibromo-4-{[2-chloro-3-(ethylamino)benzyl]oxy}benzoyl)glycine
3-(3,5-dibromo-4-{[3-chloro-5-(methylamino)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-methyl-5-(methylamino)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-(cyclobutylamino)-5-methylbenzyl]oxy}phenyl)propanoic acid
N-(3,5-dibromo-4-{[3-(cyclobutylamino)-5-methylbenzyl]oxy}benzoyl)glycine
3-(3,5-dichloro-4-{[3-(cyclobutylamino)-5-methylbenzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-chloro-5-(cyclobutylamino)benzyl]oxy}phenyl)propanoic acid
N-(3,5-dibromo-4-{[3-chloro-5-(cyclobutylamino)benzyl]oxy}benzoyl)glycine
3-(3,5-dibromo-4- \{[3-(cyclobutylamino)-5-(trifluoromethyl)benzyl]oxy\}phenyl)propanoic acid
N-(3,5-dibromo-4-\{[3-(cyclobutylamino)-5-(trifluoromethyl)benzyl]oxy\}benzoyl)glycine
3-\{3,5-dibromo-4-\{[3-cyano-5-(cyclobutylamino)benzyl]oxy\}phenyl\}propanoic acid
N-(3,5-dibromo-4-\{[2-chloro-3-(cyclobutylamino)benzyl]oxy\}benzoyl)glycine
3-\{3,5-dibromo-4-\{[2-chloro-3-(cyclobutylamino)benzyl]oxy\}phenyl\}propanoic acid
N-(3,5-dibromo-4-\{[3-(isopropylamino)-5-methylbenzyl]oxy\}benzoyl)glycine
3-\{3,5-dichloro-4-\{[3-(isopropylamino)-5-methylbenzyl]oxy\}phenyl\}propanoic acid
N-(3,5-dibromo-4-\{[3-(isopropylamino)-5-methylbenzyl]oxy\}benzoyl)glycine
N-(3,5-dibromo-4-\{[3-(isopropylamino)-5-(trifluoromethyl)benzyl]oxy\}benzoyl)glycine
3-\{3,5-dibromo-4-\{[3-(isopropylamino)-5-(trifluoromethyl)benzyl]oxy\}phenyl\}propanoic acid
N-(3,5-dibromo-4-\{[3-(isopropylamino)-5-(trifluoromethyl)benzyl]oxy\}benzoyl)glycine
3-\{3,5-dichloro-4-\{[3-(isopropylamino)-5-methylbenzyl]oxy\}phenyl\}propanoic acid
N-(3,5-dibromo-4-\{[3-(isopropylamino)-5-methylbenzyl]oxy\}benzoyl)glycine
3-\{3,5-dibromo-4-\{[3-chloro-5-(isopropylamino)benzyl]oxy\}phenyl\}propanoic acid
N-(3,5-dibromo-4-\{[3-chloro-5-(isopropylamino)benzyl]oxy\}benzoyl)glycine
3-\{3,5-dichloro-4-\{[3-(isopropylamino)-5-methylbenzyl]oxy\}phenyl\}propanoic acid
N-(3,5-dibromo-4-\{[3-(isopropylamino)-5-methylbenzyl]oxy\}benzoyl)glycine
3-\{3,5-dichloro-4-\{[3-(sec-butylamino)-5-methylbenzyl]oxy\}phenyl\}propanoic acid
N-(3,5-dibromo-4-\{[3-(sec-butylamino)-5-methylbenzyl]oxy\}benzoyl)glycine
3-\{3,5-dibromo-4-\{[3-(sec-butylamino)-5-(trifluoromethyl)benzyl]oxy\}phenyl\}propanoic acid
N-(3,5-dibromo-4-\{[3-(sec-butylamino)-5-(trifluoromethyl)benzyl]oxy\}benzoyl)glycine
3-\{3,5-dibromo-4-\{[3-(sec-butylamino)-2-chlorobenzyl]oxy\}phenyl\}propanoic acid
N-(3,5-dibromo-4-\{[3-(sec-butylamino)-2-chlorobenzyl]oxy\}benzoyl)glycine
3,5-dichloro-4-\{[3-(ethylamino)-5-methylbenzyl]oxy\}phenylacetic acid
N-(3,5-dichloro-4-\{[3-(ethylamino)-5-methylbenzyl]oxy\}benzoyl)glycine
N-(4-\{[3-amino-5-methylbenzyl]oxy\}-3,5-dichlorobenzoyl)glycine
3-(3,5-dibromo-4-\{[3-(ethylamino)-5-(fluoromethyl)benzyl]oxy\}phenyl)propanoic acid
3-(3,5-dibromo-4-\{[3-ethoxymethyl-5-(ethylamino)benzyl]oxy\}phenyl)propanoic acid
3-(4-\{3-amino-2-chlorobenzoyloxy\}-3,5-dibromophenyl)propanoic acid
3-(4-\{3-amino-2-fluorobenzoyloxy\}-3,5-dichlorophenyl)propanoic acid
3-(4-\{3-(2-carboxy-ethylamino)benzyl\}oxy)-3,5-dichlorophenyl)propanoic acid
3-(3,5-dibromo-4-\{[2-methoxy-3-(ethylamino)benzyl]oxy\}phenyl)propanoic acid
3-(3,5-dibromo-4-\{[2-fluoro-5-(isopropylamino)benzyl]oxy\}phenyl)propanoic acid
3-(3,5-dibromo-4-\{[2-fluoro-5-(cyclobutylamino)benzyl]oxy\}phenyl)propanoic acid
3-(3,5-dibromo-4-\{[2-fluoro-5-(sec-butylamino)benzyl]oxy\}phenyl)propanoic acid
3-(3,5-dibromo-4-\{[2-fluoro-5-(ethylamino)benzyl]oxy\}phenyl)propanoic acid
3-(3,5-dibromo-4-\{[2,5-dichloro-3-(ethylamino)benzyl]oxy\}phenyl)propanoic acid
3-(3,5-dibromo-4-\{[2,5-dichloro-3-(isopropylamino)benzyl]oxy\}phenyl)propanoic acid
3-(3,5-dibromo-4-\{[2,5-dichloro-3-(cyclobutylamino)benzyl]oxy\}phenyl)propanoic acid
3-(3,5-dibromo-4-\{[3-chloro-5-(1,2-dimethylpropylamino)benzyl]oxy\}phenyl)propanoic acid
3-(3,5-dibromo-4-\{[3-chloro-5-(1,2-dimethylpropylamino)benzyl]oxy\}phenyl)propanoic acid
N-(3,5-dibromo-4-\{[3-chloro-5-(1,2-dimethylpropylamino)benzyl]oxy\}phenyl)glycine
3-(3,5-dibromo-4-\{[2,5-dichloro-3-(isopropylamino)benzyl]oxy\}phenyl)-2-fluoropropionic acid
3-(3,5-dibromo-4-\{[2,5-dichloro-3-(fethylamino)benzyl]oxy\}phenyl)-2-fluoropropionic acid
3-(3,5-dibromo-4-\{[2-chloro-(ethylamino)benzyl]oxy\}phenyl)-2-fluoropropionic acid
3-(3,5-dibromo-4-\{[3-(ethylamino)-5-methylbenzyl]oxy\}phenyl)butanoic acid
3-(3,5-dibromo-4-\{[3-(isopropylamino)-5-methylbenzyl]oxy\}phenyl)butanoic acid
3-(3,5-dibromo-4-\{[3-(cyclobutylamino)-5-methylbenzyl]oxy\}phenyl)butanoic acid
3-(3,5-dibromo-4-[[2,5-dichloro-3-(ethylamino)benzyl]oxy]phenyl)butanoic acid
(E)-3-(3,5-dibromo-4-[[2,5-dichloro-3-(ethylamino)benzyl]oxy]phenyl)acrylic acid
(E)-3-(3,5-dibromo-4-[[2,5-dichloro-3-(isopropylamino)benzyl]oxy]phenyl)acrylic acid
(E)-3-(3,5-dibromo-4-[[2,5-dichloro-3-(cyclobutylamino)benzyl]oxy]phenyl)acrylic acid
N-(3,5-dibromo-4-[[2,5-dichloro-3-(ethylamino)benzyl]oxy]benzoyl)glycine
N-(3,5-dibromo-4-[[2,5-dichloro-3-(isopropylamino)benzyl]oxy]benzoyl)glycine
N-(3,5-dibromo-4-[[2,5-dichloro-3-(cyclobutylamino)benzyl]oxy]benzoyl)glycine
(S)-2-{2-(3,5-dibromo-4-[[3-chloro-5-(ethylamino)benzyl]oxy]phenyl)acetylamino}-3-phenyl-propanoic acid
(S)-2-{2-(3,5-dichloro-4-[[3-(ethylamino)-5-methylbenzyl]oxy]phenyl)acetylamino}-2-phenyl-acetic acid
3-[[3,5-dibromo-4-[[3-chloro-5-(isopropylamino)benzyl]oxy]phenyl]amino]-3-oxopropanoic acid
{4-[(E)-2-(3-amino-phenyl)-vinyl]-3,5-dibromo-benzyloxy} -acetic acid tert-butyl ester
3-(4-[[3-(acetylamino)benzyl]oxy}-3,5-dibromophenyl)propanoic acid
3-(4-[[3-(acetylamino)benzyl]oxy}-3,5-dichlorophenyl)propanoic acid
3-(4-[[3-(acetylamino)-4-methylbenzyl]oxy}-3,5-dibromophenyl)propanoic acid
3-(3,5-dibromo-4-[[3-(propionylamino)benzyl]oxy]phenyl)propanoic acid
3-(3,5-dichloro-4-[[3-(propionylamino)benzyl]oxy]phenyl)propanoic acid
3-(3,5-dibromo-4-[[3-(butyrylamino)benzyl]oxy]phenyl)propanoic acid
3-(3,5-dibromo-4-[[3-(isobutyrylamino)benzyl]oxy]phenyl)propanoic acid
3-(3,5-dichloro-4-[[3-(isobutyrylamino)benzyl]oxy]phenyl)propanoic acid
3-(3,5-dibromo-4-[[3-(isobutyrylamino)-2-methylbenzyl]oxy]phenyl)propanoic acid
3-[3,5-dibromo-4-[[3-[(3-methylbutanoyl)amino]benzyl]oxy]phenyl]propanoic acid
3-[3,5-dibromo-4-[[3-[[2E]-but-2-enoylamino]benzyl]oxy]phenyl]propanoic acid
3-[3,5-dibromo-4-[[3-[(cyclopentylcarbonyl)amino]benzyl]oxy]phenyl]propanoic acid
3-[3,5-dibromo-4-[[3-[(cyclobutylcarbonyl)amino]benzyl]oxy]phenyl]propanoic acid
N-(4-[[3-(acetylamino)benzyl]oxy}-3,5-dibromobenzoyl)glycine
N-(3,5-dibromo-4-[(3-propionylamino)benzyl]oxy)benzoyl)glycine
N-(3,5-dibromo-4-[(3-isobutyrylamino)benzyl]oxy)benzoyl)glycine
3-(4-[(3-acetylamino)-5-chlorobenzyl]oxy)-3,5-dibromophenyl)-2-fluoropropanoic acid
N-(4-[(3-acetylamino)-5-chlorobenzyl]oxy)-3,5-dibromobenzoyl)glycine
3-(4-[(3-acetylamino)-2-chlorobenzyl]oxy)-3,5-dibromophenyl)-2-fluoropropanoic acid
3-(4-[(3-acetylamino)-5-methylbenzyl]oxy)-3,5-dibromobenzoyl)glycine
N-(4-[(3-acetylamino)-2-chlorobenzyl]oxy)-3,5-dibromobenzoyl)glycine
3-(4-[(3-acetylamino)-5-chlorobenzyl]oxy)-3,5-dibromophenyl)propanoic acid
and
3-(3,5-dibromo-4-[(3-methylsulfonyl)amino]benzyl]oxy)phenyl)propanoic acid
3-(3,5-dibromo-4-[(4-methyl-3-(methylsulfonyl)amino]benzyl]oxy)phenyl)propanoic acid
3-(3,5-dibromo-4-[(2-methyl-3-(methylsulfonyl)amino]benzyl]oxy)phenyl)propanoic acid
3-(3,5-dibromo-4-[(3-methyl-5-(methylsulfonyl)amino]benzyl]oxy)phenyl)propanoic acid
3-(3,5-dibromo-4-[(3-ethylsulfonyl)amino]benzyl]oxy)phenyl)propanoic acid
3-(3,5-dibromo-4-[(3-ethylsulfonyl)amino]benzyl]oxy)phenyl)propanoic acid
3-(3,5-dibromo-4-[(3-isopropylsulfonyl)amino]benzyl]oxy)phenyl)propanoic acid
3-(3,5-dibromo-4-[(3-phenylsulfonyl)amino]benzyl]oxy)phenyl)propanoic acid
3-(3,5-dibromo-4-[(3-(3,5-dimethylisoxazol-4-yl)sulfonyl)amino]benzyl]oxy)phenyl)propanoic acid
3-(3,5-dichloro-4-[(3-methylsulfonyl)amino]benzyl]oxy)phenyl)propanoic acid
3-[3,5-dichloro-4-({3-[methylsulfonyl]amino}benzyl)oxy]phenylpropanoic acid
N-[3,5-dibromo-4-({3-[methylsulfonyl]amino}benzyl)oxy]benzoylglycine
N-[3,5-dibromo-4-({3-ethy1sulfonyl]amino}benzyl)oxy]benzoylglycine
3-[3,5-dibromo-4-({3-chloro-5-[methylsulfonyl]amino}benzyl)oxy]phenylpropanoic acid
3-[3,5-dibromo-4-({3-chloro-5-[ethylsulfonyl]amino}benzyl)oxy]phenylpropanoic acid
3-[3,5-dibromo-4-({3-[ethy1sulfonyl]amino]-5-methylbenzyl)oxy]phenylpropanoic acid
[3,5-dichloro-4-({3-[ethylsulfonyl]amino]-5-methylbenzyl)oxy]benzoylacetic acid
[3,5-dichloro-4-({3-methyl-5-[methylsulfonyl]amino}benzyl)oxy]phenylacetic acid
N-[3,5-dichloro-4-({3-methyl-5-[methylsulfonyl]amino}benzyl)oxy]benzoylglycine
N-[3,5-dichloro-4-({3-ethy1sulfonyl]amino]-5-methylbenzyl)oxy]benzoylglycine
N-[3,5-dibromo-4-({2-chloro-3-[methylsulfonyl]amino}benzyl)oxy]benzoylglycine
N-[3,5-dibromo-4-({2,5-dichloro-3-[methylsulfonyl]amino}benzyl)oxy]benzoylglycine
3-[3,5-dibromo-4-({3-ethylsulfonyl]amino}benzyl)oxy]phenylpropanoic acid
3-[3,5-dibromo-4-({3-chloro-5-[methylsulfonyl]amino}benzyl)oxy]phenylpropanoic acid
3-[3,5-dibromo-4-({2,5-dichloro-3-[methylsulfonyl]amino}benzyl)oxy]phenylpropanoic acid
3-[3,5-dibromo-4-({2-fluoro-3-[methylsulfonyl]amino}benzyl)oxy]phenylpropanoic acid
N-[3,5-dibromo-4-({3-methyl-5-[methylsulfonyl]amino}benzyl)oxy]benzoylglycine
N-[3,5-dibromo-4-({3-[methanesulfonyl]amino-phenyl-vinyl}benzyloxy)acetic acid
N-[3,5-dibromo-4-({3-methyl-5-[methanesulfonyl]amino-phenyl-ethyl}benzyloxy)acetic acid
N-[3,5-dibromo-4-({3-ethyl-4-methylquinolin-6-yl}ethyl]benzyloxy)acetic acid
(2S)-3-{3,5-dibromo-4-[(2-ethyl-4-methylquinolin-6-yl)oxy]phenyl}-2-fluoropropanoic acid

(2S)-3-{3,5-dibromo-4-[(1-ethyl-2-[(methylsulfonyl)methyl]-1H-benzimidazol-6-yl]oxy}phenyl}-2-fluoropropanoic acid

{3,5-dibromo-4-[(4-methyl-2-propylquinolin-6-yl)methyl]phenoxy}acetic acid

N-{3,5-dibromo-4-[(4-methyl-2-propylquinolin-6-yl)methyl]phenyl}glycine

3-{3,5-dibromo-4-[(8-fluoro-4-methyl-2-propylquinolin-6-yl)oxy]phenyl}-2-fluoropropanoic acid

{3,5-dibromo-4-[(8-fluoro-4-methyl-2-propylquinolin-6-yl)oxy]phenoxy}acetic acid

{3,5-dibromo-4-[(2-ethyl-4-methylquinazolin-6-yl)oxy]phenyl}-2-fluoropropanoic acid

3-{3,5-dibromo-4-[(2-ethyl-4-methylquinazolin-6-yl)oxy]phenyl}-2-fluoropropanoic acid

{3,5-dibromo-4-[(8-fluoro-4-methylquinolin-6-yl)oxy]phenyl}-2-fluoropropanoic acid

{3,5-dibromo-4-[(2-ethyl-4-methylquinolin-6-yl)oxy]phenyl}-2-fluoropropanoic acid

{3,5-dichloro-4-[(1-ethyl-2-isobutyl-1H-benzimidazol-6-yl)oxy]phenyl}acetic acid

3-{3,5-dichloro-4-[(1-ethyl-2-isobutyl-1H-benzimidazol-6-yl)oxy]phenyl}acetic acid

3-{3,5-dichloro-4-[(2-isobutyl-7-methyl-1,3-benzothiazol-6-yl)oxy]phenyl}acetic acid

3-{3,5-dichloro-4-[(2-isobutyl-7-methyl-1,3-benzothiazol-6-yl)oxy]phenyl}acetic acid

[3,5-dichloro-4-[(2-isobutyl-7-methyl-1,3-benzothiazol-6-yl)oxy]phenyl]acetic acid

[3,5-dichloro-4-[(2-isobutyl-7-methyl-1,3-benzothiazol-6-yl)oxy]phenyl]acetic acid

[3,5-dichloro-4-[(2-isobutyl-7-methyl-1,3-benzothiazol-6-yl)oxy]phenyl]acetic acid

[3,5-dichloro-4-[(2-isobutyl-7-methyl-1,3-benzothiazol-6-yl)oxy]phenyl]acetic acid

[3,5-dichloro-4-[(2-isobutyl-7-methyl-1,3-benzothiazol-6-yl)oxy]phenyl]acetic acid

(4-{[2-(acetylamino)-1-ethyl-1H-benzimidazol-6-yl]methyl}-3,5-dibromophenoxy)acetic acid
(4-\{(2-(acetylamino)-1-ethyl-1H-benzimidazol-6-yl)oxy\}-3,5-dibromophenoxy)acetic acid
3-(4-\{(2-(acetylamino)-1-ethyl-1H-benzimidazol-6-yl)oxy\}-3,5-dibromophenyl)-2-fluoropropanoic acid
3-[3,5-dibromo-4-{\{1-ethyl-2-[(methylsulfonyl)amino]-1H-benzimidazol-6-yl\}oxy}phenyl]-2-fluoropropanoic acid
3-[3,5-dibromo-4-{\{1-ethyl-2-[(ethylamino)carbonyl]-1H-benzimidazol-6-yl\}oxy}phenyl]-2-fluoropropanoic acid
3-[3,5-dibromo-4-{\{1-ethyl-2-[2-(methylamino)-2-oxoethyl]-1H-benzimidazol-6-yl\}oxy}phenyl]-2-fluoropropanoic acid
3-[3,5-dibromo-4-{\{1-ethyl-2-[2-(dimethylamino)-2-oxoethyl]-1H-benzimidazol-6-yl\}oxy}phenyl]-2-fluoropropanoic acid
3-\{(3,5-dibromo-4-\{(3-ethyl-2-isobutyl-2H-indazol-5-yl)methyl\}phenoxy\}acetic acid
3-\{(3,5-dibromo-4-\{(3-ethyl-2-isobutyl-2H-indazol-5-yl)oxy\}phenyl\}-2-fluoropropanoic acid
3-\{(3,5-dibromo-4-\{(2-isobutyl-3-methyl-2H-indazol-5-yl)oxy\}phenyl\}-2-fluoropropanoic acid
N-\{(3,5-dibromo-4-\{(3-methyl-2-phenyl-2H-indazol-5-yl)oxy\}phenyl\}glycine
N-\{(3,5-dibromo-4-\{(3-ethyl-2-isobutyl-2H-indazol-5-yl)oxy\}phenyl\}glycine
\{(3,5-dichloro-4-\{(3-ethyl-2-isobutyl-2H-indazol-5-yl)oxy\}phenyl\}acetic acid
N-\{(3,5-dibromo-4-\{(2-isobutyl-3-methyl-2H-indazol-5-yl)oxy\}phenyl\}glycine
N-\{(3,5-dibromo-4-\{(3-methyl-2-[2-(methylamino)-2-oxoethyl]-2H-indazol-5-yl\}oxy\}phenyl\}glycine
N-\{(3,5-dibromo-4-\{(3-methyl-2-[2-(methylsulfonyl)methyl]-2H-indazol-5-yl\}oxy\}phenyl\}glycine
3-(\{3,5-dibromo-4-\{(2-methyl-1H-benzimidazol-5-yl)oxy\}\}phenyl)propanoic acid
3-[3,5-dibromo-4-\{(2-methyl-1H-benzimidazol-5-yl)oxy\}phenyl]propanoic acid
\{3,5-dibromo-4-\{(2-isobutyl-1H-benzimidazol-5-yl)oxy\}phenyl\}acetic acid
4-(\{3,5-dibromo-4-\{(2-(4-methylphenyl)-1H-benzimidazo!-5-yl)oxy\}phenyl\}butanoic acid
4-(3,5-dibromo-4-\{[2-(4-fluorophenyl)-1H-benzimidazol-5-yl]oxy\}phenyl)butanoic acid
4-(3,5-dibromo-4-\{[2-(4-Chlorophenyl)-1H-benzimidazol-5-yl]oxy\}phenyl)butanoic acid
4-(3,5-dibromo-4-\{[2-(3-Chlorophenyl)-1H-benzimidazol-5-yl]oxy\}phenyl)butanoic acid
3-(3,5-dibromo-4-\{[2-(3,4-dimethylphenyl)-1H-benzimidazol-5-yl]oxy\}phenyl)propanoic acid
3-(3,5-dibromo-4-\{[2-(3-fluoro-4-methylphenyl)-1H-benzimidazol-5-yl]oxy\}phenyl)propanoic acid
3-(3,5-dibromo-4-\{[2-isobutyl-1H-benzimidazol-5-yl]oxy\}phenyl)propanoic acid
3-(3,5-dibromo-4-\{[2-(3-methylphenyl)-1H-benzimidazol-5-yl]oxy\}phenyl)propanoic acid
3-(3,5-dibromo-4-\{[2-(3-methyl-4-fluorophenyl)-1H-benzimidazol-5-yl]oxy\}phenyl)propanoic acid
3-(3,5-dibromo-4-\{[2-(4-methylphenyl)-1H-benzimidazol-5-yl]oxy\}phenyl)propanoic acid
3-(3,5-dichloro-4-\{[2-(3-methylphenyl)-1H-benzimidazol-5-yl]oxy\}phenyl)propanoic acid
3-(3,5-dibromo-4-\{[2-(2-(methylthio)-ethyl)-1H-benzimidazol-5-yl]oxy\}phenyl)propanoic acid
3-(3,5-dichloro-4-\{[2-(2-(methylthio)-ethyl)-1H-benzimidazol-5-yl]oxy\}phenyl)propanoic acid
N-(3,5-dibromo-4-\{[2-(2-(methylthio)-ethyl)-1H-benzimidazol-5-yl]oxy\}benzoyl)glycine
3-(3,5-dibromo-4-\{[2-isopropylcarbamoyl-1H-benzimidazol-5-yl]oxy\}phenyl)-2-fluoropropanoic acid
3-(3,5-dibromo-4-\{[2-ethylcarbamoyl-1H-benzimidazol-5-yl]oxy\}phenyl)-2-fluoropropanoic acid
3-(3,5-dibromo-4-\{[2-diisopropylcarbamoyl-1H-benzimidazol-5-yl]oxy\}phenyl)-2-fluoropropanoic acid
5-[2,6-Dibromo-4-(2-fluoro-2-isopropylcarbamoyl-ethyl)-phenoxy]-1H-benzoimidazole-2-carboxylic acid
3-(3,5-Dibromo-4-\{[2-(methylsulfonylamino-methyl)-1H-benzoimidazol-5-yl]oxy\}phenyl)-2-fluoro-propionic acid
[3,5-Dibromo-4-(2-cyclopentylmethyl-1H-benzoimidazol-5-yl)-phenoxy]-acetic acid
3-(3,5-Dibromo-4-\{[2-(1,1,2,2-tetrafluoro-ethyl)-1H-benzoimidazol-5-yl]oxy\}phenyl)-2-fluoro-propionic acid
[3,5-Dibromo-4-(2-(1,1,2,2-tetrafluoro-ethyl)-1H-benzoimidazol-5-yl)-phenoxy]-acetic acid
3-(3,5-Dibromo-4-\{[2-(1,1,2,2-tetrafluoro-ethyl)-1H-benzoimidazol-5-yl]oxy\}benzoylamino)-acetic acid methyl ester
3-(3,5-Dibromo-4-\{[2-(2,5-dimethyl-oxazol-4-yl)-1H-benzoimidazol-5-yl]oxy\}phenyl)-2-fluoro-propionic acid
[3,5-Dibromo-4-(2-(2,5-dimethyl-oxazol-4-yl)-1H-benzoimidazol-5-yl)-benzoylamino]-acetic acid
[3,5-Dibromo-4-(2-(2,5-dimethyl-oxazol-4-yl)-1H-benzoimidazol-5-yl)-phenoxy]-acetic acid
[3,5-Dichloro-4-(2-furan-2-yl-1H-benzoimidazol-5-yl)-benzoylaminoj-acetic acid
[3,5-Dichloro-4-(2-(1,1,2,2-tetrafluoro-ethyl)-1H-benzoimidazol-5-yl)-benzoylaminoj-acetic acid
[3,5-Dichloro-4-(2-(2,5-dimethyl-oxazol-4-yl)-1H-benzoimidazol-5-yl)-benzoylaminoj-acetic acid
[3,5-Dichloro-4-(2-furan-2-yl-1H-benzoimidazol-5-yl)-benzoylaminoj-acetic acid
[3,5-Dichloro-4-[2-(2-fluoro-phenyl)-1H-benzoimidazol-5-yl]oxy]-benzoylamino}-acetic acid
[3,5-Dichloro-4-[2-(2-methoxy-phenyl)-1H-benzoimidazol-5-yl]oxy]-benzoylamino}-acetic acid
[3,5-Dichloro-4-[2-(1-methyl-1H-pyrrol-2-yl)-1H-benzoimidazol-5-yl]oxy]-benzoylamino}-acetic acid
N-[3,5-Dibromo-4-(2-isobutyl-1H-benzoimidazol-5-yl)oxy]-phenyl]acetamide
N-[3,5-Dibromo-4-(2-isobutyl-1H-benzoimidazol-5-yl)oxy]-phenyl]malonamic acid methyl ester
3-[3,5-Dichloro-4-(2-isobutyl-1H-benzoimidazol-5-yl)oxy]-phenyl]2-fluoro-propionic acid
[3,5-Dibromo-4-[2-(2,5-dimethyl-oxazol-4-yl)-1H-benzoimidazol-5-yl]oxy]-phenoxo}]-acetic acid methyl ester
N-[3,5-Dibromo-4-(2-isobutyl-1H-benzoimidazol-5-yl)oxy]-phenyl]malonamic acid
(R)-3-[3,5-Dibromo-4-(2-isobutyl-1H-benzoimidazol-5-yl)oxy]-phenyl]2-fluoro-propionic acid
(S)-3-[3,5-Dibromo-4-(2-isobutyl-1H-benzoimidazol-5-yl)oxy]-phenyl]2-fluoro-propionic acid
(3.5-dichloro-4-{[2,3-dimethyl-1H-indol-5-yl]oxy}phenyl)acetic acid
(3.5-dichloro-4-{[2-(4-methoxyphenyl)-3-methyl-1H-indol-5-yl]oxy}phenyl)acetic acid
3-(3,5-dibromo-4-{[2-(4-methoxyphenyl)-3-methyl-1H-indol-5-yl]oxy}phenyl)propanoic acid
(3,5-dibromo-4-{[2-(4-methoxyphenyl)-3-methyl-1H-indol-5-yl]oxy}phenyl)propanoic acid
3-[3,5-dibromo-4-{[2,3-dimethyl-1H-indol-5-yl]oxy}phenyl]propanoic acid
(4-{[2-(4-bromophenyl)-3-methyl-1H-indol-5-yl]oxy}-3,5-dichlorophenyl)acetic acid
(3,5-dichloro-4-{[2-(4-hydroxyphenyl)-3-methyl-1H-indol-5-yl]oxy}phenyl)acetic acid
3-(4-{[2-(1,3-benzodioxol-5-yl)-3-ethyl-1H-indol-5-yl]oxy}-3,5-dichlorophenyl)propanoic acid
3.(4.{[2-(1,3-benzodioxol-5-yl)-3-ethyl-1H-indol-5-yl]oxy}-3,5-dibromophenyl)propanoic acid
3-{3,5-Dibromo-4-[(3-methyl-2-pyridin-4-yl-1H-indol-5-yl)oxy]phenyl}propanoic acid
3-(3,5-dibromo-4-[(2-(4-methoxyphenyl)-3-ethyl-1H-indol-5-yl)oxy]phenyl)propanoic acid
3-(3,5-dibromo-4-[(2-(4-chlorophenyl)-3-ethyl-1H-indol-5-yl)oxy]phenyl)propanoic acid
3-(3,5-dibromo-4-[(2-(4-methoxyphenyl)-3-propyl-1H-indol-5-yl)oxy]phenyl)propanoic acid
N-(3,5-dibromo-4-[(2-(4-chlorophenyl)-3-ethyl-1H-indol-5-yl)oxy]benzoyl)glycine
3-{3,5-Dibromo-4-[(2-(4-methoxyphenyl)-3-ethyl-1H-indol-5-yl)oxy]phenyl}-2-fluoro-propionic acid
N-[3,5-Dichloro-4-(2-isopropylcarbamoyl-3-methyl-1H-indol-5-yl)oxy]-phenyl]malonamic acid
5-[4-(Carboxymethyl-carbamoyl)-2,6-dichloro-phenoxy]-3-methyl-1H-indole-2-carboxylic acid methyl ester
5-[4-(Carboxymethyl-carbamoyl)-2,6-dichloro-phenoxy]-3-methyl-1H-indole-2-carboxylic acid ethyl ester
3-[3,5-Dichloro-4-(2,3-dimethyl-1H-indol-5-yl)oxy]-propionic acid
3-{3,5-Dichloro-4-t2-(4-methoxy-phenyl)-3-methyl-1H-indol-5-yl)oxy]-phenyl}-propionic acid
5-[4-(2-Carboxy-acetylamino)-2,6-bis-trifluoromethyl-phenoxy]-3-methyl-1H-indole-2-carboxylic acid.
Methyl[3,5-dibromo-4-(4-hydroxy-3-isopropyl-5-phenylethynylphenoxy)]benzoate
3,5-dibromo-4-[4-hydroxy-3-isopropyl-5-((E)-styryl)phenoxy]benzoic acid
3-{3,5-dibromo-4-[4-hydroxy-3-isopropyl-5-((E)-2-pyridin-2-yl-vinyl)phenoxy]phenyl} propionic acid;
3-{3,5-dibromo-4-[4-hydroxy-3-isopropyl-5-((E)-2-pyridin-4-yl-vinyl)phenoxy]phenyl} propionic acid
3-{3,5-dibromo-4-[4-hydroxy-3-isopropyl-5-((E)-2-pyridin-2-yl-vinyl)phenoxy]phenyl} propionic acid
3-{3,5-dibromo-4-[[3-(E)-2-(4-dimethylaminomethylphenyl)vinyl]-4-hydroxy-5-isopropylphenoxy]phenyl} propionic acid
3-(3,5-Dibromo-4-{4-hydroxy-3-isopropyl-5-[(E)-2-(4-methylthiazol-5-yl)vinyl]phenoxy}-phenyl)propionic acid
4-((E)-2-{5-[2.6-Dibromo-4-(2-carboxyethyl)phenoxy]-2-hydroxy-3-isopropylphenylvinyl)-propionic acid
3-{3,5-Dibromo-4-[4-hydroxy-3-isopropyl-5-(2-pyridin-4-yl-ethyl)-phenoxy]-phenyl}-propionic acid
3-{3,5-Dibromo-4-[4-hydroxy-3-isopropyl-5-(E)-styryl-phenoxy]-phenyl}-2-hydroxy-propionic acid
3-{3,5-Dibromo-4-[4-hydroxy-3-isopropyl-5-(E)-pyridin-4-yl-vinyl]-phenoxy]-phenyl}-2-hydroxy-propionic acid
3-{3,5-Dibromo-4-(4-hydroxy-3-isopropyl-5-phenylethyl-phenoxy)phenyl]-2-hydroxy-propionic acid
3-[4,6-Dibromo-5-[3-isopropyl-4-(5-ethyl-2-pheiiiyloxaol-4-ylmethoxy)phenoxy]-indan-1-yl] acetic acid;
(4,6-Dibromo-5-[4-(3,5-dimethylisoxazol-4-ylmethoxy)-3-isopropylphenoxy]-indan-1-yl) acetic acid;
\[ \{4,6-\text{Dibromo} \theta-5-\text{[3-isopropyl-4-(naphthalen-2-ylmethoxy)phenoxy]}\text{indan-1-yl}\} \text{acetic acid}; \]
\[ \{4,6-\text{Dibromo} \theta-5-\text{[4-(4-fluorobenzyloxy)-3-isopropylphenoxy]}\text{indan-1-yl}\} \text{acetic acid}; \]
\[ \{4,6-\text{Dibromo} \theta-5-\text{[3-isopropyl-4-(5-methylisoxazol-3-ylmethoxy)phenoxy]}\text{indan-1-yl}\} \text{acetic acid}; \]
\[ \{4,6-\text{Dibromo} \theta-5-\text{[3-isopropyl-4-(pyridin-2-ylmethoxy)phenoxy]}\text{indan-1-yl}\} \text{acetic acid}; \]

\[ 4,6-\text{Dibromo} \theta-5-\text{[3-isopropyl-4-(5-phenyl-[1,2,4]oxadiazol-3-ylmethoxy)phenoxy]}\text{indan-1-yl}\} \text{acetic acid}; \]
\[ 4-\text{[4-(4,6-Dibromo-1-carboxy-3-methyl-indan-5-yl)oxy]-2-isopropylphenoxymethyl]} \text{benzoic acid}; \]

\[ \{4,6-\text{Dibromo} \theta-5-4-\text{[2-(1H-Indol-2-yl)ethoxy]-3-isopropylphenoxy} \text{indan-1-yl}\} \text{acetic acid}; \]
\[ (4,6-\text{Dibromo} \theta-5-\text{[3-isopropyl]4-\text{[5-thiophene-3-yUE} \text{1,2,4]oxadiazol-3-yl-methoxy)}\text{phenoxy]}\text{indan-1-yl} \text{acetic acid}; \]
\[ \{5-\text{[4-\text{[4-Amino-6-phenyiamino} \text{1,3^S]triazin-2-ylmethoxy)-3-isopropylphenoxy}3-4,6-\text{dibroirioindan-1-yl} \} \text{acetic acid}; \]
3,5-Dichloro-4-(3-bromo-4-isobutyramidophenoxy)phenylacetic acid;
3,5-Dichloro-4-(4-isobutyramidophenoxy)phenylacetic acid;
3,5-Dichloro-4-(3-phenyl-4-isobutyramidophenoxy)phenylacetic acid;
3,5-Dichloro-4-(3-bromo-4-[3-methylcrotonylamido]phenoxy)phenylacetic acid;
3,5-Dichloro-4-(3-isopropylidene-1,3-dihydro-2-oxo-5-indolox)phenylacetic acid;
3,5-Dichloro-4-(3-bromo-4-acetamidophenoxy)phenylacetic acid;
3,5-Dichloro-4-(3-isopropyl-1,3-dihydro-2-oxo-5-indolox)phenylacetic acid;
3,5-Dichloro-4-(3-bromo-4-acetamidophenoxy)phenylacetic acid;
N-[3,5-dichloro-4-(4-isobutyramidophenoxy)phenylacetyl]glycine;
L-N-[3,5-dichloro-4-(4-isobutyramidophenoxy)phenylacetyl]alanine;
L-N-[3,5-dichloro-4-(4-isobutyramidophenoxy)phenylacetyl]valine;
N-[3,5-dichloro-4-(4-isobutyramidido-3-bromophenoxy)phenylacetyl]glycine;
i-Methyl-N-[3,5-dichloro-4-(4-isobutyramidido-3-bromophenoxy)phenylacetyl]-alanine;
L-N-[3,5-Dichloro-4-(4-isobutyramidido-3-bromophenoxy)phenylacetyl]valine;
3,5-Dichloro-4-(4-isobutyramidido-3-methylphenoxy)phenylacetic acid;
3,5-Dichloro-4-(4-trifluoroacetamido-3-bromophenoxy)phenylacetic acid;
3,5-Dichloro-4-(4-[2-chloropropionamido]-3-bromophenoxy)phenylacetic acid;
3,5-Dichloro-4-(4-/7-fluorobenzamido-3-bromophenoxy)phenylacetic acid;
3,5-Dichloro-4-(4-isobutyramidido-3-trifluoromethylphenoxy)phenylacetic acid;
3,5-Dichloro-4-(3- bromo-4-isobutyramidophenoxy)phenylacetic acid;
3,5-Dichloro-4-[(1,3-dihydro-2-oxo-5-imidazolox)phenylacetic acid;
3,5-Dichloro-4-(3-bromo-4-isobutyramidophenoxy)phenylcinnamic acid;
3,5-Dichloro-4-(3-bromo-4-[2-chloropropionamido]phenoxy)phenylcinnamic acid;
3,5-Dichloro-4-(3-bromo-4-isobutyramidophenoxy)phenylpropionic acid;
3,5-Dichloro-4-(3-bromo-4-/2-fluorobenzamidoplienoxy)phenylpropionic acid;
3,5-Dichloro-4-(3-bromo-4-[2-chiropropionamido]phenoxy)phenylpropionic acid;
3,5-Dichloro-4-(4-isobutyramidoplietuxoxy)phenylpropiic acid;
3,5-Dichloro-4-(4-[2-choropropionamido]phenoxy)phenylpropionic acid;
3,5-Dibromo-4-(3-methyl-1,3-dihydro-2-oxo-5-indoloxy)phenylcinnamic acid;
3,5-Dibromo-4-(3-methyl-1,3-dihydro-2-oxo-5-indoloxy)phenoxyacetic acid;
3,5-Dibromo-4-(7-2H-1,4-benzoazinoxy-3 (4H)-one)phenylpropionic acid;
3,5-Dibromo-4-(3-{((E)-2-carboxyvinyl)-4-isobutyramidoplienoxy}phenylacetic acid;
3,5-Dibromo-4-(3-bromo-4-isobutyramidophtenoxy)benzoyl phenylsulfonamide;

and the compounds showed in the table below,

<table>
<thead>
<tr>
<th>R1Q-</th>
<th>R2</th>
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<tr>
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<tr>
<td><img src="image2.png" alt="Image" /></td>
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<td>H</td>
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<tr>
<td><img src="image4.png" alt="Image" /></td>
<td>H</td>
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3,5-Dimethyl-4-(4-hydroxy-3-isopropylphenoxy)benzyltetrazole,
3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzyltetrazole,
2-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-thiazole acetic acid,

2-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-methylthiazole,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-5-hydroxy-1-naphthalenesulphonamide,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-toluenesulphonamide,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-nitrobenzenesulphonamide,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-5-dimethylamino-1-naphthalenesulphonamide,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-aminobenzenesulphonamide,
Methyl-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-2-sulphonamide] benzoate,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-2-aminobenzenesulphonamide,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-3-nitrobenzenesulphonamide,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-chlorobenzenesulphonamide,

and the compounds shown below,
and the compounds indicated in the table below:

<table>
<thead>
<tr>
<th>(-\text{NR}^\text{R}^\text{n})</th>
<th>Formula</th>
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<tbody>
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<td>C\text{2H22Br2N}2O3</td>
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<tr>
<td>2-(2-AMINOETHYL)PYRIDINE</td>
<td>C\text{2H24Br2N}2O3</td>
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<td>Name</td>
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<td>----------------------------------------------------------------------</td>
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<tr>
<td>3-(2-AMINOETHYL)PYRIDINE</td>
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<td>2-(AMINOETHYL)PYRIDINE</td>
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<tr>
<td>4-(AMINOETHYL)PYRIDINE</td>
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<tr>
<td>1-(4-METHOXYPHENYL)Piperazine dihydrochloride</td>
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<tr>
<td>1-(2-FLUOROPHENYL)Piperazine</td>
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<td>2-(2-(AMINOMETHYL)PHENYLTHIO)BENZYL ALCOHOL</td>
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<td>2-(1-CYCLOHEXYL)ETHYLAMINE</td>
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<td>2-MINOINDAN</td>
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<td>2-AMINOBENZYLBENZODIOXAN</td>
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<td>3-PHENYL-1-PROPYLAMINE</td>
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<td>2-(P-TOLYL)ETHYLAMINE</td>
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<td>2,6-DIFLUOROBENZYLAMINE</td>
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<td>BENZYLAMINE</td>
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<td>2-ETHOXYBENZYLAMINE</td>
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<td>(R)-(-)-1-CYCLO-HEXYLETHYLAMINE</td>
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<td>4-METHOXYPHENETHYLAMINE</td>
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<td>2-FLUOROBENZYLAMINE</td>
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<td>2-CHLORO-6-METHYLbenzylamine</td>
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<td>4-CHLOROBENZYLAMINE</td>
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<td>BETA-METHYLPHENETHYLAMINE</td>
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<td>(1S,2R)-(+)2-AMINO-1,2-DIPHENYLETHANOL</td>
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<td>2-FLUOROPHENETHYLAMINE</td>
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<td>2-ETHYLHEXYLAMINE</td>
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<td>3-FLUOROPHENETHYLAMINE</td>
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<td>(1S,2S)-(+)2-AMINO-3-METHOXY-1-PHENYL-1-PROANOL</td>
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<tr>
<td>NONYLAMINE</td>
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<td>2,5-DICHLOROBENZYLAMINE</td>
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<td>2-METHYLCHLORHEXYLAMINE</td>
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<td>3-METHYLCHLORHEXYLAMINE</td>
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<td>3-N-PROPXYPROPYLAMINE</td>
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<td>2,3-DIMETHYLBENZYLAMINE</td>
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<td>3-CHLOROBENZYLAMINE</td>
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<tr>
<td>4-TERT-BUTYLCHLORHEXYLAMINE</td>
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</tr>
<tr>
<td>Name</td>
<td>Formula</td>
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<tr>
<td>----------------------------------------------------------------------</td>
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<tr>
<td>Z)-N-(3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]valine</td>
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<td>L-S-Benzyl. N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]cysteine</td>
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<tr>
<td>D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]tyrosine</td>
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</tbody>
</table>

Z)-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]valine,

Z)-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyle]leucine,

L-S-Benzyl. N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]cysteine,

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]tyrosine,
i-N-d-(2,2,5,7,8-Pentamethylchroman-6-sulfbnyl),
N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl] arginine,
Z-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl][a πunobuty πc acid,
I-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]3valine,
Z-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]leucine,
i-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]proline,
Z-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]cysteine,
N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]glycine,
£-N-a-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]lysine,
D-N-a-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]lysine,
N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)be

Z-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]homoserine,
N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]glycine,
N-[3,5-Dichloro-4-(4-hydroxy-3-methylphenoxy)benzoyl]glycine,
N-[3,5-Dichloro-4-(4-hydroxy-3-ethylphenoxy)benzoyl]glycine,
D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]methionine,
Z-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]methionine,
D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]a-methylalanine,
D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartagine,
I-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]alanine,
£-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]alanine,
I-Dimethyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamate.
£-Dimethyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamate,
L-(O-/ert-butyl)methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]
glutamate,
Z,-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamic acid,
/.-N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartic acid,
£-di-ter/-butyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamate,
£)-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamic acid,
L-0-fert?-Butyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamine,
£-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamine,
Z)-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamine,
I-0-Benzyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartic acid,
L-0-/ert/-Butyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartagine,
Z,-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]l-homoserine,
I-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]homoserine,
D-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropyl phenoxy)phenylacetyl]lhomoserine.
and the compounds showed in the table below:

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<th>R</th>
<th>Mol Formel</th>
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<td>L-Val</td>
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<tr>
<td>L-Val</td>
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<tr>
<td>L-Tyr</td>
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<td>Amine</td>
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<tr>
<td>D-Leu</td>
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<td>D-Tyr</td>
<td>C_{26}H_{25}Br_{2}NO_{5}</td>
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<tr>
<td>D-Trp</td>
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<td>L-Arg</td>
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<tr>
<td>L-Pro</td>
<td>C_{22}H_{23}Br_{2}NO_{5}</td>
</tr>
</tbody>
</table>
wherein \( R_i \) – isopropyl, methyl, ethyl; \( R_i \) and \( R_3 \) may be independently selected from Br, Cl and Me; \( n = 0 \) or 1; \( R^* \) may be hydrogen, alkyl, cycloalkyl, aryl and heteroaryl; \( * \) denotes either D or L stereochemistry when \( R^* \) is not hydrogen; \( R_5 \) is hydrogen; and \( R' \) is selected from hydrogen, lower alkyl, especially ethyl and methyl.
N-[3,5-Dichloro-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)benzoyl] glycine
N-[3,5-Dichloro-4-(3-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
N-[3,5-Dichloro-4-(2-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
N-[3,5-Dichloro-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
N-[3,5-Dichloro-4-(3-cyano-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
N-[3,5-Dichloro-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
N-[3,5-Dichloro-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
N-[3,5-Dibromo-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
N-[3,5-Dimethyl-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
L-N-[3,5-Dibromo-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)phenylacetyl] valine
D-N-[3,5-Dibromo-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)phenylacetyl] phenylglycine
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenylacetyl] valine
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenylacetyl] phenylglycine
L-N-[3,5-Dibromo-4-(3,5-dimethyl-4-hydroxyphenoxy)phenylacetyl] phenylglycine
3,5-dibromo 4-(4-hydroxy-3-isopropylphenoxy)benzoic acid, 3,5-dibromo 4-{4-hydroxy-3-isopropylphenoxy} phenylacetic acid, 3,5-dibromo 4-(4-hydroxy-3-isopropylphenoxy)-benzyl iodide, 3,5-dibromo 4-(4-hydroxy-3-isopropylphenoxy)-phenylpropionic acid, 3,5-dichloro 4-(4-hydroxy-3-isopropylphenoxy) benzylalcohol, 3,5-dichloro 4-(4-hydroxy-3-isopropylphenoxy)-benzyl cyanide, 3,5-dichloro 4-(4-hydroxy-3-isopropylphenoxy)-benzyl phosphonic acid, diethyl ester, 3,5-dibromo 4-(4-hydroxy-3-isopropylphenoxy)-benzylphosphonic acid, 3,5-dimethyl 4-(4-hydroxy-3-isopropylphenoxy)-benzylalcohol, 3,5-dimethyl 4-(4-hydroxy-3-isopropylphenoxy)-phenylacetonitrile,
3,5-dibromoα-4-(4-hydroxy-3-isopropylphenoxy) cinnaric acid,
3-bromo-β-S-cholorG-4-(4-hydroxy-3-isopropylphenoxy) phenyiacetic acid,
3-chloro-5-iodo-4-(4-hydroxy-3-isopropylphenoxy) phenyiacetic acid,
3-chloro-5-ethyl-4-(4-hydroxy-3-isopropylphenoxy) phenyiacetic acid,
3-chloro-5-ethyl-4-(4-hydroxy-3-isopropylphenoxy) phenyiacetic acid,
3-chloro-4-(4-hydroxy-3-isopropylphenoxy) phenyiacetic acid,
3-chloro-4-(4-hydroxy-3-isopropylphenoxy) phenyiacetic acid,
3,5-dimethyl-4-(4-hydroxy-3-isopropylphenoxy) phenyiacetic acid,
3-ethyl-5-methyl-4-(4-hydroxy-3-isopropylphenoxy) phenyiacetic acid,
3-bromo-5-methyl-4-(4-hydroxy-3-isopropylphenoxy) phenyiacetic acid,

and the compounds below
and the compounds below:
N-[3,5-Dichloro-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)benzoyl] glycine

N-[3,5-Dichloro-4-(3-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine

N-[3,5-Dichloro-4-(2-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine

N-[3,5-Dichloro-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine

N-[3,5-Dichloro-4-(3-cyano-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine

N-[3,5-Dichloro-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine

N-[3,5-Dichloro-2-ethyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine

L-M-[3,5-Dibromo-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)phenylacetyl] valine

D-N-[3,5-Dibromo-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)phenylacetyl] phenylglycine

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenylacetyl] valine

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenylacetyl] phenylglycine

L-N-[3,5-Dibromo-4-(3,5-dimethyl-4-hydroxyphenoxy)phenylacetyl] phenylglycine

M-[3,5-Dibromo-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine

N-[3,5-Dimethyl-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine

In one embodiment of the invention the treatment involves regulation of cell-proliferation and differentiation.

In a further embodiment of the invention the disease is cancer.

Preferably the disease is basal cell carcinoma, pancreatic cancer, prostate cancer, lung cancer, breast cancer, gastric cancer, colon cancer or liver cancer.
The invention also provides a method of treating disease induced, caused or dependent on activation of the Sonic hedgehog pathway comprising administering a pharmaceutically effective quantity of a compound according to the invention to a patient in need thereof.

In one embodiment the treatment involves regulation of cell-proliferation and differentiation.

In one embodiment the invention provides a method of treatment wherein the disease is cancer.

In one embodiment the invention provides a method of treatment wherein the disease is basal cell carcinoma, pancreatic cancer, prostate cancer, lung cancer, breast cancer, gastric cancer, colon cancer or liver cancer.

The applicant also provides use of a compound according to the invention for the manufacture of a medicament for the treatment of cancer induced, caused or dependent upon activation of the Sonic hedgehog pathway.

Compounds according to the invention may exist in tautomeric, enantiomeric and diastereomeric forms, all of which are included within the scope of the invention.

All of the compounds according to the invention may be made by known methods. For details of their synthesis see WO99/00353, WO00/39077, WO01/60784, WO 01/98256, WO03/084915, WO04/007430, WO04/067482, WO05/092316, WO05/092317, WO07/003419, WO07/10226, WO07/128492, and WO07/134864.

Where the compound according to the invention is an acid or base, salts of the compounds according to the invention may be formed by reacting the free acid, or a salt thereof, or the free base, or a salt or derivative thereof, with one or more equivalents of the appropriate base or acid. The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g. ethanol, tetrahydrofuran or diethyl ether, which may be removed in vacuo, or by freeze drying. The reaction may also be a mathematical process or it may be carried out on an ion exchange resin.
Pharmaceutically acceptable salts of the compounds according to the invention include alkali metal salts, e.g. sodium and potassium salts; alkaline earth metal salts, e.g. calcium and magnesium salts; salts of the Group III elements, e.g. aluminium salts; and ammonium salts. Salts with suitable organic bases, for example, salts with hydroxylamine; lower alkyamines, e.g. methylamine or ethyamine; with substituted lower alkyamines, e.g. hydroxy substituted alkyamines; or with monocyclic nitrogen heterocyclic compounds, e.g. piperidine or morpholine; and salts with amino acids, e.g. with arginine, lysine etc, or an N-alkyl derivative thereof; or with an aminosugar, e.g. N-methyl-D-glucamine or glucosamine. The non-toxic physiologically acceptable salts are preferred, although other salts are also useful, e.g. in isolating or purifying the product.

Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various optical isomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation.

The compounds according to the invention for use in the treatment of disease will generally be administered in the form of a pharmaceutical formulation.

Thus, according to a further aspect of the invention there is provided a pharmaceutical formulation including preferably less than 80% w/w, more preferably less than 50% w/w, e.g. 0.1 to 20%, of a compound according to the invention, or a pharmaceutically acceptable salt thereof, as defined above, in admixture with a pharmaceutically acceptable diluent or carrier.

The applicant also provides a process for the production of such a pharmaceutical formulation which comprises mixing the ingredients. Examples of pharmaceutical formulations which may be used, and suitable diluents or carriers, are as follows: for intravenous injection or infusion - purified water or saline solution;
for inhalation formulations - coarse lactose;
for tablets, capsules and dragees - microcrystalline cellulose, calcium phosphate, diatomaceous earth, a sugar such as lactose, dextrose or mannitol, talc, stearic acid, starch, sodium bicarbonate and/or gelatin;
for suppositories - natural or hardened oils or waxes.

When the compound is to be used in aqueous solution, e.g. for infusion, it may be necessary to incorporate other excipients. In particular there may be mentioned chelating or sequestering agents, antioxidants, tonicity adjusting agents, pH-modifying agents and buffering agents.

Solutions containing a compound according to the invention may, if desired, be evaporated, e.g. by freeze drying or spray drying, to give a solid formulation, which may be reconstituted prior to use.

When not in solution, the compound according to the invention preferably is in a form having a mass median diameter of from 0.01 to 10μm. The formulations may also contain suitable preserving, stabilising and wetting agents, solubilisers, e.g. a water-soluble cellulose polymer such as hydroxypropyl methylcellulose, or a water-soluble glycol such as propylene glycol, sweetening and colouring agents and flavourings.

Where appropriate, the formulations may be formulated in sustained release form.

The content of compound according to the invention in a pharmaceutical formulation is generally about 0.01-about 99.9wt%, preferably about 0.1-about 50wt%, relative to the entire preparation.

The dose of the compound of according to the invention is determined in consideration of age, body weight, general health condition, diet, administration time, administration method, clearance rate, combination of drugs, the level of disease for which the patient is under treatment then, and other factors.

While the dose varies depending on the target disease, condition, subject of administration, administration method and the like, for oral administration as a therapeutic agent for the treatment of disease in a patient suffering from such a disease is from 0.01 mg - 10 g, preferably 0.1 - 100 mg, is preferably administered in a single dose or in 2 or 3 portions per day.
The potential activity of the compounds according to the invention for use in the treatment of disease may be demonstrated in the following predictive assay and screens.

1. A classical way to evaluate anti-cancer drugs for efficacy is to assess their potential to inhibit replication of tumor cells in culture dishes (in-vitro). Tumor cell-lines are characterized by their ability to divide and thus multiply the number of cells in a culture dish. This ability is denoted proliferation. If a compound or treatment (ie ionizing radiation) inhibits proliferation of cancer-cell-lines in-vitro (display antiproliferative activity) this suggests that the treatment may be efficacious as a treatment of cancers in humans or animals. Anti proliferative effects, can be assessed by measuring BrdU-incorporation. If cellular BrdU-uptake is reduced it indicates that cells divide less frequently. Proliferation, measured by the standard method BrdU incorporation, in the pancreatic cancer cell lines hPANC-I and Capan-1 was assessed for a set of representative NIOTAS with T3 as reference compound. It was showed that adding NIOTAS to cell-cultures reduced BrdU-incorporation. The concentration of NIOTAS added to the cell-cultures that was required to reduce BrdU-incorporation with 50% (IC50) was lower than the concentration of T3 required to give the same inhibition.

2. Anti proliferative effects in combination with the chemotherapeutic drugs gemcitabine and cisplatin, measured by BrdU incorporation, in the pancreatic cancer cell lines hPANC-I and Capan-1 assessed for a set of representative NIOTA and with T3 as reference compound. It was showed that NIOTAS was more potent (lower IC50) than T3.

3. Antiproliferative effects, measured by BrdU incorporation, in the prostate cancer cell lines TSU, DU145, LN-Cap and PC3 was assessed for a set of representative NIOTA with T3 as reference compound. It was showed that NIOTAS was more potent (lower IC50) than T3.

4. Antiproliferative effects (measured by BrdU incorporation) was also assessed for a set of representative NIOTA and with T3 as reference compound in
combinations with the chemotherapeutic drugs gemcitabine and cisplatin and with the anti-androgen Casiodex in the prostate cancer cell lines TSU, DU145, LN-Cap and PC3. It was showed that NIOTAS was more potent (lower IC50) than T3.

5. One characteristic feature of cancer-cell lines is their ability to grow in agar (soûd culture) and this property is not shared by other non-malignant cells. Human keratinocytes overexpressing SHh display invasive growth in agar (matrigel). It was showed that treatment with T3 or NIOTAS reduced the number of cells growing in agar. It was showed that NIOTAS was more potent (lower IC50) than T3.

6. Anti proliferative effects (measured by BrdU or 3H-Thymidine incorporation) in-vitro in cell-lines from Basal Cell carcinoma was also assessed for a set of representative NIOTA and with T3 as reference. It was showed that treatment with T3 or NIOTAS reduced the number of cells growing in agar. It was showed that NIOTAS was more potent (lower IC50) than T3.

7. Cancer cell-lines can be injected in mice with compromised immune system and form tumors in these animals. Therapeutic agents can then be evaluated by their ability to reduce growth of these tumors (in comparison with control animals. Anti proliferative effects on growth of tumors from cell-lines such as G2N2C and TbA3 inoculated in nude mice was assessed for a set of representative NIOTA and with T3 as reference. It was showed that NIOTAS was more potent (a lower dose required) than T3 to reduce growth of these tumors.

8. It was also demonstrated that a representative set of NIOTA, in contrast to T3, not are substrates for D3.

9. It was also demonstrated that a representative set of NIOTA are competitive inhibitors of D3-activity. Thus, by adding these NIOTAs to cancer cells expressing D3 the intracellular levels of T3 will not be as depressed as in corresponding control cells.

10. A topical formulation (cream, ointment or intradermal injections) of the NIOTA was applied once daily for 12 weeks on basal cell carcinoma in patients. A substantial reduction in tumor size was observed versus placebo.
In order to accurately treat a patient suffering from cancer, the treatment selected must allow be capable to stop the tumor-growth but with limited effects on rest of the body so that harm to the patient is limited. There are compelling evidence that it would be possible to stop tumor growth by increasing the intracellular levels of T3 (thereby increasing the ratio T3-TR/apo-TR inside the cancer-cells) by administering exogenous T3 to a patient. However, the high doses of exogenous T3 projected to be required that will have be given to a patient in order to reach these intracellular levels will be unacceptably high with regards to side-effects.

Therefore, the use of NIOTAS that display a blunted pharmacological activity as compared to T3 with regards to certain pharmacological effects, essentially related cardiac effects, is expected to be a superior option for such treatment.

The potency of a NIOTA with regard to anti-tumor activity in an organism can be described as the normalized dose (Mol/kg bodyweight) required to significantly reduce growth of a tumor. Immune-deficient mice were inoculated subcutaneously with tumor cells originating from from human breast, colon, liver, esophagus, kidney, prostate, pancreas or basal cell carcinoma. When subcutaneous tumors occurred the animals were treated with oral or subcutaneous administration of T3 or with the compounds denoted as experiment 1 to 7 (E1-E7) in a range of doses or with vehicle alone. Tumor growth was followed and compared with tumor growth in the vehicle group. The minimal dose required to achieve a significant reduction in tumor mass as compared to vehicle was determined in terms of the molar dose expressed as nanoMol per kilogram bodyweight per day (nmol/kg per day).

In order to assess for cardiac side-effects that are expected to restrict therapeutic use heart rates were measured in rats treated with oral or subcutaneous administration of T3 or with the compounds denoted as experiment 1 to 7 (E1-E7) in a range of doses or with vehicle alone. Tacycardia was defined as the dose resulting in more than 15% increase in heart rate as compared with vehicle group or with base-line (before treatment).
Results: Antitumor potency and tachycardia of a set of NIOTAs and T3.

<table>
<thead>
<tr>
<th>Example</th>
<th>TR-beta affinity</th>
<th>Tachycardia</th>
<th>Antitumor potency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IC50 (nM)</td>
<td>nmol/kg/day</td>
<td>nmol/kg/day</td>
</tr>
<tr>
<td>T3</td>
<td>0.10</td>
<td>3.1</td>
<td>15.0</td>
</tr>
<tr>
<td>E1</td>
<td>0.71</td>
<td>2.900</td>
<td>&lt;1.500</td>
</tr>
<tr>
<td>E2</td>
<td>0.12</td>
<td>&gt;12.000</td>
<td>&lt;2.500</td>
</tr>
<tr>
<td>E3</td>
<td>0.03</td>
<td>&gt;10.000</td>
<td>&lt;0.500</td>
</tr>
<tr>
<td>E4</td>
<td>1.05</td>
<td>&gt;9.0000</td>
<td>&lt;9.000</td>
</tr>
<tr>
<td>E5</td>
<td>0.13</td>
<td>&gt;4.90</td>
<td>&lt;2.000</td>
</tr>
<tr>
<td>E6</td>
<td>0.16</td>
<td>&gt;3.700</td>
<td>&lt;2.000</td>
</tr>
<tr>
<td>E7</td>
<td>1.16</td>
<td>&gt;34.000</td>
<td>&lt;2.000</td>
</tr>
</tbody>
</table>

E1: 2-(3,5-dichloro-4-(4-hydroxy-3-isopropylphenoxy)phenyl)acetic acid
E2: 2-(3,5-dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzamido)acetic acid
E3: 3-(3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylamino)-3-oxopropanoic acid
E4: (S)-3-(3,5-dibromo-4-(2-chloro-3-(methylsulfonamido)benzyloxy)phenyl)-2-fluoropropanoic acid
E5: (S)-3-(3,5-dibromo-4-(2-isobutyl-1H-benzo[d]imidazol-5-ylxyloxy)phenyl)-2-fluoropropanoic acid
E6: 2-(3,5-dibromo-4-(2-isobutyl-1-isopropyl-1H-benzo[d]imidazol-6-ylxyloxy)phenoxyn)acetic acid
E7: 3-(3,5-dibromo-4-(1-ethyl-2-(methylsulfonylmethyl)-1H-benzo[d]imidazol-6-ylxyloxy)phenyl)-2-fluoropropanoic acid
CLAIMS

1. A compound for the treatment of disease induced, caused or dependent on activation of the Sonic hedgehog pathway, wherein the compound is a thyromimetic lacking inner-πng iodines.

2. A compound of formula (I) or a pharmaceutically acceptable ester, amide, solvate or salt thereof, including a salt of such an ester or amide, and a solvate of such an ester, amide or salt,

\[
\begin{align*}
G &- Y - R^4 \\
R^5 &- R^6 \\
R^7 &- R^8
\end{align*}
\]

wherein:

G is a group selected from:

\[
\begin{align*}
\text{(I)} &- \text{R}^1 \text{Q} - \text{R}^3 \\
\text{(II)} &- \text{R}^1 \text{N} &\text{(III)} &- \text{R}^1 \\
\text{(IV)} &- \text{R}^6 (\text{R}^3)^n \\
\text{(V)} &- \text{R}^5 (\text{R}^3)^m
\end{align*}
\]

in group IV, N is a sp\(^2\) nitrogen with a non-bonded electron pair in a sp\(^2\) orbital;

in group V, Z is selected from C or N with the proviso that when Z is N than R\(^8\) is an electron pair;

\(n\) is an integer from 0 to 2;

R\(^4\) and R\(^5\) are independently selected from hydrogen, halogen, C\(_{1,4}\) alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, C\(_{1,4}\) alkoxy, fluoromethoxy, difluoromethoxy and trifluoromethoxy with the proviso that only one of R\(^4\) and R\(^5\) can simultaneously be hydrogen;
**R**^{6} is selected from hydrogen, halogen, trifluoromethyl, C\textsubscript{1-4} alkyl, where the alkyl can be linked through the available atoms to position W to from a saturated C\textsubscript{5} cycloalkyl as in the structure below:

![Structure](image)

**R**^{9} is selected from hydrogen and halogen;

W is selected from C\textsubscript{0-4} alkyene, C\textsubscript{0-2} alkyene C(O), C\textsubscript{2-4} alkenylene, N(R\textsuperscript{a})-C\textsubscript{i-3} alkyene, C(O)-C\textsubscript{0-1} alkyene, S(0)\textsubscript{p}-Co-3 alkyene, where p is an integer from 0 to 2, 0 -C\textsubscript{1,3} alkyene, C\textsubscript{3} alkyene-O-C\textsubscript{i-3} alkyene, C(O)N(R\textsuperscript{a})-C\textsubscript{i-3} alkyene, N(R\textsuperscript{a})(C0)-C\textsubscript{0-3} alkyene, C\textsubscript{0-3} alkyene-NR\textsuperscript{a}SO\textsubscript{2-R\textsuperscript{a}} and C\textsubscript{1,3} alkyeneC(O)N(R\textsuperscript{a})-C\textsubscript{i-3} alkyene, said alkyene or alkenylene groups or portions of groups optionally being substituted with 1 or 2 groups selected from R\textsuperscript{b}, said substitution can also be connected to R\textsuperscript{8}, to form a 5 or 6 membered ring as in the structure represented below:

![Structure](image)

Y is O or CH\textsubscript{2};

Q is selected from O or NH;

R\textsuperscript{7} is selected from -CO\textsubscript{2}R\textsuperscript{a}, -PO(OR\textsuperscript{a})\textsubscript{2}, -SO\textsubscript{2}OR\textsuperscript{a}, -C(O)CO\textsubscript{2}R\textsuperscript{a}, C(O)NR\textsuperscript{a}R\textsuperscript{a}, -SO\textsubscript{2}N(R\textsuperscript{a})\textsubscript{2}, -NR\textsuperscript{a}SO\textsubscript{2}R\textsuperscript{a}, -NR\textsuperscript{a}C(O)R\textsuperscript{a}, -C(O)NR\textsuperscript{a}SO\textsubscript{2}R\textsuperscript{a}, C\textsubscript{3-7} heterocycl, N(R\textsuperscript{a})\textsubscript{2}, -CN, -OH, and each R\textsuperscript{a} can be the same or different and can optionally be substituted with 1, 2 or 3 groups independently selected R\textsuperscript{b};

R\textsuperscript{8} is selected from a non bonded electron pair and C\textsubscript{i-3} alkyl;
R\(^1\) is independently selected from hydrogen, C\(_{1-10}\) alkyl, C\(_{3,7}\) cycloalkyl, C\(_{3,6}\) cycloalkyl-C\(_{1,3}\) alky], phenyl, benzyl and C\(_{3,7}\) heterocyclyl, -(CH\(_2\))\(_m\)-SO\(_2\)-R\(^a\), -(CH\(_2\))\(_m\)-C(O)R\(^a\), -(CH\(_2\))\(_m\)-CO-NR\(^a\)_2, -(CH\(_2\))\(_m\)-S-R\(^a\), -(CH\(_2\))\(_m\)-NR\(^a\)-SO\(_2\)-R\(^a\), -(CH\(_2\))\(_m\)-SO\(_2\)-NH-R\(^a\), -(CH\(_2\))\(_m\)-NR\(^a\)-CO-R\(^a\), said alkyl, cycloalkyl, aryl, heterocyclyl groups or portions of groups optionally being substituted with 1, 2 or 3 groups each independently selected from R\(^b\), each R\(^a\) is independently selected and optionally substituted with 1, 2 or 3 groups independently selected from R\(^b\);

m is an integer from 0 to 3;

R\(^2\) is selected from hydrogen, halogen, cyano, -NO\(_2\), C\(_{6-9}\) aryl, C\(_{1-10}\) alkyl, C\(_{1-9}\) heteroaryl, C\(_{3,8}\) cycloalkyl, C\(_{2,4}\) alkenyl said alkyl, cycloalkyl, aryl, heteroaryl and alkenyl optionally substituted with 1, 2 or 3 groups each independently selected from R\(^b\);

R\(^3\) is selected from hydrogen, halogen, C\(_{1-4}\) alkyl, cyano, C\(_{1-4}\) alkoxy, and N(R\(^a\))\(_2\), said alkyl and alkoxy optionally substituted with 1, 2 or 3 groups selected from R\(^b\);

each R\(^a\) is independently selected from hydrogen, Q\(^a\)alkyl, C\(_{2,4}\) alkenyl, benzyl, heterocyclyl and C\(_{6-10}\) aryl, said alkyl, alkenyl, or aryl groups or portions of groups optionally being substituted with 1, 2 or 3 groups independently selected R\(^b\); and

each R\(^b\) is independently selected from the group consisting of hydroxy, mercapto, amino, halogen, -CO\(_2\)R\(^a\), -C(O)H, C\(_M\) alkylthio, Arylithio, -N(R\(^a\))\(_2\), C\(_{1,9}\) alkyl, C\(_{3,8}\) cycloalkyl, C\(_{2,6}\) alkenyl, C\(_{2,4}\) alkynyl, C\(_{1,4}\) alkoxy, C\(_{6-9}\) aryl, C\(_{9}\)heterocyclyl, haloC\(_{1-4}\) alkyl, dihaloC\(_{1-4}\) alkyl, trihaloC\(_{1-4}\) alkyl, haloC\(_{1-4}\) alkoxy, dihaloC\(_{1-4}\) alkoxy, and trihaloC\(_{1-4}\) alkoxy, said alkyl. cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl optionally substituted with 1, 2 or 3 groups selected from R\(^b\),

for the treatment of disease induced, caused or dependent on activation of the Sonic hedgehog pathway.

3. A compound according to claim 2, wherein:
G is a group selected from:

in group IV, N is a sp² nitrogen with a non-bonded electron pair in a sp² orbital;
in group V, Z is selected from C or N with the proviso that when Z is N than R⁸ is an
electron pair;
n is an integer from 0 to 2;

R⁴ and R⁵ are independently selected from halogen, C₁-₄ alkyl, trifluoromethyl;
R⁶ is selected from hydrogen, halogen, C₁₂ alkyl, where the alkyl can be linked
through the available atoms to position W to form a saturated C₅ cycloalkyl as in the
structure below:

R⁹ is selected from hydrogen and halogen:

W is selected from C₀-₄ alkyne, N(R⁸)-C₁₃ alkyne, 0-C₁₃ alkyne, C(0)N(Rᵃ)-Cᵡ,
2 alkyne, N(Rᵃ)(CO)-Co.2 alkyne, said alkyne groups or portions of groups
optionally being substituted with 1 or 2 groups selected from Rᵇ, said substitution can
also be connected to Rᵃ, to form a 5 or 6 membered ring as in the structure
represented below:
Y is O;

Q is selected from O or Nil;

R^7 is selected from \(-CO_2R^8, -P0(0R^a)_{2}\), each R^a can be the same or different and can optionally be substituted with 1, 2 or 3 groups independently selected from R^b;

R^8 is selected from a non bonded electron pair and C_{5,3} alkyl;

R^1 is independently selected from hydrogen, C_{1-10} alkyl, C_{3,7}cycloalkyl, C_{3,6}cycloalkyl-C_{i-3} alkyl, phenyl, benzyl and C_{3,7} heterocyclyl, -(CH_2)_m-C(O)R^a, and -(CH2)m-CO-NR^a, said alkyl, cycloalkyl, aryl, heterocyclyl groups or portions of groups optionally being substituted with 1, 2 or 3 groups each independently selected from R^b, each R^4 is independently selected and optionally substituted with 1, 2 or 3 groups independently selected from R^b;

m is an integer from 0 to 3;

R^2 is selected from hydrogen, halogen, C_{6,11} aryl, C_{1-10} alkyl, C_{1-9} heteroaryl, C_{3-5} cycloalkyl, said alkyl, cycloalkyl, aryl and heteroaryl, optionally substituted with 1, 2 or 3 groups each independently selected from R^b;

R^3 is selected from hydrogen, halogen, C_{i-4} alkyl, Said alkyl optionally substituted with 1, 2 or 3 groups selected from R^b;

each R^a is independently selected from hydrogen and C_{i-4}alkyl, said alkyl groups or portions of groups optionally being substituted with 1, 2 or 3 groups independently selected R^b;
each R^b is independently selected from halogen, -CO_R, C_i H alkyl, C_{3,8} cycloalkyl, C_{1,4} alkoxy and C_{6-H} aryl, said alkyl, cycloalkyl, alkenyl, alkynyl, aryl and heterocyclcyl optionally substituted with 1, 2 or 3 groups selected from R^b, for the treatment of disease induced, caused or dependent on activation of the Sonic hedgehog pathway

3-(3,5-dibromo-4-\{3-(butylamino)benzyl\}oxy)phenyl)propanoic acid
3-(3,5-dibromo-4-\{3-(sec-butylamino)benzyl\}oxy)phenyl)propanoic acid
3-(3,5-dibromo-4-\{3-(sec-butylamino)-2-methylbenzyl\}oxy)phenyl)propanoic acid
3-[3,5-dibromo-4-\{(3-[2-ethylbutyl]amino)benzyl\}oxy]phenyl)propanoic acid
3-(3,5-dibromo-4-\{3-(cyclobutylamino)benzyl\}oxy)phenyl)propanoic acid
3-(3,5-dibromo-4-\{3-(cyclobutylamino)-2-methylbenzyl\}oxy)phenyl)propanoic acid
3-[3,5-dibromo-4-\{(3-[cyclohexyl]methyl)amino)benzyl\}oxy]phenyl)propanoic acid
3-(3,5-dibromo-4-\{3-(isobutylamino)benzyl\}oxy)phenyl)propanoic acid
3-\{(3-aminobenzyl)oxy\}-3,5-dichlorophenyl)propanoic acid
3-(3,5-dichloro-4-\{3-(ethyamino)-5-(trifluoromethyl)benzyl\}oxy)phenyl)propanoic acid
3-(3,5-dichloro-4-\{3-(propylamino)benzyl\}oxy)phenyl)propanoic acid
3-(3,5-dichloro-4-\{3-(isopropylamino)benzyl\}oxy)phenyl)propanoic acid
3-(4-\{3-(sec-butylamino)benzyl\}oxy)-3,5-dichlorophenyl)propanoic acid
N-\{(3-aminobenzyl)oxy\}-3,5-dibromobenzoyl)glycine
N-(3,5-dibromo-4-\{(3-tethylamino)benzyl\}oxy\}benzoyl)glycine
N-(3,5-dibromo-4-\{(3-methylamino)benzyl\}oxy\}benzoyl)glycine
N-(3,5-dibromo-4-\{(3-propylamino)benzyl\}oxy\}benzoyl)glycine
N-(3,5-dibromo-4-\{(3-isopropylamino)benzyl\}oxy\}benzoyl)glycine
N-(3,5-dibromo-4-\{(3-cyclobutylamino)benzyl\}oxy\}benzoyl)glycine
N-(3,5-dibromo-4-\{(3-sec-butylamino)benzyl\}oxy\}benzoyl)glycine
N-(3,5-dibromo-4-\{3-(ethylamino)-5-(trifluoromethyl)benzyl\}oxy\}benzoyl)glycine
N-(3,5-dibromo-4-\{3-ethylamino)-5-methylbenzyl\}oxy\}benzoyl)glycine
3-(3,5-dichloro-4-\{3-(ethylene)-5-methylbenzyl\}oxy\}phenyl)propanoic acid
3-(3,5-dibromo-4-\{3-chloro-5-(ethylene)benzyl\}oxy\}phenyl)propanoic acid
3-(3,5-dibromo-4-\{3-chloro-5-(ethylene)benzyl\}oxy\}phenyl)propanoic acid
}(3,5-dichloro-4-\{3-(ethylene)-5-methylbenzyl\}oxy\}phenyl)acetic acid
(3,5-dibromo-4-\{(3-ethylene)benzyl\}oxy\}phenyl)acetic acid

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3-(3,5-dibromo-4-{[3-cyano-5-(ethylamino)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-(ethylamino)-2-fluorobenzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[2-chloro-3-(ethylamino)benzyl]oxy}phenyl)propanoic acid
N-(3,5-dibromo-4-{[2-chloro-3-(ethylamino)benzoyl]oxy}benzoylglycine
3-(3,5-dibromo-4-{[3-chloro-5-(methy lamino)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-methyl-5-(methy lamino)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-(cyclob utylamino)-5-methylbenzyl]oxy}phenyl)propanoic acid
N-(3,5-dibromo-4-{[3-(cyclobutylamino)-5-methylbenzoyl]oxy}benzoylglycine
3-(3,5-dichloro-4-{[3-(cyclobutylamino)-5-methylbenzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-chloro-5-(cyclobutylamino)benzyl]oxy}phenyl)propanoic acid
N-(3,5-dibromo-4-{[3-chloro-5-(cyclobutylamino)benzoyl]oxy}benzoylglycine
3-(3,5-dibromo-4-{[3-(isopropylamino)-5-(trifluoromethyl)benzyl]oxy}phenyl)propanoic acid
N-(3,5-dibromo-4-{[3-(isopropylamino)-5-(trifluoromethyl)benzoyl]oxy}benzoylglycine
3-(3,5-dibromo-4-{[3-cyano-5-(trifluoromethyl)benzyl]oxy}phenyl)propanoic acid
N-(3,5-dibromo-4-{[3-(sec-butylamino)-5-chlorobenzoyl]oxy}benzoylglycine
3-(3,5-dibromo-4-{[3-(sec-butylamino)-5-methylbenzyl]oxy}phenyl)propanoic acid
N-(3,5-dibromo-4-{[3-(sec-butylamino)-5-methylbenzoyl]oxy}benzoylglycine
3-(4-{[3-(sec-butylamino)-5-methylbenzyl]oxy}-3,5-dichlorophenyl)propanoic acid
3-(3,5-dibromo-4-{[3-(sec-butylamino)-5-chlorobenzyl]oxy}phenyl)propanoic acid
N-(3,5-dibromo-4-{[3-(sec-butylamino)-5-chlorobenzoyl]oxy}benzoylglycine
3-(3,5-dibromo-4-[(3-(sec-butylamino)-5-(trifluoromethyl)benzyl]oxy]phenyl)propanoic acid
N-(3,5-dibromo-4-[(3-(sec-butylamino)-5-(trifluoromethyl)benzyl]oxy]benzoyl)glycine
3-(3,5-dibromo-4-[(3-(sec-butylamino)-2-chlorobenzyl]oxy]phenyl)propanoic acid
(3,5-dibromo-4-[(3-chloro-5-(ethylamino)benzyl]oxy]phenyl)acetic acid
(3,5-dichloro-4-[(3-(ethylamino)-5-methyl-phenyl]oxy]phenyl)acetic acid
[4-(3-amino-5-methylbenzoxyl)-3,5-dichlorophenyl]acetic acid
N-(3,5-dichloro-4-[(3-(ethylamino)-5-methylbenzyl]oxy]benzoyl)glycine
N-[(4-[3-amino-5-methylbenzyl]oxy]-3,5-dichlorobenzoyl]glycine
S-fS^-dibromo^-lfS-CethylaminoJ-S-ffluorometh^benzyloxyJpheny^propanoic acid
3-(3,5-dibromo-4-[(3-ethoxymethyl-5-(ethylamino)benzyl]oxy]phenyl)propanoic acid
3-(3,5-dibromo-4-[(3-amino-2-chlorobenzyloxy]-3,5-dichlorophenyl)propanoic acid
3-(3,5-dibromo-4-[(3-amino-2-fluorobenzyloxy]-3,5-dichlorophenyl)propanoic acid
3-(3-dibromo-4-[(2-ethoxy-3-(ethylamino)benzyl]oxy]phenyl)propanoic acid
3-(3,5-dibromo-4-[(2-methoxy-3-(ethylamino)benzyl]oxy]phenyl)propanoic acid
3-(3,5-dichloro-4-[(3-(f(cyclopropy)lamino)benzyl]oxy]phenyl)propanoic acid
3-(3,5-dibromo-4-[(2-fluoro-5-(isopropylamino)benzyl]oxy]phenyl)propanoic acid
3-(3,5-dibromo-4-[(2-fluoro-5-(cyclobutylamino)benzyl]oxy]phenyl)propanoic acid
3-(3,5-dibromo-4-[(2-chloro-3-(1,2-dimethyl-propylamino)benzyl]oxy]phenyl)propanoic acid
3-(3,5-dibromo-4-[(3-chloro-5-(1,2-dimethyl-propylamino)benzyl]oxy]phenyl)propanoic acid
3-(3,5-dibromo-4-[(2-chloro-3-(1,2-dimethyl-propylamino)benzyl]oxy]phenyl)propanoic acid
N-(3,5-dibromo-4-{[3-chloro-5-(1,2-dimethylpropylamino)benzyl]oxy}benzoyl)glycine
3-(3,5-dibromo-4-{[2,5-dichloro-3-(isopropylamino)benzyl]oxy}phenyl)-2-fluoropropanoic acid
3-(3,5-dibromo-4-{[2,5-dichloro-3-(ethylaraino)benzyl]oxy}phenyl)-2-fluoropropanoic acid
3-(3,5-dibromo-4-{[2-chloro-3-(ethylamino)benzyl]oxy}phenyl)-2-fluoropropanoic acid
3-(3,5-dibromo-4-{[3-(isopropylamino)-5-methylbenzyl]oxy}phenyl)butanoic acid
3-(3,5-dibromo-4-{[3-(cyclobutylamino)-5-methylbenzyl]oxy}phenyl)butanoic acid
(E)-3-(3,5-dibromo-4-{[2,5-dichloro-3-(ethylamino)benzyl]oxy}phenyl)acrylic acid
(E)-3-(3,5-dibromo-4-{[2,5-dichloro-3-(isopropylamino)benzyl]oxy}phenyl)acrylic acid
(E)-3-(3,5-dibromo-4-{[2,5-dichloro-3-(cyclobutylamino)benzyl]oxy}phenyl)acrylic acid
N-(3,5-dibromo-4-{[3-(ethylamino)-5-methylbenzyl]oxy}phenyl)propionic acid
N-(3,5-dibromo-4-{[3-(isopropylamino)-5-methylbenzyl]oxy}phenyl)propionic acid
N-(3,5-dibromo-4-{[3-(cyclobutylamino)-5-methylbenzyl]oxy}phenyl)propionic acid
(S)-2-{2-(3,5-dibromo-4-{[3-chloro-5-(ethylamino)benzyl]oxy}phenyl)acetylamino}-3-phenyl-propanoic acid
(S)-2-{2-(3,5-dichloro-4-{[3-(ethylamino)-5-methylbenzyl]oxy}phenyl)acetylamino]-2-phenyl-acetic acid
3-{3,5-dibromo-4-{[3-chloro-5-(isopropylamino)benzyl]oxy}phenyl}amino]-3-oxopropanoic acid
{4-{(E)-2-(3-amino-phenyl)-vinyl]-3,5-dibromo-benzyloxy} -acetic acid tert-butyl ester
3-(4-{[3-(acetylamino)benzyl]oxy}-3,5-dibromophenyl)propanoic acid
3-(4-{[3-(acetylamino)benzyl]oxy}-3,5-dichlorophenyl)propanoic acid
3-(4-{[3-(acetylamino)-4-methylbenzyl]oxy}-3,5-dibromophenyl)propanoic acid
3-(3,5-dibromo-4-{[3-(propionylamino)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{[3-(propionylamino)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-(butyrylamino)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{{3-(isobutyrylamino)benzyl}oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{{3-(isobutyrylamino)benzyl}oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{{3-(isobutyrylamino)-2-methylbenzyl}oxy}phenyl)propanoic acid
3-[3,5-dibromo-4-{{3-[(3-methylbutanoylamino)benzyl]oxy}phenyl}propanoic acid
3-[3,5-dibromo-4-{{3-[(2E)-but-2-enoylamino]benzyl}oxy}phenyl]propanoic acid
3-[3,5-dibromo-4-{{3-[(cyclopropylcarbonyl)amino]benzyl}oxy}phenyl]propanoic acid
3-[3,5-dibromo-4-{{3-[(cyclobutylcarbonyl)amino]benzyl}oxy}phenyl]propanoic acid
N-(4-{{3-(acetylamino)benzyl}oxy}-3,5-dibromobenzoyl)glycine
N-(3,5-dibromo-4-{{3-(propionylamino)benzyl}oxy}benzoyl)glycine
N-(3,5-dibromo-4-{{3-(isobutyrylamino)benzyl}oxy}benzoyl)glycine
3-(4-{{3-(acetylamino)-5-chlorobenzyl}oxy}-3,5-dibromophenyl)-2-fluoropropanoic acid
3-(4-{{3-(acetylamino)-5-chlorobenzyl}oxy}-3,5-dibromophenyl)propanoic acid
N^-ltS-facetylaminoJ-S-chlorobenzylloxyj-S^-dibromobenzoyOglycine
N-(4-{{3-(acetylamino)0-methylbenzyl}oxy}-3,5-dibromobenzoyl)glycine
N-(4-{{3-(acetylamino)-2-chlorobenzyl}oxy}-3,5-dibromobenzoyl)glycine
3-(4-{{3-(acetylamino)-2-chlorobenzyl}oxy}-3,5-dibromophenyl)-2-fluoropropanoic acid
3-(4-{{3-(acetylamino)-5-methylbenzyl}oxy}-3,5-dibromophenyl)butanoic acid
and
3-[3,5-dibromo-4-{{3-(methylsulfonyl)amino}benzyl}oxy]phenyl]propanoic acid
3-[3,5-dibromo-4-{{4-methyl-3-[(methylsulfonyl)amino]benzyl}oxy}phenyl]propanoic acid
3-[3,5-dibromo-4-{{2-methyl-3-[(methylsulfonyl)amino]benzyl}oxy}phenyl]propanoic acid
3-(3,5-dibromo-4-{{3-[(methylsulfonyl)amino]-5-(trifluoromethyl)benzyl}oxy}phenyl)propanoic acid
3-[3,5-dibromo-4-{{3-methyl-5-[(methylsulfonyl)amino]benzyI}oxy}phenyl]propanoic acid
3-[3,5-dibromo-4-{{3-[(ethylsulfonyl)amino]benzyl}oxy}phenyl]propanoic acid
3-(3,5-dibromo-4-{[3-[(ethylsulfonyl)amino]-5-(trifluoromethyl)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-[(ethylsulfonyl)amino]-2-methylbenzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-[propylsulfonyl]benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-[isopropylsulfonyl]benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-[butylsulfonyl]benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-[phenylsulfonyl]benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-[{3-[3,5-dimethylisoxazol-4-yl)sulfonyl]benzyl]oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{[3-[methylsulfonyl]amino]-5-(trifluoromethyl)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{[3-[methylsulfonyl]benzyl]oxy}phenyl)propanoic acid
N-[3,5-dibromo-4-{[3-[methylsulfonyl]benzyl]oxy}benzoyl]glycine
N-[3,5-dibromo-4-{[3-[ethylsulfonyl]benzyl]oxy}benzoyl]glycine
3-(3,5-dibromo-4-{[3-chloro-5-f(methylsulfonyl)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-chloro-5-f(ethylsulfonyl)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[3-chloro-5-f(ethylsulfonyl)benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-f(3,5-dimethylisoxazol-4-yl)sulfonyl]benzyl]oxy}phenyl)propanoic acid
3-(3,5-dichloro-4-{[3-[methylsulfonyl]amino]-5-(trifluoromethyl)benzyl]oxy}phenyl)acetic acid
3-(3,5-dichloro-4-{[3-[methylsulfonyl]amino]-5-(trifluoromethyl)benzyl]oxy}phenyl)acetic acid
N-[3,5-dichloro-4-{[3-[methylsulfonyl]amino]-5-(trifluoromethyl)benzyl]oxy}benzoyl]glycine
N-[3,5-dichloro-4-{[3-[methylsulfonyl]amino]-5-(trifluoromethyl)benzyl]oxy}benzoyl]glycine
N-[3,5-dichloro-4-{[3-chloro-5-f(methylsulfonyl)benzyl]oxy}phenyl]acetic acid
N-[3,5-dichloro-4-{[3-chloro-5-f(methylsulfonyl)benzyl]oxy}phenyl]propanoic acid
3-(3,5-dibromo-4-{[3-[methylsulfonyl]amino]-5-methylbenzyl]oxy}phenyl)acetic acid
3-(3,5-dibromo-4-{[2-chloro-3-[methylsulfonyl]amino]benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[2-chloro-3-[methylsulfonyl]amino]benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[2-chloro-3-[methylsulfonyl]amino]benzyl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[2-chloro-3-[methylsulfonyl]amino]benzyl]oxy}phenyl)propanoic acid
3-[3,5-dibromo-4-((2-chloro-3-[(methylsulfonyl)amino]benzyl)oxy)phenyl]-2-fluoropropanoic acid
3-[3,5-dibromo-4-((2,5-dichloro-3-[(methylsulfonyl)amino]benzyl)oxy)phenyl]-2-fluoropropanoic acid
3-[3,5-dibromo-4-((3-[(methylsulfonyl)amino]benzyl)oxy)phenyl]butanoic acid
N-[3,5-dibromo-4-((3-methyl-5-[(methylsulfonyl)amino]benzyl)oxy)benzoyl]glycine
{3,5-dibromo-4-[(E)-2-(3-methanesulfonylamino-phenyl)-vinyl]-benzyloxy}-acetic acid
{3,5-dibromo-4-[(E)-2-(3-methanesulfonylamino-phenyl)-ethyl]-benzyloxy}-acetic acid
{3,5-dibromo-4-{[(4-methyl-2-propylquinolin-6-yl)methyl]phenoxy} acetic acid
(2S)-3-[3,5-dibromo-4-{2-ethyl-4-n-propylquinolin-6-yl}oxy]phenyl]-2-fluoropropanoic acid
(2S)-3-[3,5-dibromo-4-((1-ethyl-2-[(methylsulfonyl)methyl]-1H-benzimidazol-6-yl)oxy]phenyl]-2-fluoropropanoic acid
{3,5-dibromo-4-[(4-methyl-2-propylquinolin-6-yl)methyl]phenoxy} acetic acid
N-[3,5-dibromo-4-[(4-methyl-2-propylquinolin-6-yl)methyl]phenyl] glycine
3-[3,5-dibromo-4-{(8-fluoro-4-ethyl-2-propylquinolin-6-yl)oxy}phenyl]propanoic acid
3-[3,5-dibromo-4-{(8-fluoro-4-methyl-2-propylquinolin-6-yl)oxy}phenyl]-2-fluoropropanoic acid
{3,5-dibromo-4-{(8-fluoro-4-methyl-2-propylquinolin-6-yl)oxy} phenoxy} acetic acid
{3,5-dibromo-4-{(2-ethyl-4-methylquinazolin-6-yl)oxy}phenyl]-2-fluoropropanoic acid
{3,5-dibromo-4-{(2-isobutyl-1-isopropyl-1H-benzimidazol-6-yl)methyl]phenoxy} acetic acid
N-[3,5-dibromo-4-((1-ethyl-2-isobutyl-1H-benzimidazol-6-yl)methyl]phenyl]glycine
3-[3,5-dibromo-4-{(2-[(dimethylamino)methyl]-1-ethyl-1H-benzimidazol-6-yl)oxy}phenyl]l-2-fluoropropanoic acid
{3,5-dichloro-4-[(1-ethyl-2-isobutyl-1H-benzimidazol-6-yl)oxy]phenyl] acetic acid
3-[3,5-dibromo-4-{(2-ethyl-4-methylquinazolin-6-yl)oxy}phenyl]-2-fluoropropanoic acid
B-IS^-dibromo^-KS^-dimethylcinnolin-6-yOoxyJphenyll^-fluoropropanoic acid
3-{3,5-dibromo-4-{(2-isobutyl-7-methyl-1,3-benzothiazol-6-y1)oxy3phenyl}-2-fluoropropanoic acid
[3,5-dichloro-4-{(2-isobutyl-7-methyl-1,3-benzothiazol-6-y1)oxy}phenyl]acetic acid
3-{3,5-dibromo-4-{(7-fluoro-2-isobutyl-1,3-benzoxazol-6-y1)oxy}phenyl}-2-fluoropropanoic acid
[3,5-dibromo-4-{(1-ethyl-2-[(methylsulfonyl)methyl]-1H-benzimidazol-6-y1)methyl]phenoxy]acetic acid
[3,5-dichloro-4-{(1-ethyl^-^-methylsulfonyl)methyl]-1H-benzimidazol-6-y1}oxy]phenyl]acetic acid
(4-{[2-(acetylamino)-1-ethyl-1H-benzimidazol-6-y1]methyl}-3,5-dibromophenoxy)acetic acid
(4-{[2-(acetylamino)-1-ethyl-lH-benzimidazol-6-y1]oxy}-3,5-dibromophenoxy)acetic acid
3-{4-{[2-(acetylamino)-1-ethyl-1H-benzimidazol-6-y1]oxy}-3,5-dibromophenyl)-2-fluoropropanoic acid
3-{3,5-dibromo-4-{[1-ethyl-2-[(methylsulfonyl)amino]-1H-benzimidazol-6-y1]oxy}phenyl]-2-fluoropropanoic acid
3-{3,5-dibromo-4-{(1-ethyl-2-[(ethylamino)carbonyl]-1H-benzimidazol-6-y1]oxy}phenyl]-2-fluoropropanoic acid
3-{3,5-dibromo-4-{[2-[2-(methylamino)-2-oxoethyl]-1-ethyl-1H-benzimidazol-6-y1]oxy}phenyl]-2-fluoropropanoic acid
[3,5-dibromo-4-{[1-ethyl-2-[2-(dimethylamino)-2-oxoethyl]-1-ethyl-1H-benzimidazol-6-y1]oxy}phenyl]-2-fluoropropanoic acid
{3,5-dibromo-4-{[3-ethyl-2-isobutyl-2H-indazol-5-y1)methyl]phenoxy}acetic acid
3-{3,5-dibromo-4-[(3-ethyl-2-isobutyl-2H-indazol-5-y1)oxy]phenyl}-2-fluoropropanoic acid
3-{3,5-dibromo-4-{[2-isobutyl-3-methyl-2H-indazol-5-y1]oxy}phenyl}-2-fluoropropanoic acid
N-{3,5-dibromo-4-{[3-methyl-2-phenyl-2H-indazol-5-y1]oxy}phenyl]glycine
N-{3,5-dibromo-4-[(3-ethyl-2-isobutyl-2H-indazol-5-y1)oxy]phenyl] glycine
{3,5-dichloro-4-[(3-ethyl-2-isobutyl-2H-indazol-5-y1)oxy]phenyl]acetic acid
N-{3,5-dibromo-4-[(2-isobutyl-3-methyl-2H-indazol-5-yl)oxy]phenyl}glycine
N-[3,5-dibromo-4-[(3-methyl-2-[2-(methylamino)-2-oxoethyl]-2H-indazol-5-yl)oxy]phenyl]glycine
N-[3,5-dibromo-4-[(3-methyl-2-[(methylsulfonyl)methyl]-2H-indazol-5-yl)oxy]phenyl]glycine
3-(3,5-dibromo-4-[[2-(3-methoxyphenyl)-1H-benzimidazol-5-yl]oxy]phenyl)propanoic acid
3-(3,5-dibromo-4-[[2-(methyl-1H-benzimidazol-5-yl)oxy]phenyl]propanoic acid
{3,5-dibromo-4-[2-(2,2-dimethylpropyl)-1H-benzimidazol-5-yl]oxy}acetic acid
3-(3,5-dibromo-4-[[2-(3-methyl-4-fluorophenyl)-1H-benzimidazol-5-yl]oxy]phenyl)-2-fluoropropanoic acid
3-(3,5-dibromo-4-[[2-(3-methyl-4-fluorophenyl)-1H-benzimidazol-5-yl]oxy]phenyl)propanoic acid
3-(3,5-dibromo-4-[[2-(3-methyl-4-fluorophenyl)-1H-benzimidazol-5-yl]oxy]phenyl)propanoic acid
3-(3,5-dibromo-4-[[2-(3-methyl-4-fluorophenyl)-1H-benzimidazol-5-yl]oxy]phenyl)propanoic acid
3-(3,5-dibromo-4-[[2-(3-methyl-4-fluorophenyl)-1H-benzimidazol-5-yl]oxy]phenyl)propanoic acid
{3,5-dibromo-4-[2-(cyclopropylmethyl)-1H-benzimidazol-5-yl]oxy}phenoxy}acetic
acid
{3,5-dibromo-4-[2-propyl-1H-benzimidazol-5-yl]oxy}phenoxy}acetic acid
S-fB^-dichloro^-JPKS-methylphenyO-1H-benzimidazol-S-yl oxyJphenyOpropanoic acid
3-(3,5-dibromo-4-{[2-(2-(2-thio-ethyl)-1H-benzimidazol-5-yl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4-{[2-(2-(methylthio)-ethyl)-1H-benzimidazol-5-yl]oxy}phenyl)-2-fluoropropanoic acid
N-(3,5-dibromo-4-{[2-(methylthio)-ethyl]-1H-benzimidazol-5-yl]oxy}benzoyl)glycine
3-(3,5-dibromo-4-{[2-isopropylcarbamoyl-1H-benzimidazol-5-yl]oxy}phenyl)-2-fluoropropanoic acid
3-(3,5-dibromo-4-{[2-ethylcarbamoyl-1H-benzimidazol-5-yl]oxy}phenyl)-2-fluoropropanoic acid
3-(3,5-dibromo-4-{[2-diisopropylcarbamoyl-1H-benzimidazol-5-yl]oxy}phenyl)-2-fluoropropanoic acid
5-[2,6-Dibromo-4-(2-fluoro-2-isopropylcarbamoyl-ethyl)-phenoxy]-1H-benzoimidazole-2-carboxylic acid
3-{3,5-Dibromo-4-[2-(methylsulfonylamino-methyl)-1H-benzoimidazol-5-yl]oxy}-propionic acid
3-{3,5-Dibromo-4-[2-(3-fluoro-4-methyl-phenyl)-1H-benzoimidazol-5-yl]oxy}-propionic acid
[3,5-Dibromo-4-(2-cyclopentylmethyl-1H-benzoimidazol-5-yl)oxy phenoxy]-acetic acid
3-{3,5-Dibromo-4-[2-(1,1,2,2-tetrafluoro-ethyl)-1H-benzoimidazol-5-yl]oxy}-phenyl)-2-fluoro-propionic acid
{3,5-Dibromo-4-[2-(1,1,2,2-tetrafluoro-ethyl)-1H-benzoimidazol-5-yl]oxy}-phenoxy]-acetic acid
{3,5-Dibromo-4-[2-(1,1,2,2-tetrafluoro-ethyl)-1H-benzoimidazol-5-yl]benzoylamino}-acetic acid
{3,5-Dibromo-4-[2-(1,1,2,2-tetrafluoro-ethyl)-1H-benzoimidazol-5-yl]benzoylamino}-acetic acid methyl ester
3-\{3,5-Dibromo-4-[2-(2,5-dimethyl-oxazol-4-yl)-1H-benzoimidazol-5-yl oxy]-phenyl\}-2-fluoro-propionic acid

\{3,5-Dibromo-4-[2-(2,5-dimethyl-oxazol-4-yl)-1H-benzoimidazol-5-yl oxy]-benzoylamino\}-acetic acid

\{3,5-Dibromo-4-[2-(2,5-dimethyl-oxazol-4-yl)-1H-benzoimidazol-5-yl oxy]-phenoxy\}-acetic acid

\{3,5-Dichloro-4-[2-(1,1,2,2-tetrafluoro-ethyl)-1H-benzoimidazol-5-yl oxy]-benzoylamino\}-acetic acid

\{3,5-Dichloro-4-[2-(2,5-dimethyl-oxazol-4-yl)-1H-benzoimidazol-5-yl oxy]-benzoylamino\}-acetic acid

\{3,5-Dichloro-4-[2-furan-2-yl-1H-benzoimidazol-5-yl oxy]-benzoylamino\}-acetic acid

\{3,5-Dichloro-4-[2-(2-fluoro-phenyl)-1H-benzoimidazol-5-yl oxy]-benzoylamino\}-acetic acid

\{3,5-Dichloro-4-[2-(methoxy-phenyl)-1H-benzoimidazol-5-yl oxy]-benzoylamino\}-acetic acid

\{3,5-Dichloro-4-[2-(1-methyl-1H-pyrrol-2-yl)-1H-benzoimidazol-5-yl oxy]-benzoylamino\}-acetic acid

N-[3,5-Dibromo-4-(2-isobutyl-1H-benzoimidazol-5-yl oxy)-phenyl]-acetamide

N-[3,5-Dibromo-4-(2-isobutyl-3H-benzoimidazol-5-yl oxy)-phenyl]-malonamic acid methyl ester

3-[3,5-Dichloro-4-(2-isobutyl-1H-benzoimidazol-5-yl oxy)-phenyl]-2-fluoro-propionic acid

\{3,5-Dibromo-4-[2-(2,5-dimethyl-oxazol-4-yl)-1H-benzoimidazol-5-yl oxy]-phenoxy\}-acetic acid methyl ester

N-[3,5-Dibromo-4-(2-isobutyl-1H-benzoimidazol-5-yl oxy)-phenyl]-malonamic acid

(R)-3-[3,5-Dibromo-4-(2-isobutyl-1H-benzoimidazol-5-yl oxy)-phenyl]-2-fluoro-propionic acid

(S)-3-[3,5-Dibromo-4-(2-isobutyl-1H-benzoimidazol-5-yl oxy)-phenyl]-2-fluoro-propionic acid

(3,5-dichloro-4-[[2,3-dimethyl-1H-indol-5-yl]oxy]phenyl)acetic acid

(3,5-dichloro-4-[[2-(4-methoxyphenyl)-3-methyl-1H-indol-5-yl]oxy]phenyl)acetic acid
3-(3,5-dibromo-4-{[2-(4-methoxyphenyl)-3-methyl-1H-indol-5-yl]oxy}phenyl)propanoic acid
(3,5-dibromo-4-{f2-(4-methoxyphenyl)-3-methyl-1H-indol-5-yl]oxy}phenoxy)acetic acid
3- (3,5-dibromo-4-[(2,3-dimethyl-1H-indol-5-yl)oxy]phenyl) propanoic acid
(4-{[2-(4-bromophenyl)-3-methyl-1H-indol-5-yl]oxy}-3,5-dichlorophenyl)acetic acid
(3,5-dichloro-4-{[2-(4-hydroxyphenyl)-3-methyl-1H-indol-5-yl]oxy}phenyl)acetic acid
3-(4-{[2-(1,3-benzodioxol-5-yl)-3-ethyl-1H-indol-5-yl]oxy})-3,5-dichlorophenyl)propanoic acid
3-(4-{[2-(1,3-benzodioxol-5-yl)-3-ethyl-1H-indol-5-yl]oxy})-3,5-dibromophenyl)propanoic acid
3- [3,5-Dibromo-4 [(3-methyl-2-pyridin-4-yl -1H-indol-5-yl)oxy]phenyl ]propanoic acid
3-(3,5-dibromo-4- {[2-(4-methoxyphenyl)-3-ethyl]- 1H-indol-5-yl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4- {[2-(4-chlorophenyl)-3-ethyl-1H-indol-5-yl]oxy}phenyl)propanoic acid
3-(3,5-dibromo-4- {[2-(4-methoxyphenyl)-3-propyl-1H-indol-5-yl]oxy}phenyl)propanoic acid
N-(3,5-dibromo-4-{[2-(4-chlorophenyl)-3-ethyl-1H-indol-5-yl]oxy}benzoyl)glycine
3-{3,5-Dibromo-4-[3-ethyl-2-(4-methoxy-phenyl)-1H-indol-5-yloxy]-phenyl}]-2-fluoro-propionic acid
N-[3,5-Dichloro-4-(2-isopropylcarbamoyl]-3 -methyl- 1H-indol-5-yloxy)-phenyl]-malonamic acid
5-[4-(Carboxymethyl-carbamoyl)-2,6-dichloro-phenoxy]-3-methyl-1H-indole-2-carboxylic acid methyl ester
5-[4-(Carboxymethyl-carbamoyl)-2,6-dichloro-phenoxy]-3-methyl-1H-indole-2-carboxylic acid ethyl ester
3-[3,5-Dichloro-4-(2,3-dimethyl- 1H-indol-5-yloxy)-phenyl]-propionic acid
3-{3,5-Dichloro-4-[2-(4-methoxy-phenyl)-3-methyl-1H-indol-5-yloxy]-phenyl}]-propionic acid
5-[4-(2-Carboxy-acety!amino)-2,6-bis-trifluoromethyl-phenoxy]-3-methyl-1H-indole-2-carboxylic acid.
Methyl[3,5-dibromo-4-(4-hydroxy-3-isopropyl-5-phenylethynylphenoxy)]benzoate
3,5-dibromo-4-{4-hydroxy-3-isopropyl-5-((E)-styryl)phenoxy}benzoic acid
3-{3,5-dibromo-4-[4-hydroxy-3-isopropyl-5-((E)-styryl)phenoxy]phenyl}propionic acid
3-{3,5-dibromo-4-[4-hydroxy-3-isopropyl-5-((E)-2-pyridin-4-yl-vinyl)phenoxy]phenyl}propionic acid
3-{3,5-dibromo-4-[4-hydroxy-3-isopropyl-5-((E)-2-pyridin-2-yl-vinyl)phenoxy]phenyl}propionic acid
3-{3,5-dibromo-4-[4-hydroxy-3-isopropyl-5-((E)-2-pyrazine-2-yl-vinyl)phenoxy]phenyl}propionic acid
3-{3,5-dibromo-4-[4-hydroxy-3-isopropyl-5-((E)-2-(4-dimethylaminomethylphenyl)vinyl)phenoxy]phenyl}propionic acid
4-{(E)-2-{5-[2,6-Dibromo-4-(2-carboxyethyl)phenoxy]-2-hydroxy-3-isopropylphenoxy}vinyl}propionic acid
3-{3,5-Dibromo-4-[4-hydroxy-3-isopropyl-5-(2-pyridin-4-yl-ethyl)-phenoxy]phenyl}propionic acid
3-[3,5-Dibromo-4-(4-hydroxy-3-isopropyl-5-phenylethyl-phenoxy)phenyl]-2-hydroxy-propionic acid
3-{3,5-Dibromo-4-[4-hydroxy-3-isopropyl-5-((E)-2-pyridin-4-yl-vinyl)-phenoxy]phenyl}propionic acid
3-{3,5-Dibromo-4-[4-hydroxy-3-isopropyl-5-(2-pyridin-4-yl-ethyl)-phenoxy]phenyl}-2-hydroxy-propionic acid
{4,6-Dibromo-5-[3-isopropylpyridine-4-(5-methyl-2-phenylloxazol-4-ylmethoxy)phenoxy]indan-1-yl} acetic acid;
{4,6-Dibromo-5-[4-(3,5-dimethyloxazol-4-ylmetboxy)-3-isopropylphenoxy]indan-1-yl} acetic acid;
{4,6-Dibromo-5-[3-isopropyl-4-(naphthaien-2-ylmethoxy)phenoxy]indan-1-yl} acetic acid;

{4,6-Dibromo-5-[4-(4-fluorobenzoyloxy)-3-isopropylphenoxy] indan-1-yl} acetic acid;

{4,6-Dibromo-5-[3-isopropyl-4-(5-methylisoxazol-3-ylmethoxy)phenoxy]indan-1-yl} acetic acid;

{4,6-Dibromo-5-i3-isopropyl-4-(pyridin-2-ylmethoxy)phenoxy)indan-1-yl} acetic acid;

4,6-Dibromo-5-[3-isopropyl-4-(5-phenyl-2,4]oxadiazol-3-ylmethoxy)phenoxy]indan-1-yl} acetic acid,

4-[4-(4,6-Dibromo-1-carboxymethylindan-5-yl)oxy]-2-isopropylphenoxy]benzoic acid;

(4,6-Dibromo-5-[4-(5-thiophen-3-yl)ethoxy]-3-isopropylphenoxy]indan-1-yl} acetic acid;

{4,6-Dibromo-5-[3-isopropyl-4-(5-thiophen-3-yl)ethoxy]-1,2,4]oxadiazol-3-ylmethoxy)phenoxy]indan-1-yl} acetic acid;

{S-[4-(4-Amino-6-phenylamino[1,3,5]triazin-2-ylmethoxyy)-3-isopropylphenoxy]-4,6-dibromoindan-1-yl} acetic acid;
3,5-Dichloro-4-(3-bromo-4-isobutyramidophenoxy)phenylacetic acid; 
3,5-Dichloro-4-(4-isobutyramidophenoxy)phenylacetic acid; 
3,5-Dichloro-4-(3-phenyl-4-isobutyramidophenoxy)phenylacetic acid; 
3,5-Dichloro-4-(3-bromo-4-[3-methylcrotonylamidophenoxy)phenylacetic acid; 
3,5-Dichloro-4-(3-isopropylidene-1,3-dihydro-2-oxy-5-indoloxy)phenylacetic acid; 
3,5-Dichloro-4-(3-isopropyl-1,3-dihydro-2-oxy-5-indoloxy)phenylacetic acid; 
3,5-Dichloro-4-(3-bromo-4-acetamidophenoxy)phenylacetic acid; 
3,5-Dichloro-4-(4-acetamido-3-phenylphenoxy)phenylacetic acid; 
N-[3,5-dichloro-4-(4-isobutyramidophenoxy)phenylacetyl]glycine; 
L-N-[3,5-dichloro-4-(4-isobutyramidophenoxy)phenylacetyl]alanine; 
L-N-[3,5-dichloro-4-(4-isobutyramidophenoxy)phenylacetyl]valine; 
N-[3,5-dichloro-4-(4-isobutyramid-3-bromophenoxy)phenylacetyl]glycine; 
i-Methyl-N-[3,5-dichloro-4-(4-isobutyramid-3-bromophenoxy)phenylacetyl]-alanine; 
L-N-[3,5-Dichloro-4-(4-isobutyramidophenoxy)phenylacetyl]valine; 
3,5-Dichloro-4-(4-isobutyramidophenoxy)phenylacetic acid; 
3,5-Dichloro-4-(4-trifluoroacetamidophenoxy)phenylacetic acid; 
3,5-Dichloro-4-(4-[2-chloropropionamido]-3-bromophenoxy)phenylacetic acid; 
3,5-Dichloro-4-(4-p-fluorobenzamidophenoxy)phenylacetic acid; 
3,5-Dichloro-4-(4-isobutyramidophenoxy)phenylacetic acid; 
3,5-Dichloro-4-(3-chloro-4-isobutyramidophenoxy)phenylacetic acid; 
3,5-Dichloro-4-(1,3-dihydro-2-oxy-5-ixQidazolophenoxy)phenylacetic acid; 
3,5-Dichloro-4-(3-bromo-4-isobutyramidophenoxy)phenylcinnamic acid; 
3,5-Dichloro-4-(3-bromo-4-isobutyramidophenoxy)phenylpropionic acid;
3,5-Dichloro-4-(3-bromo-4-p-fluorobenzazinophenoxy)phenylpropiolic acid;
3,5-Dichloro-4-(3-bromo-4-[2-chloropropionamido]phenoxy)phenylpropionic acid;
3,5-Dichloro-4-(4-isobutyramidophenoxy)phenylpropionic acid;
3,5-Dibromo-4-(4-[2-chloropropionamido]phenoxy)phenylcinnamic acid;
3,5-Dibromo-4-(3-methyl-1,3-dihydro-2-oxy-5-indolox)phenylcinnamic acid;
3,5-Dibromo-4-(3-methyl-1,S-dihydro-oxy-S-indololxyphenoxycetic acid;
3,5-Diisopropyl-4-(7-2H-1,4-benzoxazinony-3(4H)-one)phenylpropionic acid;
3,5-Dichloro-4-[3-((E)-2-carboxyvinyl)-4-isobutyramidophenoxy]phenylacetic acid;
3,5-Dichloro-4-(3-bromo-4-isobutyramidophenoxy)benzoylphenylsulfonamide;

and the compounds showed in the table below,
3,5-Dimethyl-4-(4-hydroxy-3-isopropylphenoxy)benzyltetrazole,
3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzyltetrazole,
2-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzy]4-thiazole acetic acid,

2-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-methylthiazole,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-5-hydroxy-1-naphthalenesulphonamide,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-toluenesulphonamide,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-nitrobenzenesulphonamide,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl sulfamide,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-aminobenzenesulphonamide,
Methyl-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-2-sulphonamide] benzoate,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-(2-aminoethyl)benzenesulphonamide,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-(2-aminomethyl)benzenesulphonamide,

and the compounds shown below,
$R = \begin{align*}
&\begin{array}{c}
\text{H} \\
\text{H}
\end{array} \\
&\begin{array}{c}
\text{N} \\
\text{H}
\end{array} \\
&\begin{array}{c}
\text{H} \\
\text{N}
\end{array} \\
&\begin{array}{c}
\text{H} \\
\text{N}
\end{array} \\
&\begin{array}{c}
\text{H} \\
\text{N}
\end{array} \\
&\begin{array}{c}
\text{H} \\
\text{N}
\end{array} \\
&\begin{array}{c}
\text{H} \\
\text{N}
\end{array} \\
&\begin{array}{c}
\text{H} \\
\text{N}
\end{array} \\
&\begin{array}{c}
\text{H} \\
\text{N}
\end{array} \\
&\begin{array}{c}
\text{H} \\
\text{N}
\end{array} \\
&\begin{array}{c}
\text{H} \\
\text{N}
\end{array}
\end{align*}$

and the compounds indicated in the table below,

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<th>$\text{-NR'}{R''}$</th>
<th>Formula</th>
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<td>3-(AMINOMETHYL)PYRIDINE</td>
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<tr>
<td>2-(2-AMINOETHYL)PYRIDINE</td>
<td>C24H24Br2N2O3</td>
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<td>NR'R''</td>
<td>Formula</td>
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<tr>
<td>3-(2-AMINOETHYL)PYRIDINE</td>
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<td>1-(4-METHOXYPHENYL)PIPERAZINE DIHYDROCHLORIDE</td>
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<td>1-(2-FLUOROPHENYL)PIPERAZINE</td>
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<td>4-TERT-BUTYLCYCLOHEXYLAMINE</td>
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Z.-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aminobutyric acid,
L.-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]valine,
Z.-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]leucine,
Z.-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]cysteine,
N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]glycine,
D.-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]lysine,
D.-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]methionine,
Z.-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]phenylalanine,
N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]phenylglycine,
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N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]glycine,
D.-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]lysine,
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Z)-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]a-methylalanine, 
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Z,-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]alanine; 
I-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]alanine, 
I-Dimethyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamate, 
L-Di-fer-Butyln-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamate, 
I-(0-er/-butyi)methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamate, 
I-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamic acid, 
L-N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartic acid, 
D-di-fer?-butyiN-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamate, 
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamic acid, 
L-0-;er/-Butyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamine, 
I-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamine, 
H-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamine, 
I-0-Benzy]-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartic acid, 
L-0/-er/-Butyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]asparagine, 
I-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]homoserine, 
Z,-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]homoserine, 
r>-Methyi-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]homoserine. 

and the compounds showed in the table below,

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wherein $R_1 = \text{isopropyl, methyl, ethyl}; R_i$ and $R_3$ may be independently selected from Br, Cl and Me; $n = \text{Oo or 1}; R^* \text{ may be hydrogen, alkyl, cycloalkyl, aryl and heteroaryl}; ^* \text{denotes either D or L stereochemistry when } R^* \text{ is not hydrogen}; R_5 \text{ is hydrogen}; \text{and } R' \text{ is selected from hydrogen, lower alkyl, especially ethyl and methyl.}
N-[3,5-Dichloro-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)benzoyl] glycine
N-[3,5-Dichloro-4-(3-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
N-[3,5-Dichloro-4-(2-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
N-[3,5-Dichloro-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
N-[3,5-Dichloro-4-(3-cyano-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
N-[3,5-Dichloro-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
N-[3,5-Dichloro-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
N-[3,5-Dibromo-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
N-[3,5-Dimethyl-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine
L-N-[3,5-Dibromo-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)phenylacetyl] valine
D-N-[3,5-Dibromo-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)phenylacetyl] phenylglycine
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenylacetyl] valine
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenylacetyl] phenyl glycine
L-N-[3,5-Dibromo-4-(3.5-dimethyl-4-hydroxyphenoxy)phenylacetyl] phenylglycine
3,5-dibromo 4-(4-hydroxy-3-isopropylphenoxy)benzoic acid,
3,5-dibromo 4-(4-hydroxy-3-isopropylphenoxy) benzylalcohol,
3,5-dibromo 4-(4-hydroxy-3-isopropylphenoxy) phenylacetic acid,
3,5-dichloro 4-(4-hydroxy-3-isopropylphenoxy) benzoic acid,
3,5-dichloro 4-(4-hydroxy-3-isopropylphenoxy) benzylalcohol,
3,5-dichloro 4-(4-hydroxy-3-isopropylphenoxy) phenylpropionic acid,
3,5-dimethyl 4-(4-hydroxy-3-isopropylphenoxy) benzoic acid,
3,5-dimethyl 4-(4-hydroxy-3-isopropylphenoxy) benzylalcohol,
3,5-dimethyl 4-(4-hydroxy-3-isopropylphenoxy) phenylacetotrile,
3, 5-dibromo-4-(4-hydroxy-3-isopropylphenoxy) cinnamic acid,
3-bromo-S-chloro-4-(4-hydroxy-3-isopropylphenoxy) phenylacetic acid,
3-chloro-5-iodo-4-(4-hydroxy-3-isopropylphenoxy) phenylacetic acid,
3-chloro-5-methyl-4-(4-hydroxy-3-isopropylphenoxy) phenylacetic acid,
3-chloro-4-ethyl-4-(4-hydroxy-3-isopropylphenoxy) phenylacetic acid,
3-chloro-4-(4-hydroxy-3-isopropylphenoxy) phenylacetic acid,
3, 5-dimethyl-4-(4-hydroxy-3-isopropylphenoxy) phenylacetic acid,
3-ethyl-5-methyl-4-(4-hydroxy-3-isopropylphenoxy) phenylacetic acid,
3-bromo-5-methyl-4-(4-hydroxy-3-isopropylphenoxy) phenylacetic acid,
and the compounds below
and the compounds below:
N-[3,5-Dichloro-4-(4-hydroxy-3-isopropyl-5-πiethytphenoxy)benzoyl] glycine

N_L3,5-Dichloro-4-(3-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine

N-[3,5-Dichloro-4-(2-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine

N-[3,5-Dichloro-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine

N-[3,5-Dichloro-4-(3-cyano-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine

N-[3,5-Dichloro-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine

N-[3,5-Dichloro-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine

L-N-[3,5-Dibromo-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)phenylacetyl] valine

D-N-[3,5-Dibromo-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)phenylacetyl] phenylglycine

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenylacetyl] valine

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenylacetyl] phenylglycine

L-N-[3,5-Dibromo-4-(3,5-dimethyl-4-hydroxyphenoxy)phenylacetyl] phenylglycine

N-[3,5-Dibromo-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine

M-[3,5-Dimethyl-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine

4. A compound for the treatment of disease induced, caused or dependent on activation of the Sonic hedgehog pathway according to any of claims 1 to 4 wherein the treatment involves regulation of cell-proliferation and differentiation.

5. A compound for the treatment of disease induced, caused or dependent on activation of the Sonic hedgehog pathway according to any of claims 1 to 4, wherein the disease is cancer.
7. A compound for the treatment of disease induced, caused or dependent on activation of the Sonic hedgehog pathway according to any of claims 1 to 4, wherein the disease is basal cell carcinoma, pancreatic cancer, prostate cancer, lung cancer, breast cancer, gastric cancer, colon cancer or liver cancer.

8. A method of treating disease induced, caused or dependent on activation of the Sonic hedgehog pathway comprising administering a pharmaceutically effective quantity of a compound according to any of claims 1 to 4 to a patient in need thereof.

9. A method of treatment according to claim 8, wherein the treatment involves regulation of cell-proliferation and differentiation.

10. A method of treatment according to claim 9, wherein the disease is cancer.

11. A method of treatment according to claim 10, wherein the disease is basal cell carcinoma, pancreatic cancer, prostate cancer, lung cancer, breast cancer, gastric cancer, colon cancer or liver cancer.
Figure 1
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**


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)
A61K

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

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

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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* Further documents are listed in the continuation of Box C

**Date of the actual completion of the international search**
14 April 2009

**Date of mailing of the international search report**
24/04/2009

**Name and mailing address of the ISA/Office**
European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040,
Fax (+31-70) 340-3316

**Authorized officer**
Steendijk, Martin

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* Special categories of cited documents

- 'A' document defining the general state of the art which is not considered to be of particular relevance
- 'E' earlier document but published on or after the international filing date
- 'I' document which may throw doubts on prior claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- 'O' document referring to an oral disclosure, use, exhibition or other means
- 'P' document published prior to the international filing date but later than the priority date claimed

- 'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- 'X' document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to solve the same problem as with the invention
- 'Y' document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is taken alone
- 'Z' document member of the same patent family
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<td>wo 2006/123229 A (ORCHID RES LAB LTD [IN]; PANDEY SURENDRAKUMAR SATYANARA [IN]; SINGH GA) 23 November 2006 (2006-11-23) cl aim 12</td>
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<td>wo 2005/092317 A (KAROBIO AB [SE]; GARCIA COLLAZO ANA MARIA [SE]; ERICSSON THOMAS ANDERS) 6 October 2005 (2005-10-06) cited in the application cl aim 1 page 2, line 23</td>
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<td>wo 00/39077 A (KAROBIO AB [SE]; HANGELAND JON [US]; ZHANG MINSHENG [US]; CARINGAL YOL) 6 July 2000 (2000-07-06) cited in the application cl aim 1 page 4, line 11</td>
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<td>PETERSON BLAKE R: &quot;Small-molecule triggers of tadpole metamorphosis&quot; ACS CHEMICAL BIOLOGY, vol. 1, no. 9, 2006, pages 559-561, XP002523532 ISSN: 1554-8929(print) 1554-8937(ele abstract</td>
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