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(71) Applicant(s)
Vanderbilt University

(72) Inventor(s)
Lee, Taekyu;Tarr, James C.;Jeon, Kyuok;Salovich, James M.;Shaw, Subrata;Veerasamy, Nagarathanam;Kim, Kwangho;Christov, Plamen P.;Olejniczak, Edward T.;Zhao, Bin;Fesik, Stephen W.;Bian, Zhiguo

(74) Agent / Attorney
Griffith Hack, Level 10 161 Collins St, MELBOURNE, VIC, 3000, AU

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(71) Applicant: **VANDERBILT UNIVERSITY** [US/US]; 305 Kirkland Hall, 2201 West End Avenue, Nashville, TN 37240 (US).

(72) Inventors: **LEE, Taekyu**; 1057 Walnut Bend Lane, Brentwood, TN 37027 (US). **TARR, James, C.**; 324 Wisteria Drive, Franklin, TN 37064 (US). **JEON, Kyuok**; 918 Tote Lane, Nashville, TN 37211 (US). **SALOVICH, James, M.**; 119 Twin Oaks Drive, Nashville, TN 37211 (US). **SHAW, Subrata**; 3631a Redmon Street, Nashville, TN 37209 (US). **VEERASAMY, Nagarathanam**; c/o Vanderbilt University, 305 Kirkland Hall, 2201 West End Avenue, Nashville, TN 37240 (US). **KIM, Kwangho**; 6784 Chritiansted Lane, Nashville, TN 37211 (US). **CHRISTOV, Plamen, P.**; 902 Pebble Beach Cove, Mount Juliet, TN 37122 (US). **OLEJNICZAK, Edward, T.**; 429 Caledonian Court, Nashville, TN 37211 (US). **ZHAO, Bin**; 5533 Nevil Point, Brentwood, TN 37027 (US). **FESIK, Stephen, W.**; 31 Annandale, Nashville, TN 37215 (US). **BIAN, Zhiguo**; 12895 West Sanctuary Lane, LAKE Bluff, IL 60044 (US).

(74) Agent: **REYNOLDS, Anne, M.**; Michael Best & Friedrich LLP, 100 East Wisconsin Avenue, Suite 3300, Milwaukee, WI 53202-4108 (US).

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(54) Title: SUBSTITUTED INDOLE MCL-1 INHIBITORS

(57) Abstract: The present disclosure provides for compounds that inhibit the activity of an anti- apoptotic Bcl-2 family member Myeloid cell leukemia-1 (Mcl-1) protein. The present disclosure also provides for pharmaceutical compositions as well as methods for using compounds for treatment of diseases and conditions (e.g., cancer) characterized by the over- expression or dysregulation of Mcl-1 protein.

SUBSTITUTED INDOLE MCL-1 INHIBITORS

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. provisional application serial number 62/304,124, filed March 4, 2016, and U.S. provisional application serial number 62/402,903, filed, September 30, 2016, the entire contents of each being incorporated herein by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

[0002] This invention was made with government support under Award DP1OD006933/DP1CA174419, awarded by the National Institutes of Health; under Contract No. HHSN261200800001E, awarded by the NCI Experimental Therapeutics (NExT) Program; and under Grant No. P50CA098131, awarded by the NCI SPORE grant in breast cancer. The government has certain rights in the invention.

TECHNICAL FIELD

[0003] The present disclosure pertains to compounds that inhibit the activity of an anti-apoptotic Bcl-2 family member Myeloid cell leukemia-1 (Mcl-1) protein, compositions containing the compounds, and methods of treating cancer involving over-expressed or dysregulated Mcl-1 protein.

BACKGROUND

[0004] Abnormal regulation of apoptosis is now recognized to play an important role in the development of cancer. The apoptosis pathway can be initiated by various extracellular and intracellular stresses, including growth factor deprivation, DNA damage, oncogene induction, and cytotoxic drugs (Danial, N. N. and Korsmeyer, SJ. *Cell* (2004) 116, 205-219). The death signal leads to the oligomerization of the pro-apoptotic proteins Bax and Bak. Upon activation, they permeabilize the mitochondrial outer membrane and release apoptogenic factors into the cytoplasm. This process is tightly regulated by both pro-apoptotic (Bax, Bak, Bad, Bid, Bim, Bmf, NOXA, PUMA) and anti-apoptotic (Bcl-2, Bcl-xL, Bcl-w, Bcl2-A1, Mcl-1) members of the Bcl-2 family of proteins. Recent data suggests that the anti-apoptotic Bcl-2 proteins function to protect the cell from apoptotic insults, primarily by preventing disruption of mitochondrial outer membrane integrity by binding to the pro-apoptotic proteins as described in Adams, J. M. and Cory S. *Oncogene* (2007) 26, 1324-1337; Willis, S. N. et

al. *Science* (2007) 315,856-859. Because tumor cells are under stress, alterations in their apoptotic signaling pathways are believed to be crucial for survival. Recent data implicates down-regulated apoptosis in the onset of cancer. Research has shown, for example, that anti-apoptotic proteins, are over-expressed in many cancer cell types as described in Beroukhim, R. et al. *Nature* (2010) 463, 899-905; Zhang J. Y., *Nature Reviews Drug Discovery*, (2002) 1, 101; Kirkin, V. et al. *Biochimica et Biophysica Acta* (2004) 1644, 229-249; and Amundson, S.A. et al. *Cancer Research* (2000) 60, 6101-6110. This dysregulation results in the survival of cells that would otherwise have undergone apoptosis such as cancer cells. This suggests that neutralizing the function of anti-apoptotic Bcl-2 proteins may offer an effective strategy for the elimination of cancer cells. In addition, resistance to chemotherapy which is a major cause of treatment failure and poor prognosis in many cancers can be caused by the upregulation of anti-apoptotic Bcl-2 family proteins.

[0005] An important anti-apoptotic member of the Bcl-2 family is Myeloid cell leukemia-1 (Mcl-1). Mcl-1 is one of the most frequently amplified anti-apoptotic genes in human cancers including prostate, lung, pancreatic, breast, ovarian, and cervical cancers, as well as melanoma, B-cell chronic lymphocytic leukemia (B-CLL), *acute myeloid leukemia (*AML) and *acute lymphoblastic leukemia (*ALL) (Beroukhim et al. *Nature* (2010) 463, 899-905). Moreover, its overexpression is implicated as a resistance factor for multiple therapies including widely prescribed microtubule-targeted agents for breast cancers, such as paclitaxel and vincristine as well as Gemcitabine, a first-line treatment option for pancreatic cancer (Wei et al. *Cancer Chemother Pharmacol* (2008) 62, 1055-1064 and Wertz et al. *Nature* (2011) 471, 110-114). These data suggest that Mcl-1 is an important target for a wide variety of cancers.

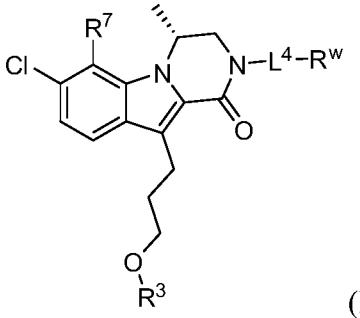
[0006] In many cancer cell types, the cancer cell's survival is attributed to the dysregulation of the apoptotic pathway caused by the over-expression of one or more anti-apoptotic Bcl-2 protein family members. Because of the important role for Bcl-2 family of proteins in regulating apoptosis in both cancerous and non-cancerous cells, and the inter-cell variability of Bcl-2 family protein expression, it could be advantageous to have a small molecule inhibitor that selectively targets and preferably binds to one type or a subset of anti-apoptotic Bcl-2 protein(s). A selective compound also may confer certain advantages in the clinical setting, by providing flexibility to select a dosing regimen to reduce on-target toxic effects in normal cells.

[0007] Because Mcl-1 protein is an important Bcl-2 family member associated with a number of diseases, there is a need for compounds which bind to and inhibit the activity of

Mcl-1 protein.

SUMMARY

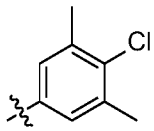
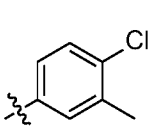
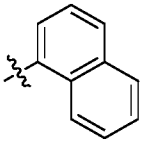
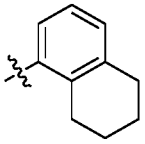
[0007a] In one aspect there is provided a compound having formula:



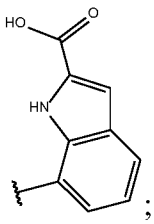
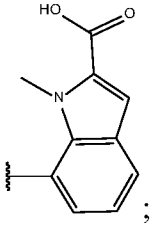
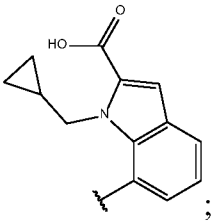
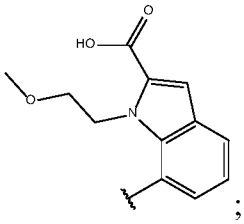
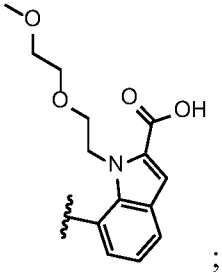
(I-a-1),

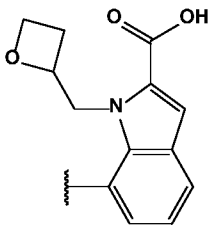
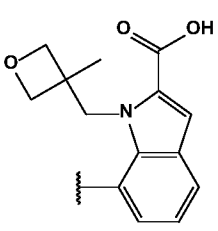
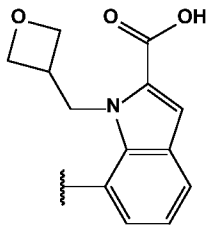
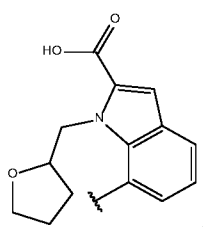
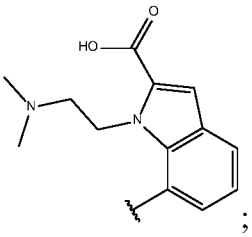
or a pharmaceutically acceptable salt thereof,

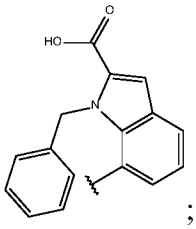
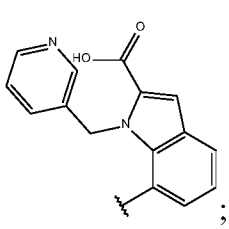
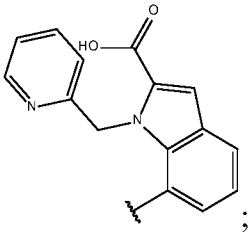
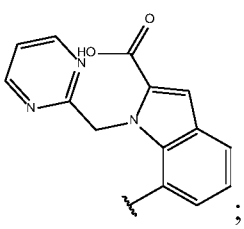
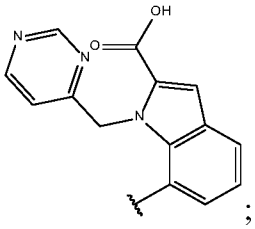
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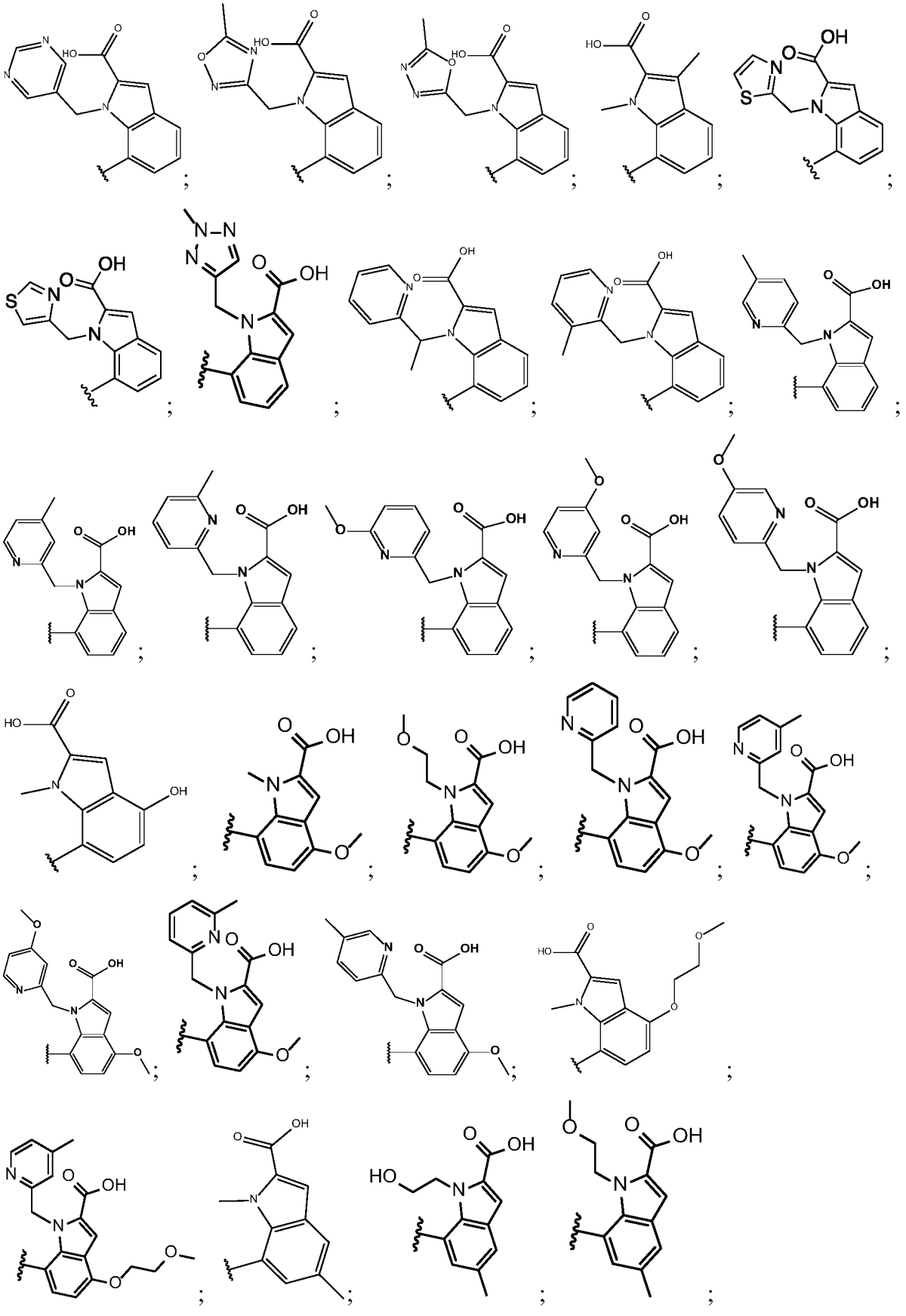
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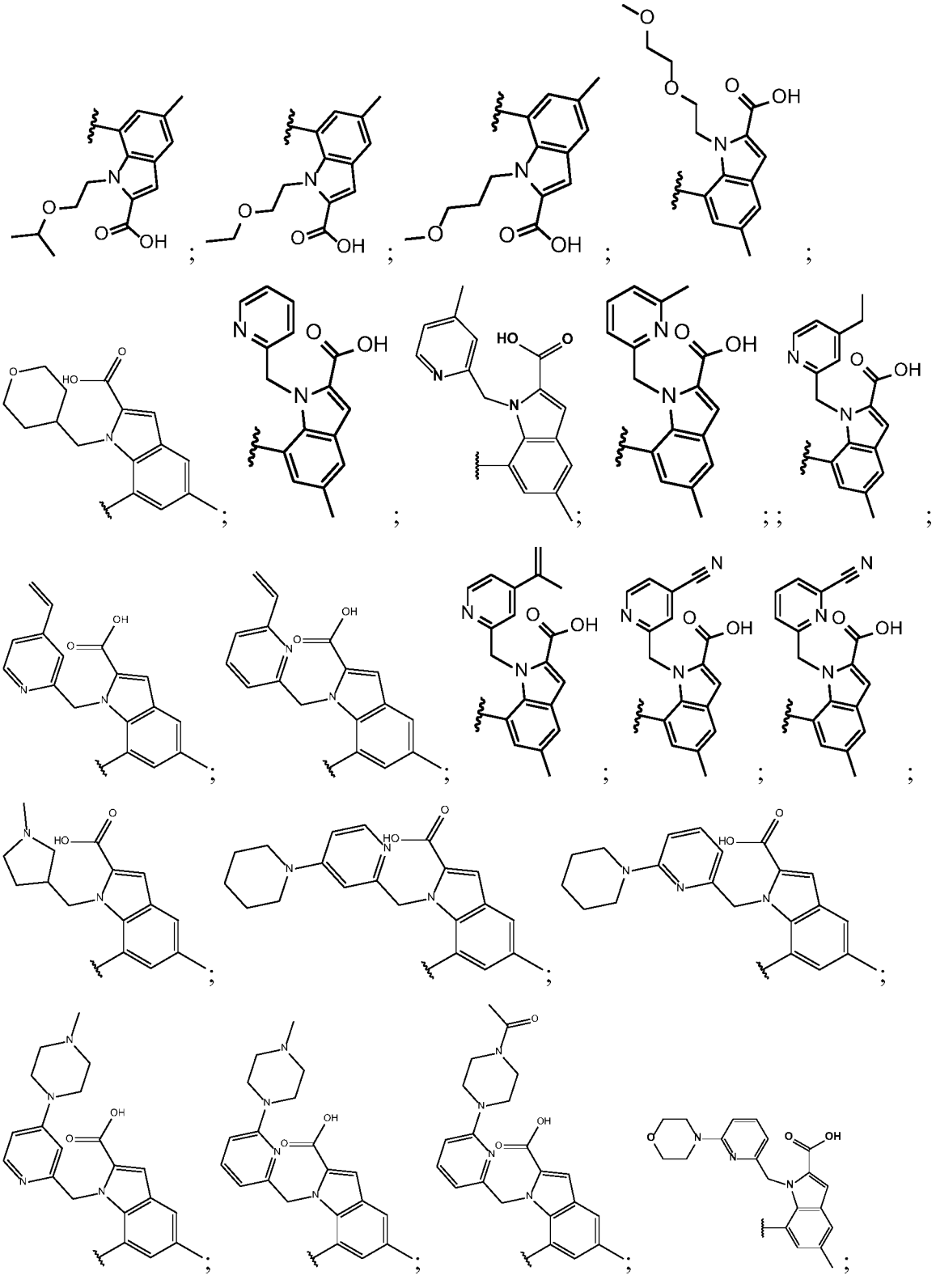
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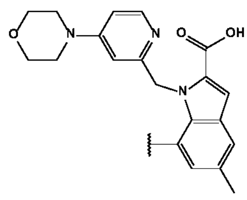
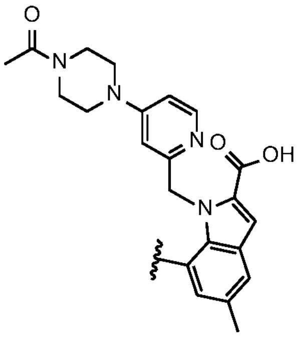
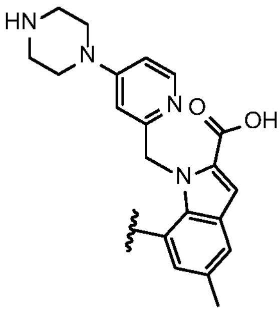
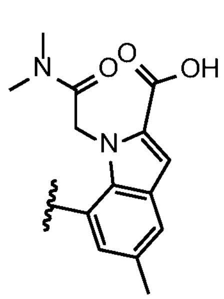
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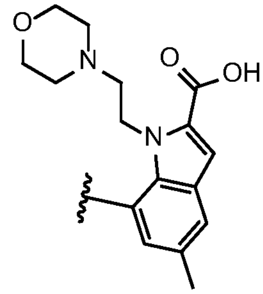
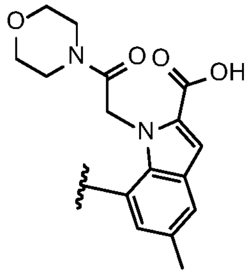
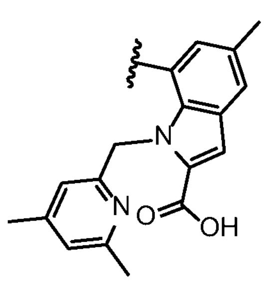
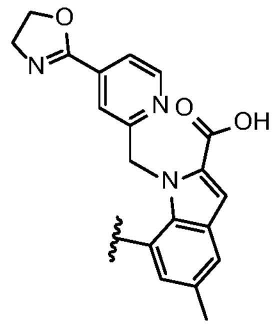
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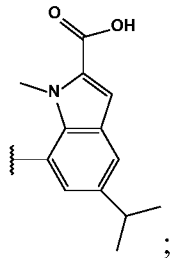
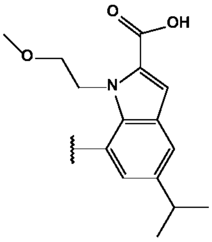
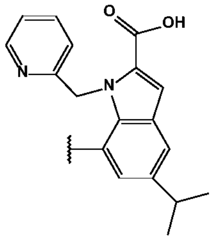
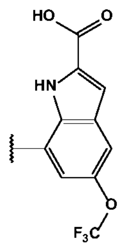
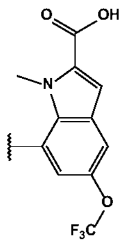
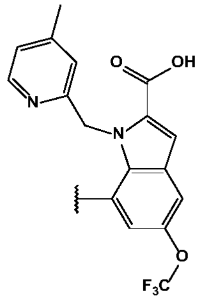
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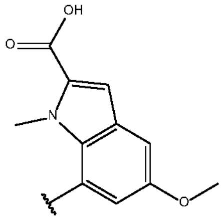
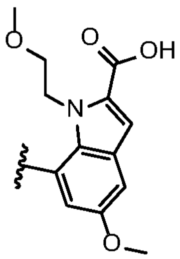
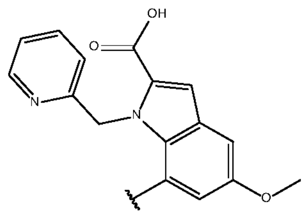
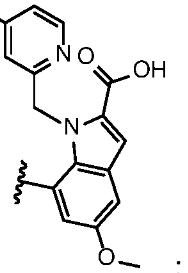


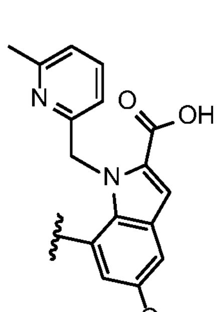
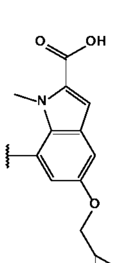
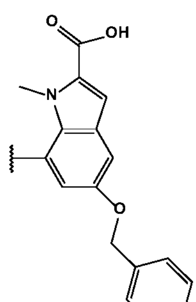
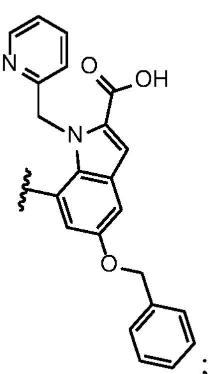
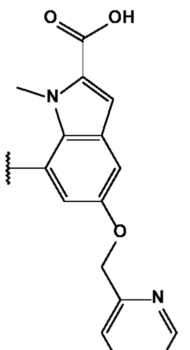


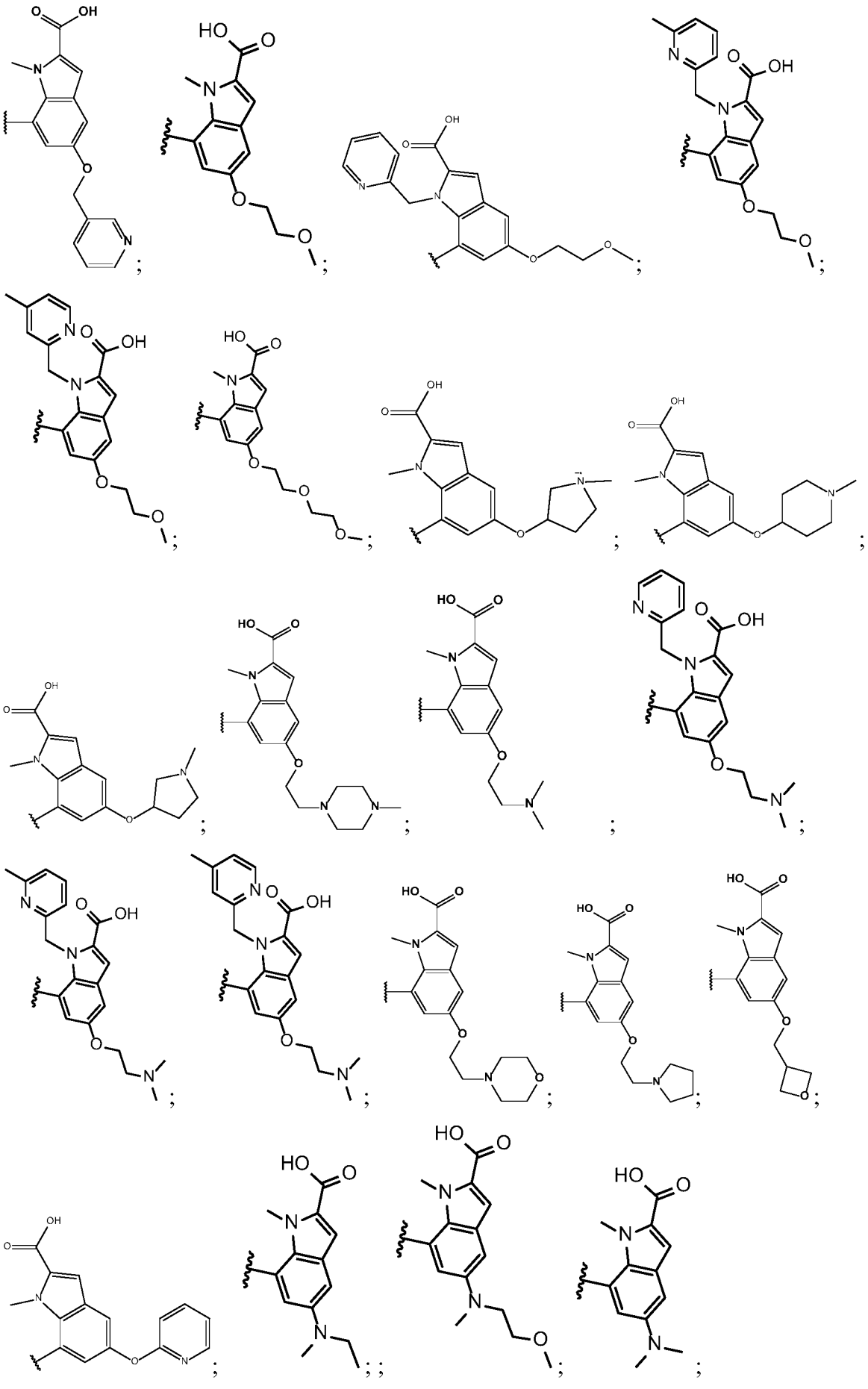
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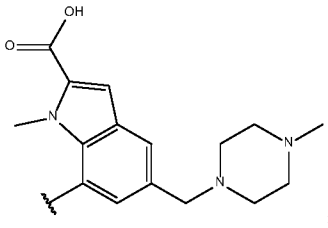
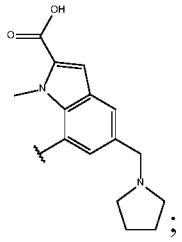
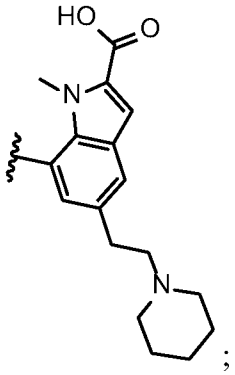
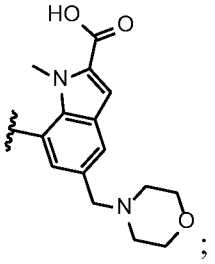
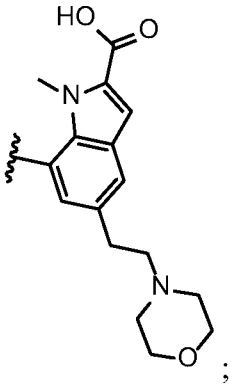
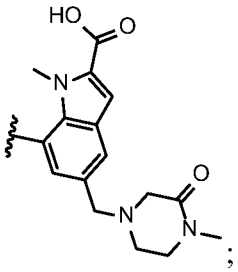
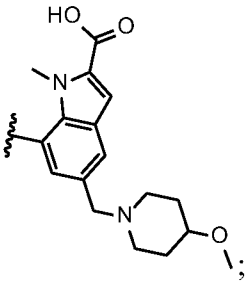
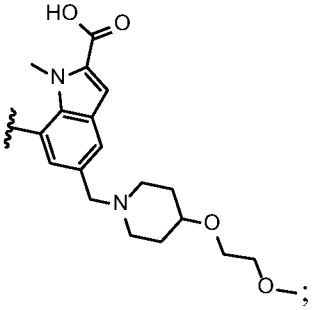
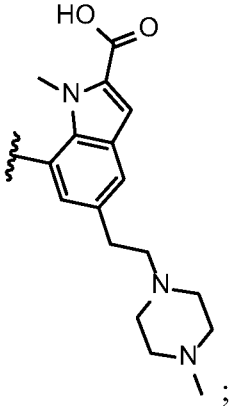
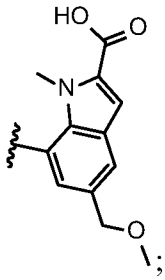
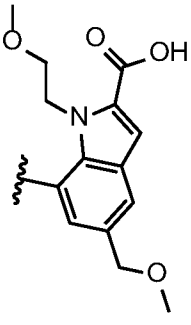
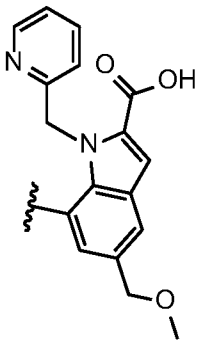
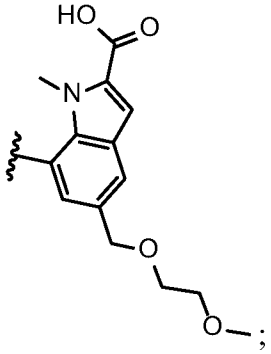
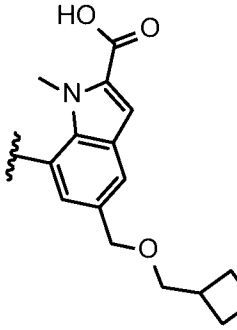
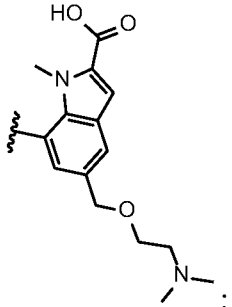
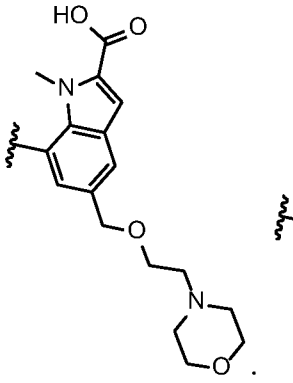
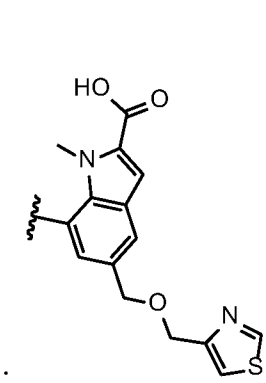
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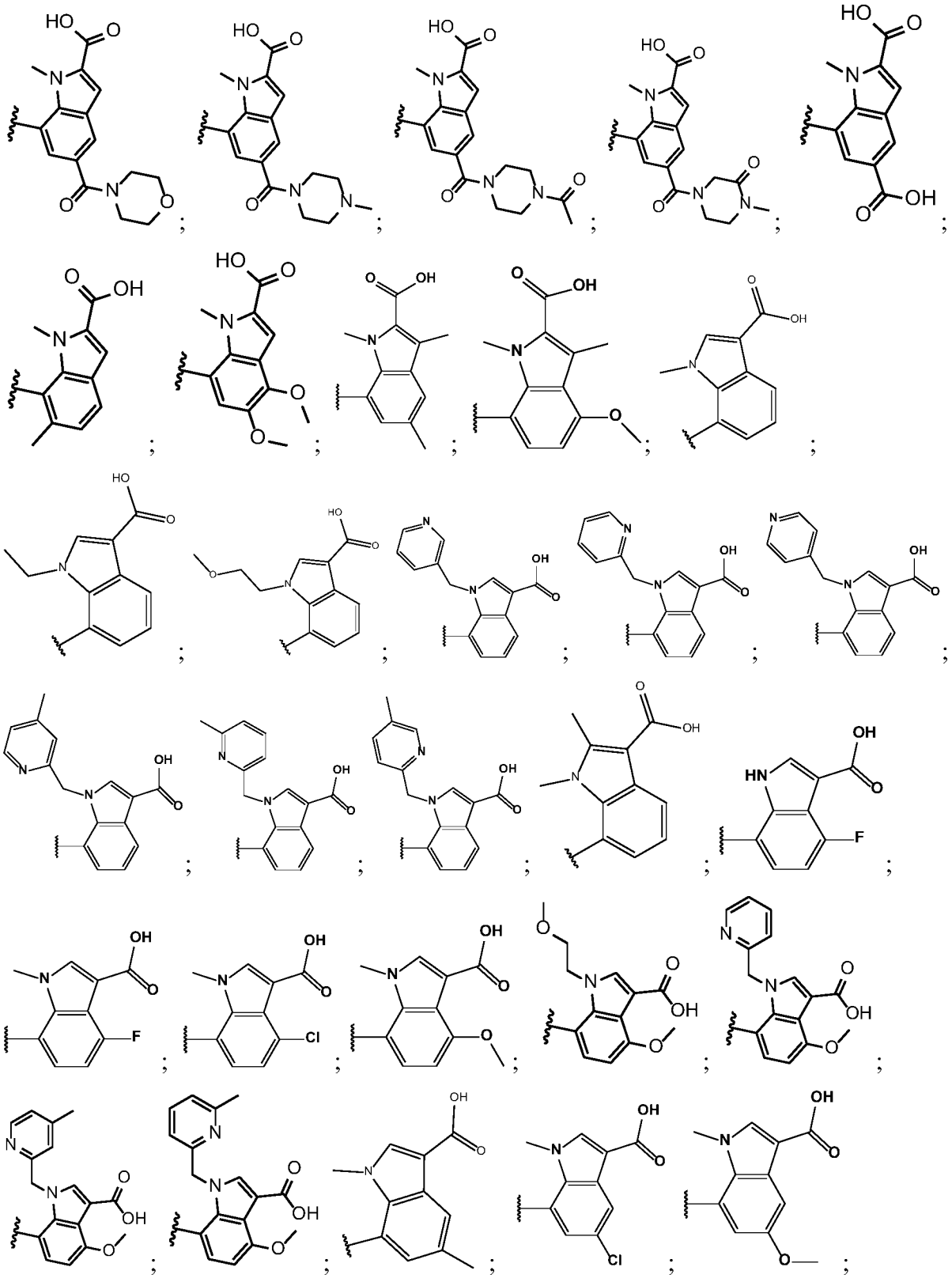
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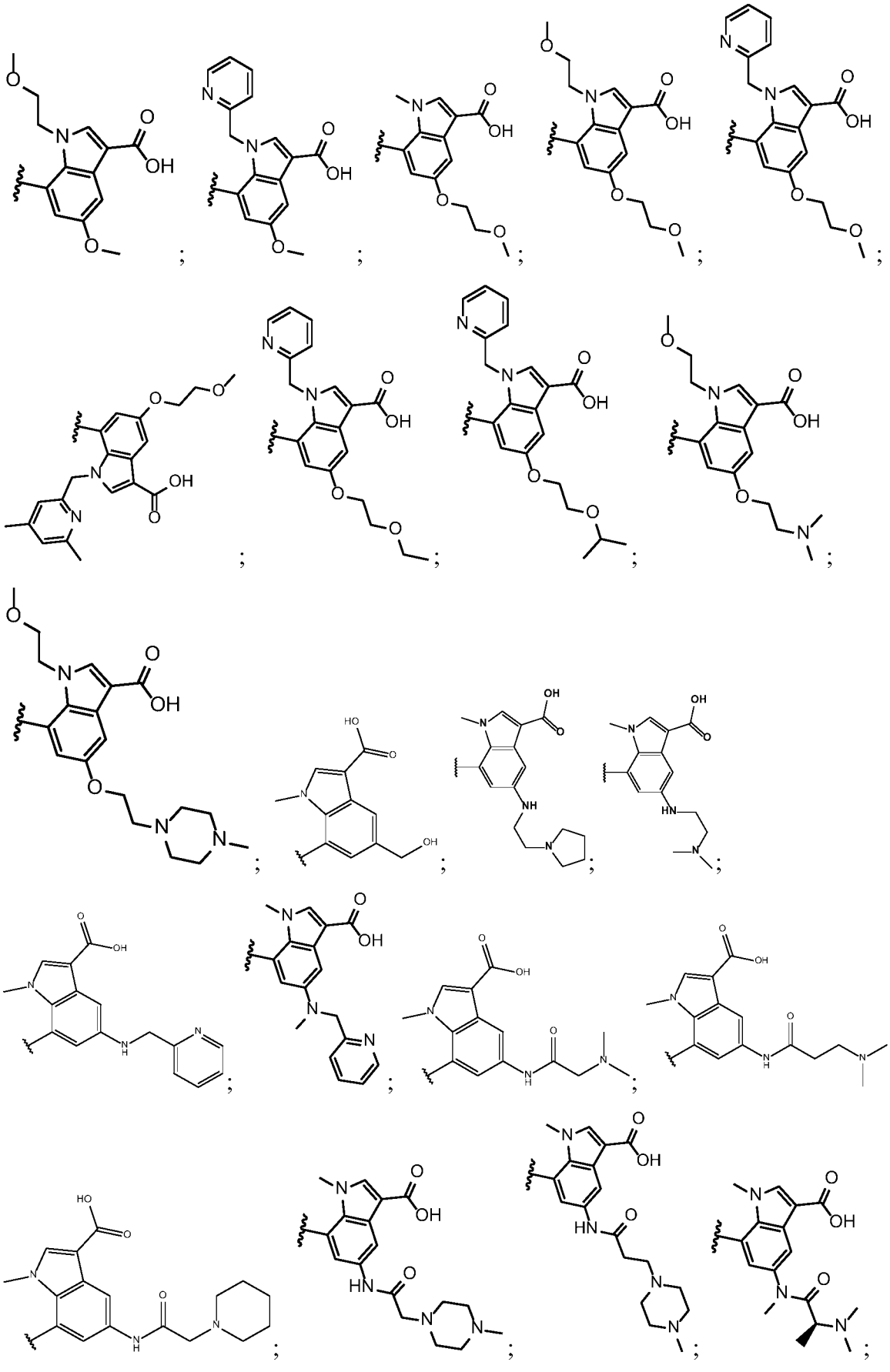
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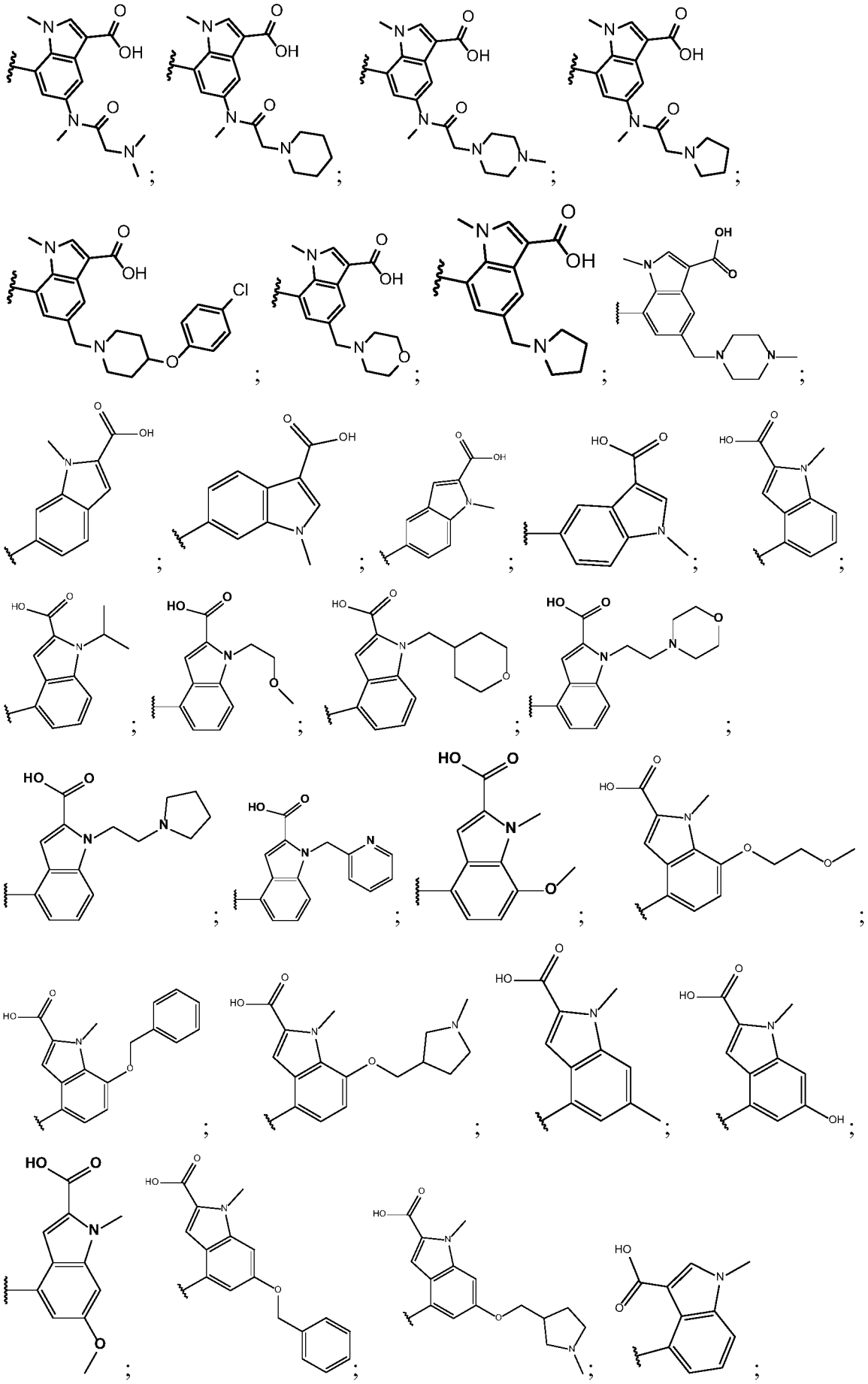
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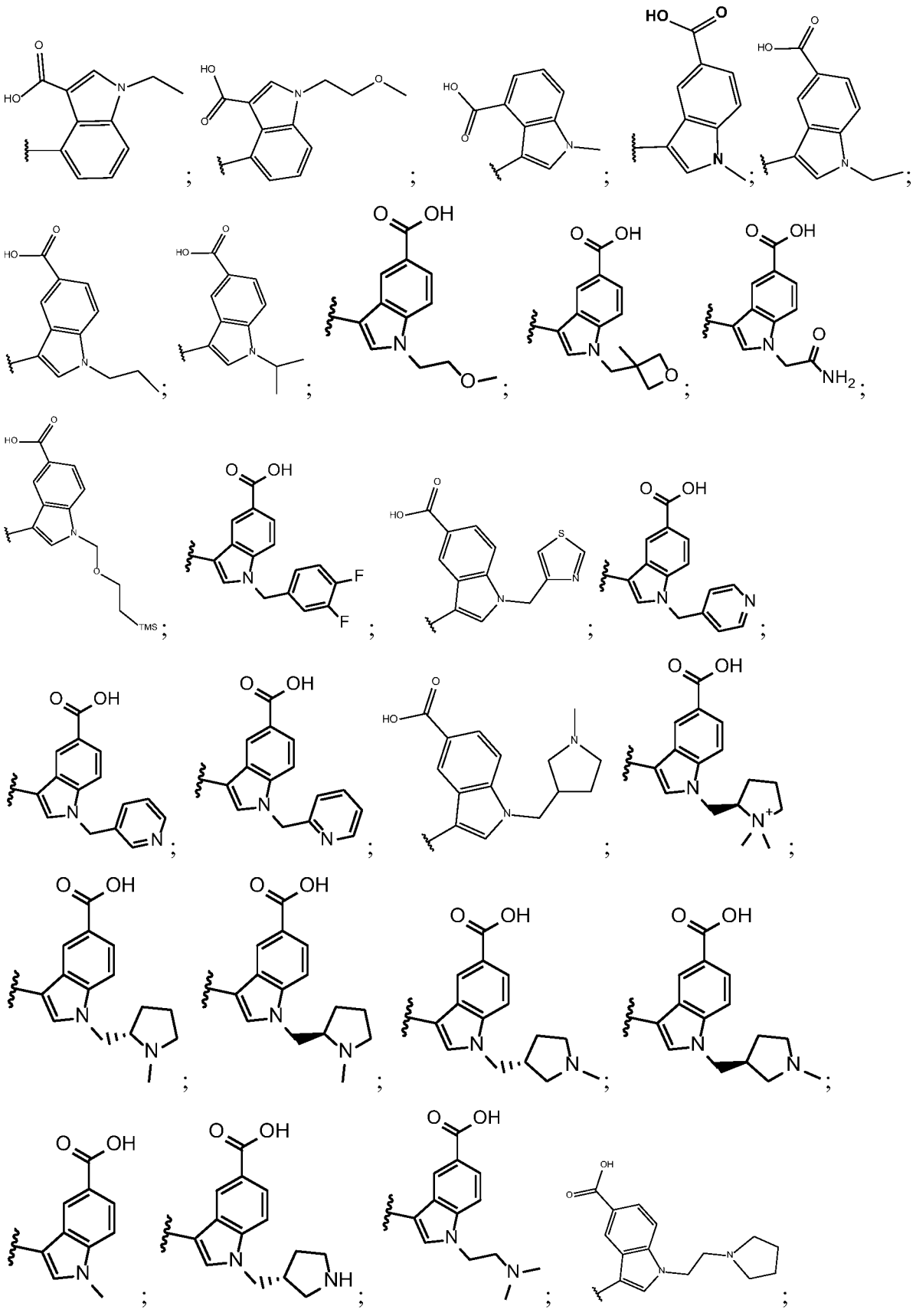
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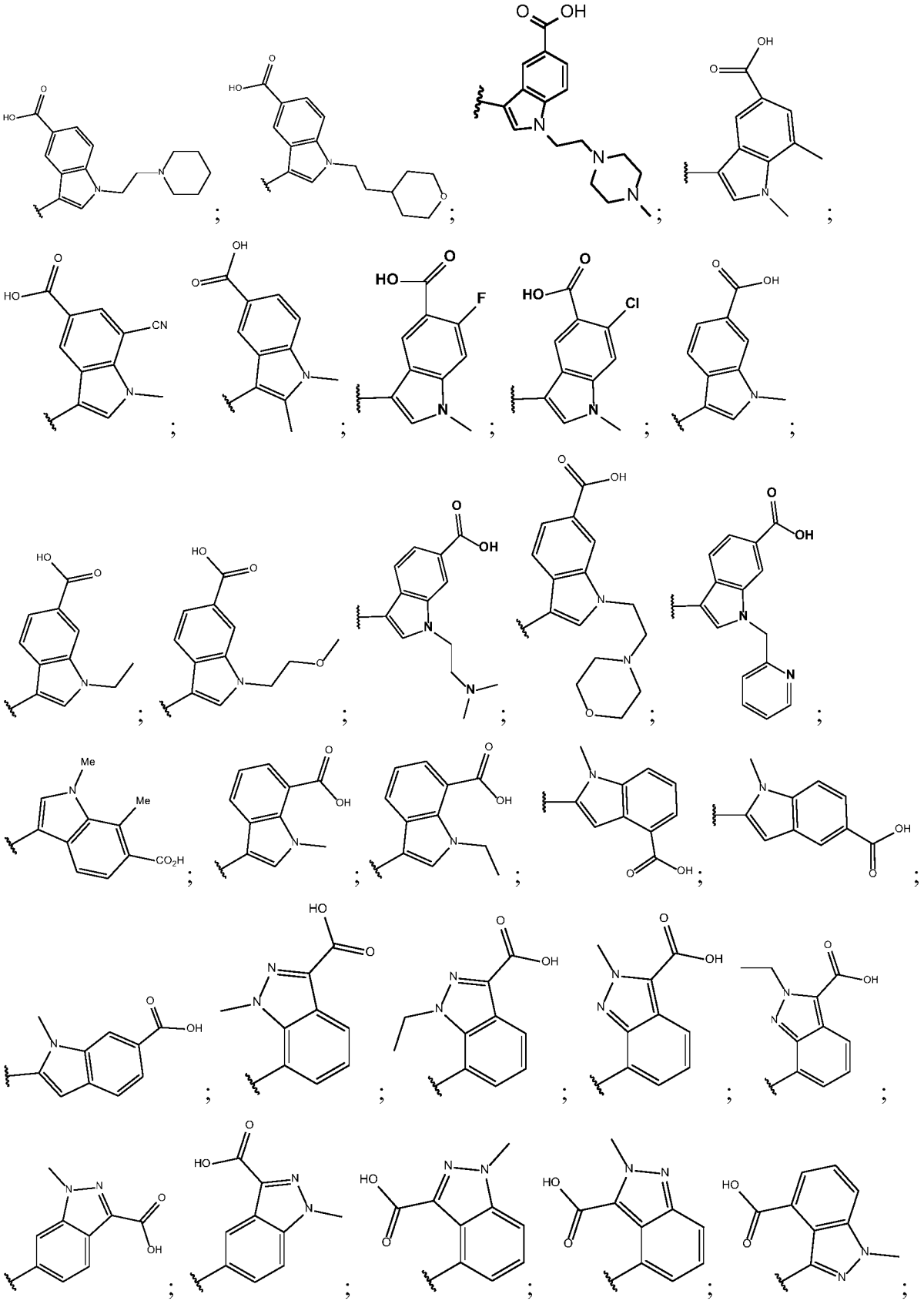
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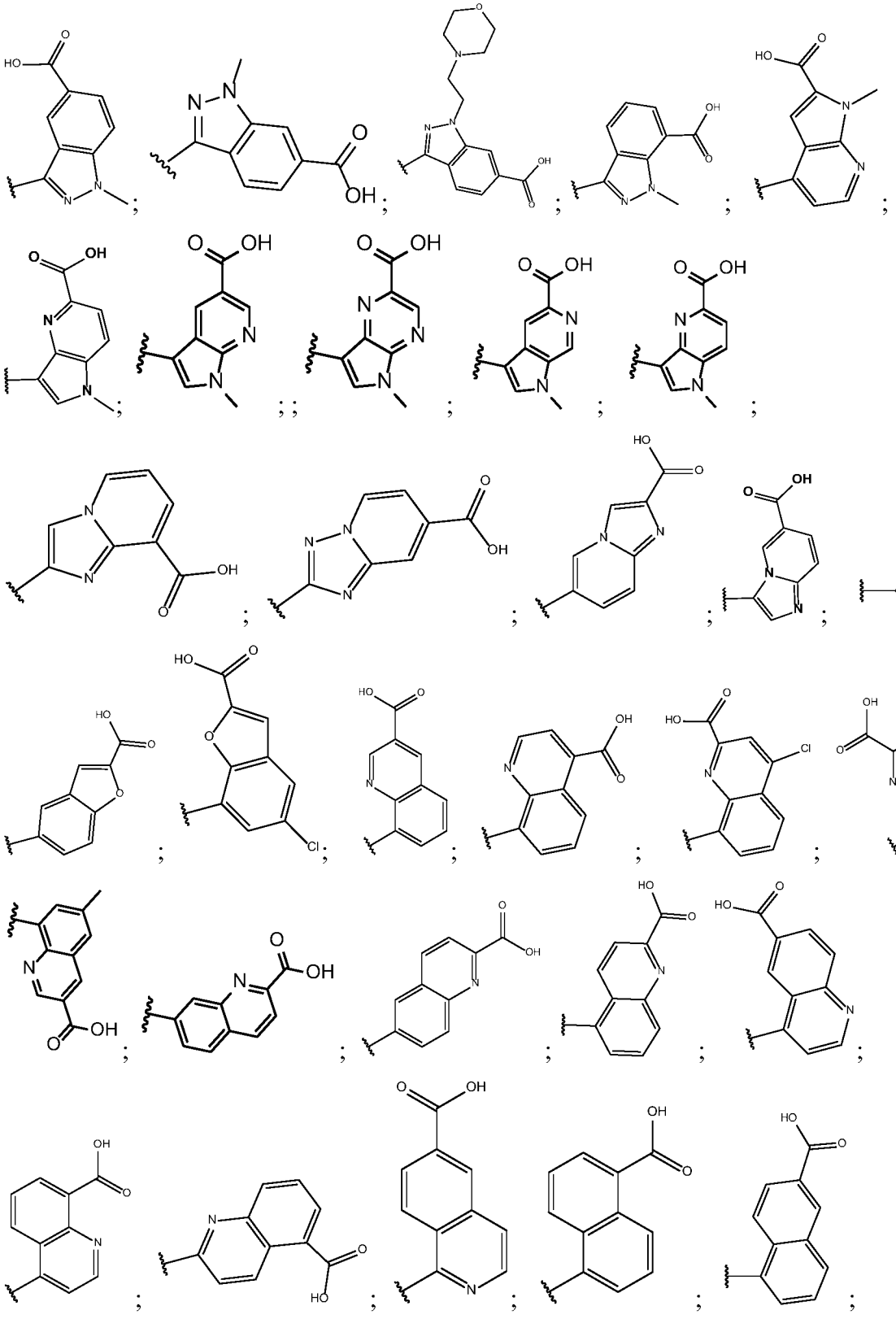


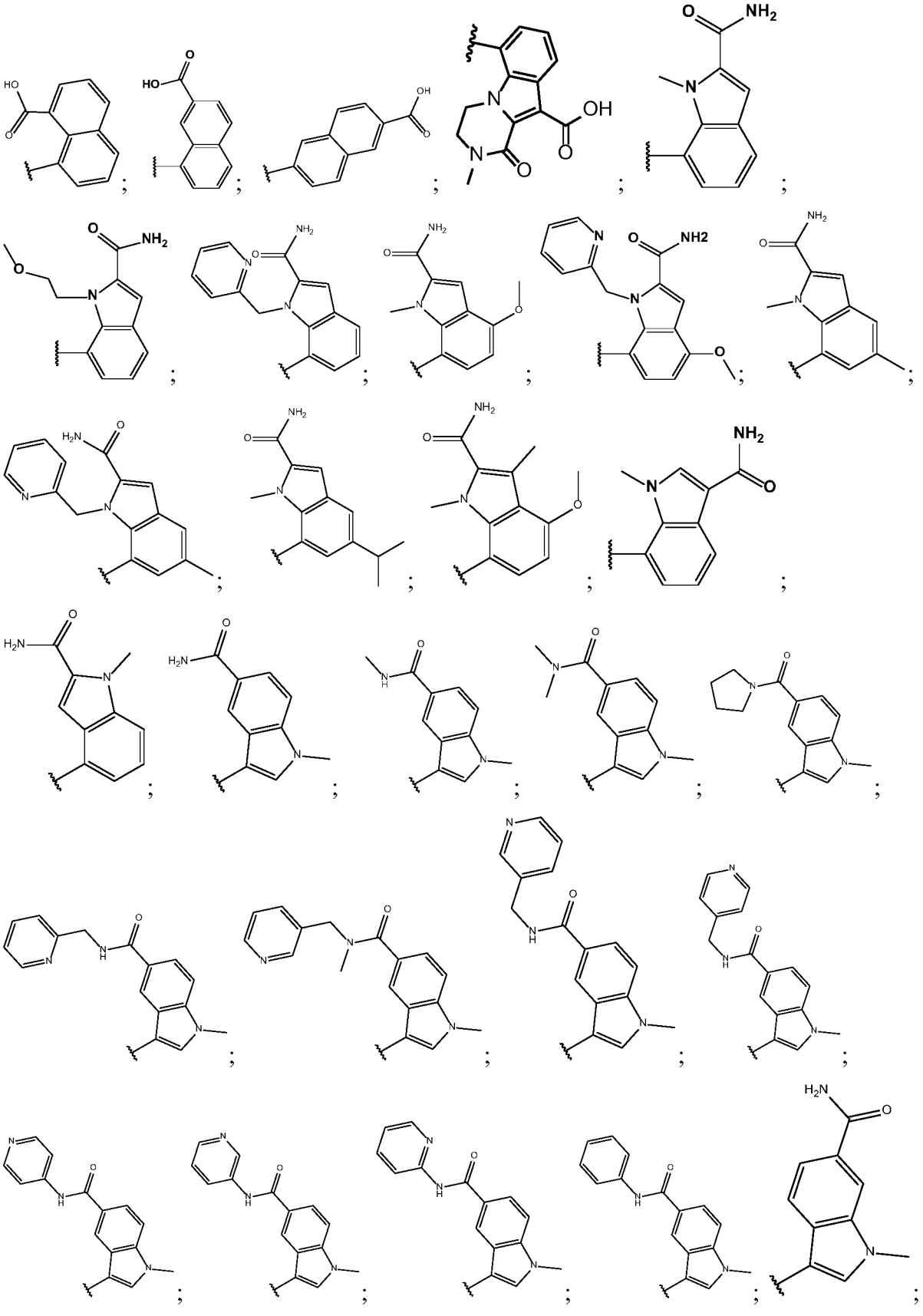


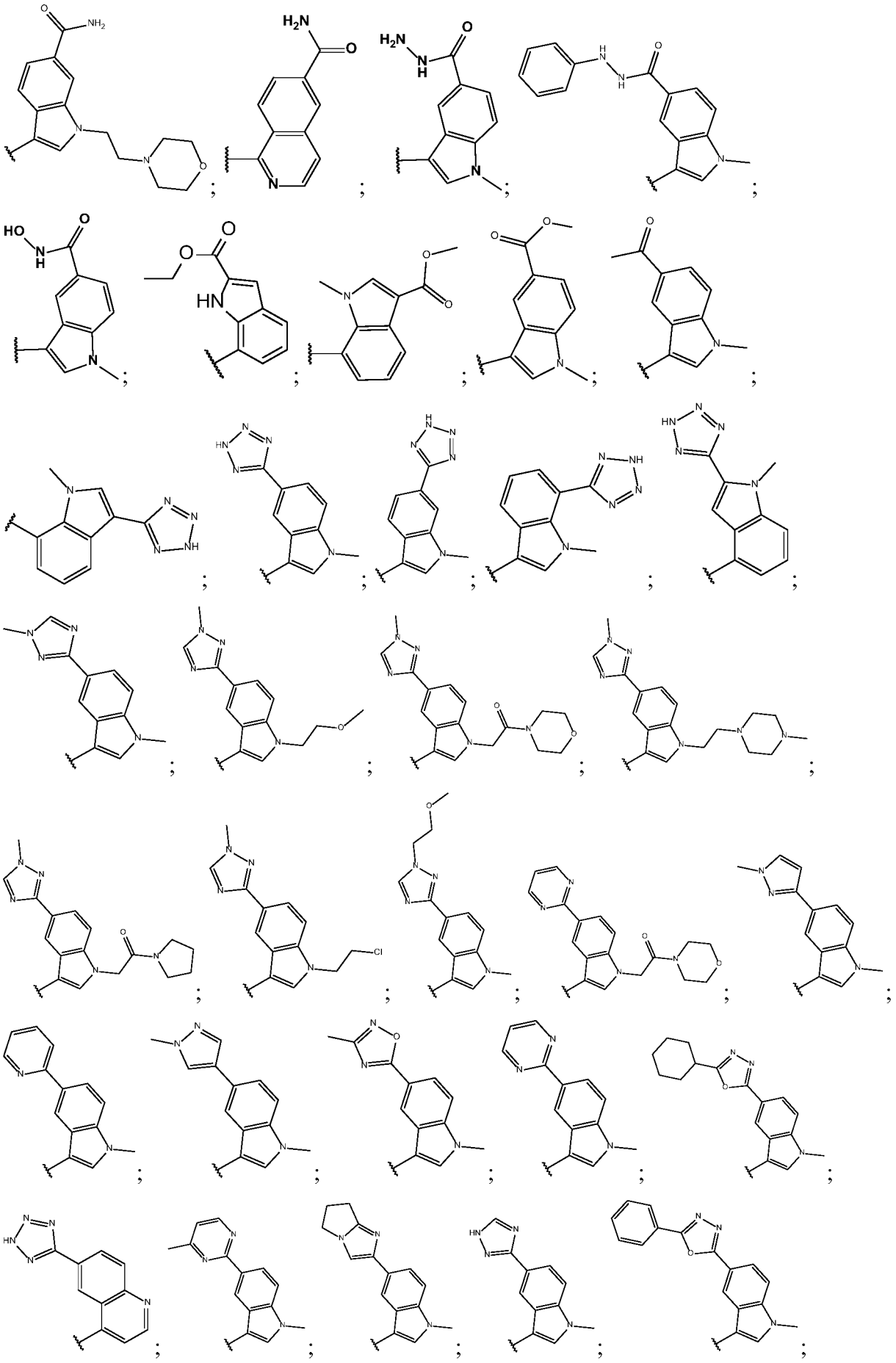


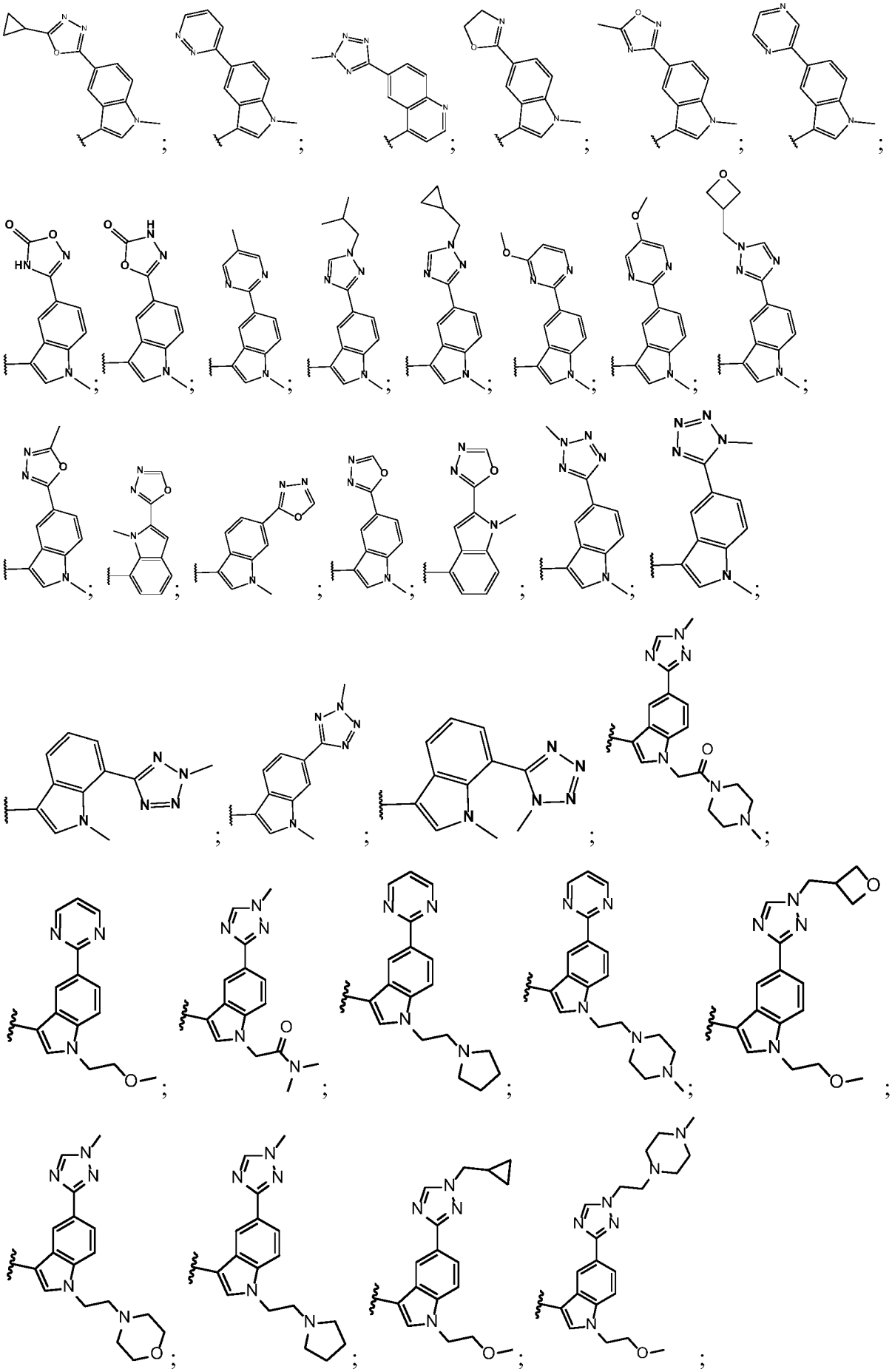




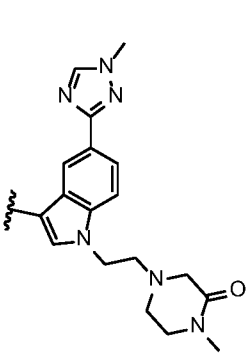
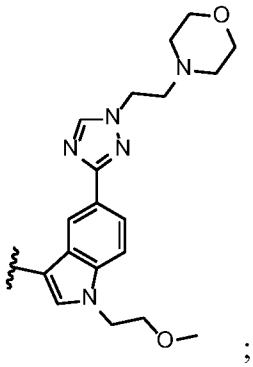
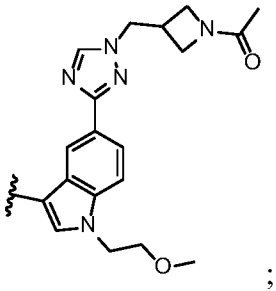
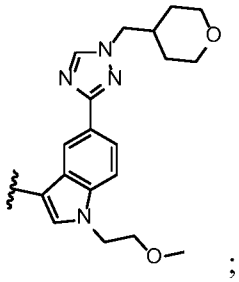
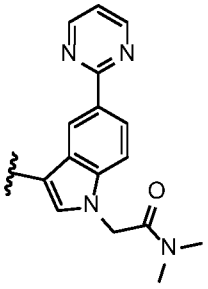
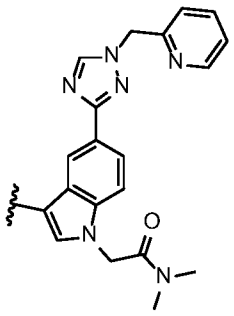
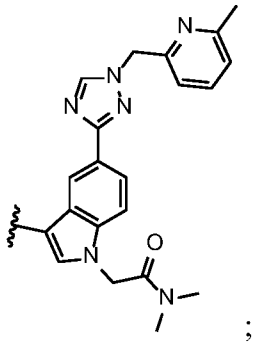
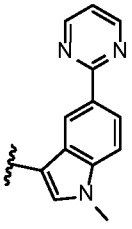
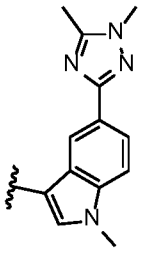
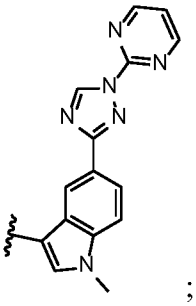
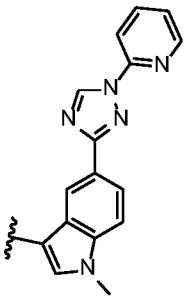
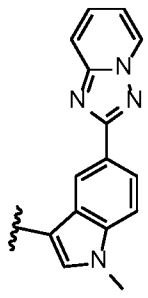
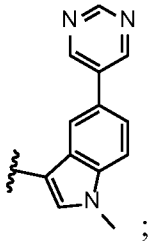
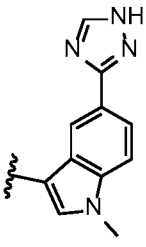
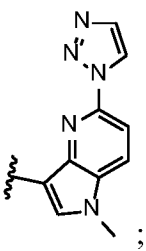
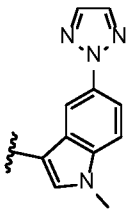
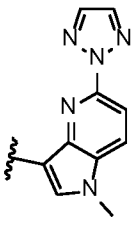
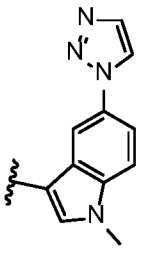
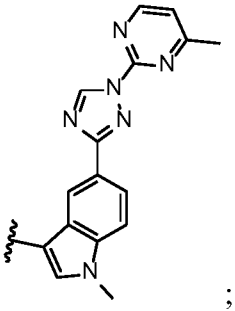
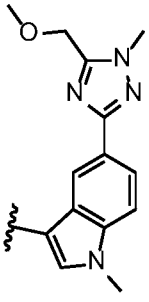
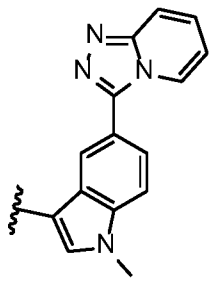
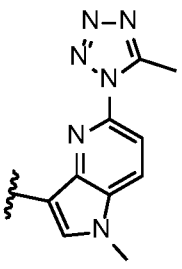
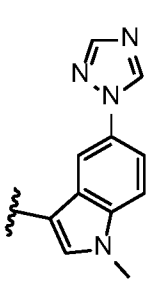
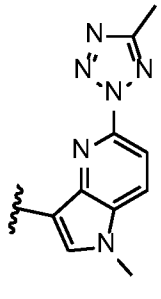
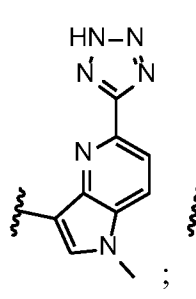
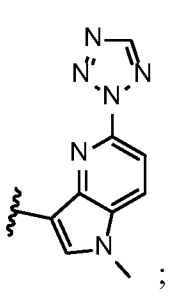
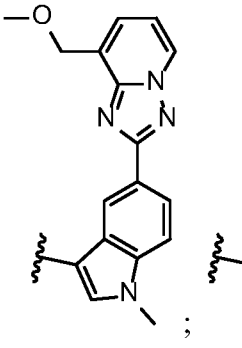
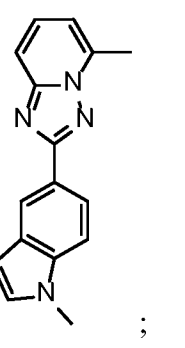






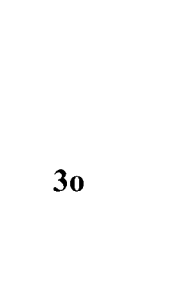


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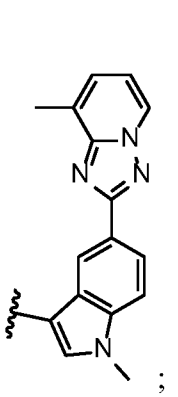
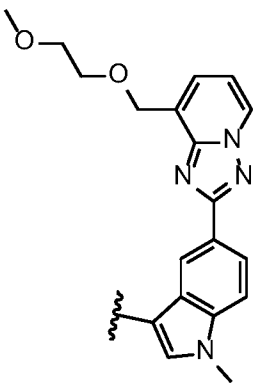
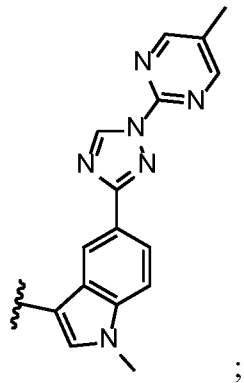
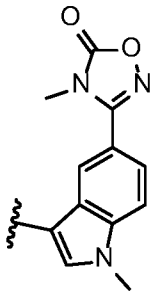
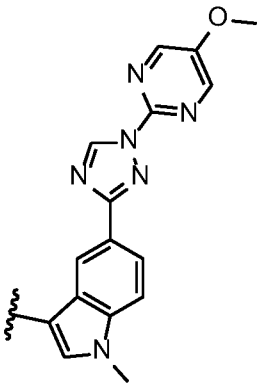
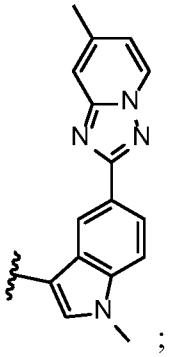
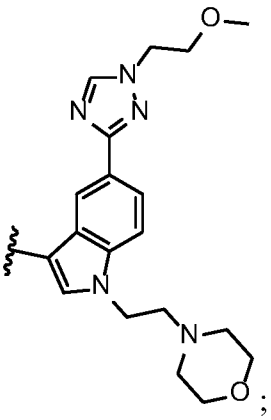
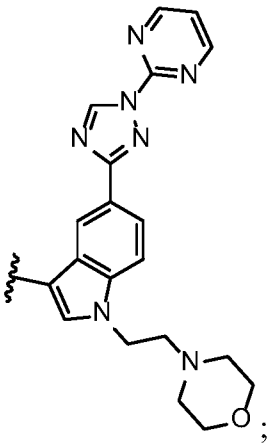
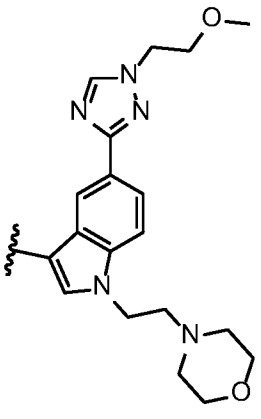
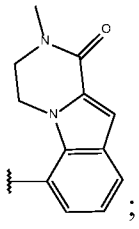
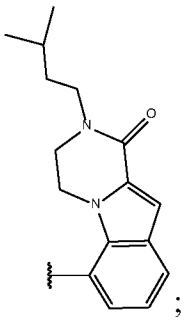
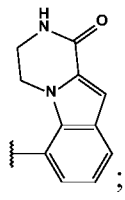
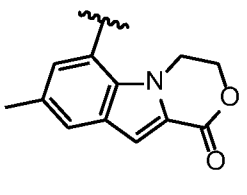
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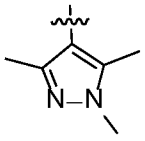
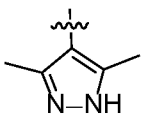
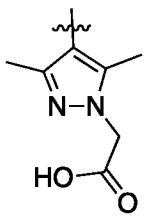
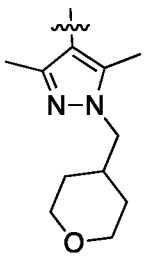
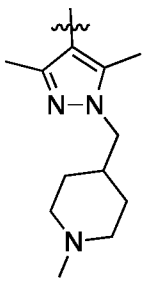
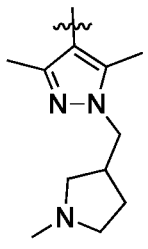
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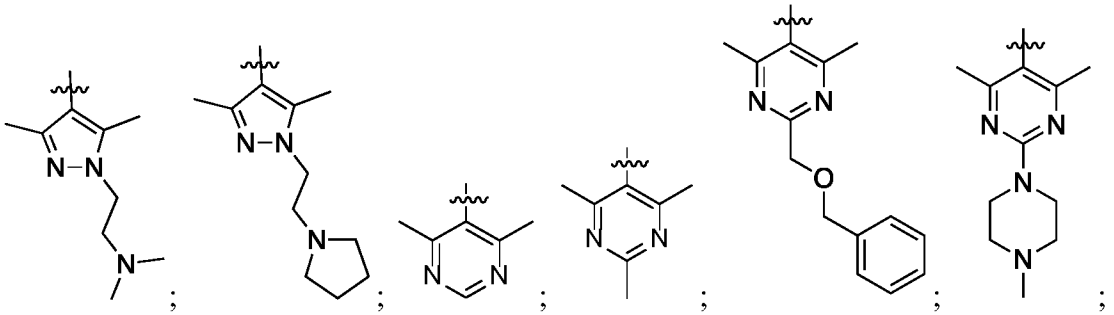
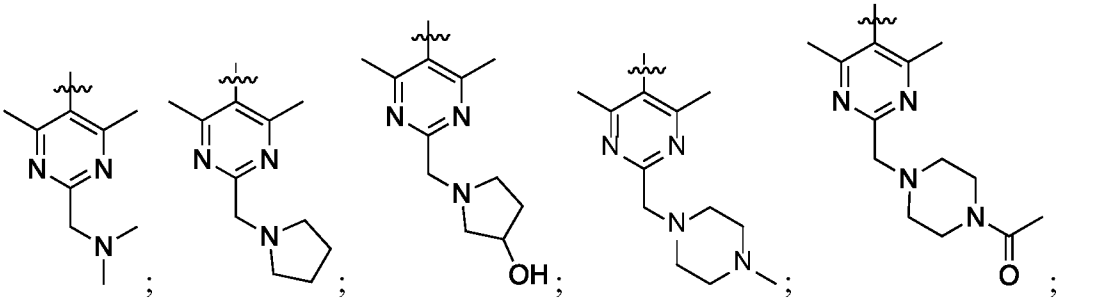
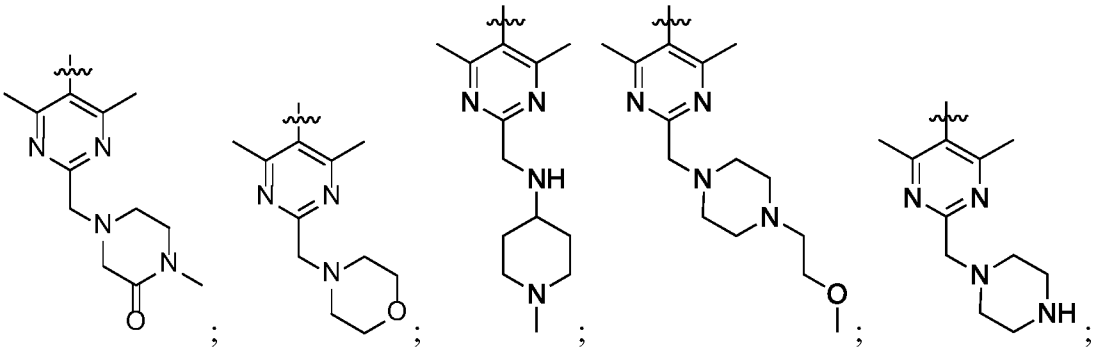
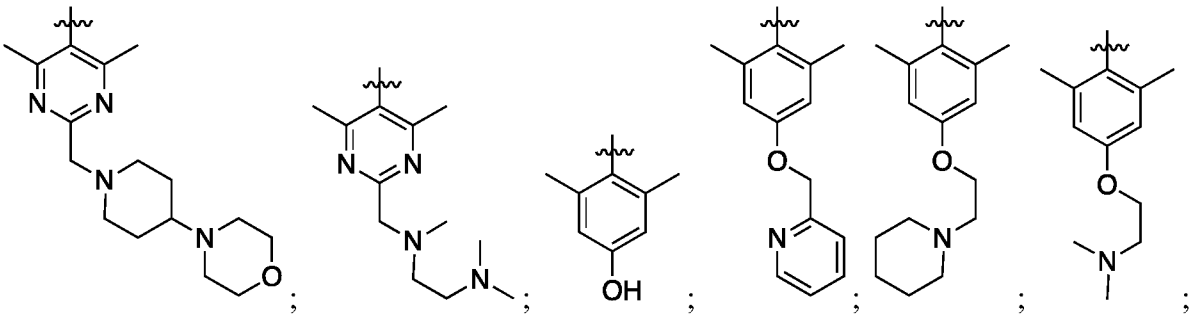
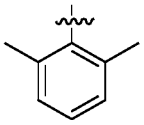
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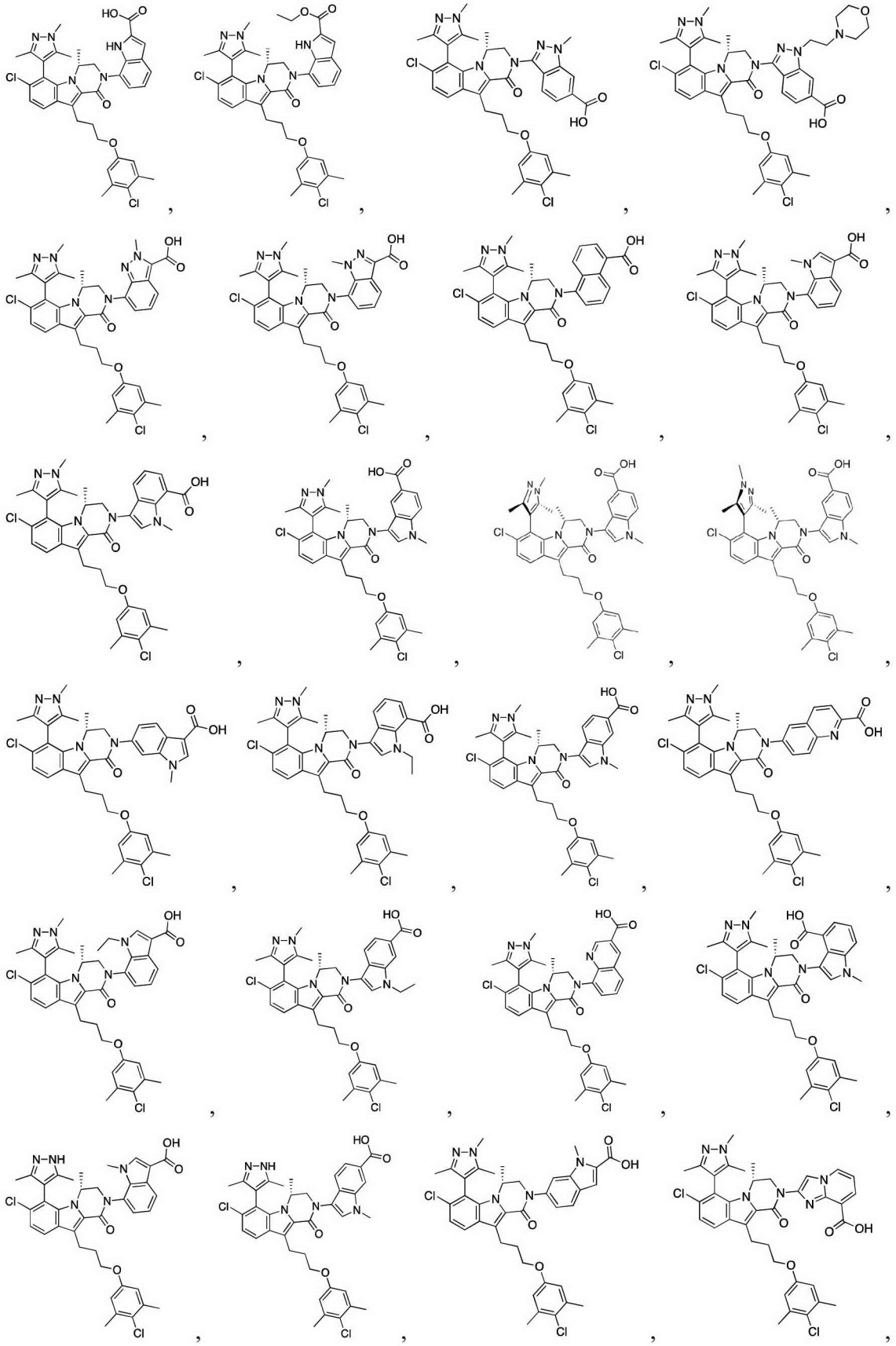
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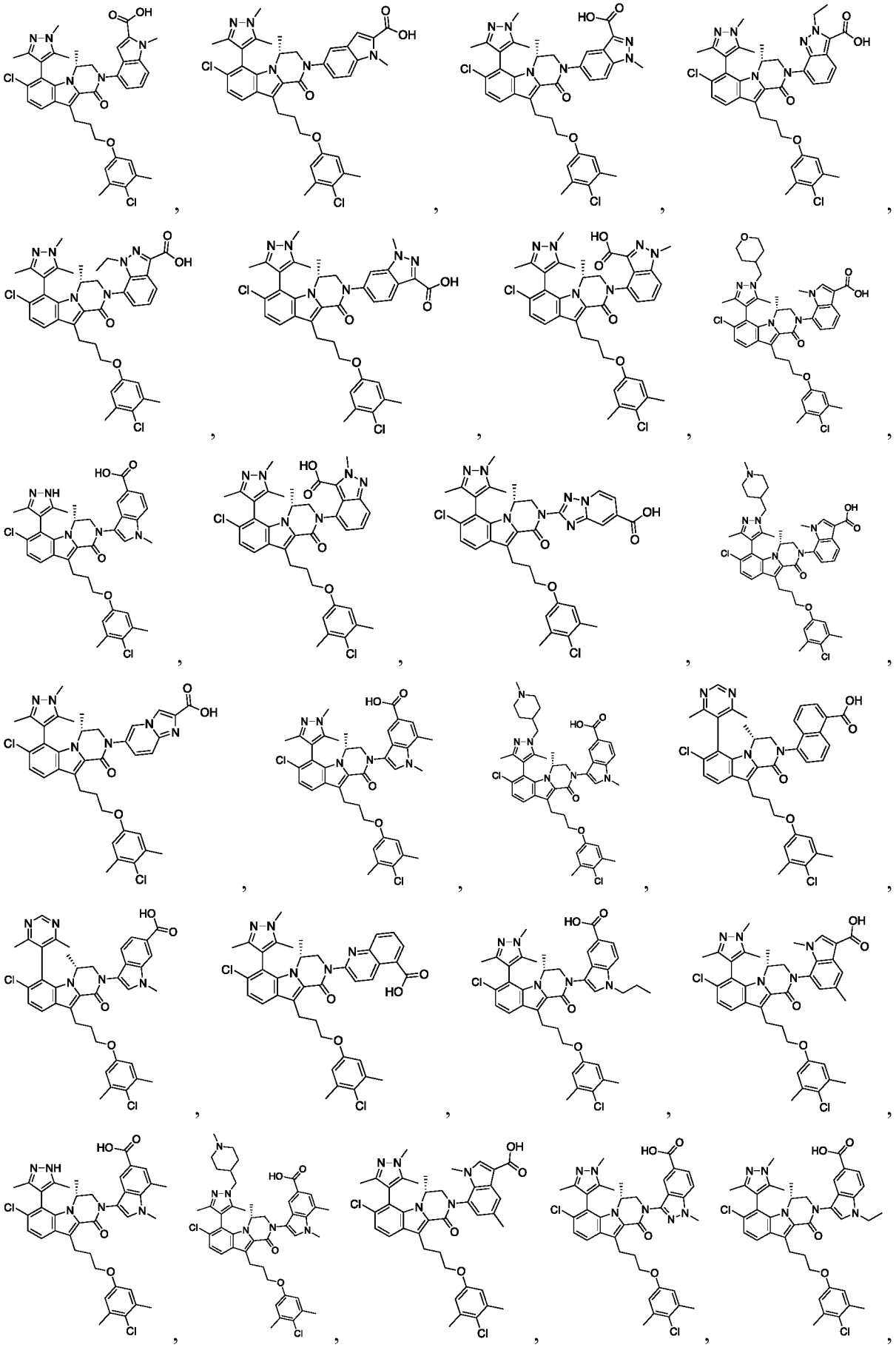






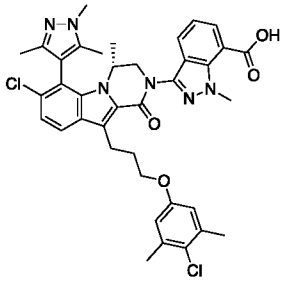
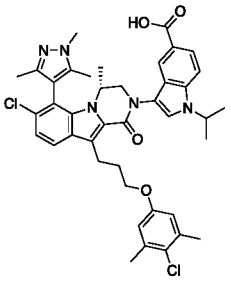
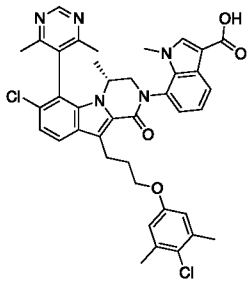
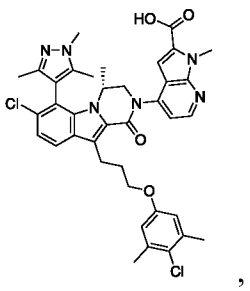
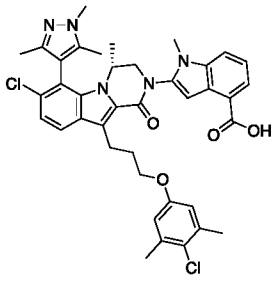
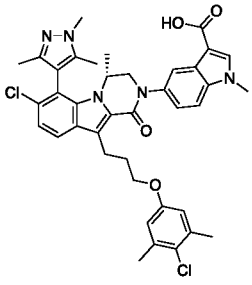
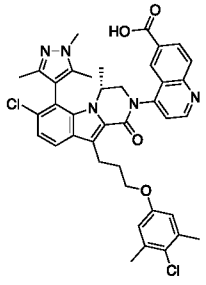
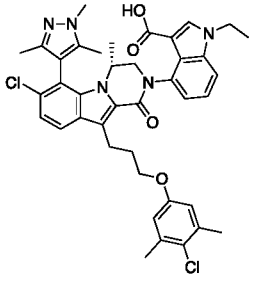
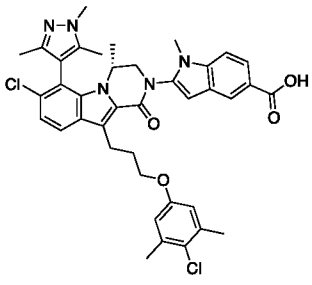
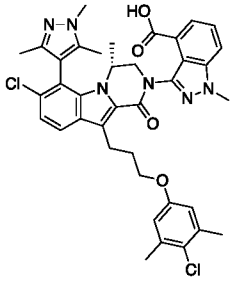
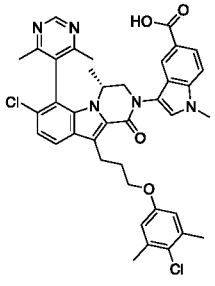
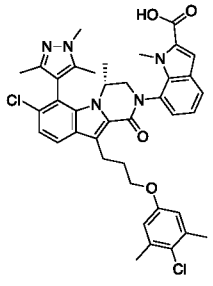
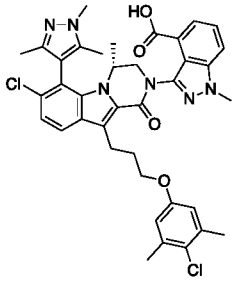
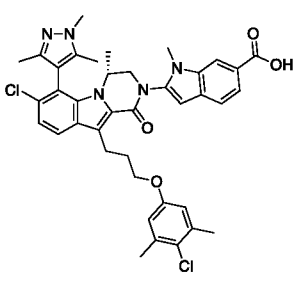
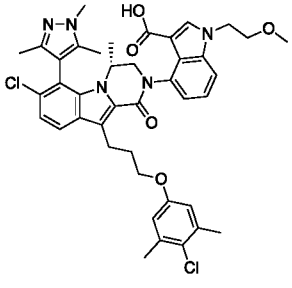
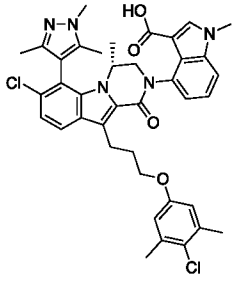
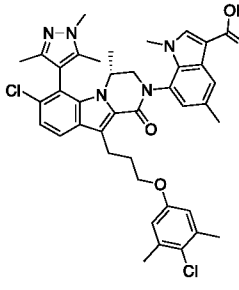
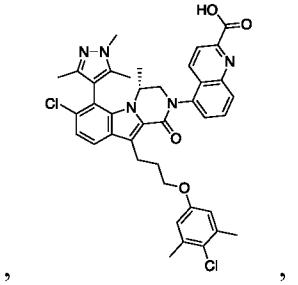
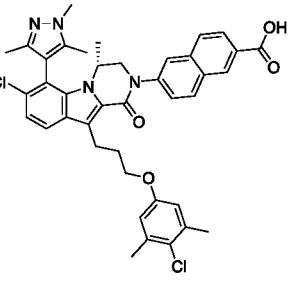
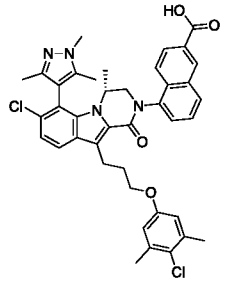
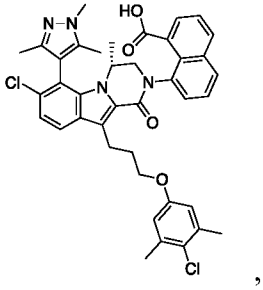
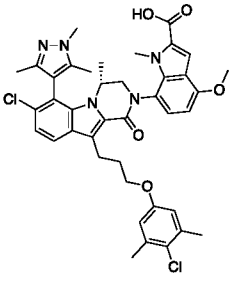
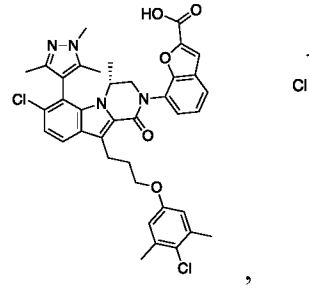
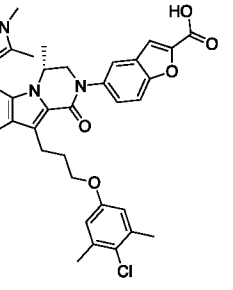
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[0007b] In another aspect there is provided a compound selected from the group consisting of:



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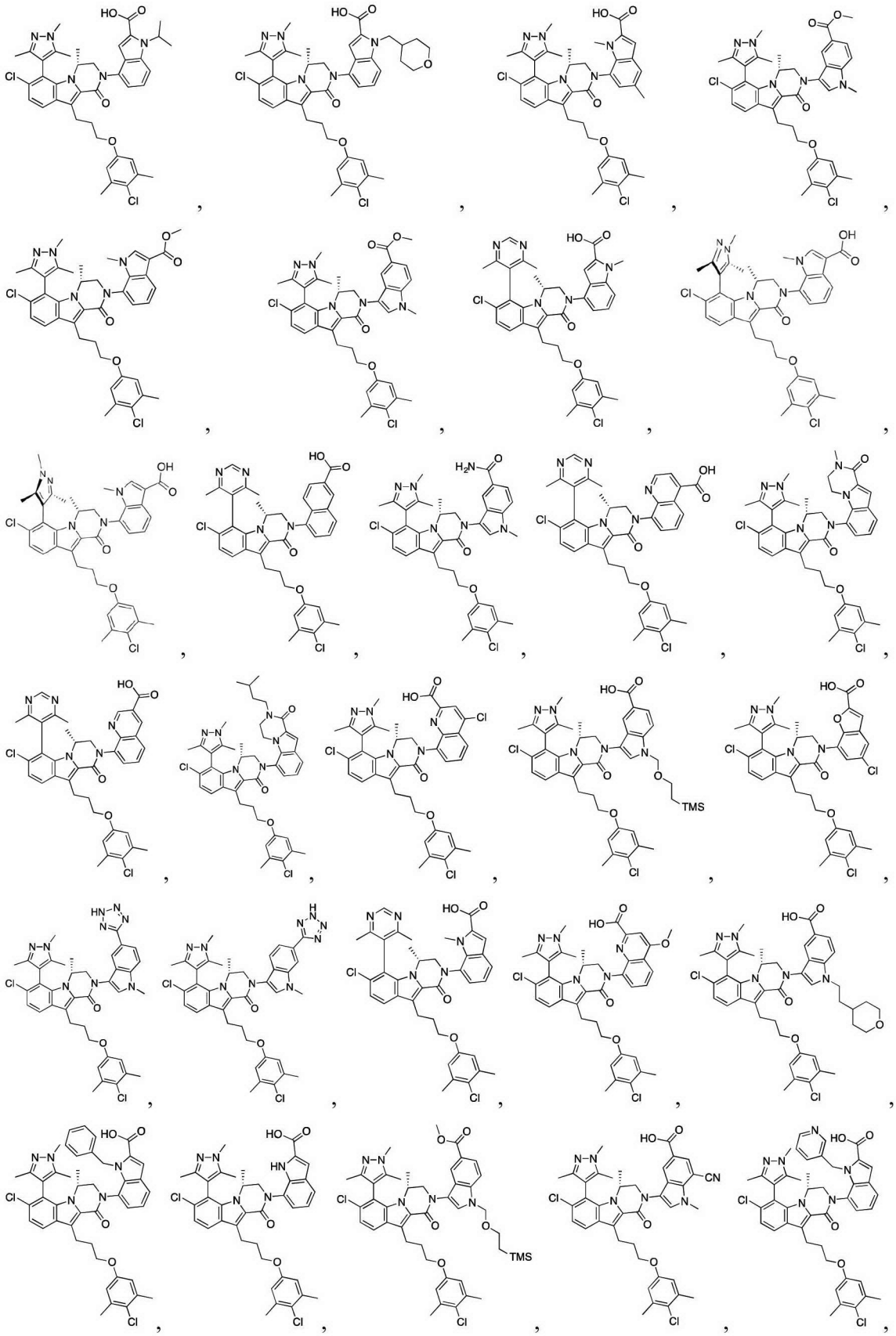

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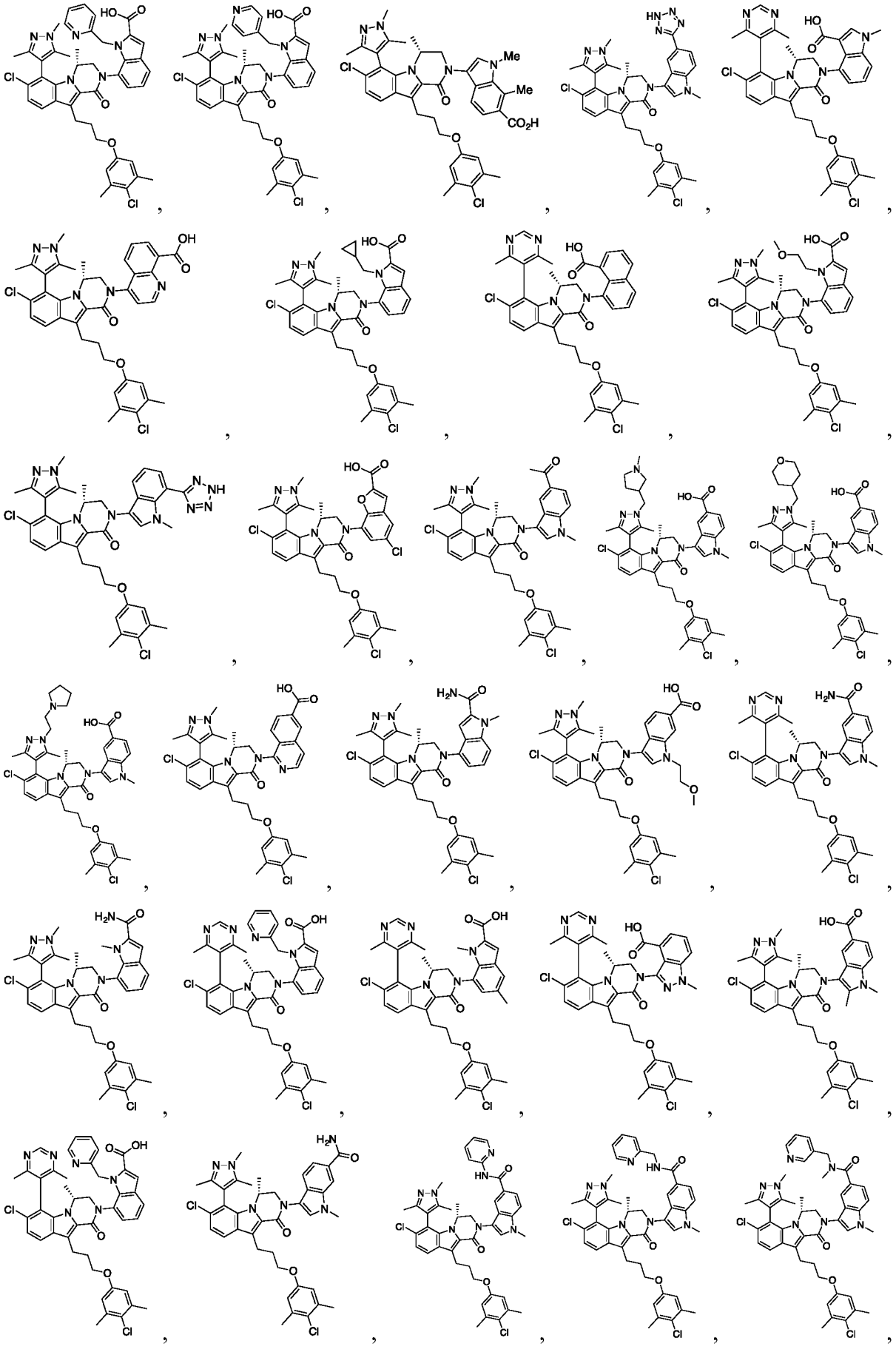
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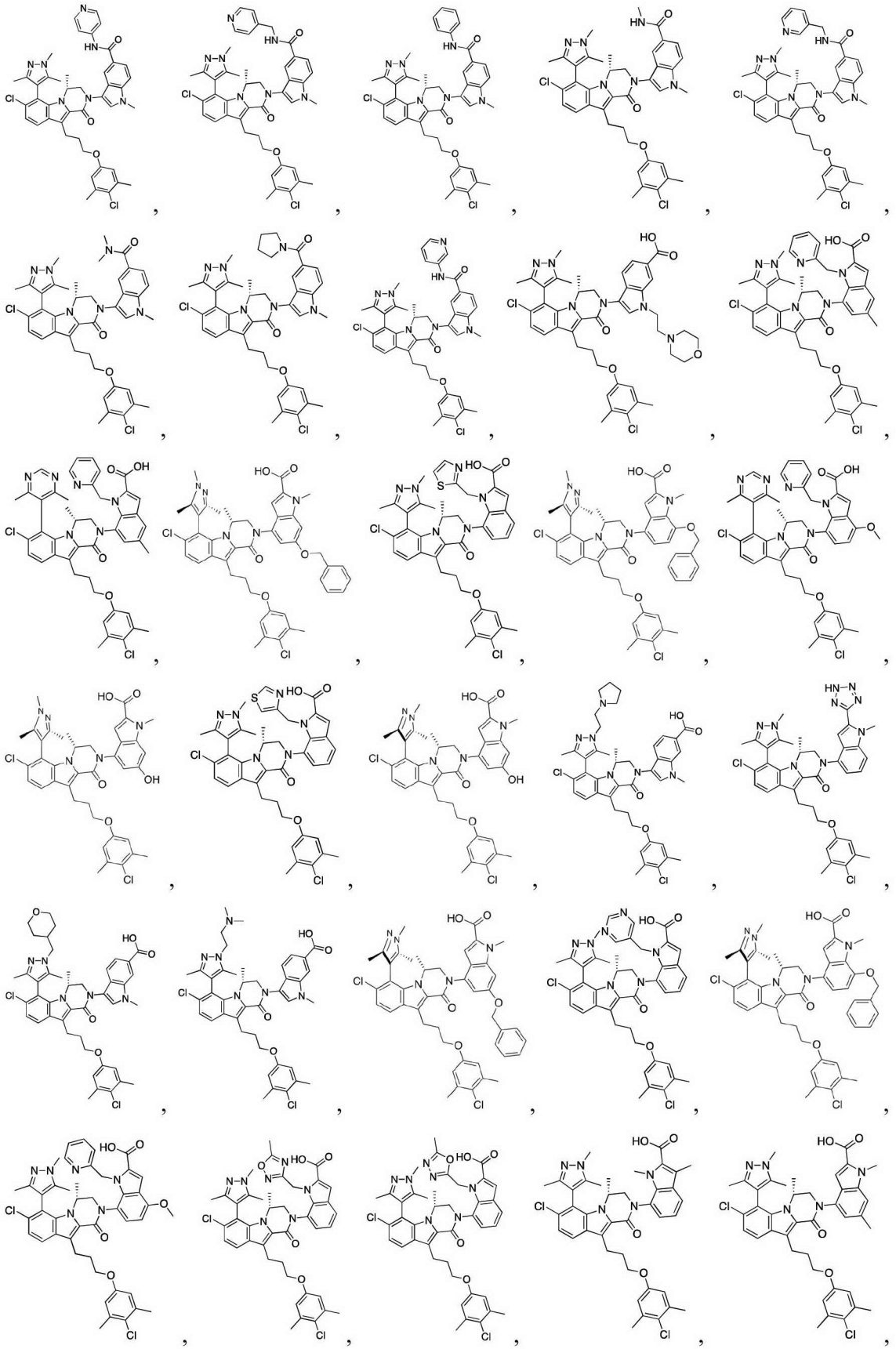
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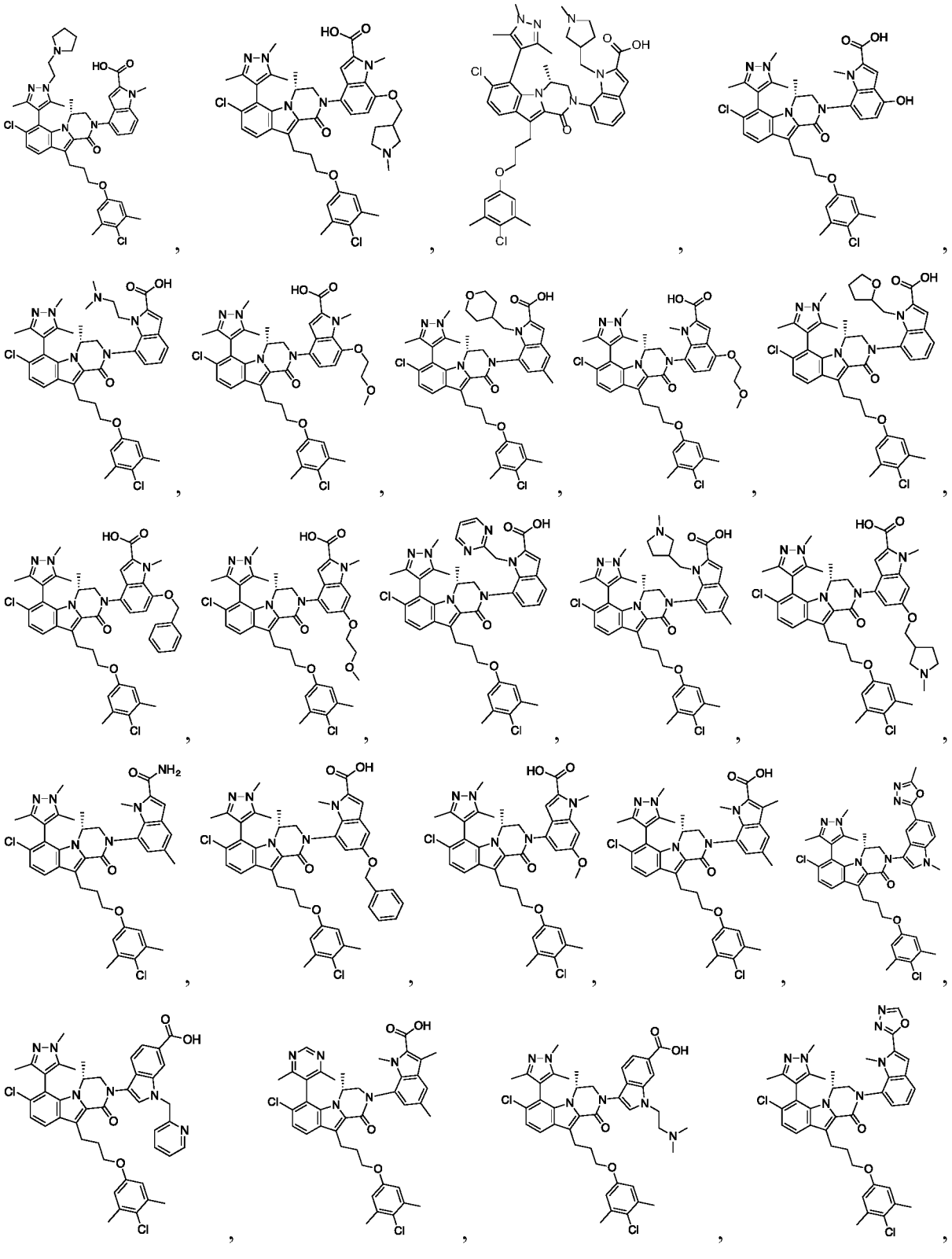
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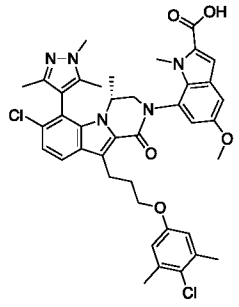
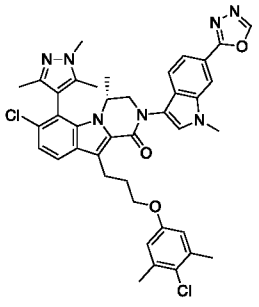
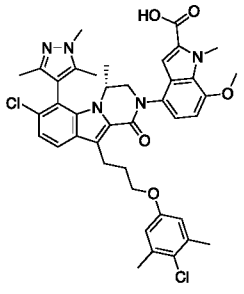
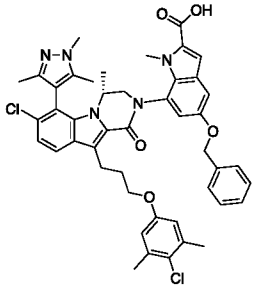
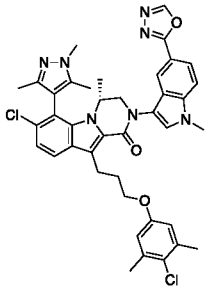
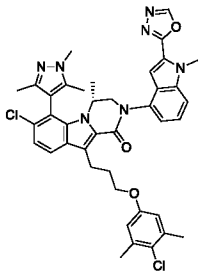
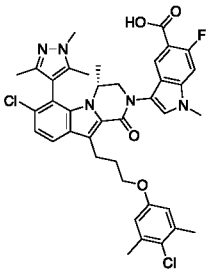
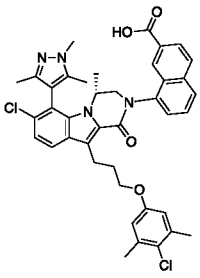
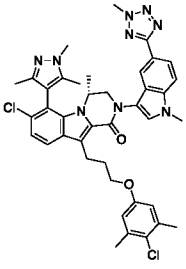
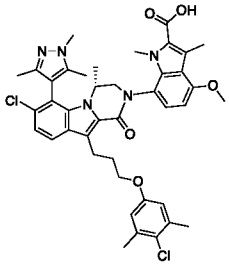
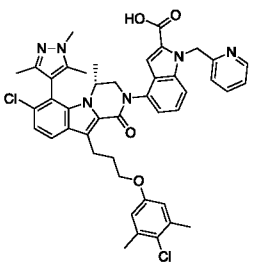
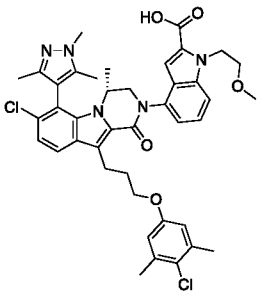
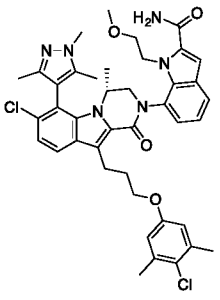
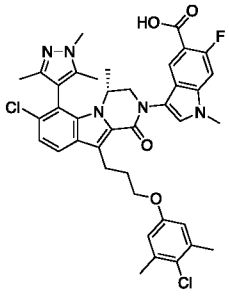
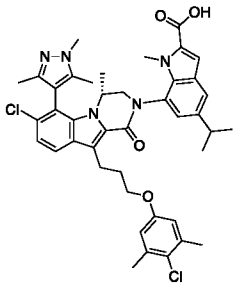
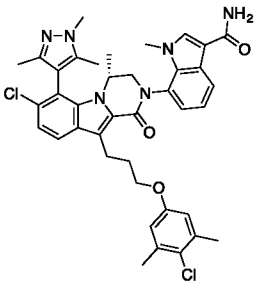
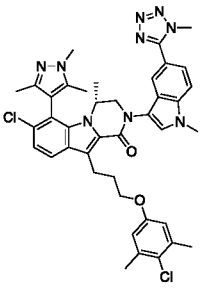
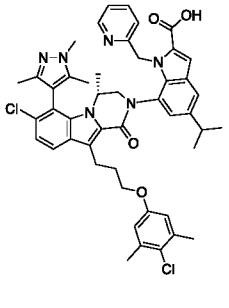
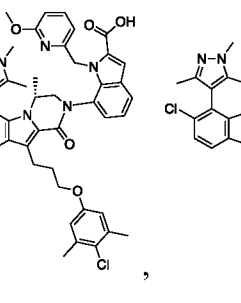
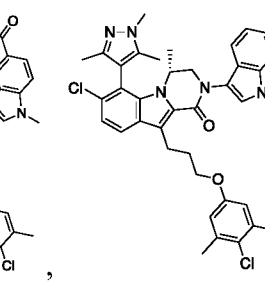
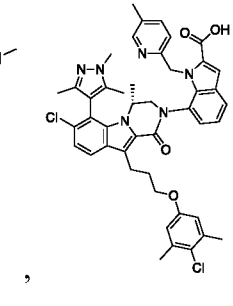


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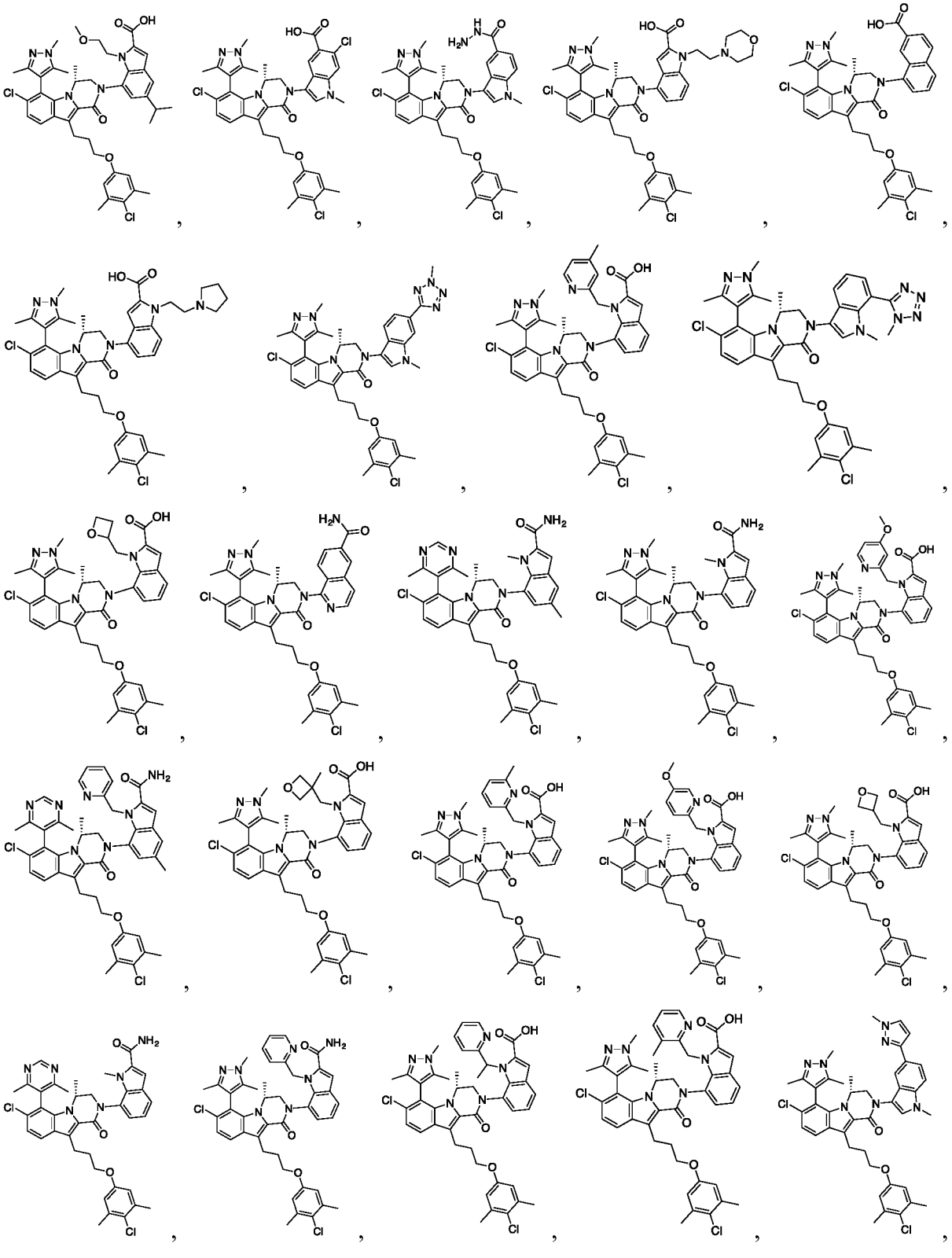
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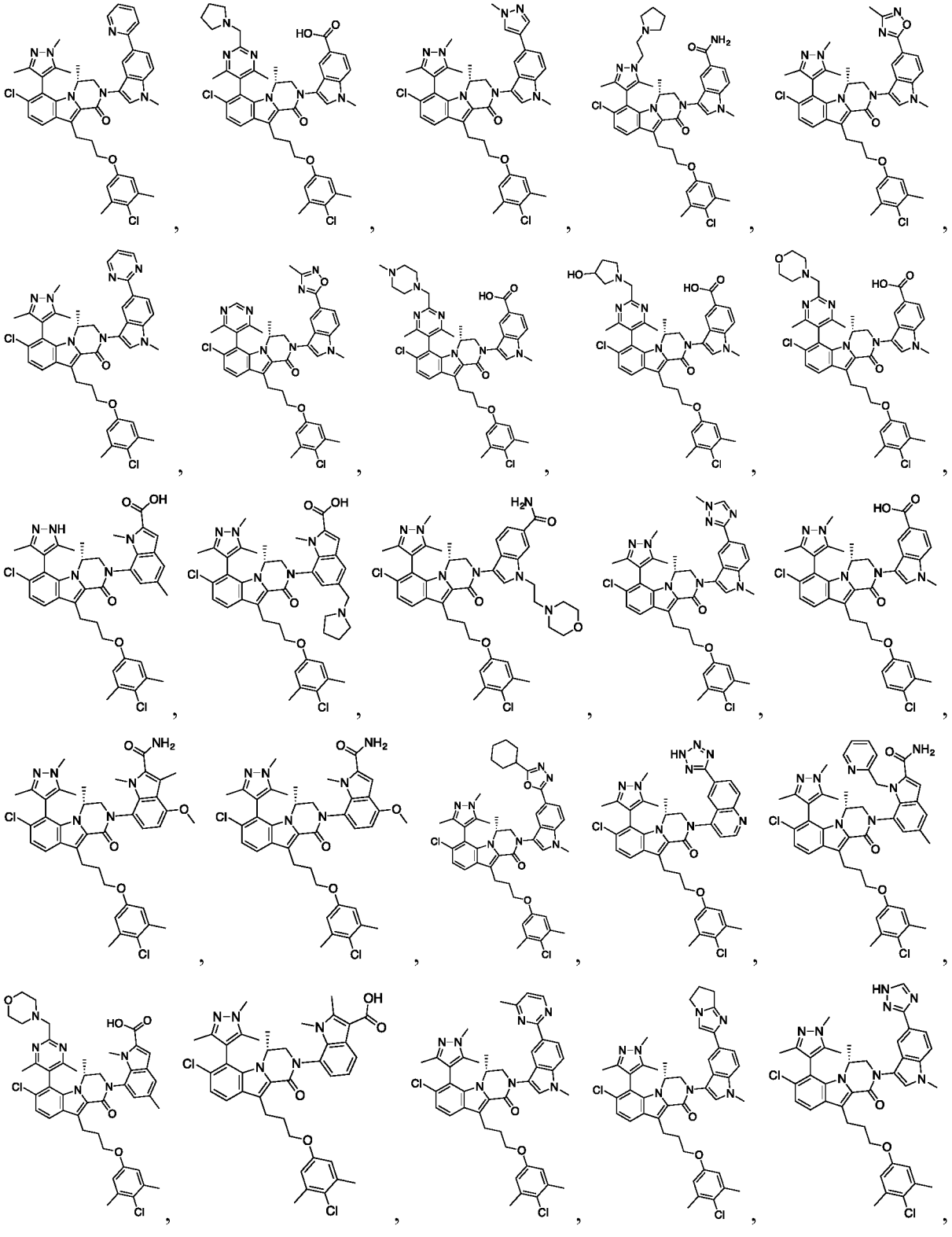
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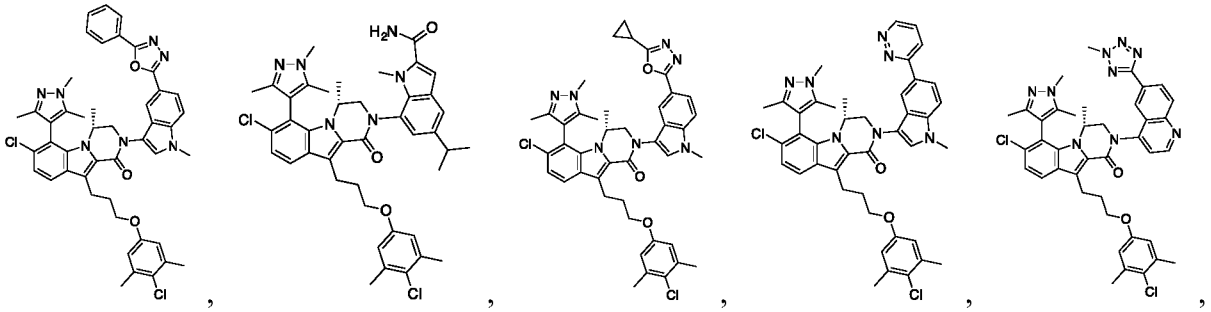
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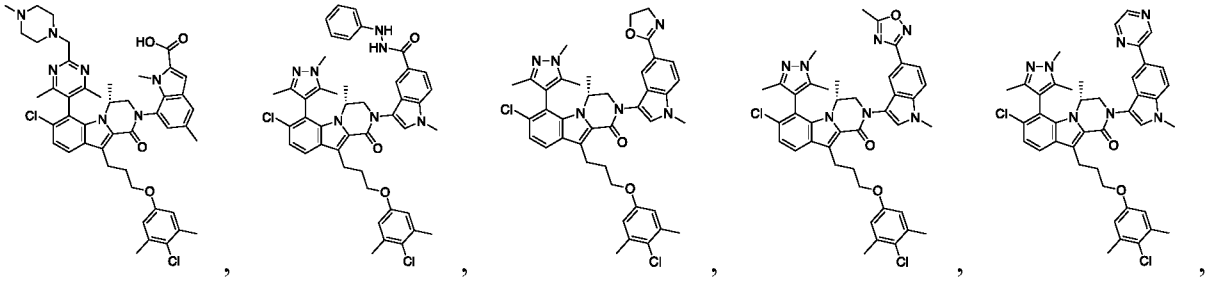
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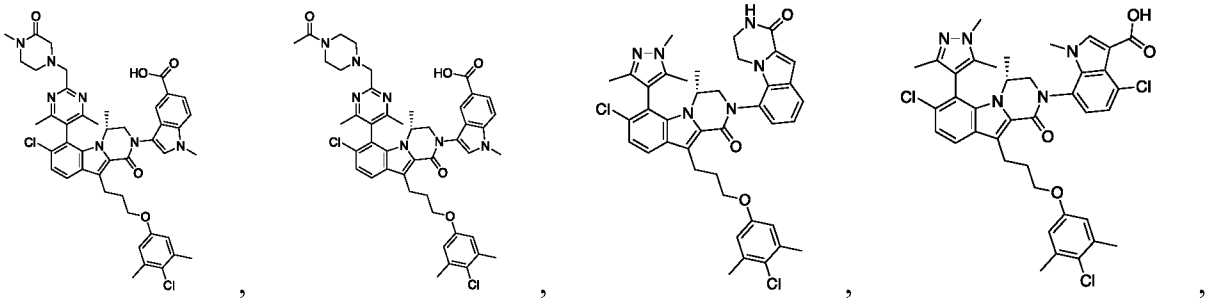


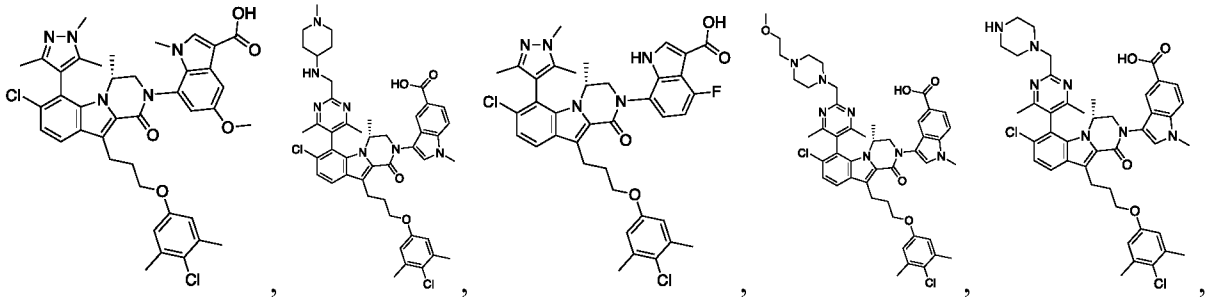


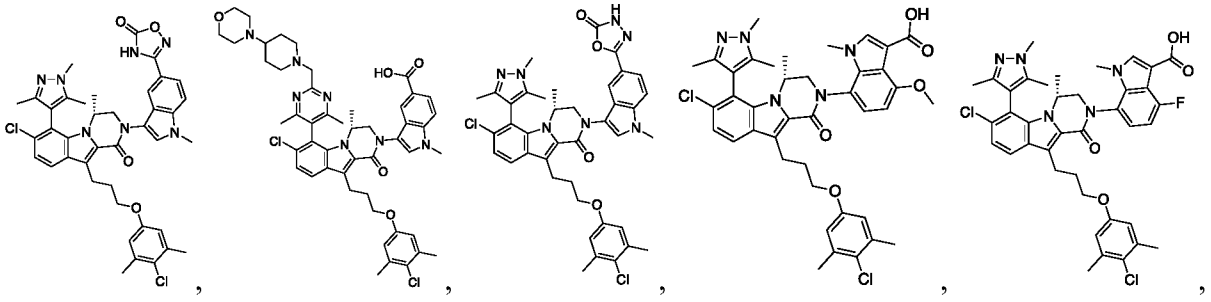
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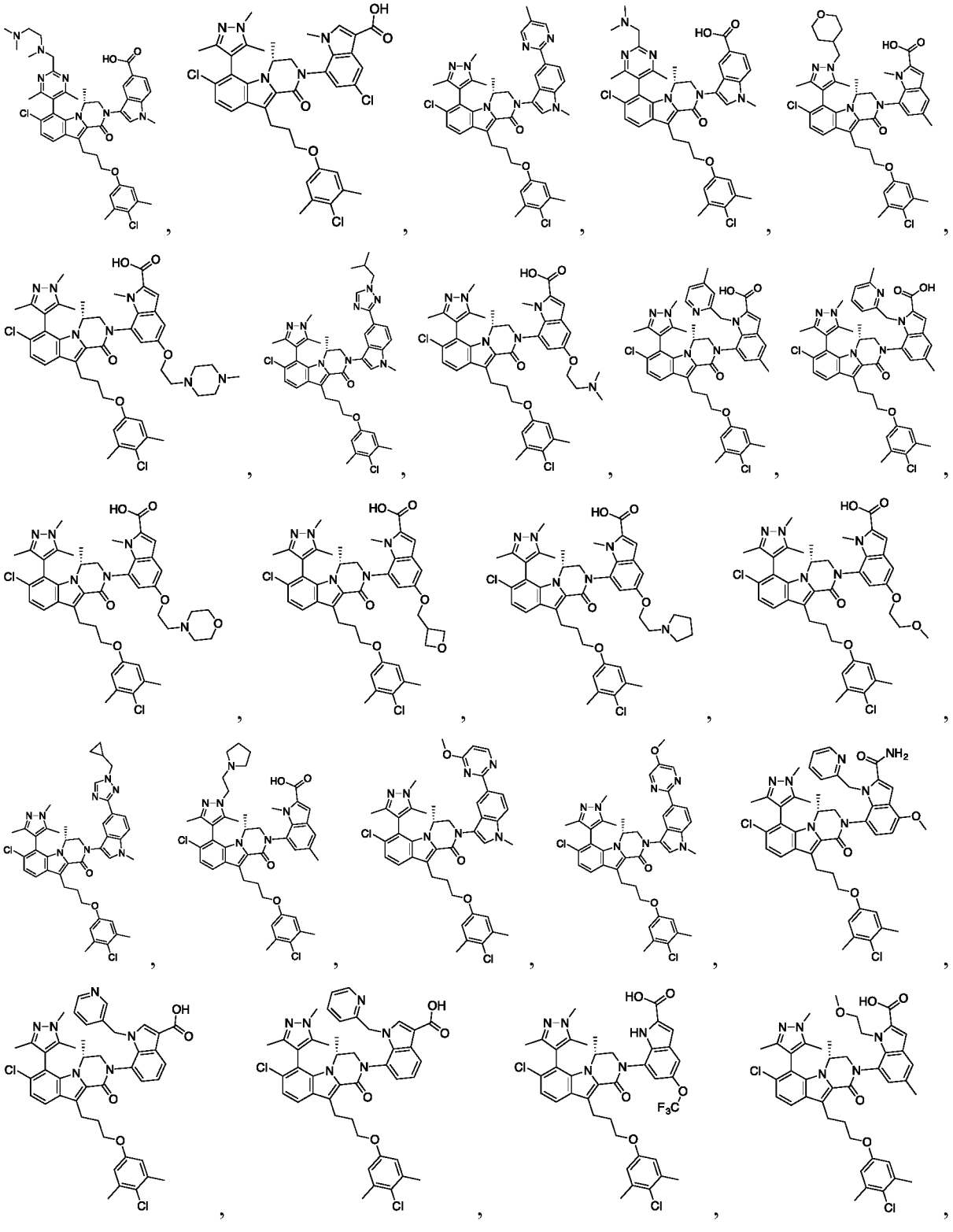


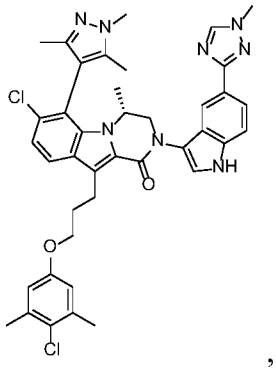
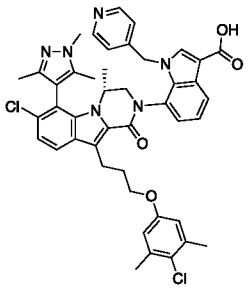
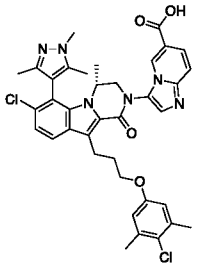
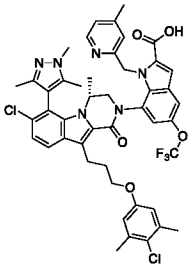
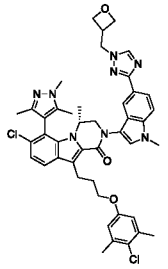
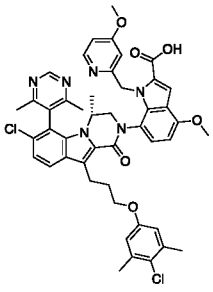
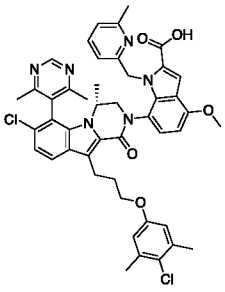
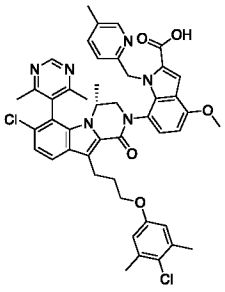
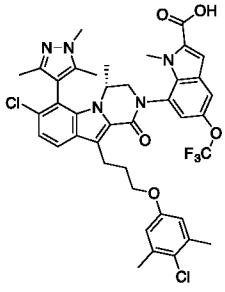
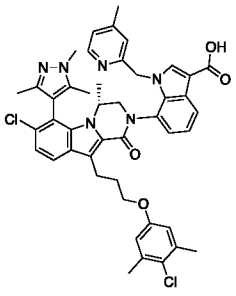
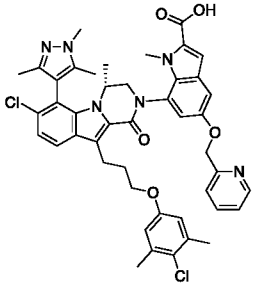
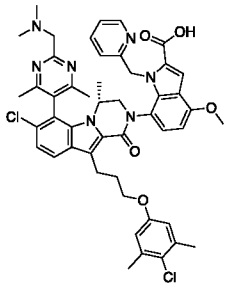
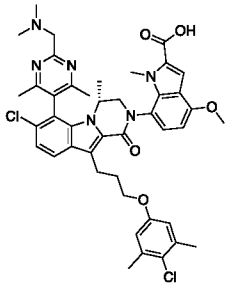
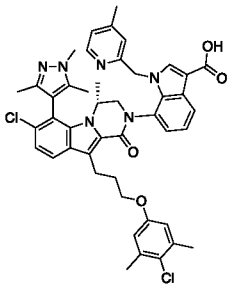
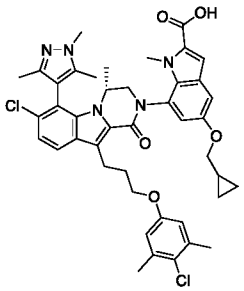
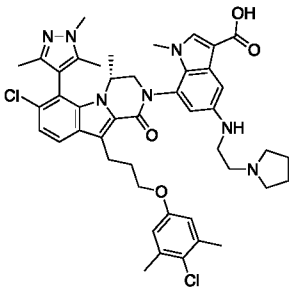
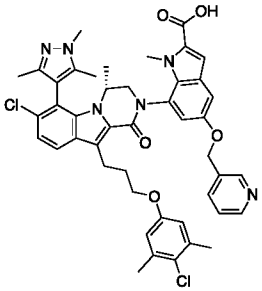
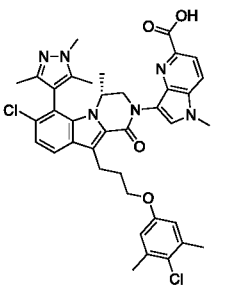
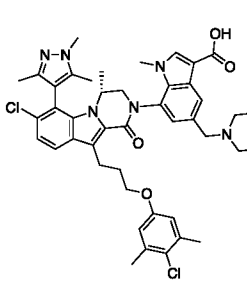
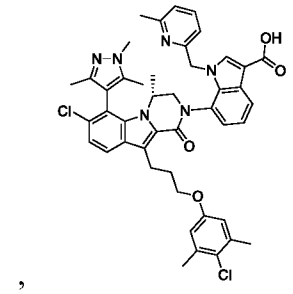
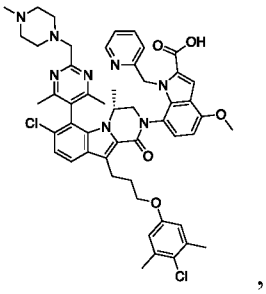
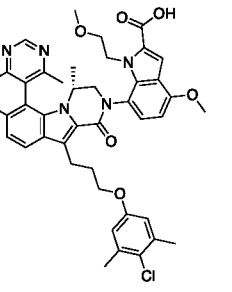











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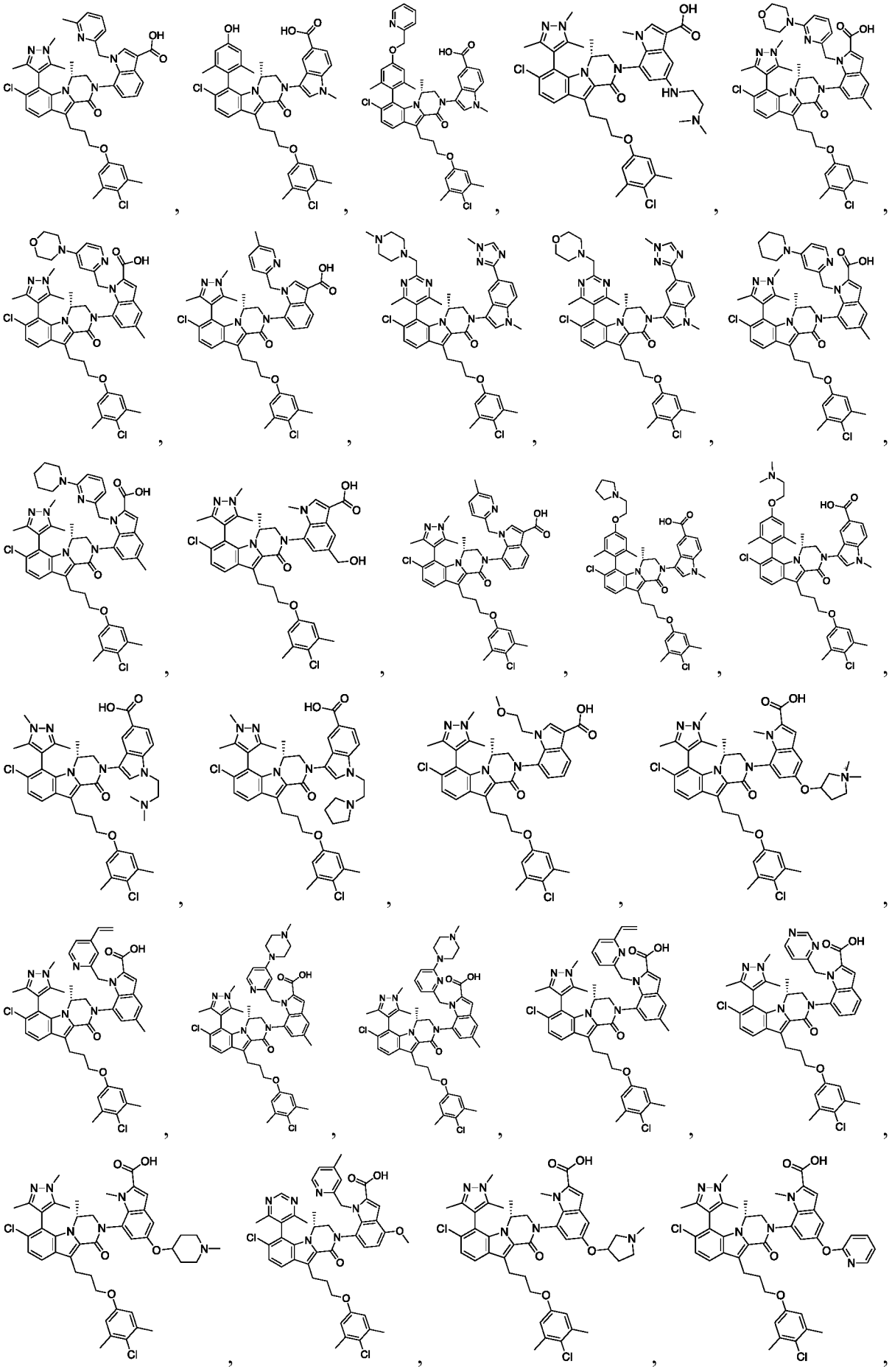
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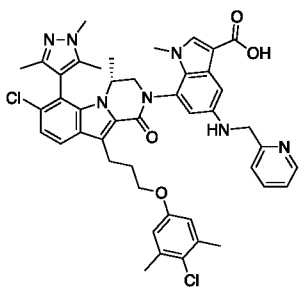
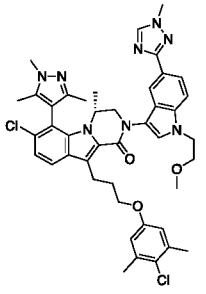
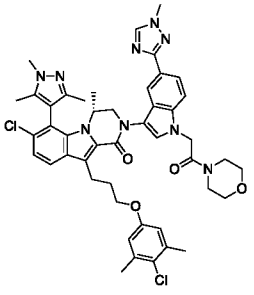
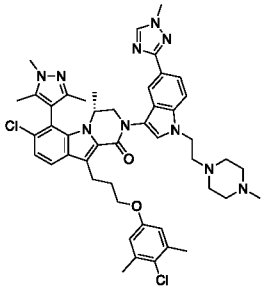
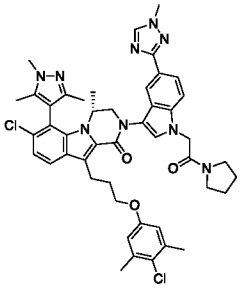
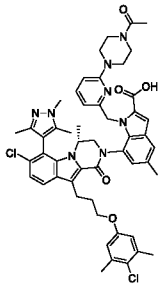
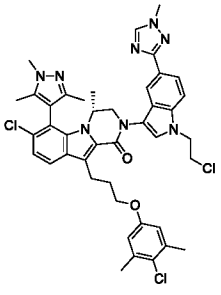
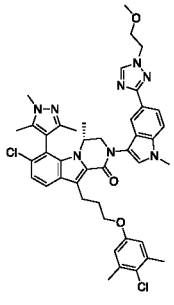
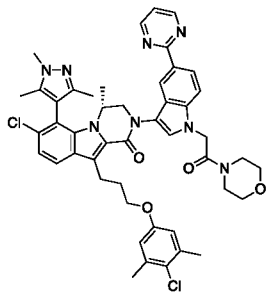
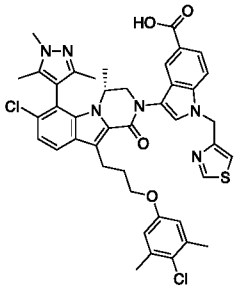
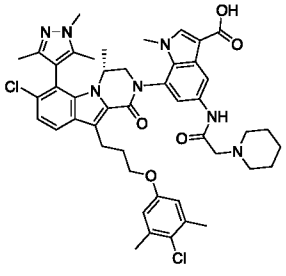
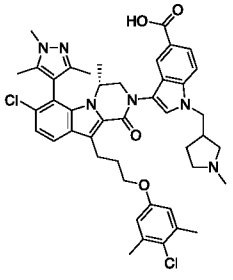
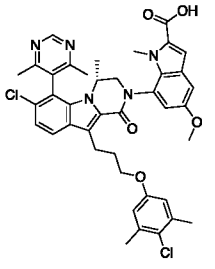
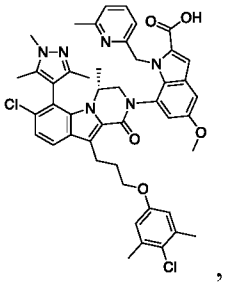
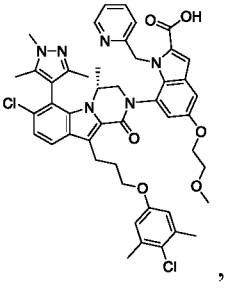
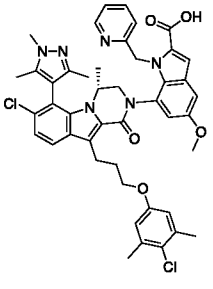
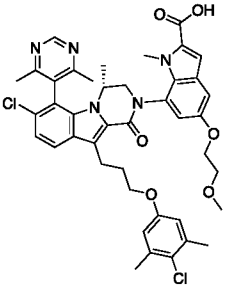
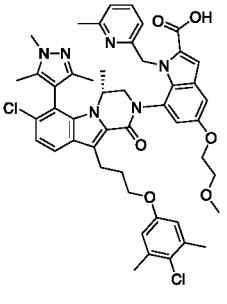
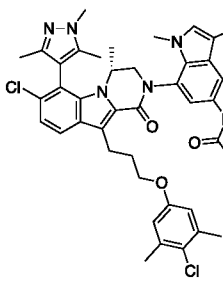
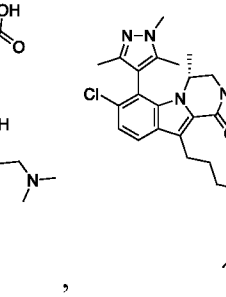
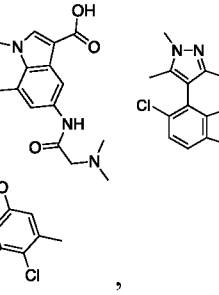
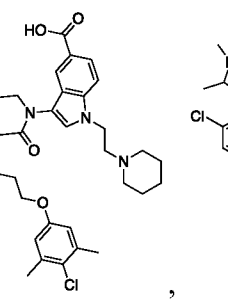
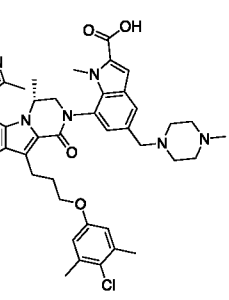
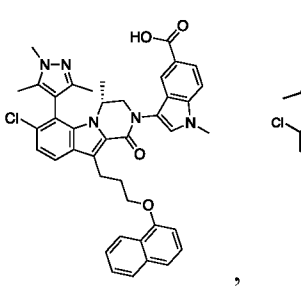
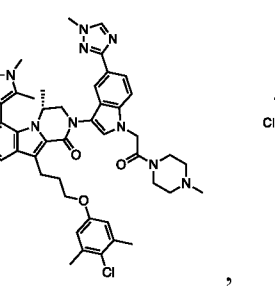
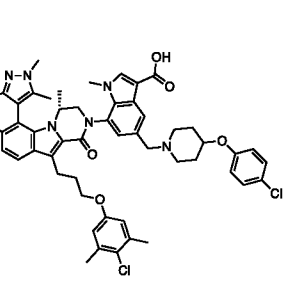
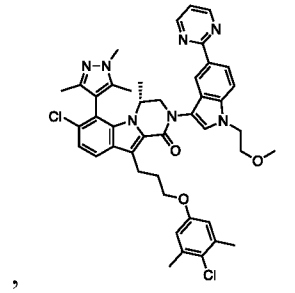
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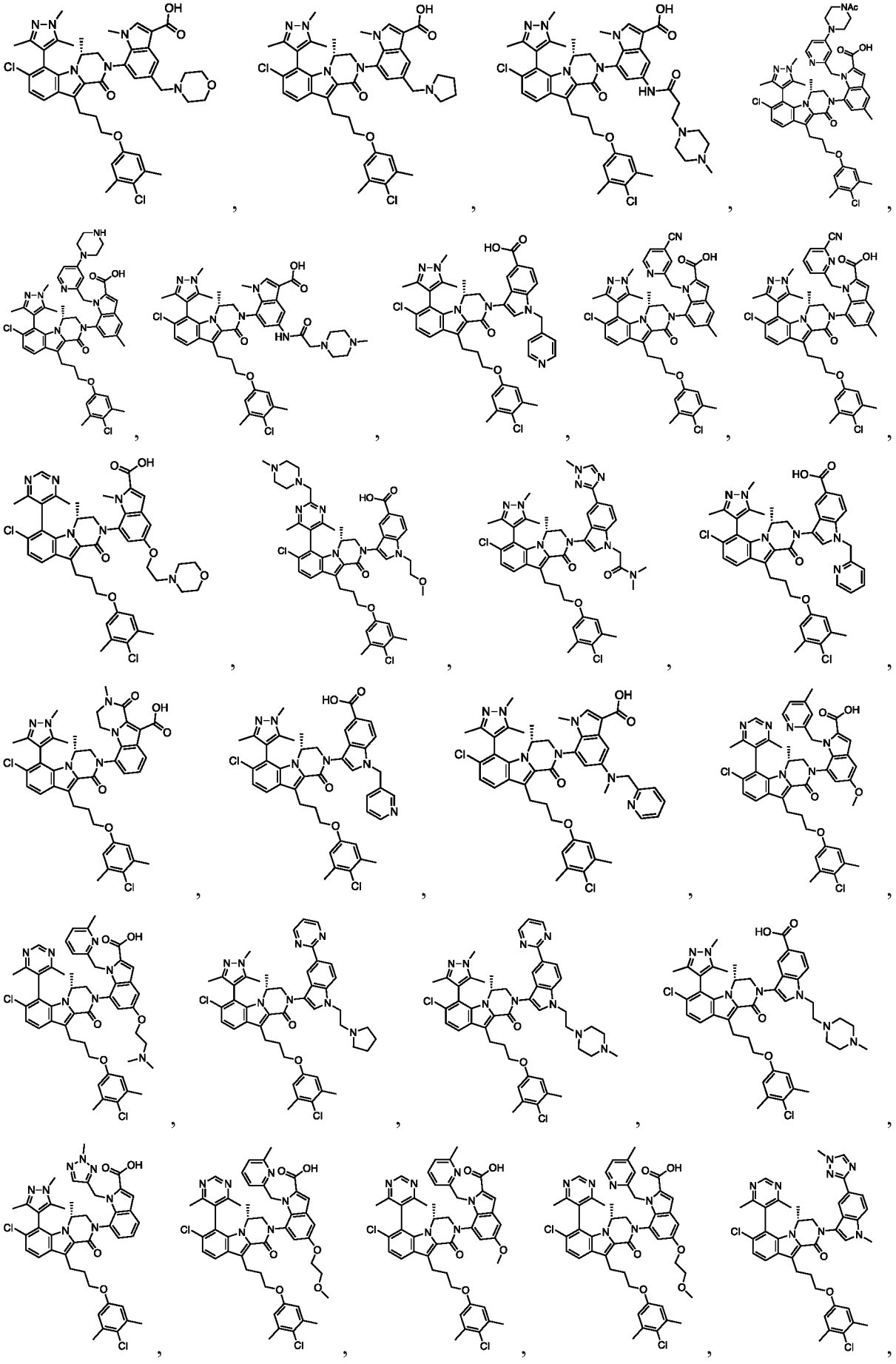
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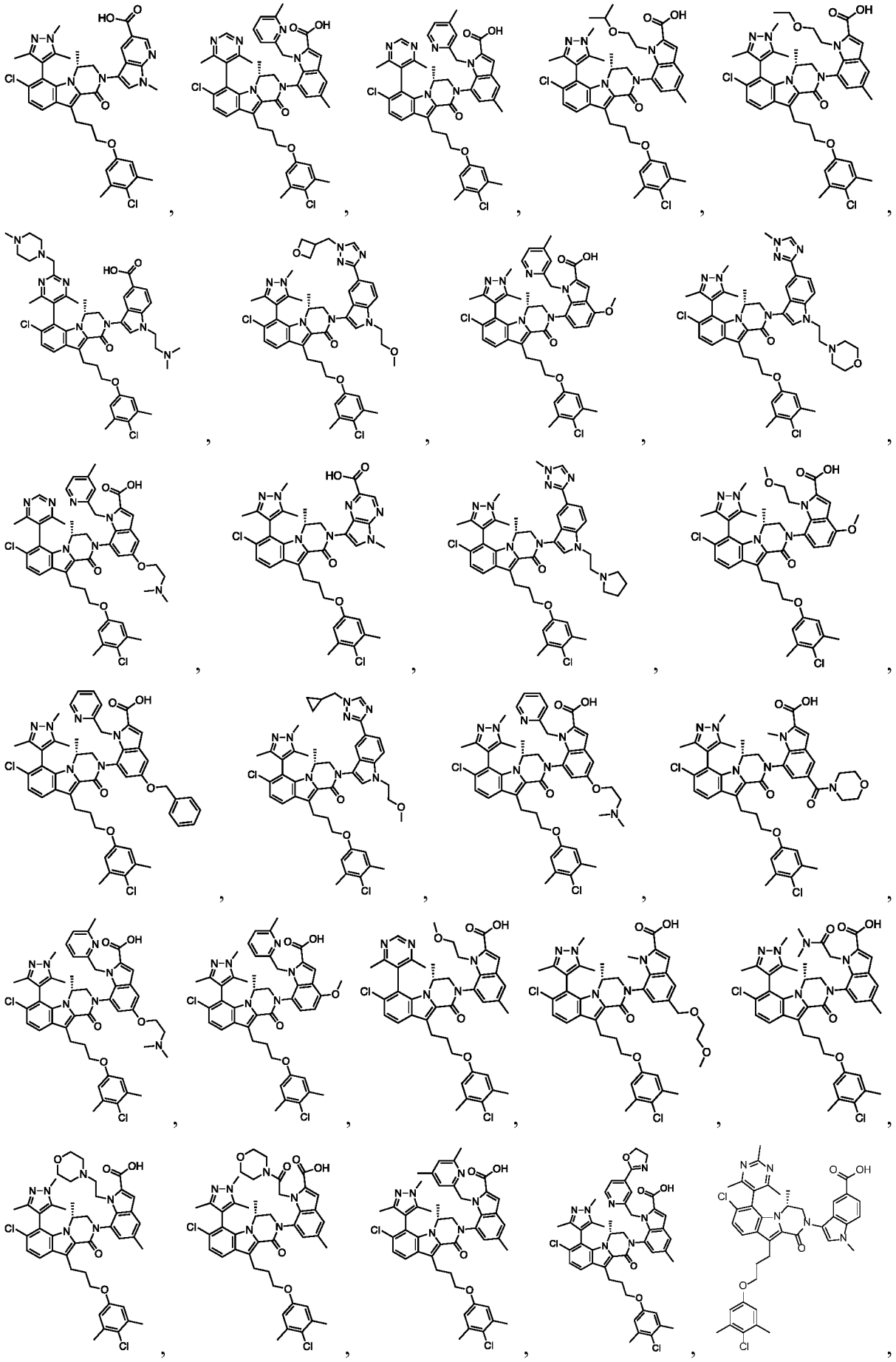
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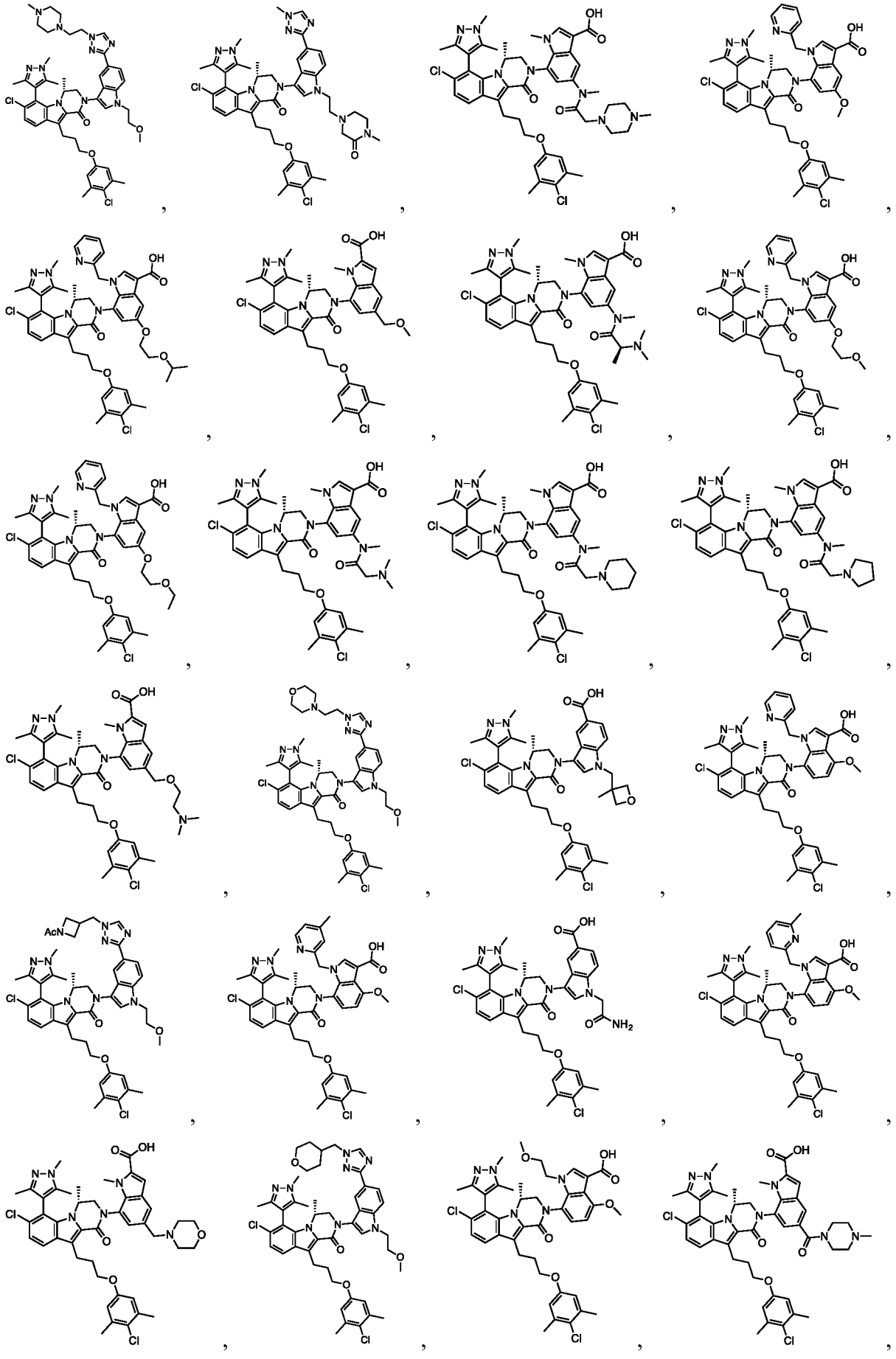
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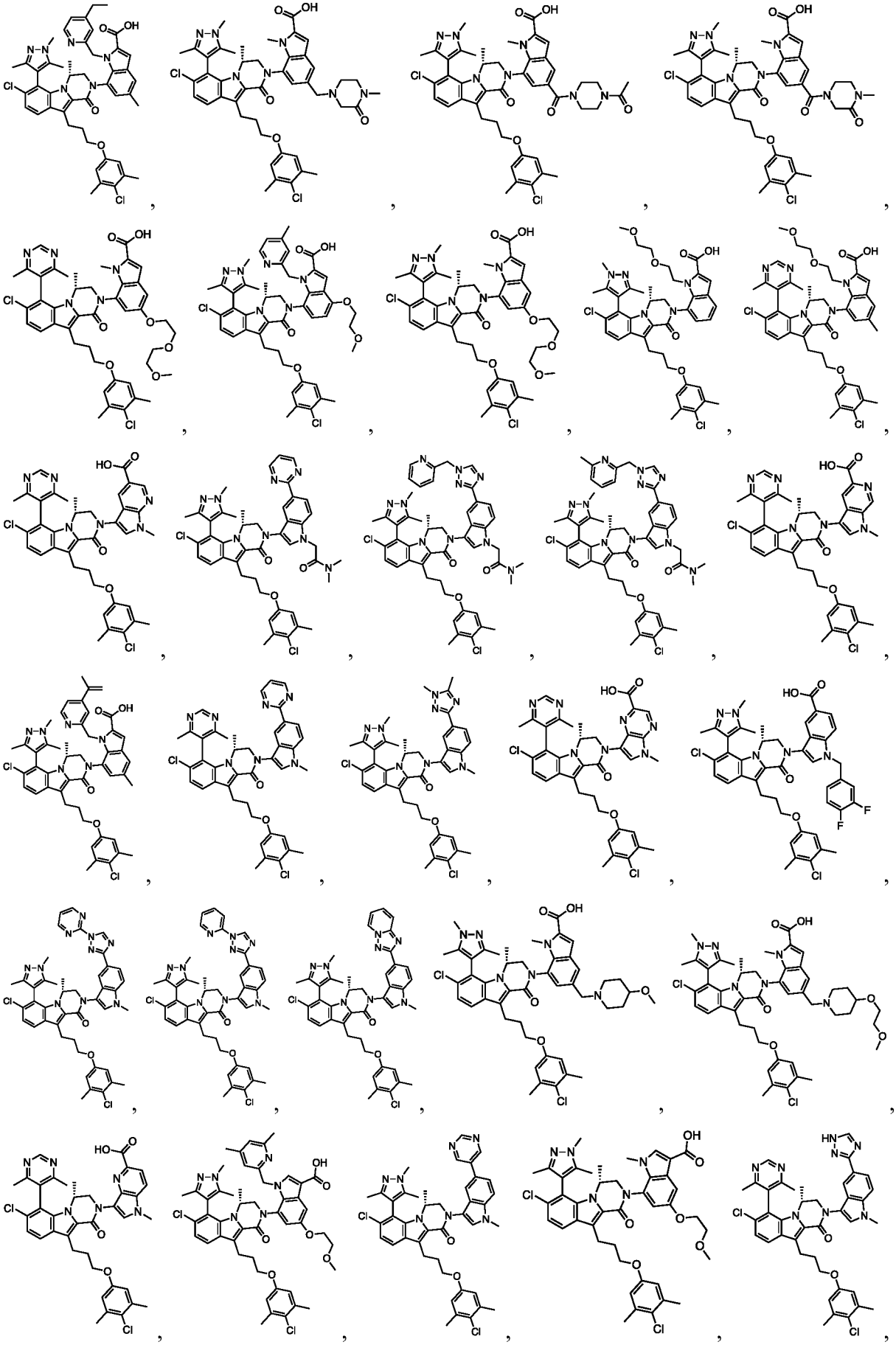
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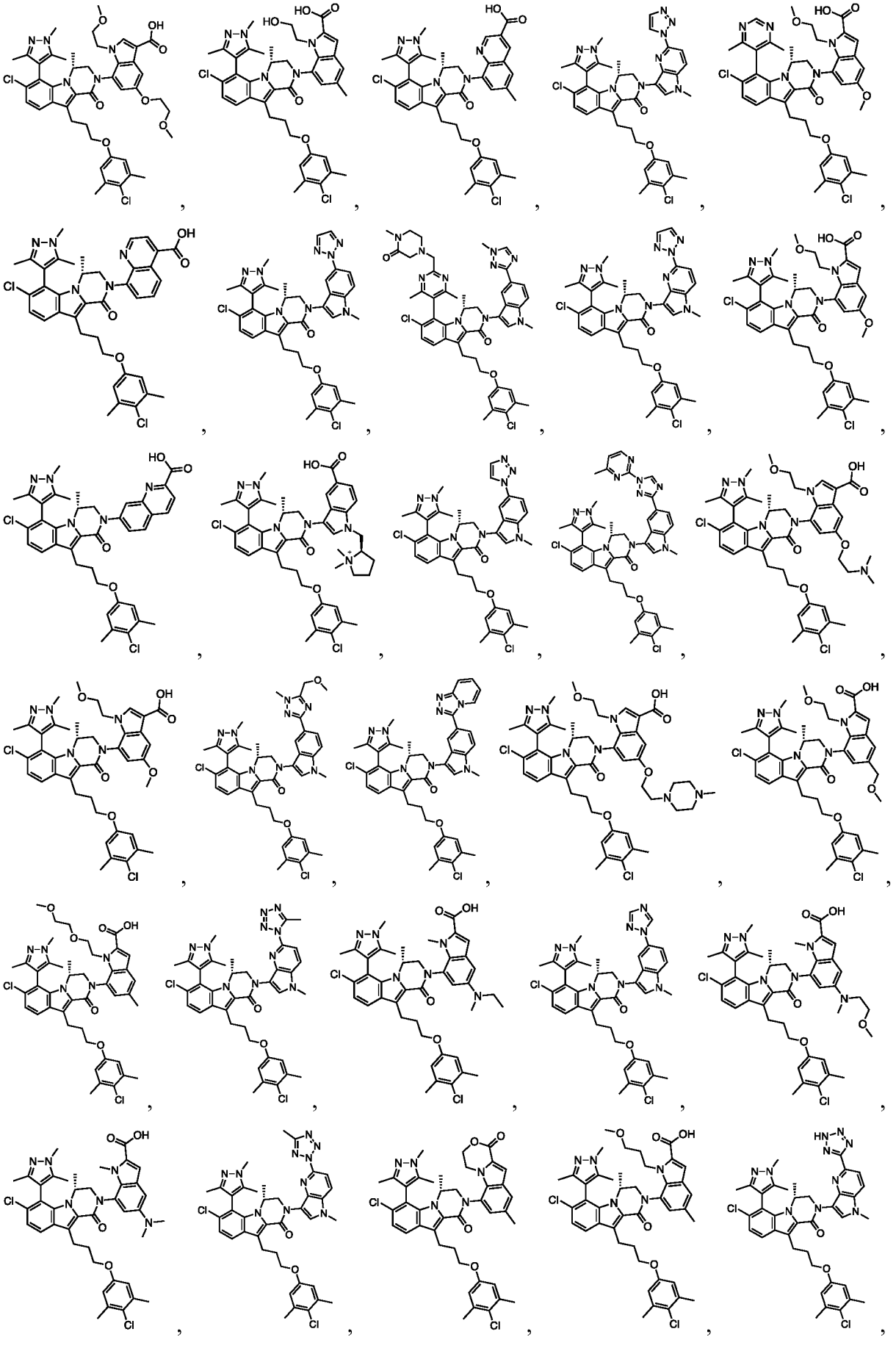
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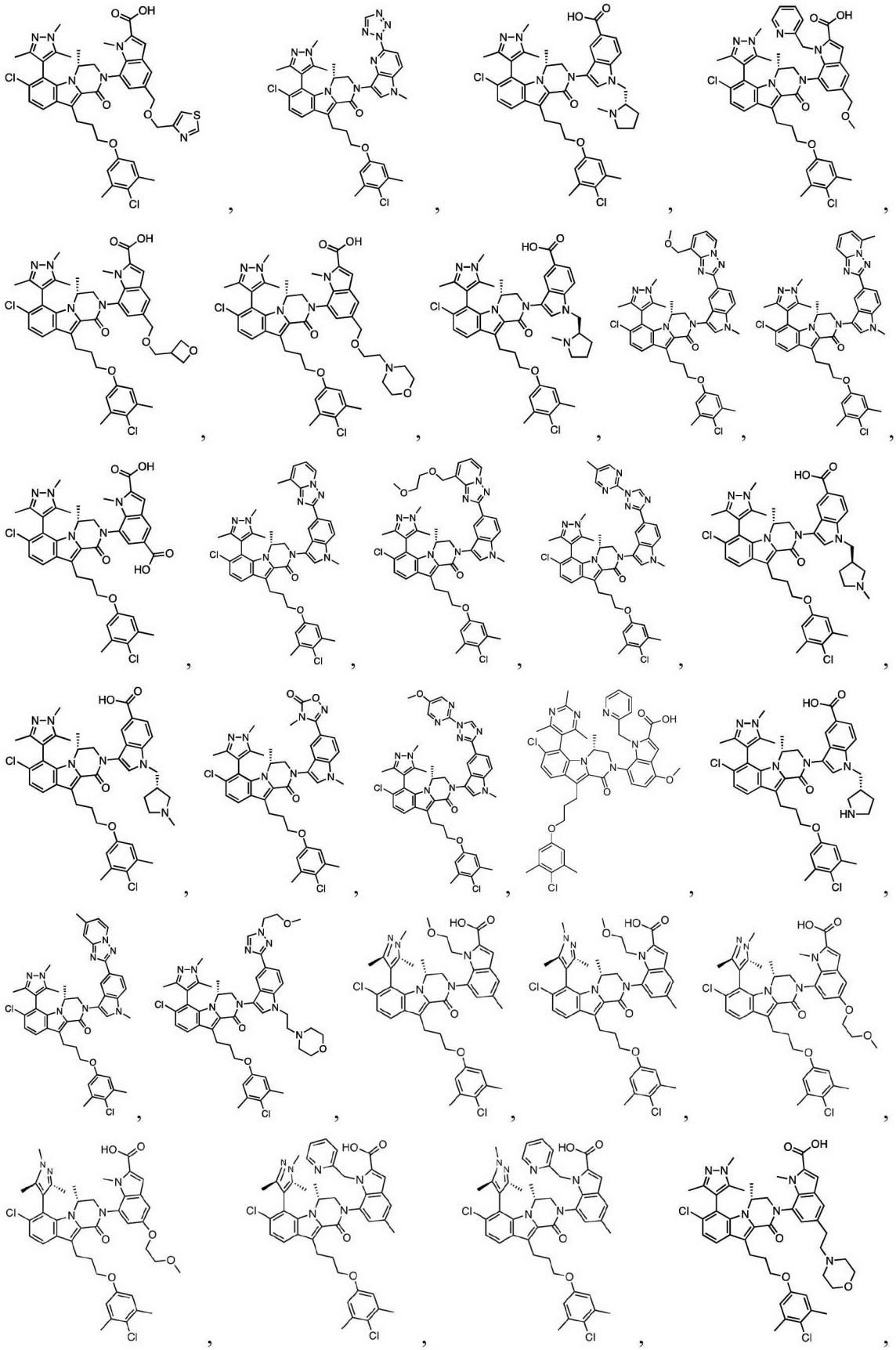
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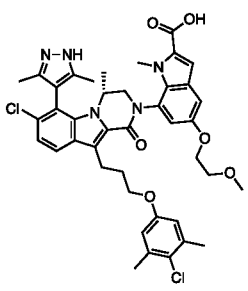
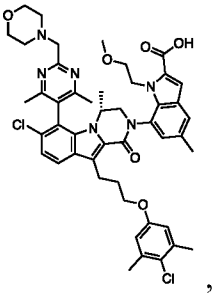
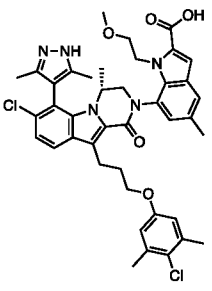
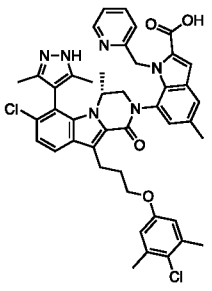
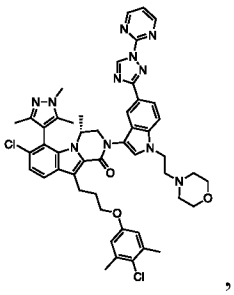
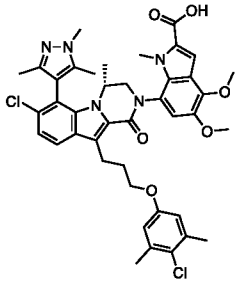
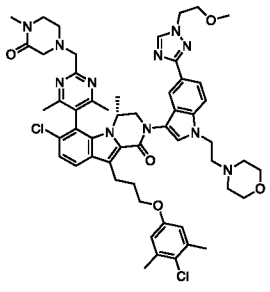
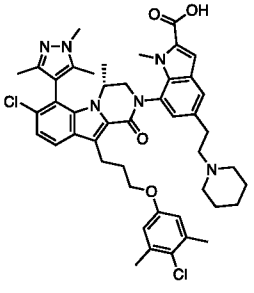
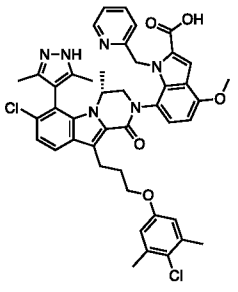
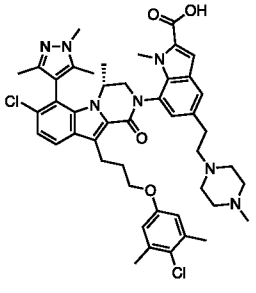
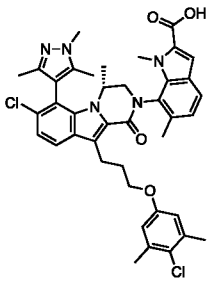
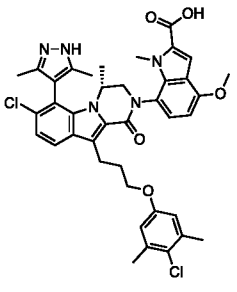
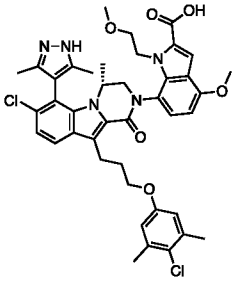
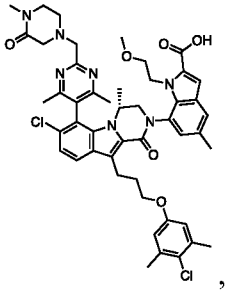
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or a pharmaceutically acceptable salt thereof.

[0007c] In another aspect there is provided a pharmaceutical composition comprised of a compound as defined herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0007d] In another aspect there is provided a method of modulating the activity of the Bcl-2 family of proteins comprising administering to a mammalian patient in need thereof a therapeutically effective amount of at least one compound as defined herein, or a pharmaceutically acceptable salt thereof, and, optionally, an additional therapeutic agent.

[0007e] In another aspect there is provided a method for treating diseases or disorders associated with the expression or over-expression of Mcl-1, comprising administering to a

subject in need thereof, a therapeutically effective amount of a compound as defined herein, or a pharmaceutically acceptable salt thereof, wherein:

the diseases or disorders are selected from the group consisting of acoustic neuroma, acute leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia (monocytic, myeloblastic, adenocarcinoma, adrenocortical cancer, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute T-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, bone cancer, brain cancer, brain stem glioma, breast cancer, bronchogenic carcinoma, cervical cancer, cholangiocarcinoma, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myleogeneous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, duodenal cancer, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fallopian tube carcinoma, fibrosarcoma, follicular lymphoma, gastric carcinoma, germ cell testicular cancer, gestational trophobalstic disease, glioblastoma, gall bladder cancer, head and neck cancer, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, liposarcoma, lung cancer both small cell lung cancer and non-small cell lung cancer, lymphagioendothelio-sarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma, including Diffuse Large B-celllymphoma, follicular lymphoma, Hodgkin's lymphoma and non-Hodgkin's lymphoma, malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, leukemia, lymphoma, medullary carcinoma, medulloblastoma, melanoma (cutaneous or intraocular), meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, parathyroid cancer, peripheral T -cell lymphoma, pinealoma, pituitary adenoma, polycythemia vera, prostate cancer including hormone-insensitive (refractory) prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small intestine cancer, solid tumors (carcinomas and sarcomas), small cell lung cancer, spinal axis tumors, spleen cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, testicular cancer (including germ cell testicular cancer), thyroid cancer, urethra cancer, uterine cancer, Waldenstram's

macroglobulinemia, testicular tumors, vaginal cancer, vulva cancer, Wilms' tumor, embryonal rhabdomyosarcoma, pediatric acute lymphoblastic leukemia, pediatric acute myelogenous leukemia, pediatric alveolar rhabdomyosarcoma, pediatric anaplastic ependymoma, pediatric anaplastic large cell lymphoma, pediatric anaplastic medulloblastoma, pediatric atypical teratoidlrhabdoid tumor of the central nervous system, pediatric biphenotypic acute leukemia, pediatric Burkitts lymphoma, pediatric cancers of Ewing's family of tumors such as primitive neuroectodermal rumors, pediatric diffuse anaplastic Wilm's tumor, pediatric favorable histology Wilm's tumor, pediatric glioblastoma, pediatric medulloblastoma, pediatric neuroblastoma, pediatric neuroblastoma-derived myelocytomatosis, pediatric pre-B-cell cancers (such as leukemia), pediatric psteosarcoma, pediatric rhabdoid kidney tumor, pediatric rhabdomyosarcoma, and pediatric T-cell cancers such as lymphoma and skin cancer.

[0007f] In another aspect there is provided a method for preventing, inhibiting, or treating the progression or onset of diseases or disorders associated with the expression or over-expression of anti-apoptotic Bcl-2 family protein members, particularly Mcl-1 protein, comprising administering to a mammalian patient in need of prevention, inhibition, or treatment a therapeutically effective amount of at least one compound as defined herein, or a pharmaceutically acceptable salt thereof, and, optionally, an additional therapeutic agent wherein:

(a) the diseases or disorders are selected from the group consisting of acoustic neuroma, acute leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia (monocytic, myeloblastic, adenocarcinoma, adrenocortical cancer, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute T-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, bone cancer, brain cancer, brain stem glioma, breast cancer, bronchogenic carcinoma, cervical cancer, cholangiocarcinoma, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myleogeneous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, duodenal cancer, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fallopian tube carcinoma, fibrosarcoma, follicular lymphoma, gastric carcinoma, germ cell testicular cancer, gestational trophobalstic disease, glioblastoma, gall bladder cancer, head and neck cancer, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer,

leiomyosarcoma, liposarcoma, lung cancer both small cell lung cancer and non-small cell lung cancer, lymphagioendothelio-sarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma, including Diffuse Large B-celllymphoma, follicular lymphoma, Hodgkin's lymphoma and non-Hodgkin's lymphoma, malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, leukemia, lymphoma, medullary carcinoma, medulloblastoma, melanoma (cutaneous or intraocular), meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, parathyroid cancer, peripheral T -cell lymphoma, pinealoma, pituitary adenoma, polycythemia vera, prostate cancer including hormone-insensitive (refractory) prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small intestine cancer, solid tumors (carcinomas and sarcomas), small cell lung cancer, spinal axis tumors, spleen cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, testicular cancer (including germ cell testicular cancer), thyroid cancer, urethra cancer, uterine cancer, Waldenstram's macroglobulinemia, testicular tumors, vaginal cancer, vulva cancer, Wilms' tumor, embryonal rhabdomyosarcoma, pediatric acute lymphoblastic leukemia, pediatric acute myelogenous leukemia, pediatric alveolar rhabdomyosarcoma, pediatric anaplastic ependymoma, pediatric anaplastic large cell lymphoma, pediatric anaplastic medulloblastoma, pediatric atypical teratoidlrhabdoid tumor of the central nervous system, pediatric biphenotypic acute leukemia, pediatric Burkitts lymphoma, pediatric cancers of Ewing's family of tumors such as primitive neuroectodermal rumors, pediatric diffuse anaplastic Wilm's tumor, pediatric favorable histology Wilm's tumor, pediatric glioblastoma, pediatric medulloblastoma, pediatric neuroblastoma, pediatric neuroblastoma-derived myelocytomatosis, pediatric pre-B-cell cancers (such as leukemia), pediatric psteosarcoma, pediatric rhabdoid kidney tumor, pediatric rhabdomyosarcoma, and pediatric T-cell cancers such as lymphoma and skin cancer; and

(b) the additional therapeutic agent is selected from the group of anti-cancer agents consisting of alkylating agents, angiogenesis inhibitors, antibodies, antimetabolites, antimitotics, antiproliferatives, aurora kinase inhibitors, Bcl-2 family protein (for example, Bcl-xL, Bcl-2, Bcl-w) inhibitors, Bcr-Abl kinase inhibitors, biologic response modifiers, cyclin-dependent kinase inhibitors, cell cycle inhibitors, cyclooxygenase-2 inhibitors, leukemia viral oncogene homolog (ErbB2) receptor inhibitors, growth factor inhibitors, heat

shock protein (HSP)-90 inhibitors, histone deacetylase (HDAC) inhibitors inhibitors, hormonal therapies, inhibitors of apoptosis proteins (lAPs), immunologicals, intercalating antibiotics, kinase inhibitors, mammalian target of rapamycin inhibitors, mitogen-activated extracellular signal-regulated kinase inhibitors, microRNA's, small inhibitory ribonucleic acids (siRNAs), non-steroidal anti-inflammatory drugs (NSAID's), poly ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitors, platinum chemotherapeutics, polo-like kinase inhibitors, proteasome inhibitors, purine analogs, pyrimidine analogs, receptor tyrosine kinase inhibitors, retinoids/deltoids plant alkaloids and topoisomerase inhibitors.

[0007g] In another aspect there is provided a use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating diseases or disorders associated with the expression or over-expression of Mcl-1, wherein:
the diseases or disorders are selected from the group consisting of acoustic neuroma, acute leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia (monocytic, myeloblastic, adenocarcinoma, adrenocortical cancer, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute T-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, bone cancer, brain cancer, brain stem glioma, breast cancer, bronchogenic carcinoma, cervical cancer, cholangiocarcinoma, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myleogeneous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, duodenal cancer, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fallopian tube carcinoma, fibrosarcoma, follicular lymphoma, gastric carcinoma, germ cell testicular cancer, gestational trophobalstic disease, glioblastoma, gall bladder cancer, head and neck cancer, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, liposarcoma, lung cancer both small cell lung cancer and non-small cell lung cancer, lymphagioendothelio-sarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma, including Diffuse Large B-celllymphoma, follicular lymphoma, Hodgkin's lymphoma and non-Hodgkin's lymphoma, malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, leukemia, lymphoma, medullary carcinoma, medulloblastoma, melanoma (cutaneous or intraocular), meningioma, mesothelioma, multiple myeloma, myelogenous leukemia,

myeloma, myxosarcoma, neuroblastoma, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, parathyroid cancer, peripheral T -cell lymphoma, pinealoma, pituitary adenoma, polycythemia vera, prostate cancer including hormone-insensitive (refractory) prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small intestine cancer, solid tumors (carcinomas and sarcomas), small cell lung cancer, spinal axis tumors, spleen cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, testicular cancer (including germ cell testicular cancer), thyroid cancer, urethra cancer, uterine cancer, Waldenstram's macroglobulinemia, testicular tumors, vaginal cancer, vulva cancer, Wilms' tumor, embryonal rhabdomyosarcoma, pediatric acute lymphoblastic leukemia, pediatric acute myelogenous leukemia, pediatric alveolar rhabdomyosarcoma, pediatric anaplastic ependymoma, pediatric anaplastic large cell lymphoma, pediatric anaplastic medulloblastoma, pediatric atypical teratoidlrhabdoid tumor of the central nervous system, pediatric biphenotypic acute leukemia, pediatric Burkitts lymphoma, pediatric cancers of Ewing's family of tumors such as primitive neuroectodermal rumors, pediatric diffuse anaplastic Wilm's tumor, pediatric favorable histology Wilm's tumor, pediatric glioblastoma, pediatric medulloblastoma, pediatric neuroblastoma, pediatric neuroblastoma-derived myelocytomatosis, pediatric pre-B-cell cancers (such as leukemia), pediatric psteosarcoma, pediatric rhabdoid kidney tumor, pediatric rhabdomyosarcoma, and pediatric T-cell cancers such as lymphoma and skin cancer.

[0007h] In another aspect there is provided a use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, and, optionally, an additional therapeutic agent, in the manufacture of a medicament for preventing, inhibiting, or treating the progression or onset of diseases or disorders associated with the expression or over-expression of anti-apoptotic Bcl-2 family protein members, wherein:

(a) the diseases or disorders are selected from the group consisting of acoustic neuroma, acute leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia (monocytic, myeloblastic, adenocarcinoma, adrenocortical cancer, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute T-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, bone cancer, brain cancer, brain stem glioma, breast cancer, bronchogenic carcinoma, cervical cancer, cholangiocarcinoma, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myleogeneous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell

lymphoma, duodenal cancer, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fallopian tube carcinoma, fibrosarcoma, follicular lymphoma, gastric carcinoma, germ cell testicular cancer, gestational trophobalstic disease, glioblastoma, gall bladder cancer, head and neck cancer, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, liposarcoma, lung cancer both small cell lung cancer and non-small cell lung cancer, lymphagioendothelio-sarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma, including Diffuse Large B-celllymphoma, follicular lymphoma, Hodgkin's lymphoma and non-Hodgkin's lymphoma, malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, leukemia, lymphoma, medullary carcinoma, medulloblastoma, melanoma (cutaneous or intraocular), meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, parathyroid cancer, peripheral T -cell lymphoma, pinealoma, pituitary adenoma, polycythemia vera, prostate cancer including hormone-insensitive (refractory) prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small intestine cancer, solid tumors (carcinomas and sarcomas), small cell lung cancer, spinal axis tumors, spleen cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, testicular cancer (including germ cell testicular cancer), thyroid cancer, urethra cancer, uterine cancer, Waldenstram's macroglobulinemia, testicular tumors, vaginal cancer, vulva cancer, Wilms' tumor, embryonal rhabdomyosarcoma, pediatric acute lymphoblastic leukemia, pediatric acute myelogenous leukemia, pediatric alveolar rhabdomyosarcoma, pediatric anaplastic ependymoma, pediatric anaplastic large cell lymphoma, pediatric anaplastic medulloblastoma, pediatric atypical teratoidlrhabdoid tumor of the central nervous system, pediatric biphenotypic acute leukemia, pediatric Burkitts lymphoma, pediatric cancers of Ewing's family of tumors such as primitive neuroectodermal rumors, pediatric diffuse anaplastic Wilm's tumor, pediatric favorable histology Wilm's tumor, pediatric glioblastoma, pediatric medulloblastoma, pediatric neuroblastoma, pediatric neuroblastoma-derived myelocytomatosis, pediatric pre-B-cell cancers (such as leukemia),

pediatric psteosarcoma, pediatric rhabdoid kidney tumor, pediatric rhabdomyosarcoma, and pediatric T-cell cancers such as lymphoma and skin cancer; and

(b) the additional therapeutic agent is selected from the group of anti-cancer agents consisting of alkylating agents, angiogenesis inhibitors, antibodies, antimetabolites, antimitotics, antiproliferatives, aurora kinase inhibitors, Bcl-2 family protein (for example, Bcl-xL, Bcl-2, Bcl-w) inhibitors, Bcr-Abl kinase inhibitors, biologic response modifiers, cyclin-dependent kinase inhibitors, cell cycle inhibitors, cyclooxygenase-2 inhibitors, leukemia viral oncogene homolog (ErbB2) receptor inhibitors, growth factor inhibitors, heat shock protein (HSP)-90 inhibitors, histone deacetylase (HDAC) inhibitors inhibitors, hormonal therapies, inhibitors of apoptosis proteins (lAPs), immunologicals, intercalating antibiotics, kinase inhibitors, mammalian target of rapamycin inhibitors, mitogen-activated extracellular signal-regulated kinase inhibitors, microRNA's, small inhibitory ribonucleic acids (siRNAs), non-steroidal anti-inflammatory drugs (NSAID's), poly ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitors, platinum chemotherapeutics, polo-like kinase inhibitors, proteasome inhibitors, purine analogs, pyrimidine analogs, receptor tyrosine kinase inhibitors, retinoids/deltoids plant alkaloids and topoisomerase inhibitors.

[0008] In some embodiments, the present disclosure provides compounds, and pharmaceutically acceptable compositions thereof, that are effective as inhibitors of Mcl-1.

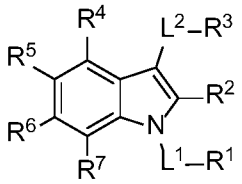
[0009] Compounds of the present disclosure, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with MCl-1. Such diseases, disorders, or conditions include those described herein.

[0010] Compounds provided by this disclosure are also useful for the study of Mcl-1 in biological and pathological phenomena and the comparative evaluation of new Mcl-1 inhibitors *in vitro* or *in vivo*.

DETAILED DESCRIPTION

1. General Description of Compounds of the Disclosure:

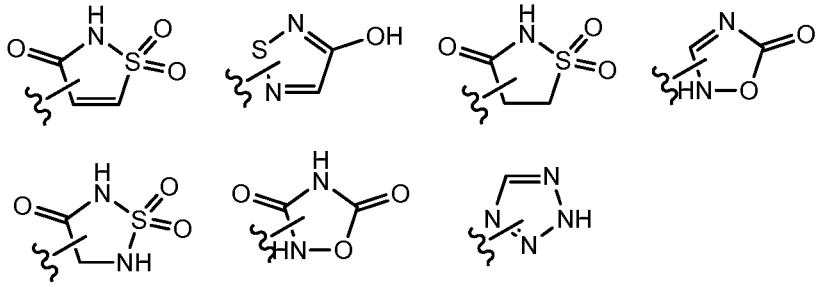
[0011] In one aspect, the present disclosure provides inhibitors of Mcl-1. In some embodiments, such compounds include those of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein: L^1 is selected from a covalent bond or an optionally substituted bivalent straight or branched C_{1-6} hydrocarbon chain wherein one or more methylene units are optionally and independently replaced with −Cy−; −Cy− is an optionally substituted bivalent ring independently selected from phenylene, 3-8 membered saturated or partially unsaturated carbocyclylene, 5-6 membered heteroarylene having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 3-8 membered saturated or partially unsaturated heterocyclylene having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; L^2 is an optionally substituted bivalent straight or branched C_{3-6} hydrocarbon chain wherein one or two methylene units of L^2 are optionally and independently replaced with −O−, −S−, or −N(R')−, and wherein two substituents of L^2 are optionally taken together to form an optionally substituted bivalent ring selected from 3-8

membered saturated or partially unsaturated carbocyclylene or 3-8 membered saturated or partially unsaturated heterocyclylene having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each R' is independently selected from hydrogen or optionally substituted C_{1-4} alkyl; R^1 is selected from hydrogen, halogen, R, −OR, −SR, −S(O)R, $-S(O)_2R$, $-S(O)_2N(R)_2$, $-N(R)_2$, $-C(O)N(R)_2$, −C(O)R, −N(R)C(O)R, −N(R)C(O)OR, $-N(R)C(O)N(R)_2$, $-N(R)S(O)_2R$, $-N(R)S(O)_2N(R)_2$, −C(O)OH, $-C(O)R^x$, $-S(O)_2OH$, $-S(O)R^y$, or $-S(O)_2R^y$; R^2 is selected from $-C(O)-L^3-R^z$, $-C(O)N(R)-L^3-R^z$, $-C(O)N(R)-C(R)_2-L^3-R^z$, $-C(O)O-L^3-R^z$ or $-C(O)S-L^3-R^z$; L^3 is selected from a covalent bond or an optionally substituted bivalent straight or branched C_{1-8} hydrocarbon chain wherein one or more methylene units are optionally and independently replaced with −Cy−, −O−, −S−, −N(R)−, −N(R)C(O)−, $-N(R)S(O)_2-$, −C(O)−, −C(O)N(R)−, −S(O)−, $-S(O)_2-$, or $-S(O)_2N(R)-$; R^z is selected from hydrogen, −Cy−R, R, −OR, −SR, −S(O)R, $-S(O)_2R$, $-S(O)_2N(R)_2$, $-N(R)_2$, $-C(O)N(R)_2$, −C(O)R, −N(R)C(O)R, −N(R)C(O)OR, $-N(R)C(O)N(R)_2$, $-N(R)S(O)_2R$, $-N(R)S(O)_2N(R)_2$, −C(O)OH, $-C(O)R^x$, $-S(O)_2OH$, or $-S(O)_2R^y$, or is selected from:

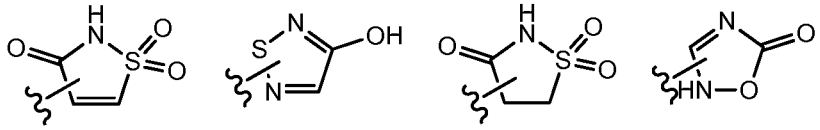


; R^x is selected from $-C(O)OR$, $-N(R)S(O)_2CF_3$, −N(R)C(O)R, −N(R)C(O)OR, $-N(R)C(O)N(R)_2$, or $-N(R)S(O)_2R$; R^y is selected from $-N(R)C(O)CF_3$, −N(R)C(O)R, or $-N(R)C(O)N(R)_2$; each R is independently selected from hydrogen or an optionally substituted group selected from C_{1-12} aliphatic or a ring selected from a 3-10 membered saturated or partially unsaturated carbocyclic ring, phenyl, a 6-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 3-8 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen or sulfur, an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen or sulfur, or a 12-15 membered tricyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen or sulfur; R^3 is an optionally substituted ring

selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of R^4, R^5, and R^6 is independently selected from R, halogen, $-CN$, $-NO_2$, $-C(O)OR'$, $-OR'$, $-SR'$, $-C(O)N(R')_2$ $-N(R')_2$, $-S(O)_2N(R')_2$, $-N(R')S(O)_2CF_3$, $-C(O)R'$, $-N(R')C(O)R'$, $-S(O)R'$, $-S(O)_2R'$, $-N(R')C(O)OR'$, and $-N(R')S(O)_2R'$; R^7 is selected from hydrogen, halogen, $-CN$, $-NO_2$, $-C(O)OR$, $-OCF_3$, $-OR$, $-SR$, $-S(O)_2OR$, $-P(O)(OH)_2$, $-C(O)N(R)_2$, $-N(R)_2$, $-S(O)_2N(R)_2$, $-N(R)S(O)_2CF_3$, $-C(O)N(R)S(O)_2R$, $-S(O)_2N(R)C(O)OR$, $-S(O)_2N(R)C(O)N(R)_2$, $-C(O)R$, $-C(O)N(R)S(O)_2CF_3$, $-N(R)C(O)R$, $-OC(O)R$, $-OC(O)N(R)_2$, $-C(NR)N(R)_2$, $-N(R)C(NR)N(R)_2$, $-S(O)R$, $-S(O)_2R$, $-N(R)C(O)OR$, or $-N(R)S(O)_2R$, or an optionally substituted group selected from C_{1-6} aliphatic or a ring selected from a 3-8 membered saturated or partially unsaturated carbocyclic ring, phenyl, a 3-8 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an 8-14 membered bicyclic or polycyclic saturated, partially unsaturated or aryl ring, a 7-14 membered bicyclic or polycyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-14 membered bicyclic or polycyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and optionally R^1 and R^2, R^1 and R^7, R^4 and R^5, R^5 and R^6 and/or R^6 and R^7 are taken together with their intervening atoms to form an optionally substituted ring selected from a 3-8 membered saturated or partially unsaturated carbocyclic ring, phenyl, a 3-8 membered saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0012] In other embodiments are compounds of formula (I), or a pharmaceutically acceptable salt, thereof, wherein L^1 is selected from a covalent bond or an optionally substituted bivalent straight or branched C_{1-6} hydrocarbon chain wherein one or more methylene units are optionally and independently replaced with $-Cy-$; $-Cy-$ is an optionally substituted bivalent ring independently selected from phenylene, 3-8 membered saturated or

partially unsaturated carbocyclylene, 5-6 membered heteroarylene having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 3-8 membered saturated or partially unsaturated heterocyclylene having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; L^2 is an optionally substituted bivalent straight or branched C_{3-6} hydrocarbon chain wherein one or two methylene units of L^2 are optionally and independently replaced with −O−, −S−, or −N(R')−, and wherein two substituents of L^2 are optionally taken together to form an optionally substituted bivalent ring selected from 3-8 membered saturated or partially unsaturated carbocyclylene or 3-8 membered saturated or partially unsaturated heterocyclylene having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each R' is independently selected from hydrogen or optionally substituted C_{1-4} alkyl; R^1 is selected from hydrogen, halogen, R, −OR, −SR, −S(O)R, $-S(O)_2R$, $-S(O)_2N(R)_2$, $-N(R)_2$, $-C(O)N(R)_2$, −C(O)R, −N(R)C(O)R, −N(R)C(O)OR, $-N(R)C(O)N(R)_2$, $-N(R)S(O)_2R$, $-N(R)S(O)_2N(R)_2$, −C(O)OH, $-C(O)R^x$, $-S(O)_2OH$, $-S(O)R^y$, or $-S(O)_2R^y$; R^2 is selected from $-C(O)-L^3-R^z$, $-C(O)N(R)-L^3-R^z$, $-C(O)N(R)-C(R)_2-L^3-R^z$, $-C(O)O-L^3-R^z$ or $-C(O)S-L^3-R^z$; L^3 is selected from a covalent bond or an optionally substituted bivalent straight or branched C_{1-8} hydrocarbon chain wherein one or more methylene units are optionally and independently replaced with −Cy−, −O−, −S−, −N(R)−, −N(R)C(O)−, $-N(R)S(O)_2-$, −C(O)−, −C(O)N(R)−, −S(O)−, $-S(O)_2-$, or $-S(O)_2N(R)-$; R^z is selected from hydrogen, −Cy−R, R, −OR, −SR, −S(O)R, $-S(O)_2R$, $-S(O)_2N(R)_2$, $-N(R)_2$, $-C(O)N(R)_2$, −C(O)R, −N(R)C(O)R, −N(R)C(O)OR, $-N(R)C(O)N(R)_2$, $-N(R)S(O)_2R$, $-N(R)S(O)_2N(R)_2$, −C(O)OH, $-C(O)R^x$, $-S(O)_2OH$, or $-S(O)_2R^y$, or is selected from:



; R^x is selected from −C(O)OR, $-N(R)S(O)_2CF_3$, −N(R)C(O)R, −N(R)C(O)OR, $-N(R)C(O)N(R)_2$, or $-N(R)S(O)_2R$; R^y is selected from $-N(R)C(O)CF_3$, −N(R)C(O)R, or $-N(R)C(O)N(R)_2$; each R is independently selected from hydrogen or an optionally substituted group selected from C_{1-12} aliphatic or a ring selected from a 3-10 membered saturated or partially unsaturated carbocyclic ring, phenyl, a 6-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 3-8 membered saturated or partially unsaturated heterocyclic ring having 1-2

heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen or sulfur; R^3 is an optionally substituted ring selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of R^4, R^5, and R^6 is independently selected from R, halogen, $-CN$, $-NO_2$, $-C(O)OR'$, $-OR'$, $-SR'$, $-C(O)N(R')_2$ $-N(R')_2$, $-S(O)_2N(R)_2$, $-N(R')S(O)_2CF_3$, $-C(O)R'$, $-N(R')C(O)R'$, $-S(O)R'$, $-S(O)_2R'$, $-N(R')C(O)OR'$, and $-N(R')S(O)_2R'$; R^7 is selected from hydrogen, halogen, $-CN$, $-NO_2$, $-C(O)OR$, $-OCF_3$, $-OR$, $-SR$, $-S(O)_2OR$, $-P(O)(OH)_2$, $-C(O)N(R)_2$, $-N(R)_2$, $-S(O)_2N(R)_2$, $-N(R)S(O)_2CF_3$, $-C(O)N(R)S(O)_2R$, $-S(O)_2N(R)C(O)OR$, $-S(O)_2N(R)C(O)N(R)_2$, $-C(O)R$, $-C(O)N(R)S(O)_2CF_3$, $-N(R)C(O)R$, $-OC(O)R$, $-OC(O)N(R)_2$, $-C(NR)N(R)_2$, $-N(R)C(NR)N(R)_2$, $-S(O)R$, $-S(O)_2R$, $-N(R)C(O)OR$, or $-N(R)S(O)_2R$, or an optionally substituted group selected from C_{1-6} aliphatic or a ring selected from a 3-8 membered saturated or partially unsaturated carbocyclic ring, phenyl, a 3-8 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an 8-14 membered bicyclic or polycyclic saturated, partially unsaturated or aryl ring, a 7-14 membered bicyclic or polycyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-14 membered bicyclic or polycyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and optionally R^1 and R^2, R^1 and R^7, R^4 and R^5, R^5 and R^6 and/or R^6 and R^7 are taken together with their intervening atoms to form an optionally substituted ring selected from a 3-8 membered saturated or partially unsaturated carbocyclic ring, phenyl, a 3-8 membered saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6

membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

2. Compounds and Definitions:

[0013] Compounds of this disclosure include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0014] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic or polycyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle," "cycloaliphatic" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms. In some embodiments, "cycloaliphatic" (or "carbocycle" or "cycloalkyl") refers to a monocyclic C3-C6 hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0015] The term "lower alkyl" refers to a C1-4 straight or branched alkyl group. Exemplary lower alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tert-butyl.

[0016] The term "lower haloalkyl" refers to a C1-4 straight or branched alkyl group that is substituted with one or more halogen atoms.

[0017] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen; or a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR+ (as in N-substituted pyrrolidinyl)).

[0018] The term "unsaturated," as used herein, means that a moiety has one or more units of unsaturation.

[0019] As used herein, the term "bivalent C1-8 (or C1-6) saturated or unsaturated, straight or branched, hydrocarbon chain", refers to bivalent alkylene, alkenylene, and alkynylene chains that are straight or branched as defined herein.

[0020] The term "alkylene" refers to a bivalent alkyl group. An "alkylene chain" is a polymethylene group, i.e., $-(CH_2)n-$, wherein n is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0021] The term "alkenylene" refers to a bivalent alkenyl group. A substituted alkenylene chain is a polymethylene group containing at least one double bond in which one or more hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0022] The term "halogen" means F, Cl, Br, or I.

[0023] The term "aryl" used alone or as part of a larger moiety as in "aralkyl," "aralkoxy," or "aryloxyalkyl," refers to monocyclic or bicyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring." In certain embodiments of the present disclosure, "aryl" refers to an aromatic ring system which includes, but not limited to, phenyl, naphthyl, anthracyl and the like, which may be optionally substituted. Also included within the scope of the term "aryl," as it is used herein, is a group in which an aromatic ring is fused to one or more non–aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like.

[0024] The terms "heteroaryl" and "heteroar–," used alone or as part of a larger moiety, e.g., "heteroaralkyl," or "heteroaralkoxy," refer to groups having 5 to 10 ring atoms, or 5 to 15 ring atoms, preferably 5, 6, or 9 ring atoms; having 6, 10, or 14 π electrons shared in a

cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. The terms "heteroaryl" and "heteroar–", as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Non-limiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4H–quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, pyrido[2,3–b]–1,4–oxazin–3(4H)–one, 3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole, 3,4-dihydro-1H-[1,4]oxazino[4,3-a]indol-1-one, 1,2,3,4-tetrahydropyrazino[1,2-a]indole, and 3,4-dihydropyrazino[1,2-a]indol-1(2H)-one. A heteroaryl group may be mono–, bicyclic, or tricyclic. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring," "heteroaryl group," or "heteroaromatic," any of which terms include rings that are optionally substituted. The term "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[0025] As used herein, the terms "heterocycle," "heterocyclyl," "heterocyclic radical," and "heterocyclic ring" are used interchangeably and refer to a stable 5– to 7–membered monocyclic or 7–10–membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms. When used in reference to a ring atom of a heterocycle, the term "nitrogen" includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 1–3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4–dihydro–2H–pyrrolyl), NH (as in pyrrolidinyl), or +NR (as in N–substituted pyrrolidinyl).

[0026] A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothiophenyl pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl. The terms "heterocycle," "heterocyclyl," "heterocyclyl ring," "heterocyclic

group," "heterocyclic moiety," and "heterocyclic radical," are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3H–indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl, where the radical or point of attachment is on the heterocyclyl ring. A heterocyclyl group may be mono– or bicyclic. The term "heterocyclylalkyl" refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted.

[0027] As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[0028] As described herein, compounds of the disclosure may contain "optionally substituted" moieties. In general, the term "substituted," whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this disclosure are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0029] Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$, $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; $-CH=CHPh$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR-$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$;

$-(CH_2)_{0-4}C(O)N(R°)S(O)_2R°$; $-C(S)NR°_2$; $-C(S)SR°$; $-SC(S)SR°$, $-(CH_2)_{0-4}OC(O)NR°_2$; $-C(O)N(OR°)R°$; $-C(O)C(O)R°$; $-C(O)CH_2C(O)R°$; $-C(NOR°)R°$; $-(CH_2)_{0-4}SSR°$; $-(CH_2)_{0-4}S(O)R°$; $-(CH_2)_{0-4}S(O)_2R°$; $-(CH_2)_{0-4}S(O)_2OR°$; $-(CH_2)_{0-4}OS(O)_2R°$; $-S(O)_2NR°_2$; $-S(O)_2N(R°)C(O)R°$; $-(CH_2)_{0-4}S(O)R°$; $-N(R°)S(O)_2NR°_2$; $-N(R°)S(O)_2R°$; $-N(OR°)R°$; $-C(NH)NR°_2$; $-P(O)_2R°$; $-P(O)R°_2$; $-OP(O)R°_2$; $-OP(O)(OR°)_2$; $-SiR°_3$; $-$(C1–4 straight or branched alkylene)$O-N(R°)_2$; or $-$(C1–4 straight or branched alkylene)$C(O)O-N(R°)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, an optionally substituted group selected from C_{1-12} aliphatic or a ring selected from a 3-10 membered saturated or partially unsaturated carbocyclic ring, phenyl, a 6-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 3-8 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen or sulfur, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or $-CH_2-$(5-6 membered heteroaryl ring), or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[0030] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^•$, $-$(halo$R^•$), $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^•$, $-(CH_2)_{0-2}CH(OR^•)_2$; $-O$(halo$R^•$), $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^•$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^•$, $-(CH_2)_{0-2}SR^•$, $-(CH_2)_{0-2}S(O)R^•$, $-(CH_2)_{0-2}S(O)_2R^•$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^•$, $-(CH_2)_{0-2}NR^•_2$, $-NO_2$, $-SiR^•_3$, $-OSiR^•_3$, -C(O)$SR^•$, $-$(C1–4 straight or branched alkylene)$C(O)OR^•$, or $-SSR^•$ wherein each $R^•$ is unsubstituted or where preceded by "halo" is substituted with one or more halogens, and is independently selected from an C_{1-12} aliphatic or a ring selected from a 3-10 membered saturated or partially unsaturated carbocyclic ring, phenyl, a 6-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 3-8 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered

heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen or sulfur, $-CH_2Ph$, or $-O(CH_2)_{0-1}Ph$. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

[0031] Suitable divalent substituents on a suitable carbon atom of an "optionally substituted" group include the following: =O, =S, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0032] Suitable substituents on the aliphatic group of R^* include halogen, $-R^\bullet$, -(halo$R^\bullet$), $-OH$, $-OR^\bullet$, $-O$(halo$R^\bullet$), $-CN$, $-C(O)R^\bullet$, $-C(O)OH$, $-C(O)OR^\bullet$, $-C(O)NR^\bullet_2$, $-SR^\bullet$, $-S(O)R^\bullet$, $-S(O)_2R^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0033] Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include $-R^\dagger$, $-NR^\dagger_2$, $-C(O)R^\dagger$, $-C(O)OR^\dagger$, $-C(O)C(O)R^\dagger$, $-C(O)CH_2C(O)R^\dagger$, $-S(O)_2R^\dagger$, $-S(O)_2NR^\dagger_2$, $-C(S)NR^\dagger_2$, $-C(NH)NR^\dagger_2$, $-C(NR^\dagger)NR^\dagger_2$, or $-N(R^\dagger)S(O)_2R^\dagger$; wherein each $R^\dagger$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted $-OPh$, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^\dagger$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected

from nitrogen, oxygen, or sulfur.

[0034] Suitable substituents on the aliphatic group of $R^{\dagger}$ are independently halogen, $-R^{\bullet}$, -(halo$R^{\bullet}$), –OH, $-OR^{\bullet}$, –O(halo$R^{\bullet}$), –CN, –C(O)OH, $-C(O)OR^{\bullet}$, $-C(O)NR^{\bullet}_2$, $-SR^{\bullet}$, $-S(O)R^{\bullet}$, $-S(O)_2R^{\bullet}$, $-NH_2$, $-NHR^{\bullet}$, $-NR^{\bullet}_2$, or $-NO_2$, wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0035] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1–19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this disclosure include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like.

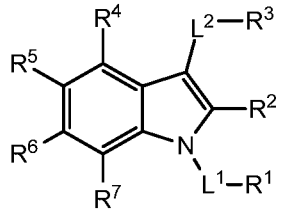
[0036] Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and N+(C1–4alkyl)$_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide,

hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate.

[0037] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the disclosure. Unless otherwise stated, all tautomeric forms of the compounds of the disclosure are within the scope of the disclosure. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a 13C- or 14C-enriched carbon are within the scope of this disclosure. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present disclosure.

3. Description of Exemplary Embodiments:

[0038] In one aspect, disclosed is a compound of formula (I):

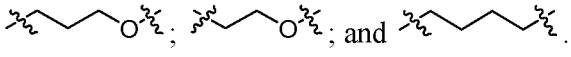


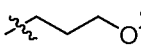
(I)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, L^1, and L^2 are as defined above.

[0039] In certain embodiments, R^2 is selected from $-C(O)-L^3-R^z$, $-C(O)N(R)-L^3-R^z$, $-C(O)N(R)-C(R)_2-L^3-R^z$, or $-C(O)S-L^3-R^z$.

[0040] In certain embodiments, L^2 is selected from:

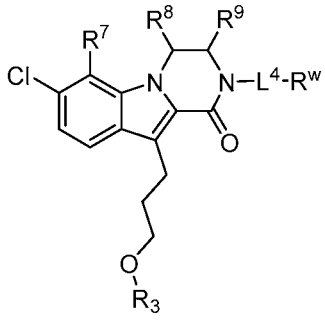


[0041] In certain embodiments, L^2 is 

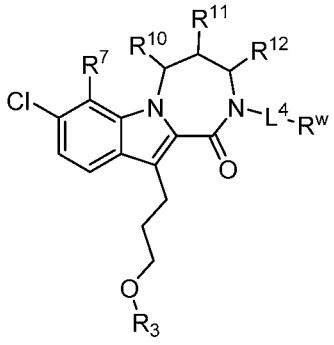
[0042] In certain embodiments, R^4 is hydrogen; R^5 is hydrogen; and R^6 is halogen, C_1-C_6-haloalkyl, or cyclopropyl.

[0043] In certain embodiments, R^6 is chloro.

[0044] In certain embodiments, the compound of formula (I) has formula (I-a) or (I-b):

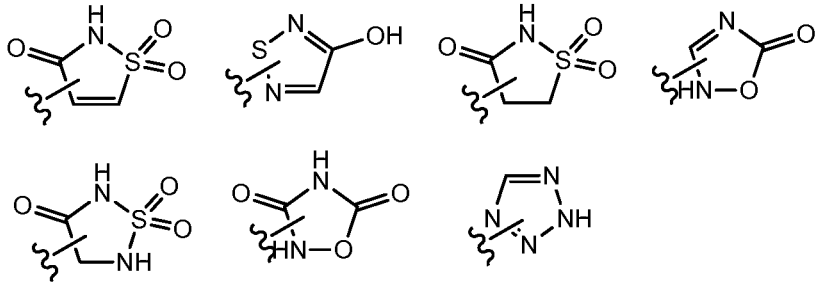


(I-a); or



(I-b);

or a pharmaceutically acceptable salt thereof, wherein: L^4 is independently selected from a covalent bond or an optionally substituted bivalent straight or branched C_{1-8} hydrocarbon chain wherein one or more methylene units are optionally and independently replaced with –Cy'–, –O–, –S–, –N(R)–, –N(R)C(O)–, –N(R)S(O)$_2$–, –C(O)–, –C(O)N(R)–, –S(O)–, –S(O)$_2$–, or –S(O)$_2$N(R)–; –Cy'– is an optionally substituted bivalent ring independently selected from phenylene, 3-8 membered saturated or partially unsaturated carbocyclylene, 5-6 membered heteroarylene having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 3-8 membered saturated or partially unsaturated heterocyclylene having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an 8-10 membered bicyclic arylene or heteroarylene having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered saturated or partially unsaturated heterocyclylene having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; R^w is selected from hydrogen, –Cy'–R, R, –OR, –SR, –S(O)R, –S(O)$_2$R, –S(O)$_2$N(R)$_2$, –N(R)$_2$, –C(O)N(R)$_2$, –C(O)R, –N(R)C(O)R, –N(R)C(O)OR, –N(R)C(O)N(R)$_2$, –N(R)S(O)$_2$R, –N(R)S(O)$_2$N(R)$_2$, –C(O)OH, –C(O)OR, –C(O)R^x, –S(O)$_2$OH, or –S(O)$_2$$R^y$, or is selected from:

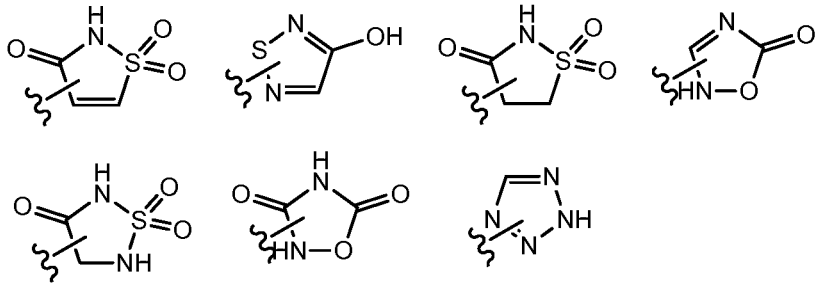


; R^x is selected from –C(O)OR, –N(R)S(O)$_2$CF$_3$, –N(R)C(O)R, –N(R)C(O)OR, –N(R)C(O)N(R)$_2$, or –N(R)S(O)$_2$R; R^y is selected from –N(R)C(O)CF$_3$, –N(R)C(O)R, or –N(R)C(O)N(R)$_2$; each R is independently selected from hydrogen or an optionally substituted group selected from

C_{1-12} aliphatic or a ring selected from a 3-10 membered saturated or partially unsaturated carbocyclic ring, phenyl, a 6-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 3-8 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen or sulfur; each of R^5, R^6, R^8, R^9, R^{10}, R^{11}, and R^{12} is independently selected from R, halogen, $-CN$, $-NO_2$, $-C(O)OR'$, $-OR'$, $-SR'$, $-C(O)N(R')_2$ $-N(R')_2$, $-S(O)_2N(R)_2$, $-N(R')S(O)_2CF_3$, $-C(O)R'$, $-N(R')C(O)R'$, $-S(O)R'$, $-S(O)_2R'$, $-N(R')C(O)OR'$, and $-N(R')S(O)_2R'$; each R' is independently selected from hydrogen or optionally substituted C_{1-4} alkyl; and R^7 is selected from hydrogen, halogen, $-CN$, $-NO_2$, $-C(O)OR$, $-OCF_3$, $-OR$, $-SR$, $-S(O)_2OR$, $-P(O)(OH)_2$, $-C(O)N(R)_2$, $-N(R)_2$, $-S(O)_2N(R)_2$, $-N(R)S(O)_2CF_3$, $-C(O)N(R)S(O)_2R$, $-S(O)_2N(R)C(O)OR$, $-S(O)_2N(R)C(O)N(R)_2$, $-C(O)R$, $-C(O)N(R)S(O)_2CF_3$, $-N(R)C(O)R$, $-OC(O)R$, $-OC(O)N(R)_2$, $-C(NR)N(R)_2$, $-N(R)C(NR)N(R)_2$, $-S(O)R$, $-S(O)_2R$, $-N(R)C(O)OR$, or $-N(R)S(O)_2R$, or an optionally substituted group selected from C_{1-6} aliphatic or a ring selected from a 3-8 membered saturated or partially unsaturated carbocyclic ring, phenyl, a 3-8 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an 8-14 membered bicyclic or polycyclic saturated, partially unsaturated or aryl ring, a 7-14 membered bicyclic or polycyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-14 membered bicyclic or polycyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0045] In certain embodiments, of formula (I-a) or (I-b), or a pharmaceutically acceptable salt thereof, L^4 is independently selected from a covalent bond or an optionally substituted bivalent straight or branched C_{1-8} hydrocarbon chain wherein one or more methylene units are optionally and independently replaced with $-Cy'-$, $-O-$, $-S-$, $-N(R)-$, $-N(R)C(O)-$, $-N(R)S(O)_2-$, $-C(O)-$, $-C(O)N(R)-$, $-S(O)-$, $-S(O)_2-$, or $-S(O)_2N(R)-$; $-Cy'-$ is an optionally substituted bivalent ring independently selected from phenylene, 3-8 membered saturated or partially unsaturated carbocyclylene, 5-6 membered heteroarylene having 1-4

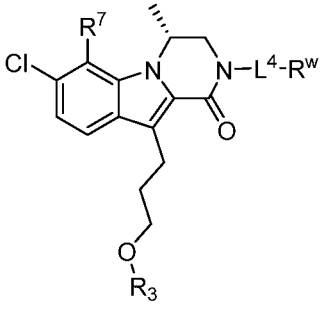
heteroatoms independently selected from nitrogen, oxygen, or sulfur, 3-8 membered saturated or partially unsaturated heterocyclylene having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an 8-10 membered bicyclic arylene or heteroarylene having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered saturated or partially unsaturated heterocyclylene having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; R^w is selected from hydrogen, R, −Cy'−R, −OR, −SR, −S(O)R, $-S(O)_2R$, $-S(O)_2N(R)_2$, $-N(R)_2$, $-C(O)N(R)_2$, −C(O)R, −N(R)C(O)R, −N(R)C(O)OR, $-N(R)C(O)N(R)_2$, $-N(R)S(O)_2R$, $-N(R)S(O)_2N(R)_2$, −C(O)OH, −C(O)OR, $-C(O)R^x$, $-S(O)_2OH$, or $-S(O)_2R^y$, or is selected from:



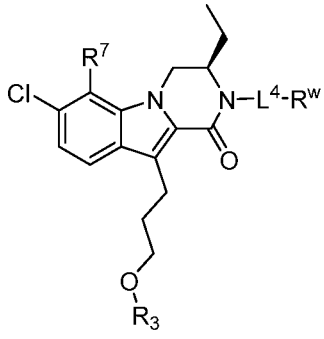
; R^x is selected from −C(O)OR, $-N(R)S(O)_2CF_3$, −N(R)C(O)R, −N(R)C(O)OR, $-N(R)C(O)N(R)_2$, or $-N(R)S(O)_2R$; R^y is selected from $-N(R)C(O)CF_3$, −N(R)C(O)R, or $-N(R)C(O)N(R)_2$; each R is independently selected from hydrogen or an optionally substituted group selected from C_{1-12} aliphatic or a ring selected from a 3-10 membered saturated or partially unsaturated carbocyclic ring, phenyl, a 6-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 3-8 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen or sulfur, an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen or sulfur, or a 12-15 membered tricyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen or sulfur; each of R^5, R^6, R^8, R^9, R^{10}, R^{11}, and R^{12} is independently selected from R, halogen, −CN, $-NO_2$, −C(O)OR', −OR', −SR', $-C(O)N(R')_2$ $-N(R')_2$, $-S(O)_2N(R')_2$, $-N(R')S(O)_2CF_3$, −C(O)R', −N(R')C(O)R', −S(O)R', $-S(O)_2R'$, −N(R')C(O)OR', and $-N(R')S(O)_2R'$; each R' is independently selected from hydrogen or optionally substituted C_{1-4} alkyl; and R^7 is selected from hydrogen, halogen, −CN, $-NO_2$, −C(O)OR, $-OCF_3$, −OR, −SR, $-S(O)_2OR$, $-P(O)(OH)_2$, $-C(O)N(R)_2$, $-N(R)_2$, $-S(O)_2N(R)_2$, $-N(R)S(O)_2CF_3$, $-C(O)N(R)S(O)_2R$, $-S(O)_2N(R)C(O)OR$,

$-S(O)_2N(R)C(O)N(R)_2$, $-C(O)R$, $-C(O)N(R)S(O)_2CF_3$, $-N(R)C(O)R$, $-OC(O)R$, $-OC(O)N(R)_2$, $-C(NR)N(R)_2$, $-N(R)C(NR)N(R)_2$, $-S(O)R$, $-S(O)_2R$, $-N(R)C(O)OR$, or $-N(R)S(O)_2R$, or an optionally substituted group selected from C_{1-6} aliphatic or a ring selected from a 3-8 membered saturated or partially unsaturated carbocyclic ring, phenyl, a 3-8 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an 8-14 membered bicyclic or polycyclic saturated, partially unsaturated or aryl ring, a 7-14 membered bicyclic or polycyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-14 membered bicyclic or polycyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

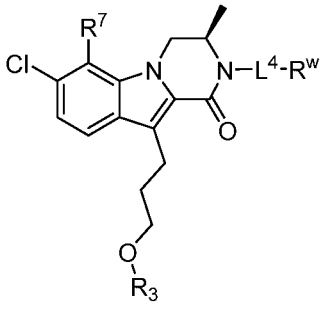
[0046] In certain embodiments, the compound of formula (I) has formula:



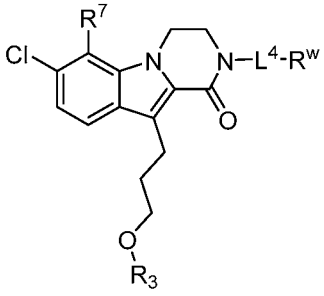
(I-a-1);



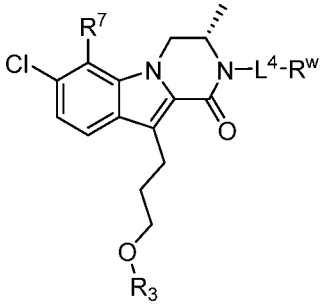
(I-a-2);



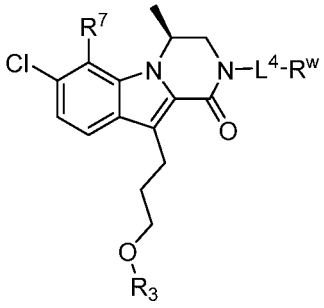
(I-a-3);



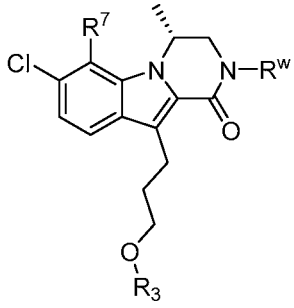
(I-a-4);

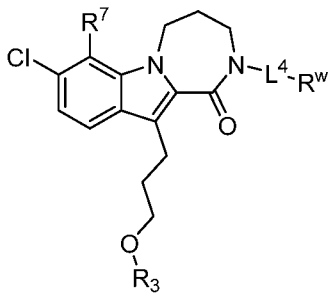


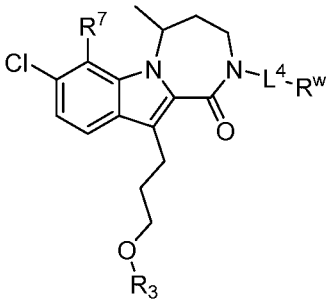
(I-a-5);

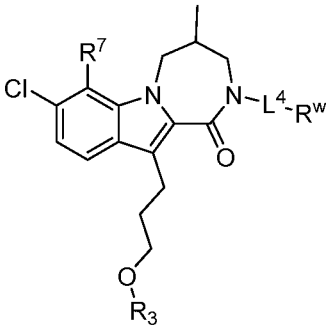


(I-a-6);

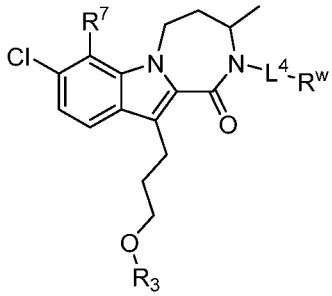



(I-a-7);


(I-b-1);

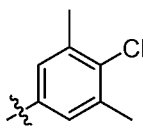

(I-b-2);

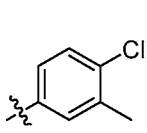
(I-b-3); or

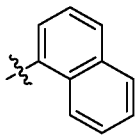

(I-b-4).

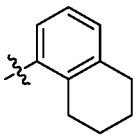
[0047] In certain embodiments, formula (I-a-1) is formula (I-a-7).

[0048] In certain embodiments, R^3 is selected from:

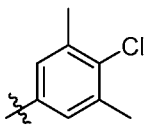

;

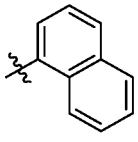

;


; and


.

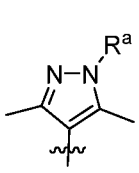
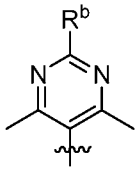
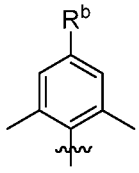
[0049] In certain embodiments, R^3 is selected from


; and

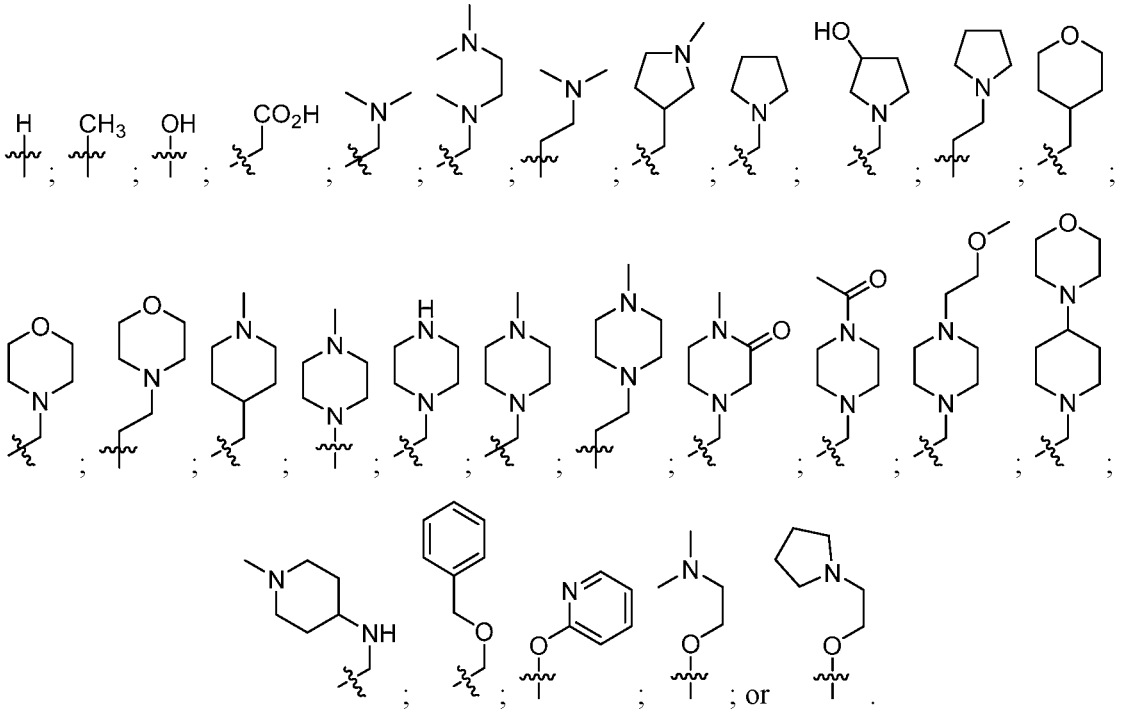

.

[0050] In certain embodiments, R^7 is an optionally substituted group selected from phenyl and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen. Exemplary optional substituents include, but are not limited to, halogen, oxo (=O), =S, cyano, nitro, fluoroalkyl, alkoxyfluoroalkyl, fluoroalkoxy, alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, heteroalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkylalkyl, cycloalkenylalkyl, heteroarylalkyl, arylalkyl, heterocyclylalkyl, hydroxy, hydroxyalkyl, alkoxy, alkylthio, alkoxyalkyl, alkylene, aryloxy, arylthio, phenoxy, benzyloxy, amino, alkylamino, dialkylamino, acylamino, aminoalkyl, arylamino,

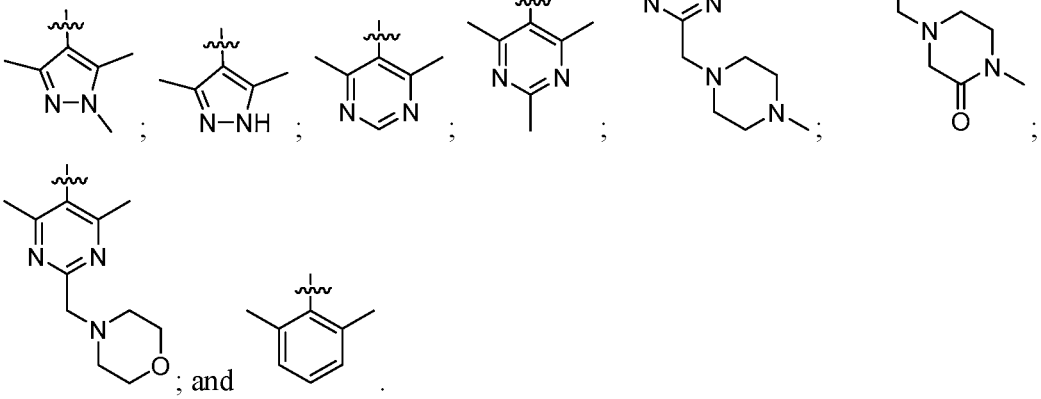
diarylamino, sulfonylamino, sulfinylamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, sulfinyl, -COOH, ketone, alkoxycarbonyl, aryloxycarbonyl, amide, carbamate, acyl, boronic acid, and boronic ester.

[0051] In certain embodiments, R^7 is  ;  ; or  ; and R^a and R^b are each independently hydrogen, hydroxy, alkyl, heteroalkyl, heterocyclyl, or heterocyclylalkyl, wherein said alkyl, heteroalkyl, heterocyclyl, and heterocyclylalkyl are independently substituted by 0, 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of halogen, oxo (=O), =S, cyano, nitro, fluoroalkyl, alkoxyfluoroalkyl, fluoroalkoxy, alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, heteroalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkylalkyl, cycloalkenylalkyl, heteroarylalkyl, arylalkyl, heterocyclylalkyl, hydroxy, hydroxyalkyl, alkoxy, alkylthio, alkoxyalkyl, alkylene, aryloxy, arylthio, phenoxy, benzyloxy, amino, alkylamino, dialkylamino, acylamino, aminoalkyl, arylamino, diarylamino, sulfonylamino, sulfinylamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, sulfinyl, -COOH, ketone, alkoxycarbonyl, aryloxycarbonyl, amide, carbamate, acyl, boronic acid, and boronic ester.

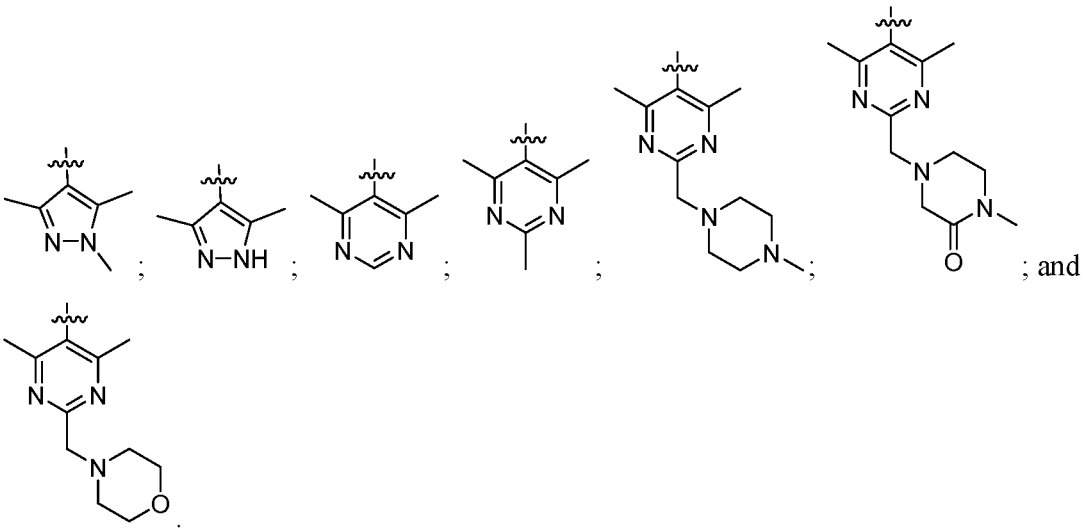
[0052] In certain embodiments, R^a and R^b are selected from:



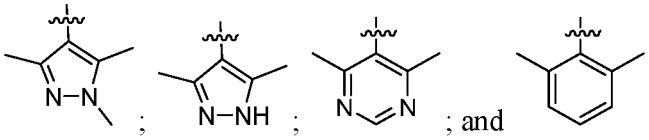
[0053] In certain embodiments, R^7 is selected from:


; and

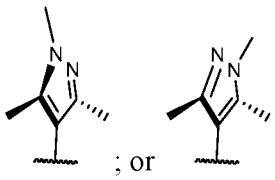
[0054] In certain embodiments, R^7 is selected from:


; and

[0055] In certain embodiments, R^7 is selected from:


; and

[0056] In certain embodiments, R^7 is

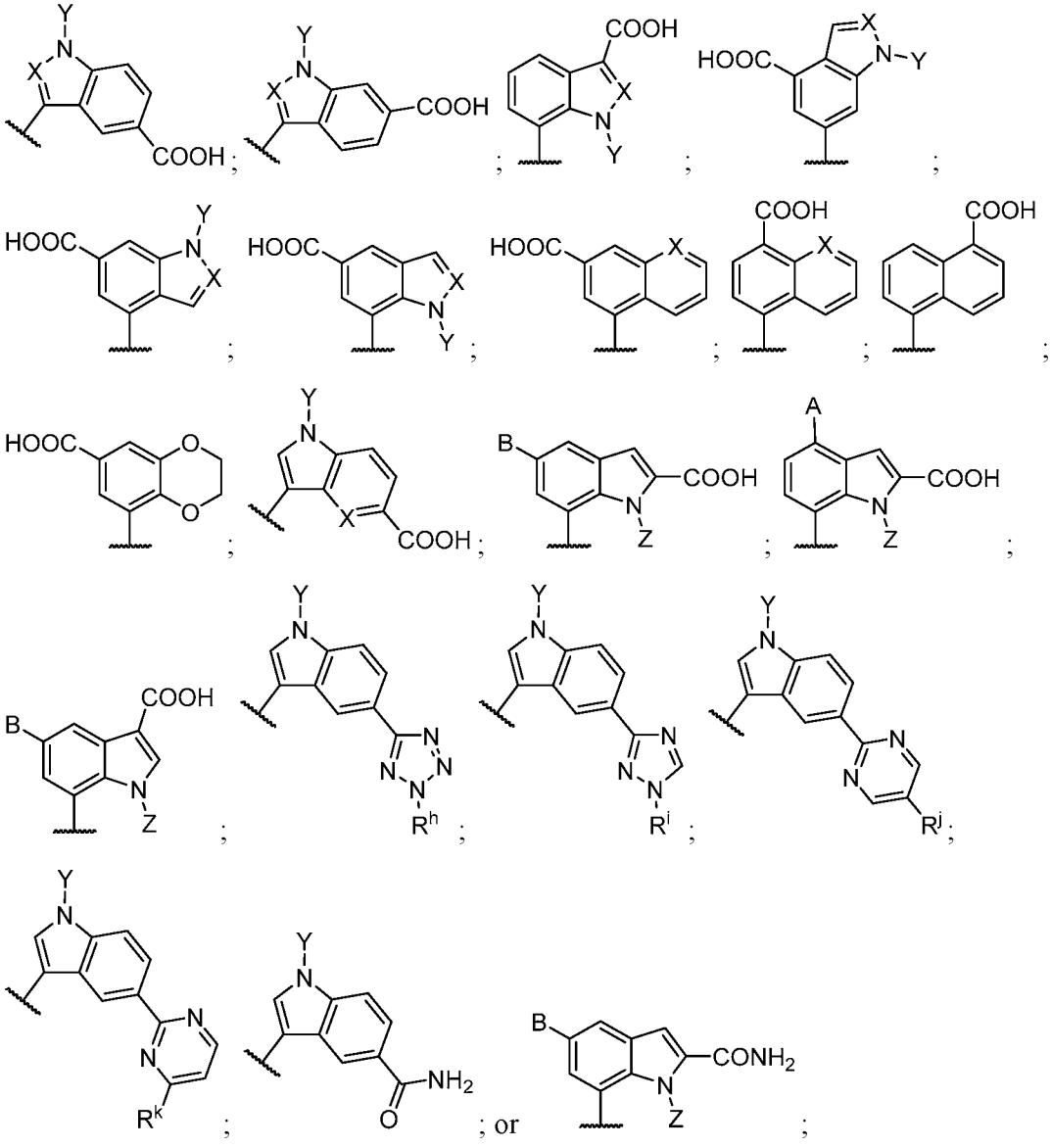

; or

[0057] In certain embodiments, L^4-R^w is an optionally substituted 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, an optionally substituted 8-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms

independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

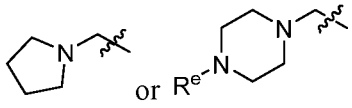
[0058] In other embodiments, L^4-R^w is an optionally substituted 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, an optionally substituted 8-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 1,2,3,4-tetrahydropyrazino[1,2-a]indole, or an optionally substituted 3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole.

[0059] In certain embodiments, L^4-R^w is



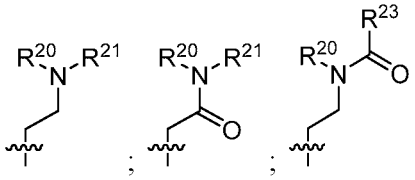
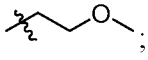
wherein

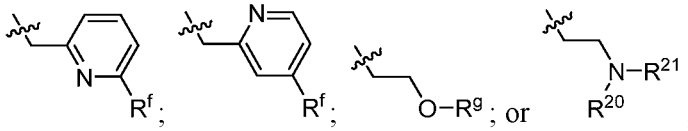
A and B are each independently hydrogen, halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, halogen, $-OR^c$, $-CH_2OR^d$,



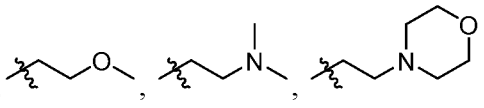
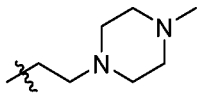
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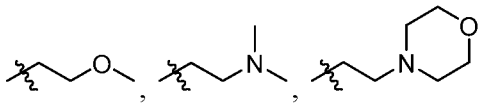
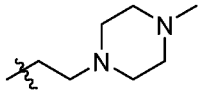
X is C(H), C(C_1-C_4-alkyl), C(C_1-C_4-haloalkyl) or N;

Y is hydrogen, C_1-C_4-alkyl,  ; or  ;

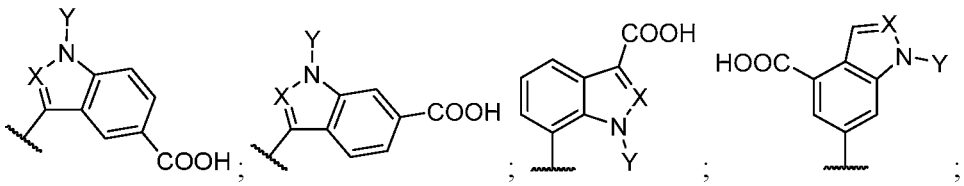
Z is  ;

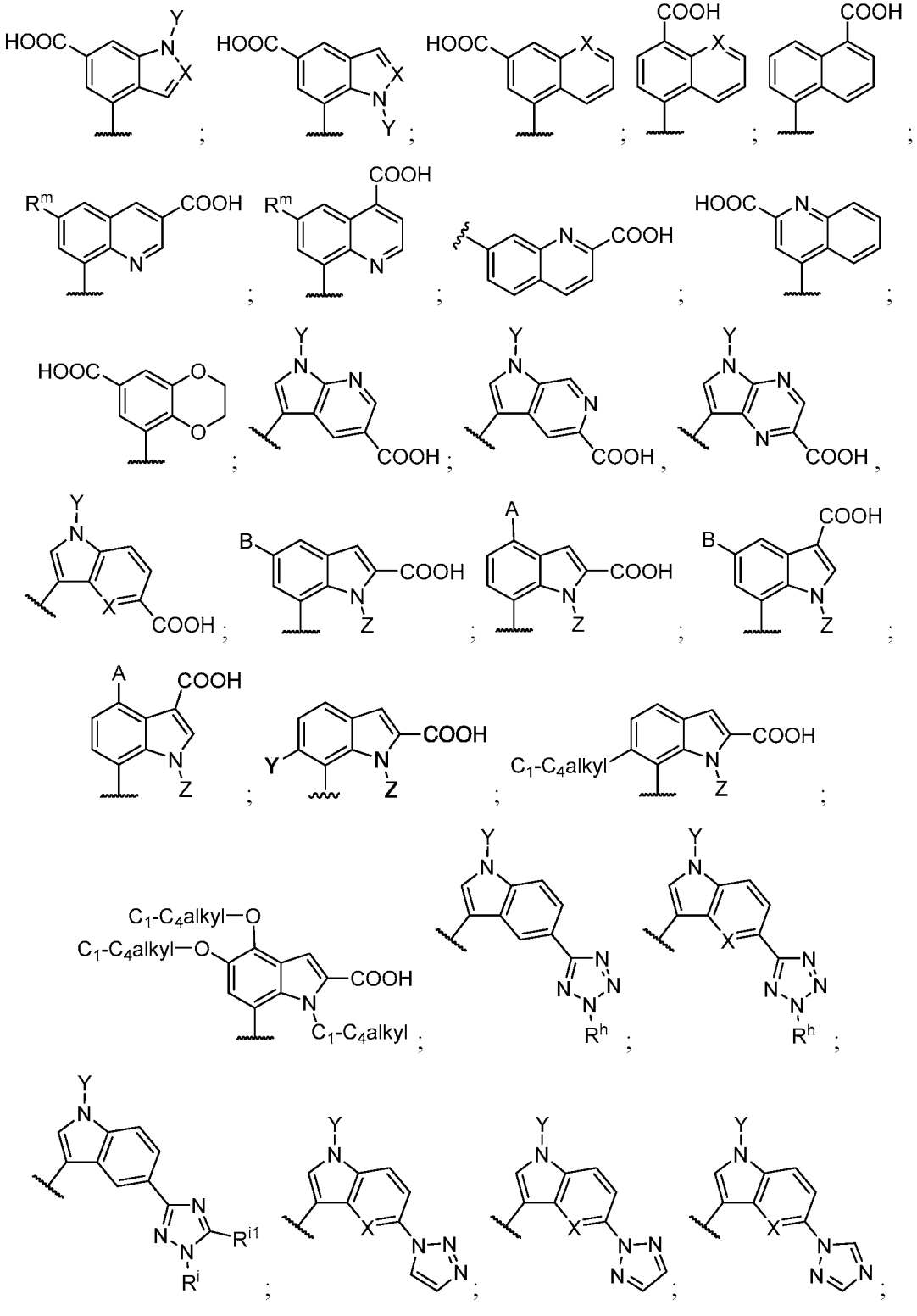
R^{20} and R^{21} are each independently hydrogen or C_1-C_4-alkyl, or R^{20} and R^{21} together with the nitrogen to which they are attached can form an optionally substituted 4-8 membered heterocyclic ring;

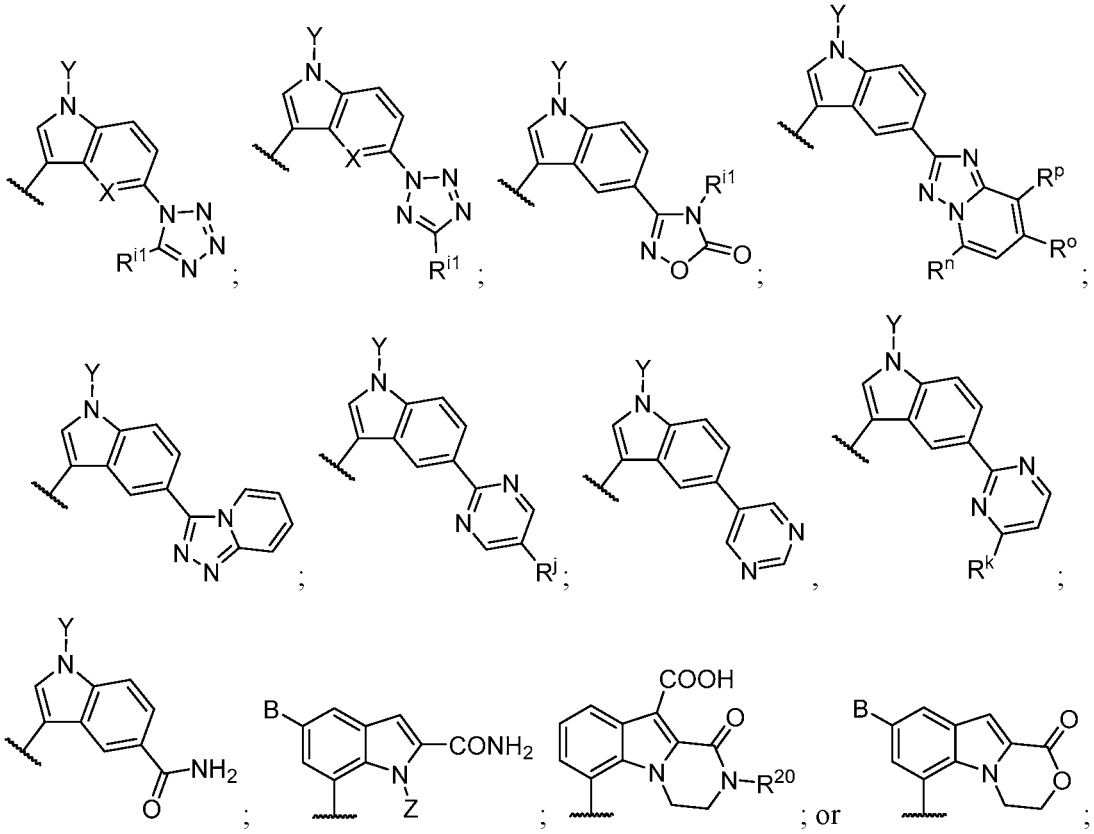
R^c is C_1-C_4-alkyl, C_2-C_4-alkenyl,  , or  ;

R^d is C_1-C_4-alkyl; R^e is C_1-C_4-alkyl; R^f is C_1-C_4-alkyl, C_2-C_4-alkenyl, or cyano; R^g is C_1-C_4-alkyl; R^h is C_1-C_4-alkyl; R^i is C_1-C_4-alkyl,  , or  ; R^j is C_1-C_4-alkyl or C_1-C_4-alkoxy; and R^k is C_1-C_4-alkyl.

[0060] In certain embodiments, L^4-R^w is

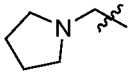


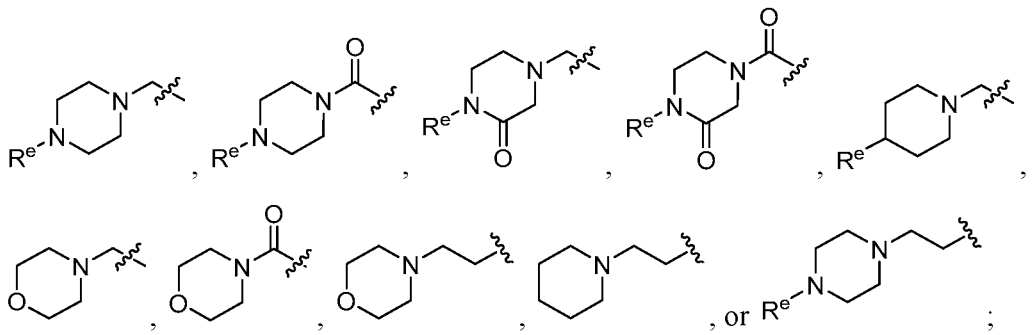




wherein

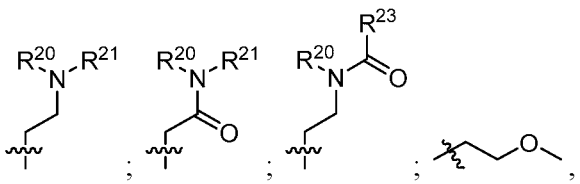
A and B are each independently hydrogen, halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, halogen, -OR^c, -CH_2OR^c, $CH_2CH_2OC_1$-C_4alkyl, –$NHC(O)R^i$, –$N(C_1$-C_4alkyl)$C(O)R^i$, –NR^cR^c, $CH_2N(R^c)_2$, $CH_2CH_2N(R^c)_2$, COOH,

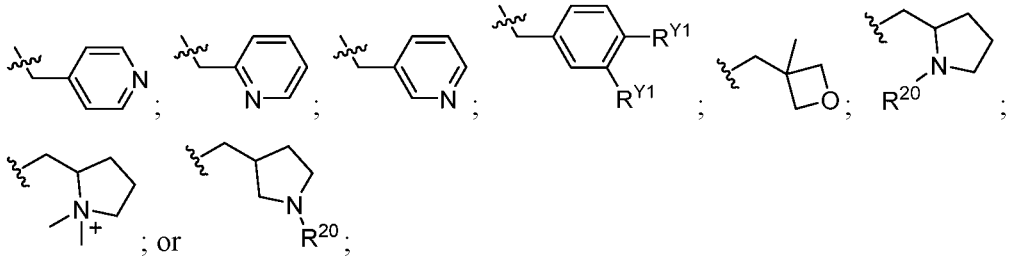




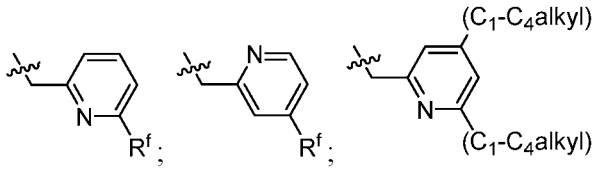
X is C(H), C(C_1-C_4-alkyl), C(C_1-C_4-haloalkyl) or N;

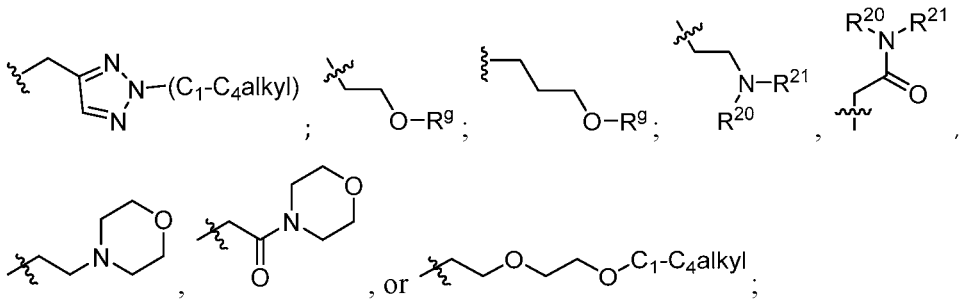
Y is hydrogen, C_1-C_4-alkyl,



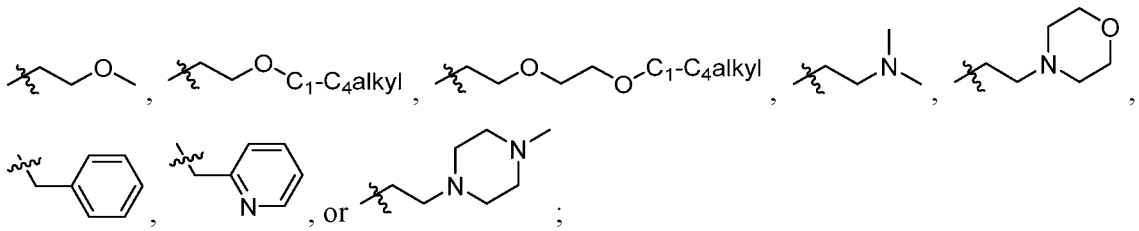


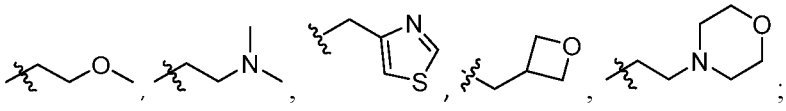
R^{Y1}, at each occurrence, is independently a halogen;

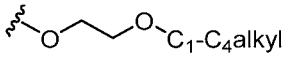
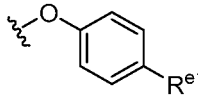
Z is C_1-C_4-alkyl 

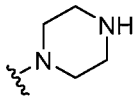
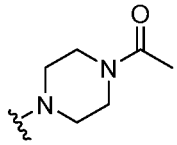
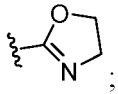


R^{20} and R^{21} are each independently hydrogen or C_1-C_4-alkyl, or R^{20} and R^{21} together with the nitrogen to which they are attached can form an optionally substituted 4-8 membered heterocyclic ring;

R^c, at each occurrence, is independently hydrogen, C_1-C_4-alkyl, C_2-C_4-alkenyl, 

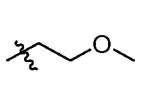
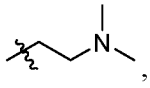
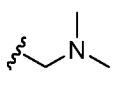
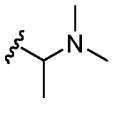
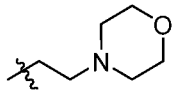
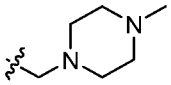
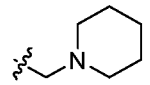
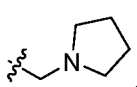
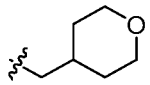
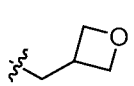
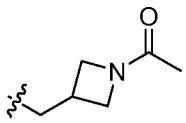
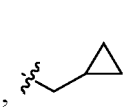
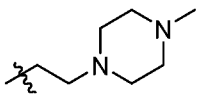
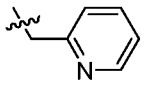
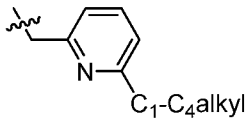
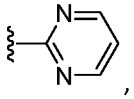
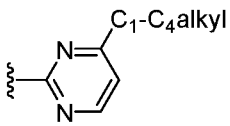
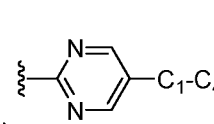
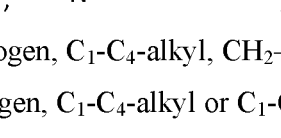
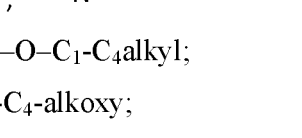
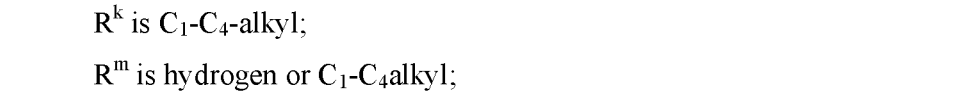
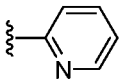
R^d is C_1-C_4-alkyl 

R^e is C_1-C_4-alkyl, $-OC_1$-C_4-alkyl,  $C(O)C_1$-C_4alkyl, or  , where R^{e1} is halogen;

R^f is hydrogen, C_1-C_4-alkyl, C_2-C_4-alkenyl, cyano,  ,  , or  ;

R^g is hydrogen or C_1-C_4-alkyl;

R^h is hydrogen or C_1-C_4-alkyl;

R^i is hydrogen, C_1-C_4-alkyl,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  ;

R^{i1} is hydrogen, C_1-C_4-alkyl, CH_2–O–C_1-C_4alkyl;

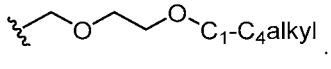
R^j is hydrogen, C_1-C_4-alkyl or C_1-C_4-alkoxy;

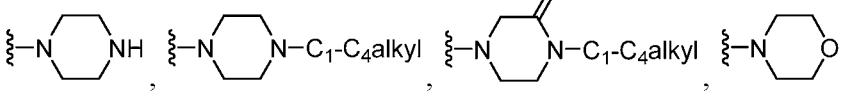
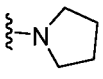
R^k is C_1-C_4-alkyl;

R^m is hydrogen or C_1-C_4alkyl;

R^n is hydrogen or C_1-C_4alkyl;

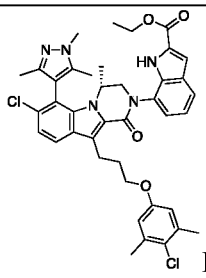
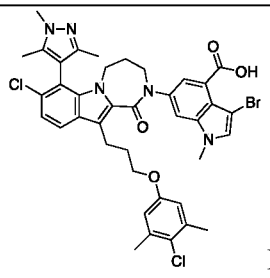
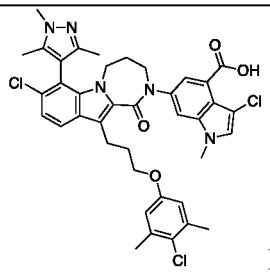
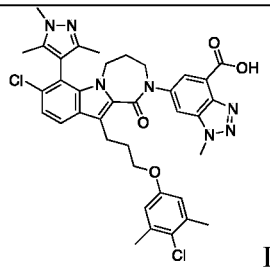
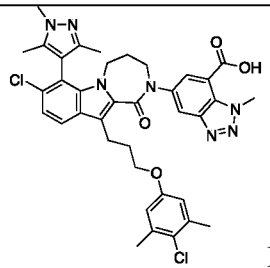
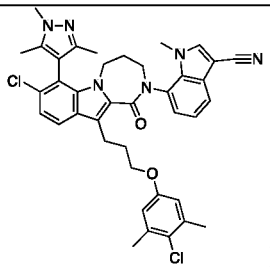
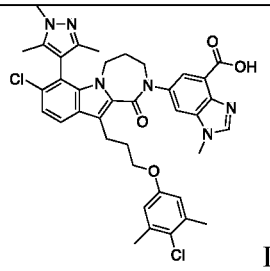
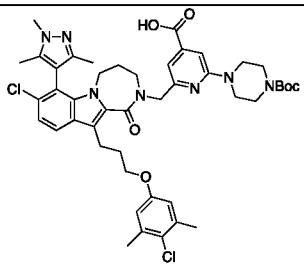
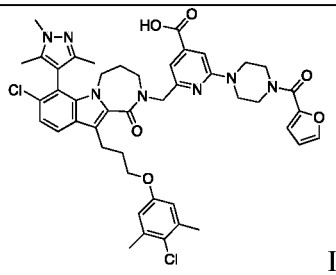
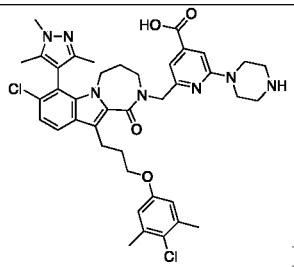
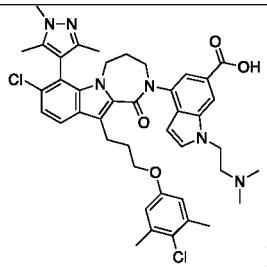
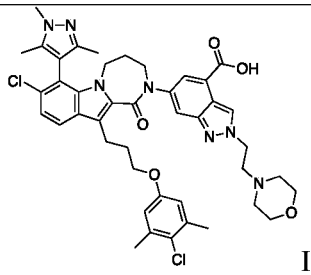
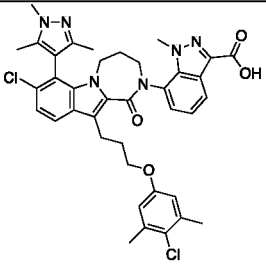
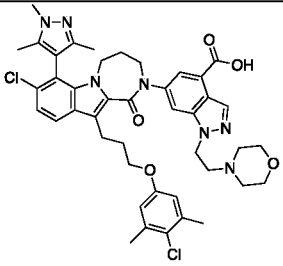
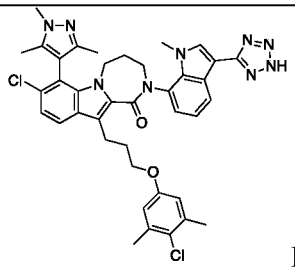
R^o is hydrogen or C_1-C_4alkyl; and

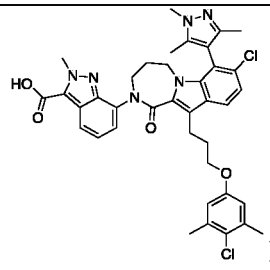
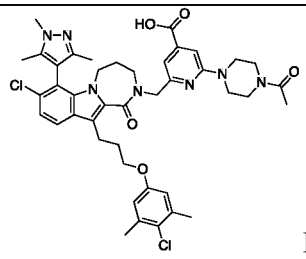
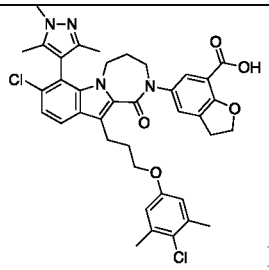
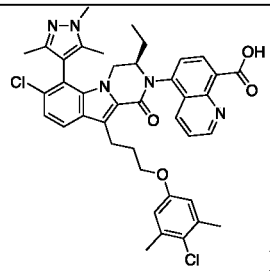
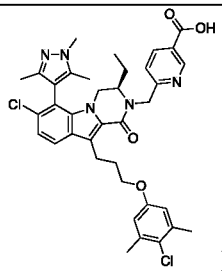
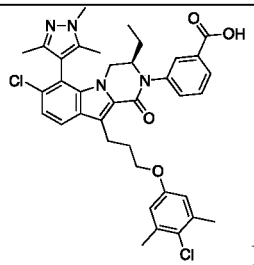
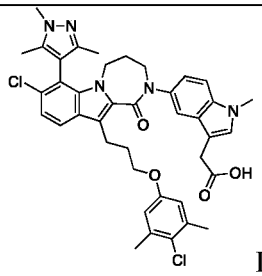
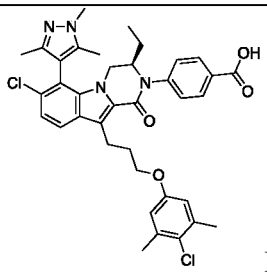
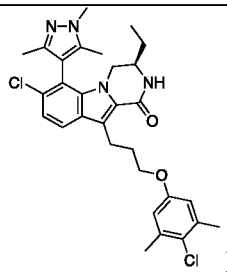
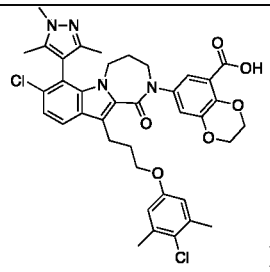
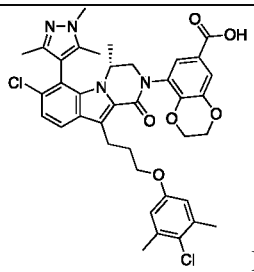
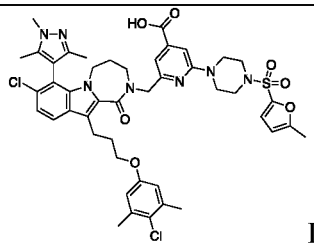
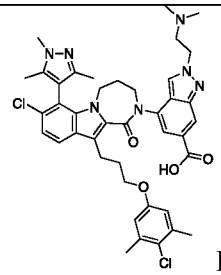
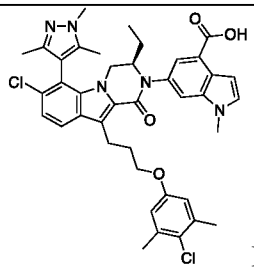
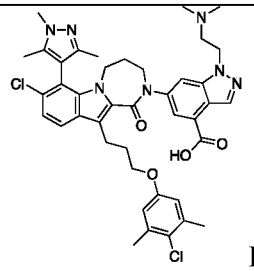
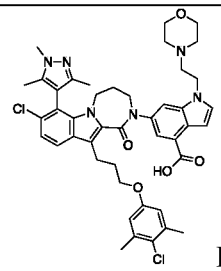
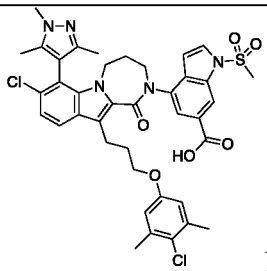
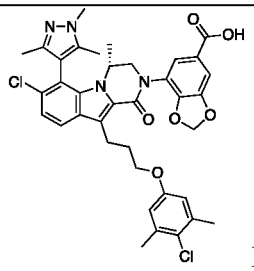
R^p is hydrogen, C_1-C_4alkyl, CH_2OC_1-C_4alkyl, or  .

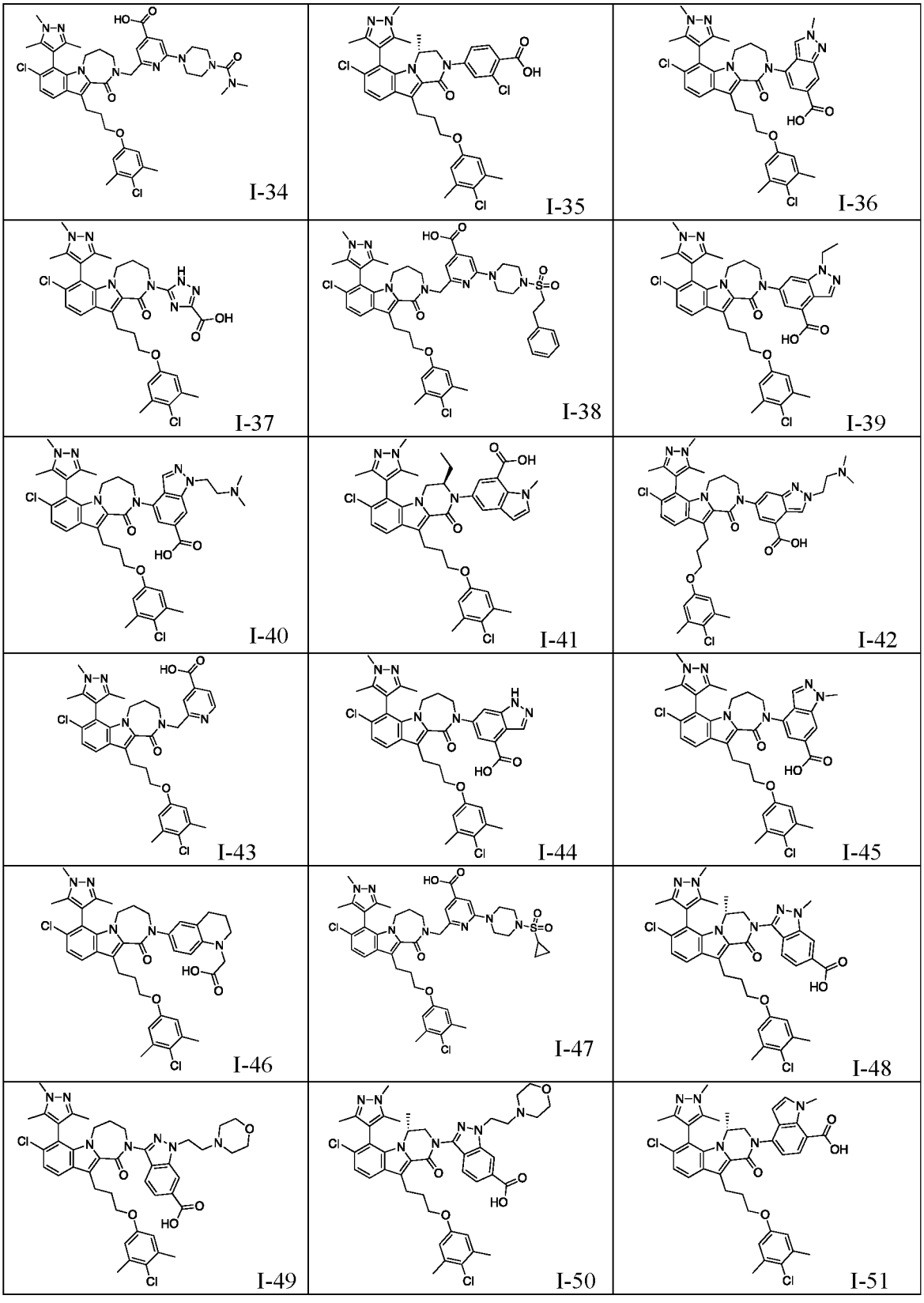
[0061] In certain embodiments, the optionally substituted 4-8 membered heterocyclic ring formed by R^{20} and R^{21} together with the nitrogen to which they are attached is selected from the group consisting of  , and  .

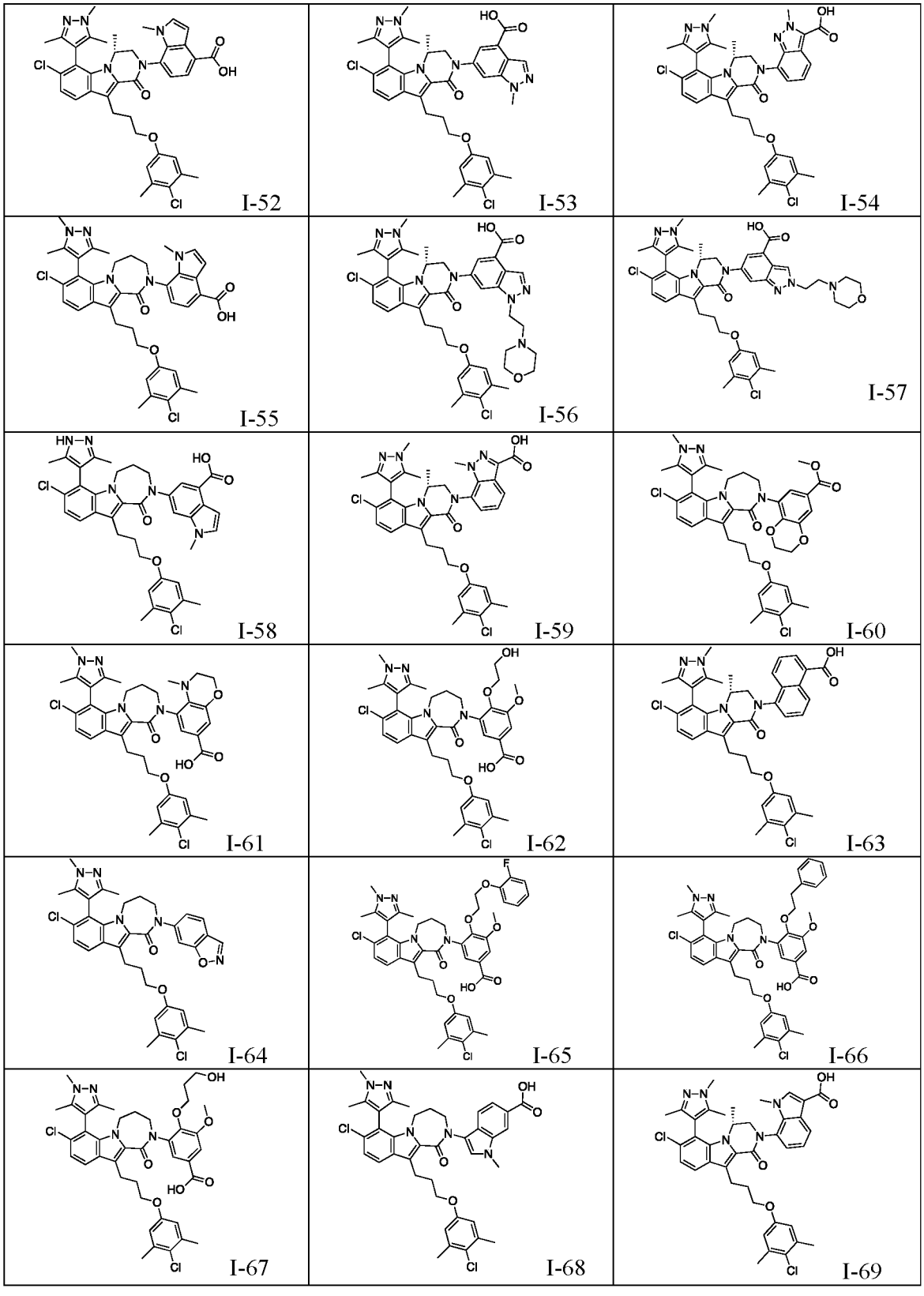
[0062] In certain embodiments, the compound of formula (I) is selected from the group consisting of the compounds in Table 1, or a pharmaceutically acceptable salt thereof.

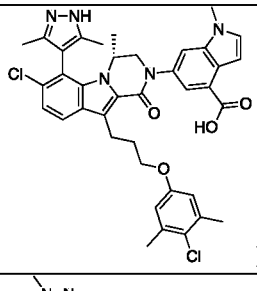
Table 1. Exemplary compounds.

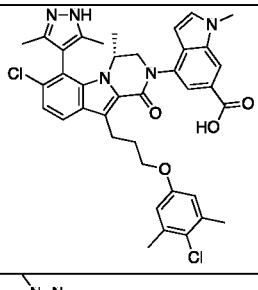
 I-1	 I-2	 I-3
 I-4	 I-5	 I-6
 I-7	 I-8	 I-9
 I-10	 I-11	 I-12
 I-13	 I-14	 I-15

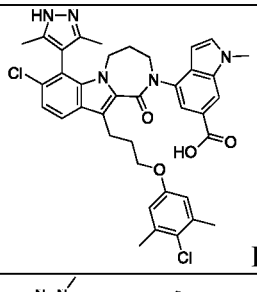
 I-16	 I-17	 I-18
 I-19	 I-20	 I-21
 I-22	 I-23	 I-24
 I-25	 I-26	 I-27
 I-28	 I-29	 I-30
 I-31	 I-32	 I-33

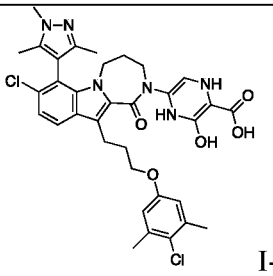

I-34
I-35
I-36
I-37
I-38
I-39
I-40
I-41
I-42
I-43
I-44
I-45
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I-47
I-48
I-49
I-50
I-51

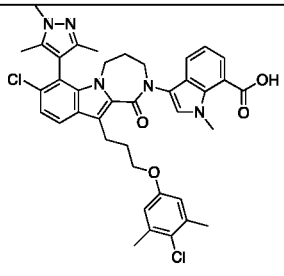

I-52
I-53
I-54
I-55
I-56
I-57
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I-60
I-61
I-62
I-63
I-64
I-65
I-66
I-67
I-68
I-69

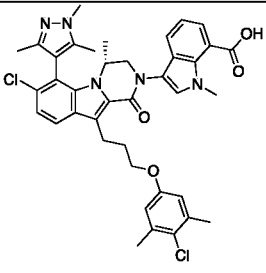

I-70

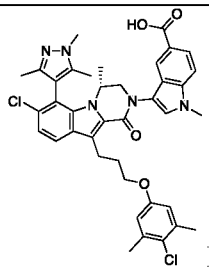

I-71

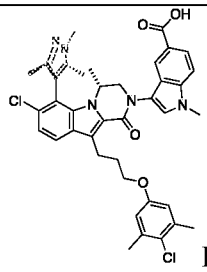

I-72

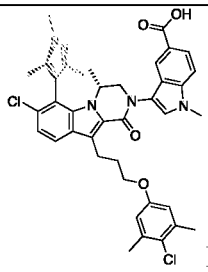

I-73

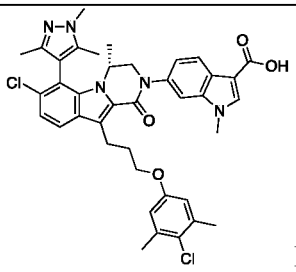

I-74

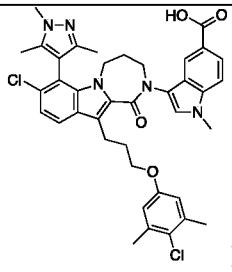

I-75

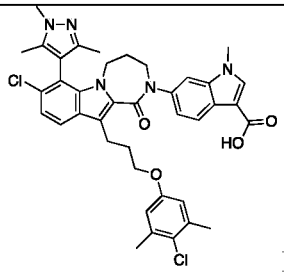

I-76

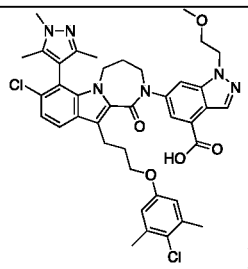

I-77

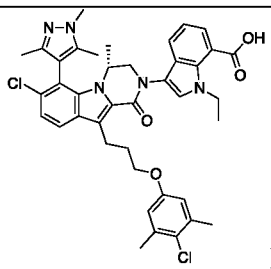

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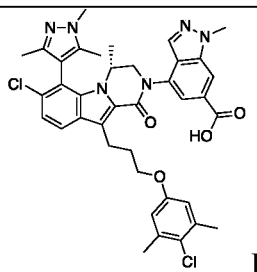

I-79

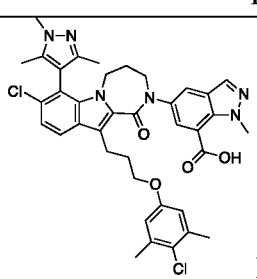

I-80

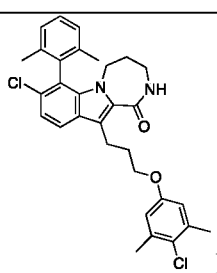

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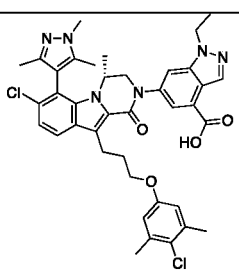

I-82

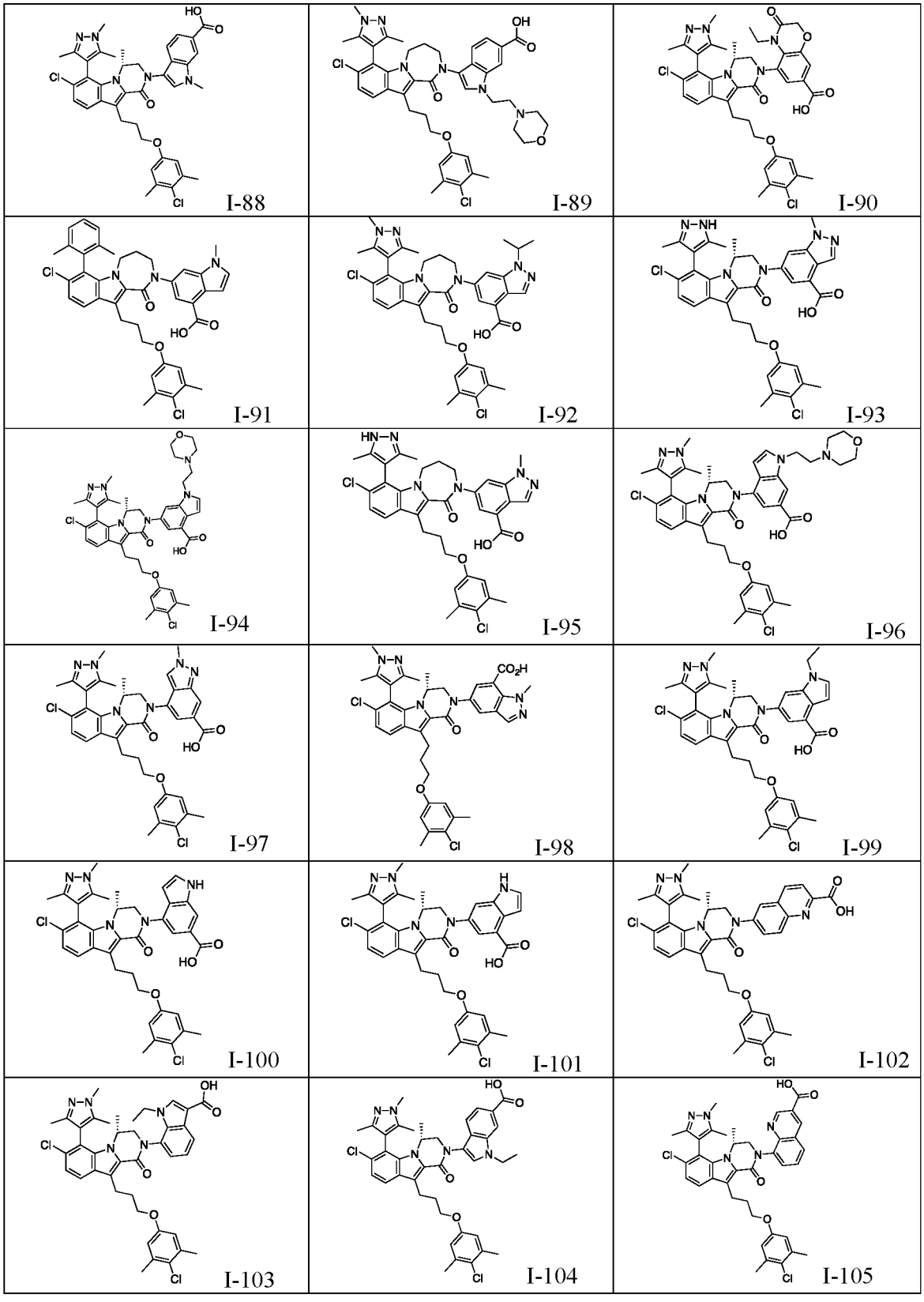

I-83

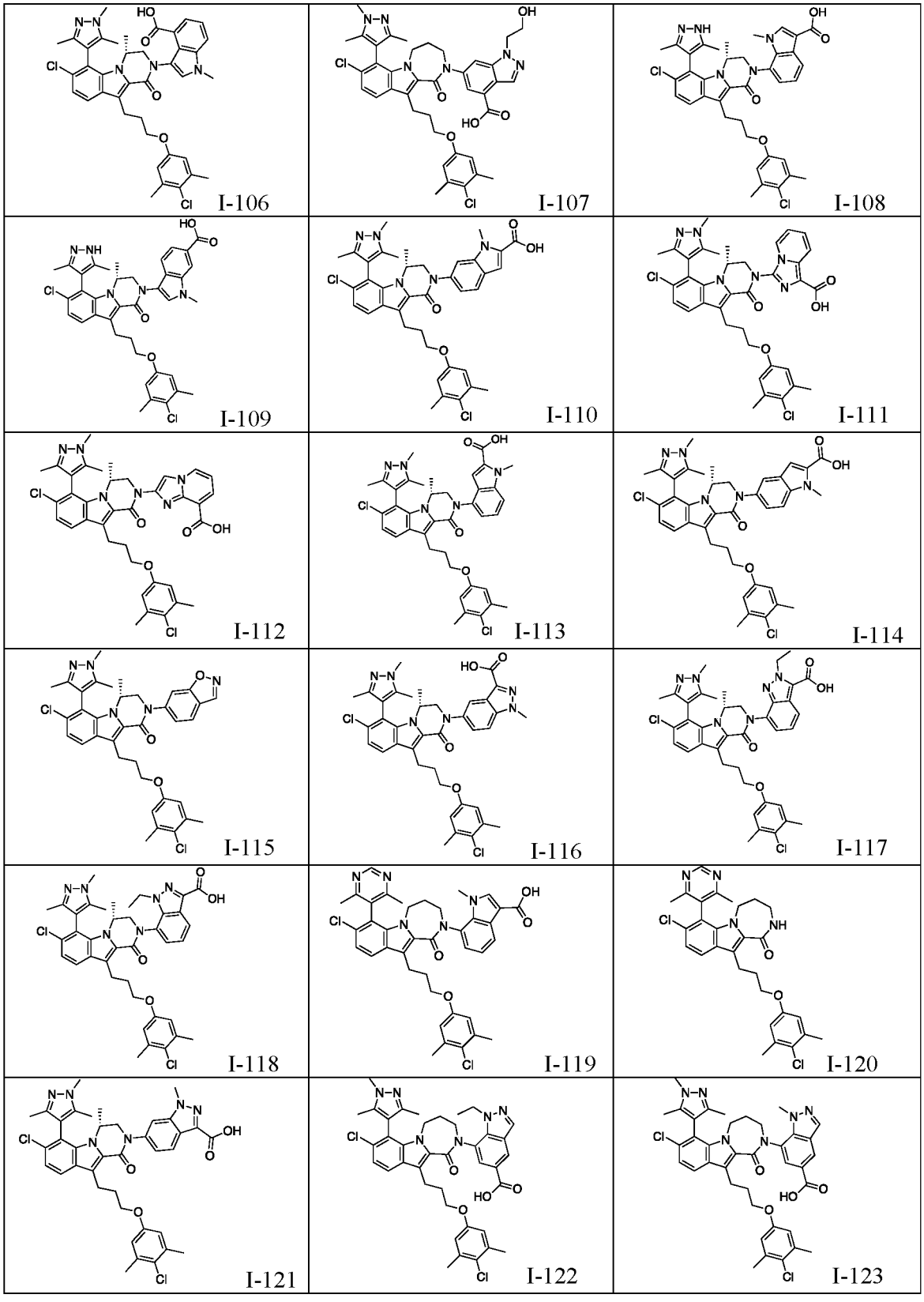

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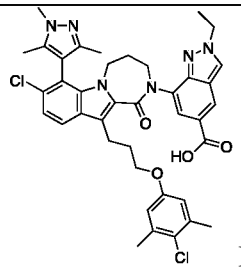
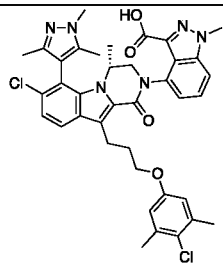
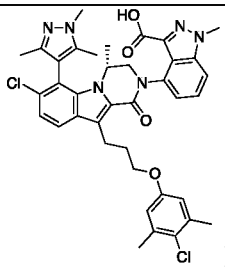
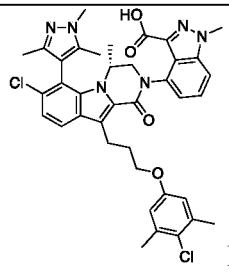
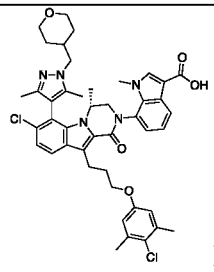
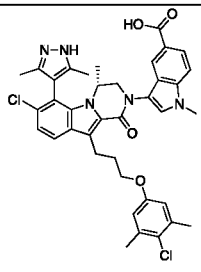
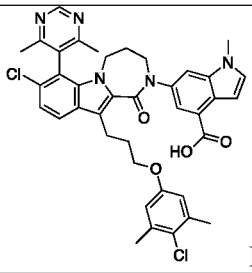
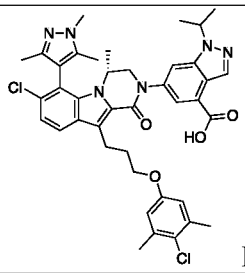
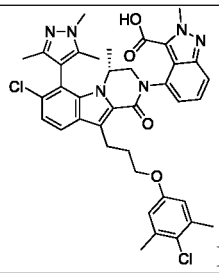
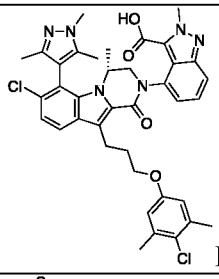
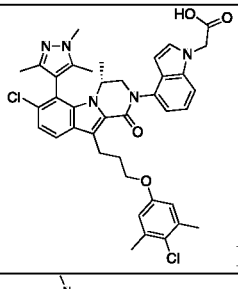
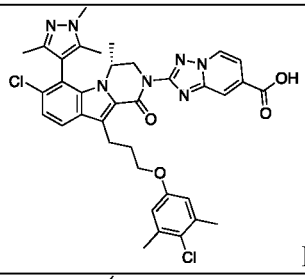
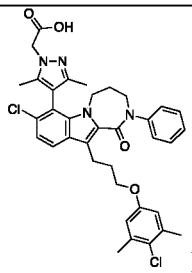
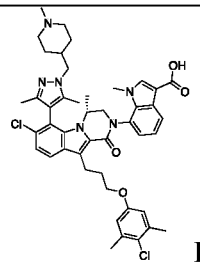
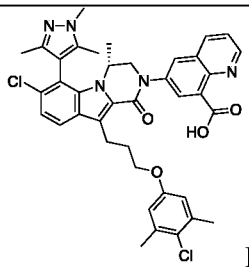
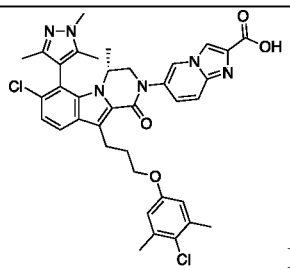
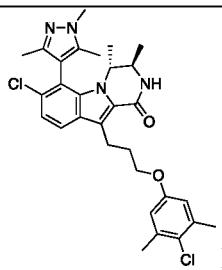
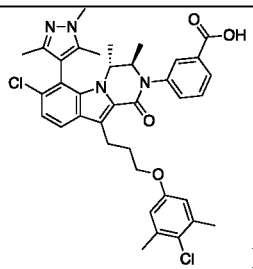

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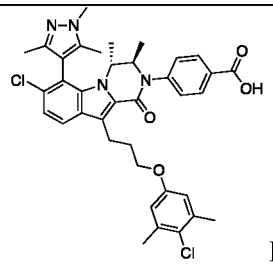
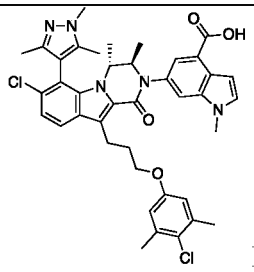
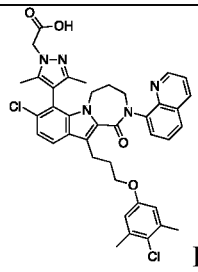
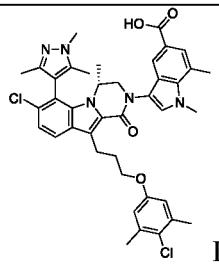
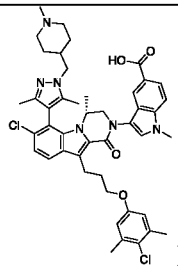
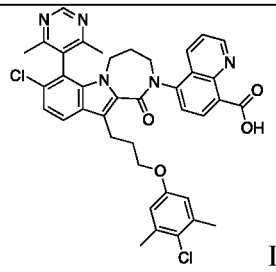
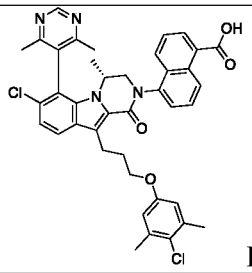
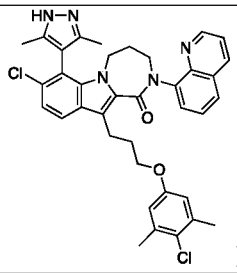
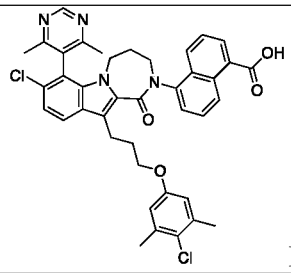
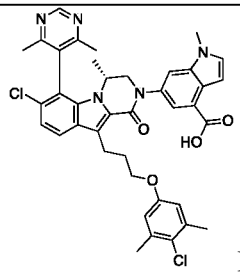
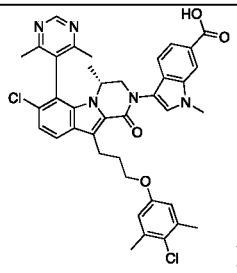
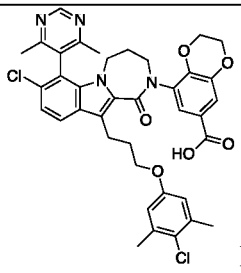
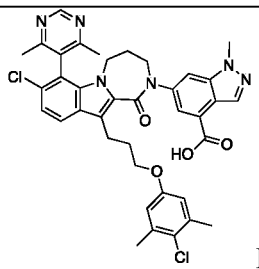
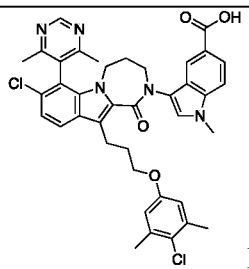
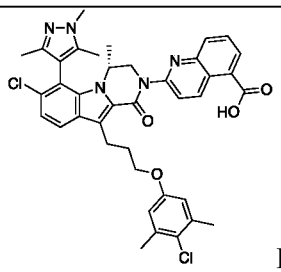
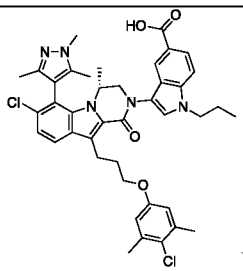
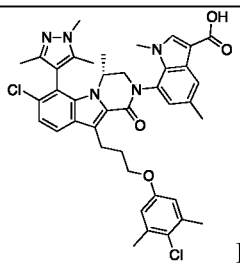
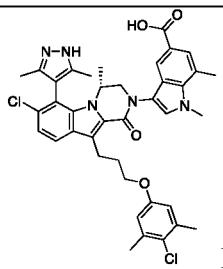

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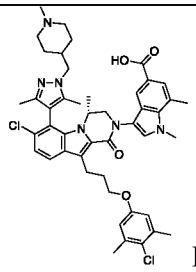
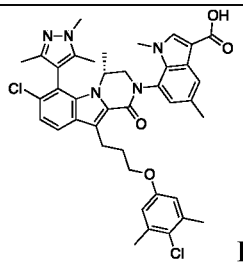
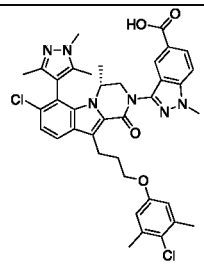
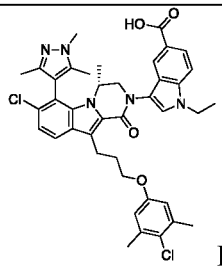
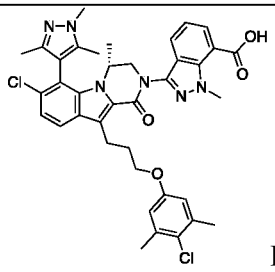
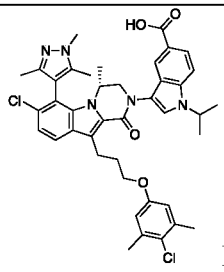
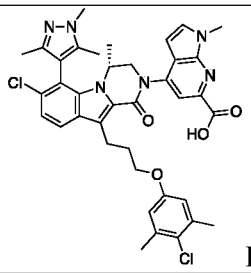
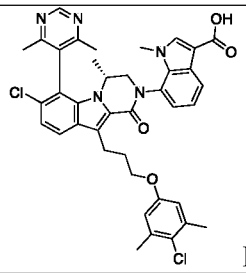
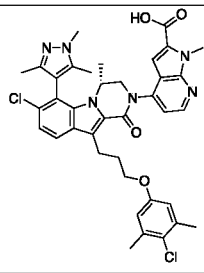
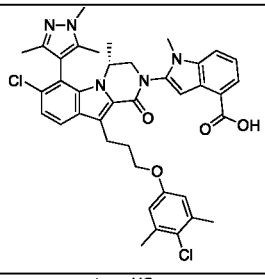
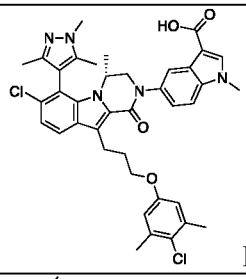
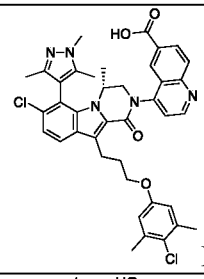
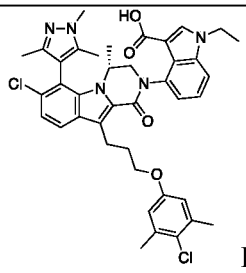
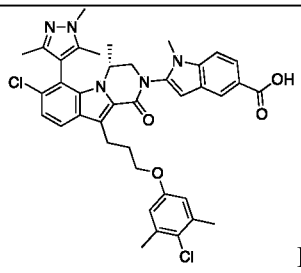
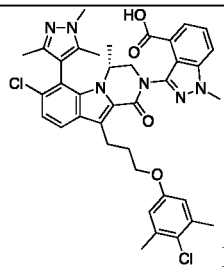
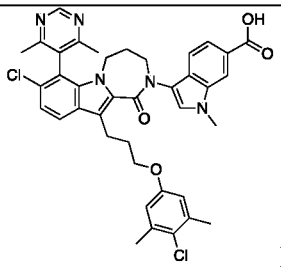
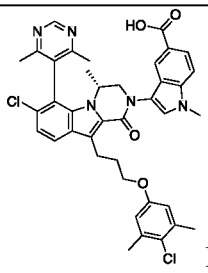
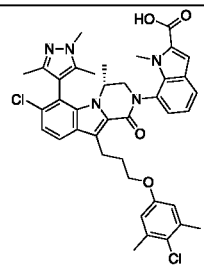

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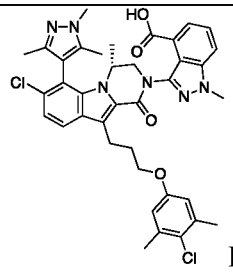
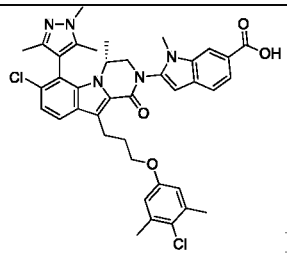
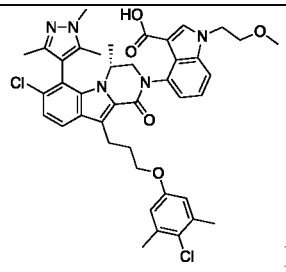
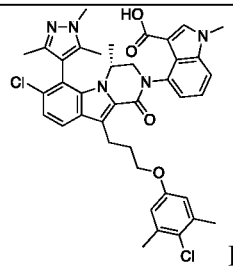
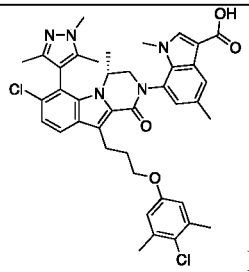
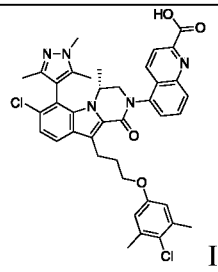
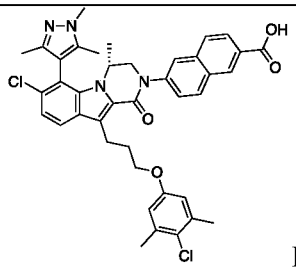
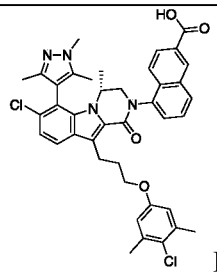
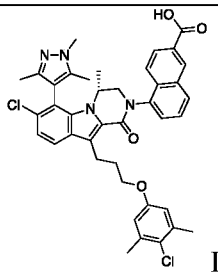
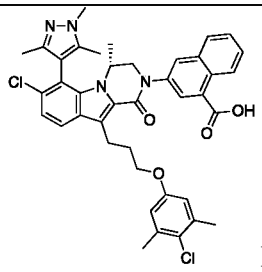
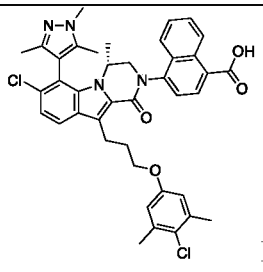
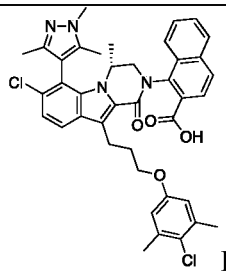
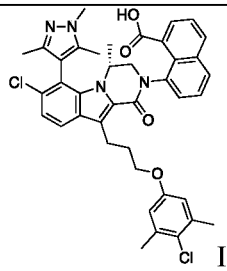
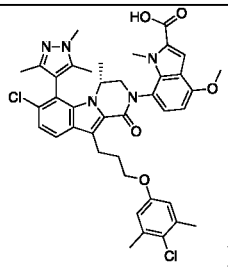
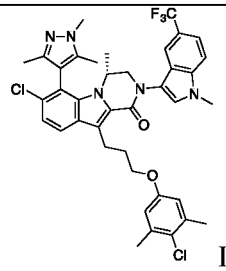
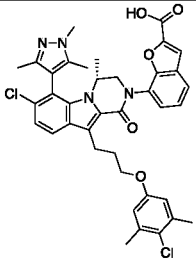
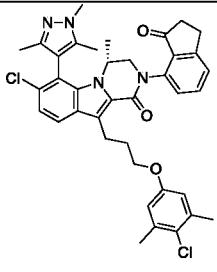
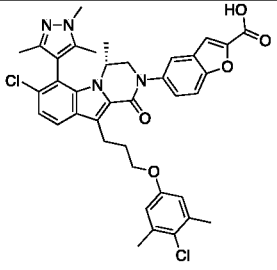

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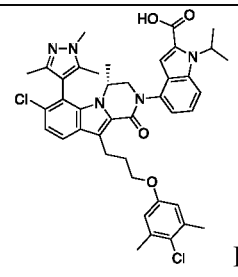
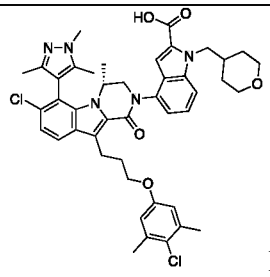
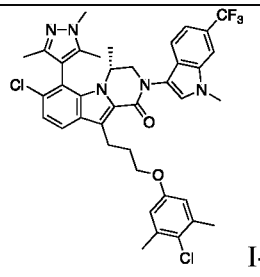
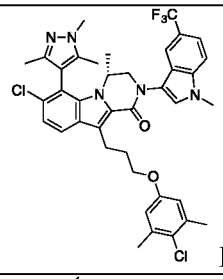
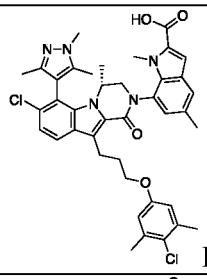
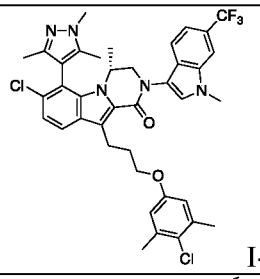
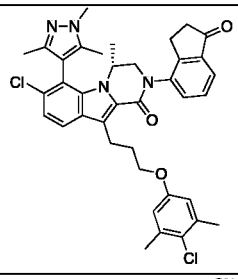
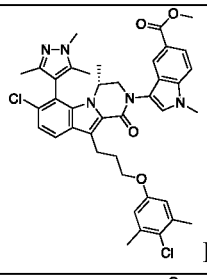
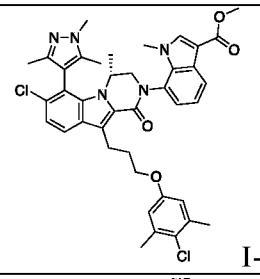
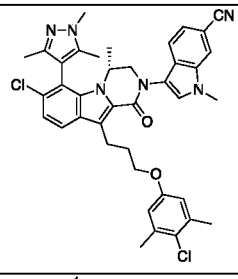
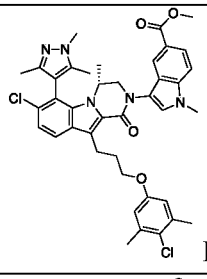
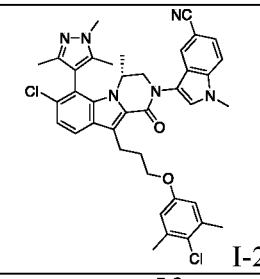
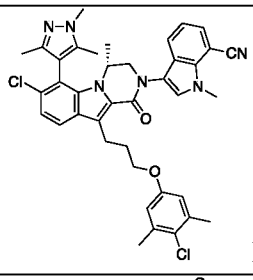
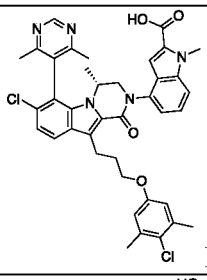
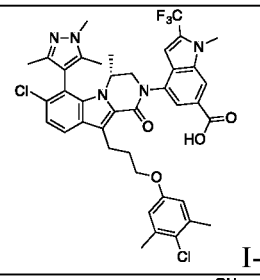
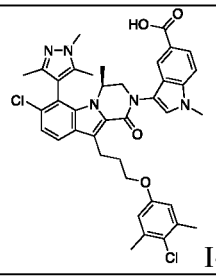
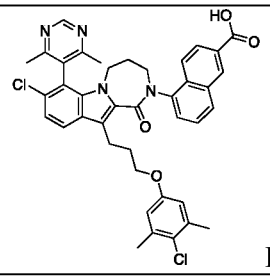
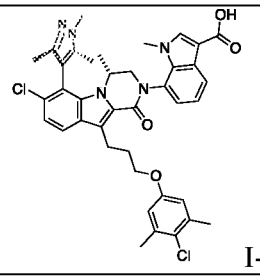

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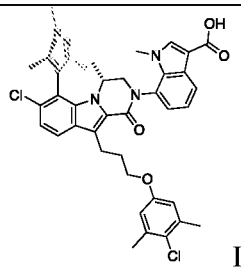
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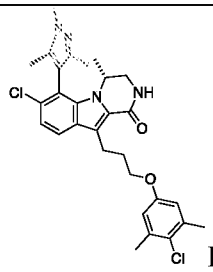
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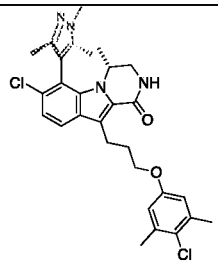
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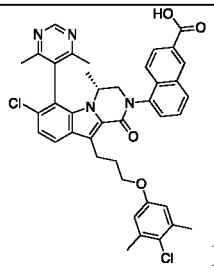
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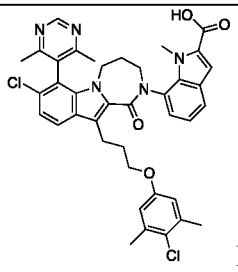
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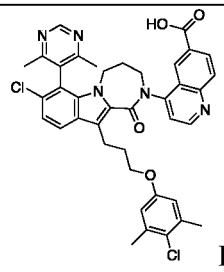

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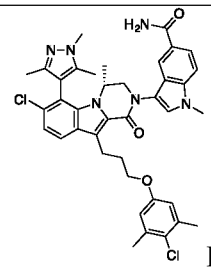

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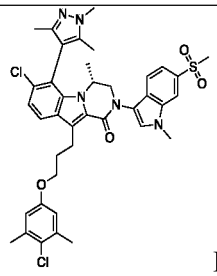

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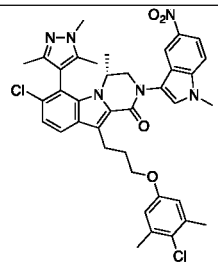

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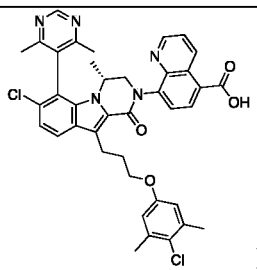

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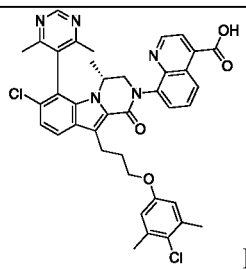

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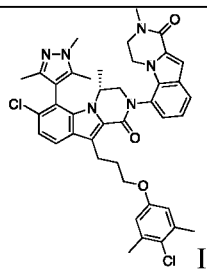

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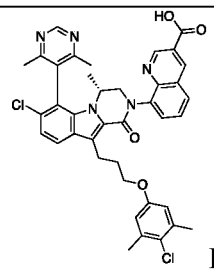

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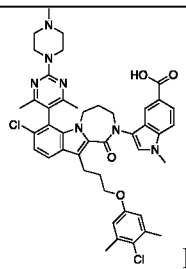

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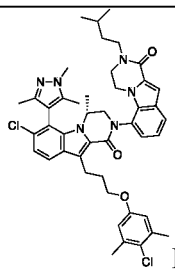

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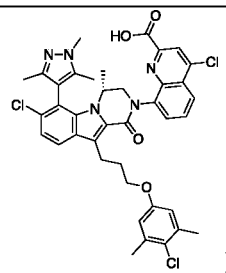

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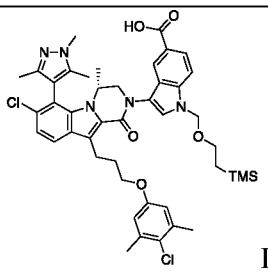

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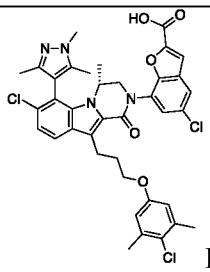

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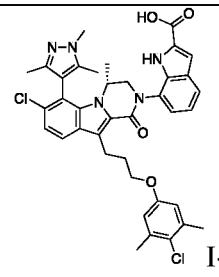
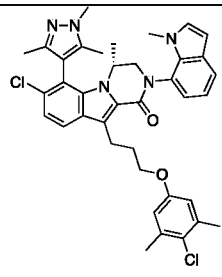
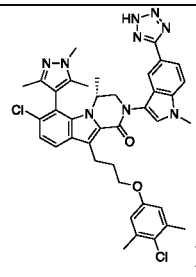
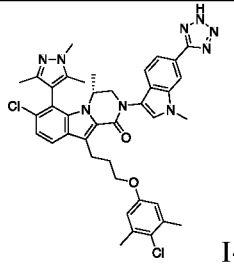
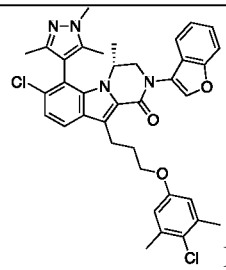
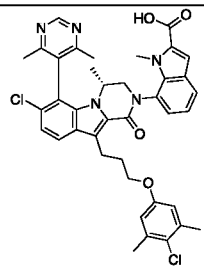
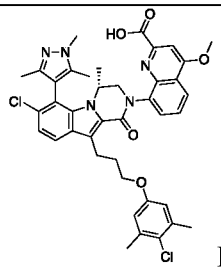
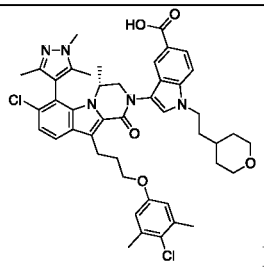
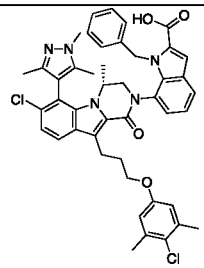
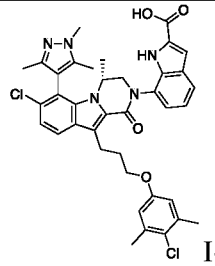
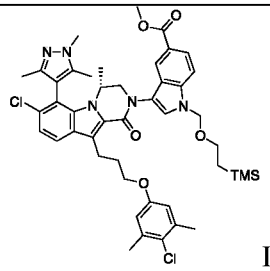
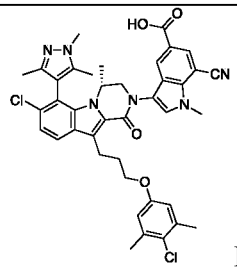
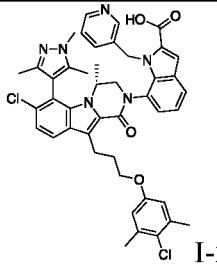
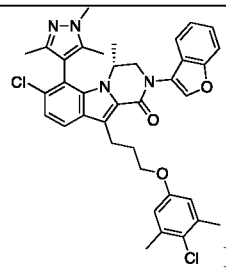
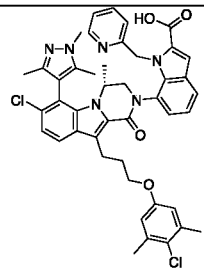
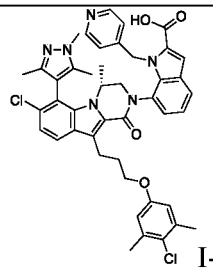
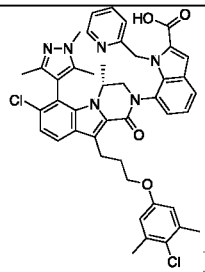
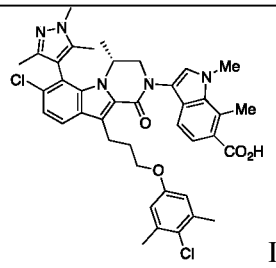

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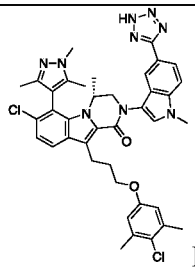
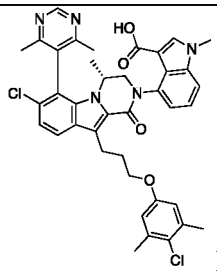
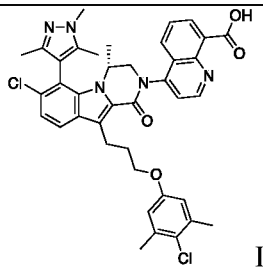
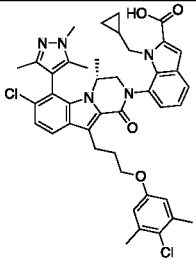
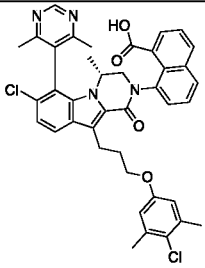
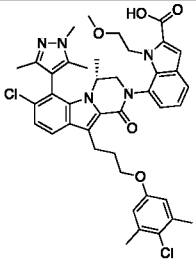
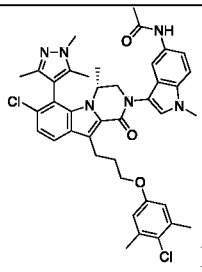
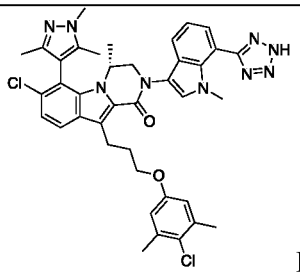
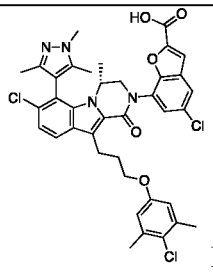
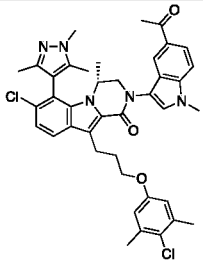
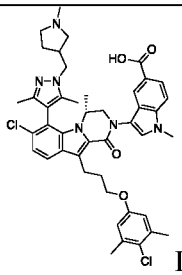
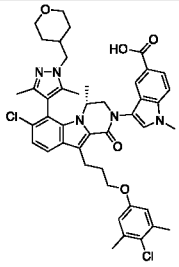
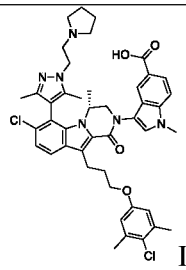
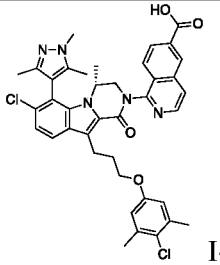
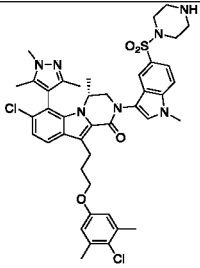
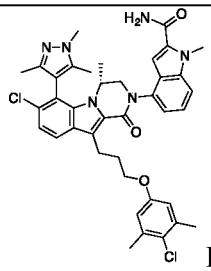
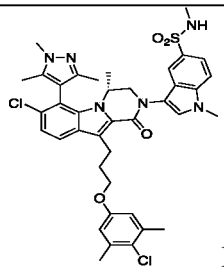
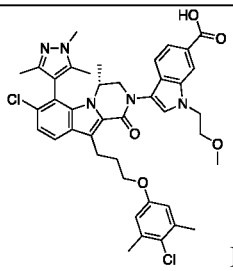

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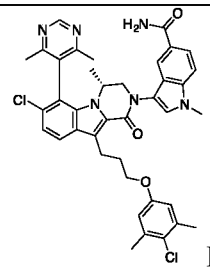
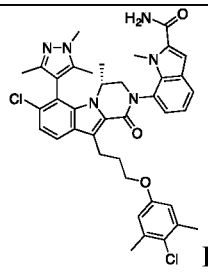
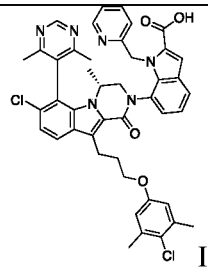
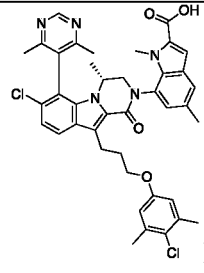
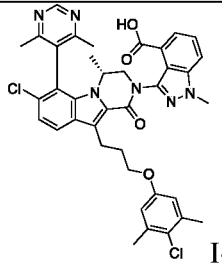
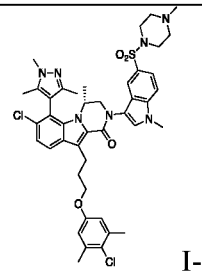
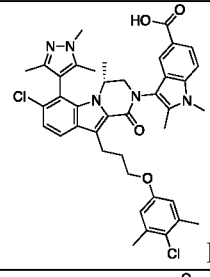
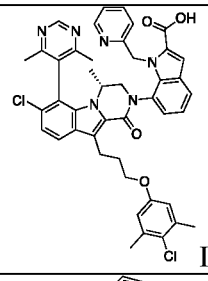
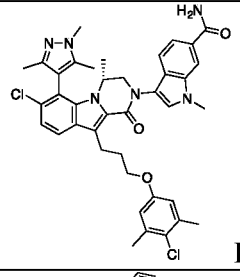
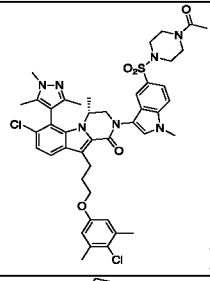
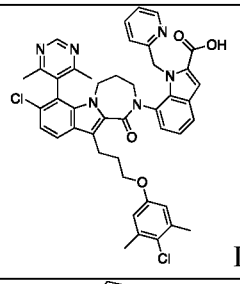
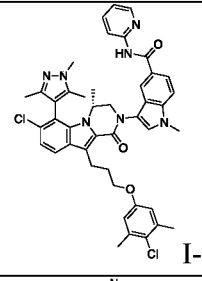
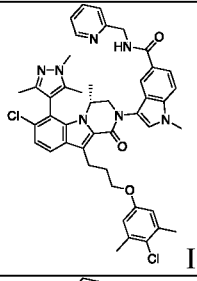
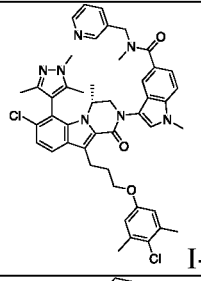
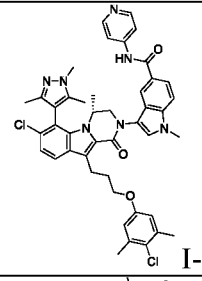
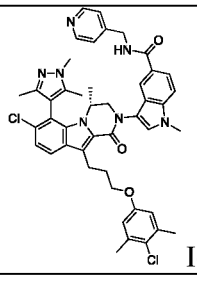
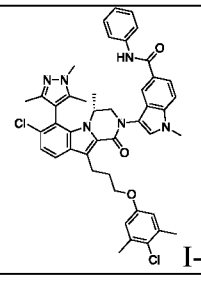
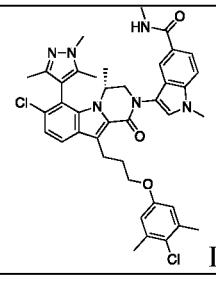

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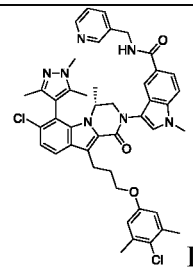
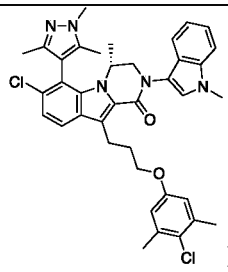
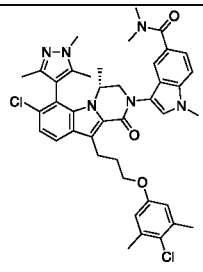
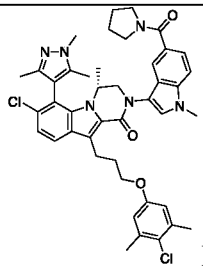
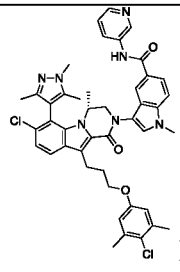
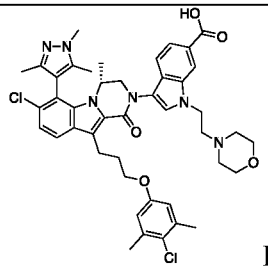
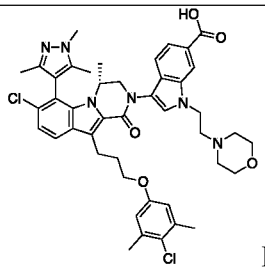
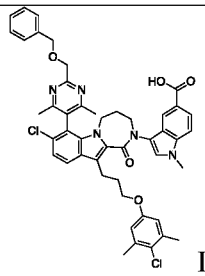
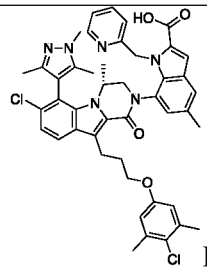
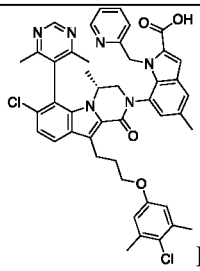
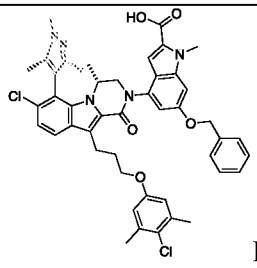
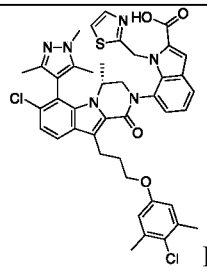
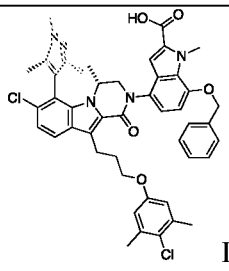
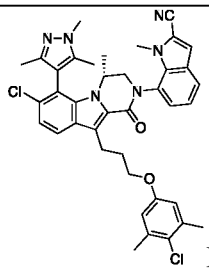
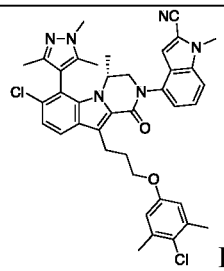
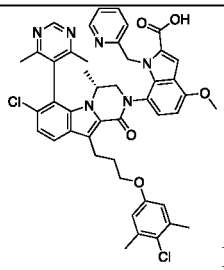
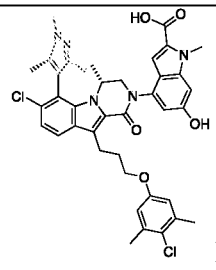
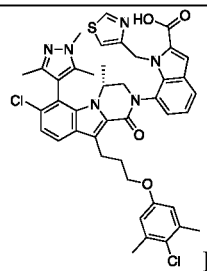

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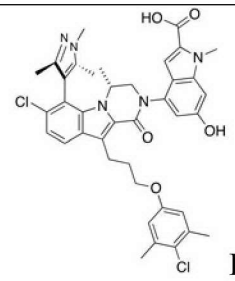
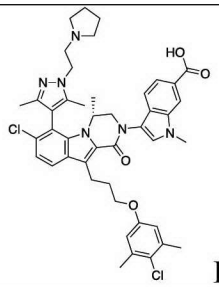
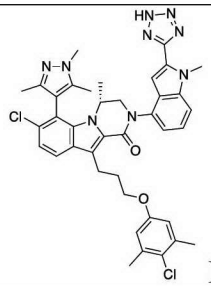
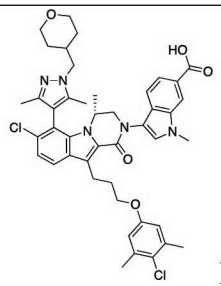
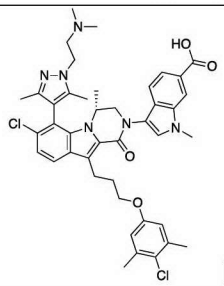
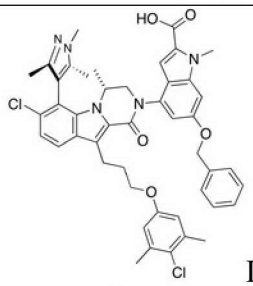
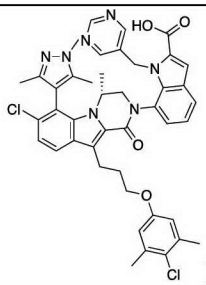
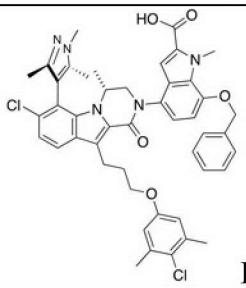
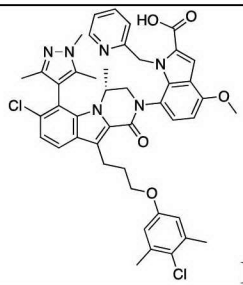
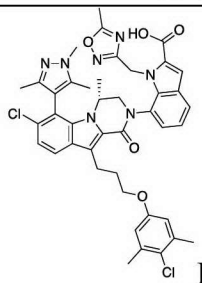
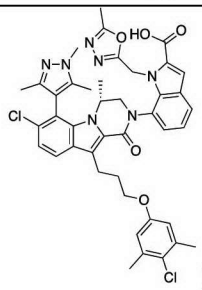
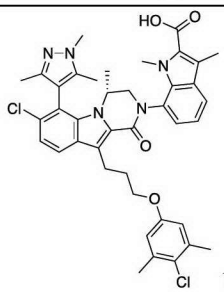
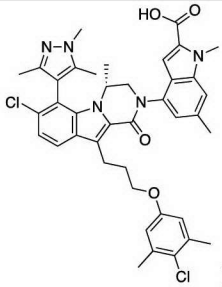
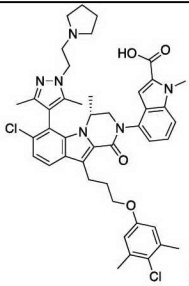
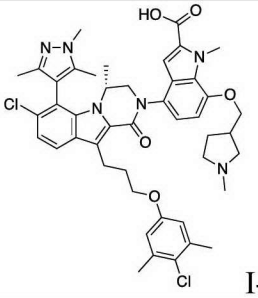
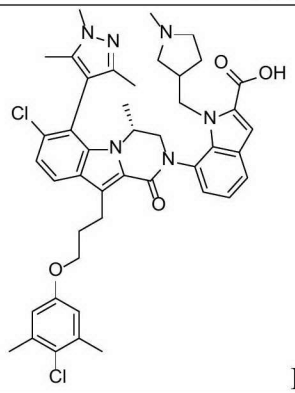
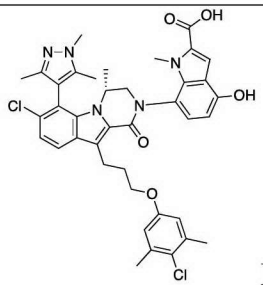
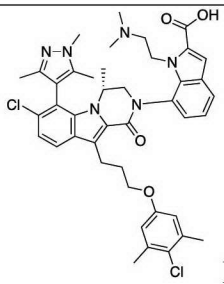

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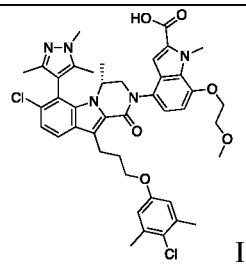
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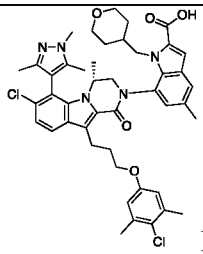
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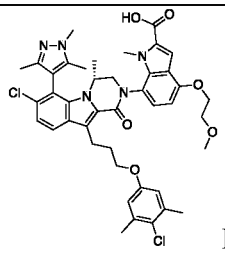
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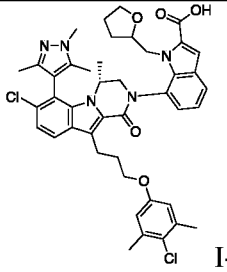
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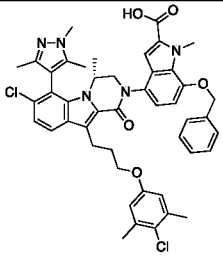
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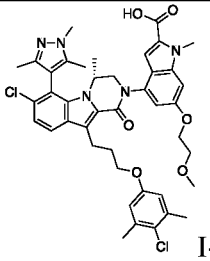

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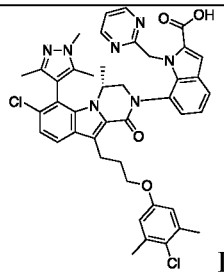

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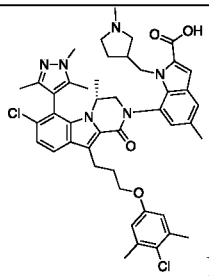

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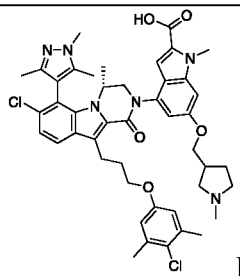

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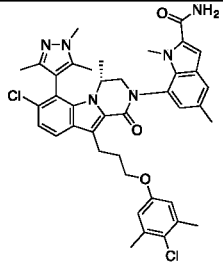

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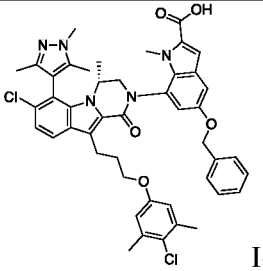

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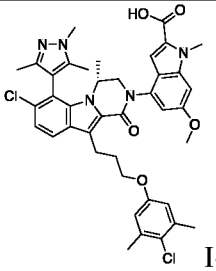

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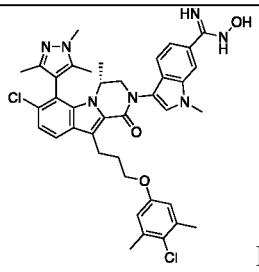

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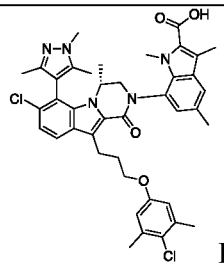

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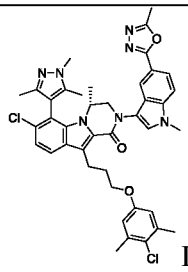

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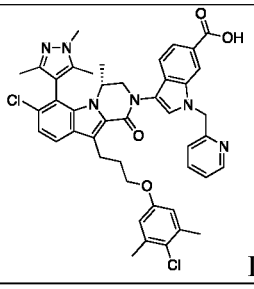

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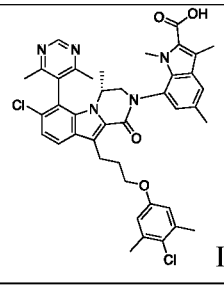

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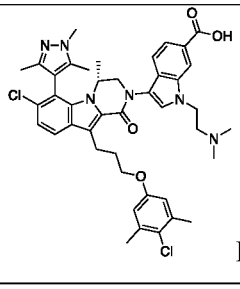

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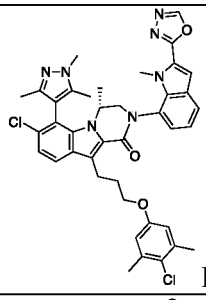
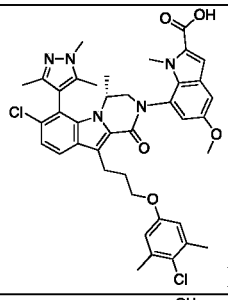
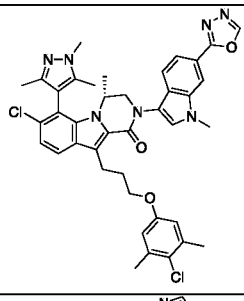
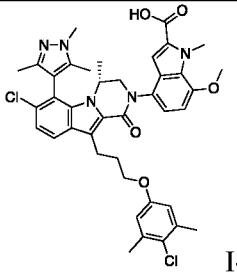
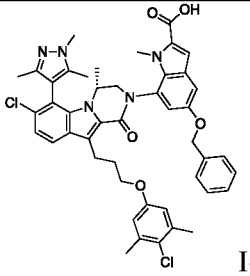
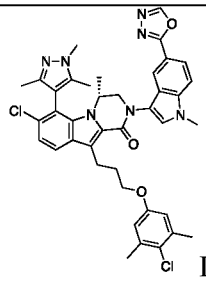
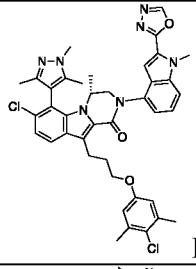
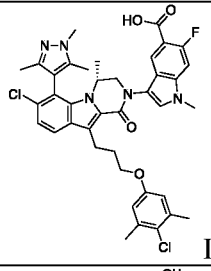
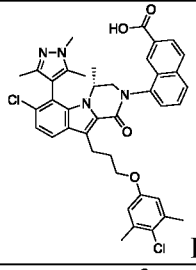
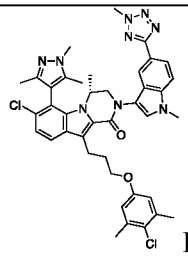
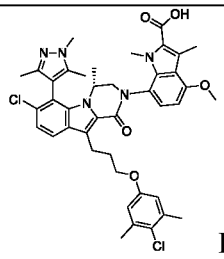
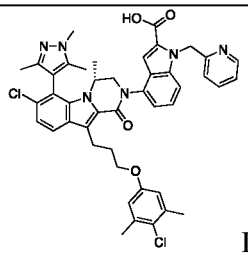
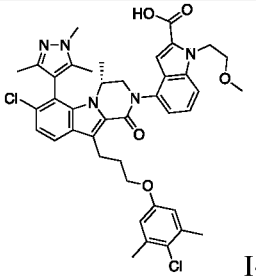
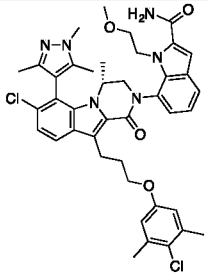
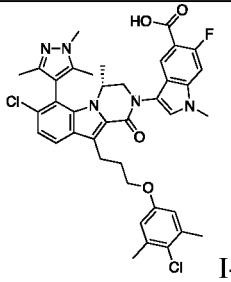
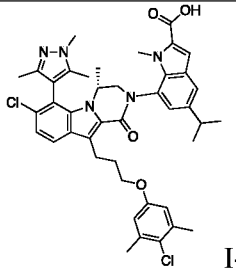
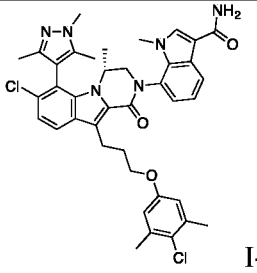
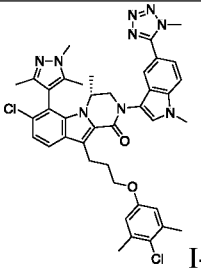

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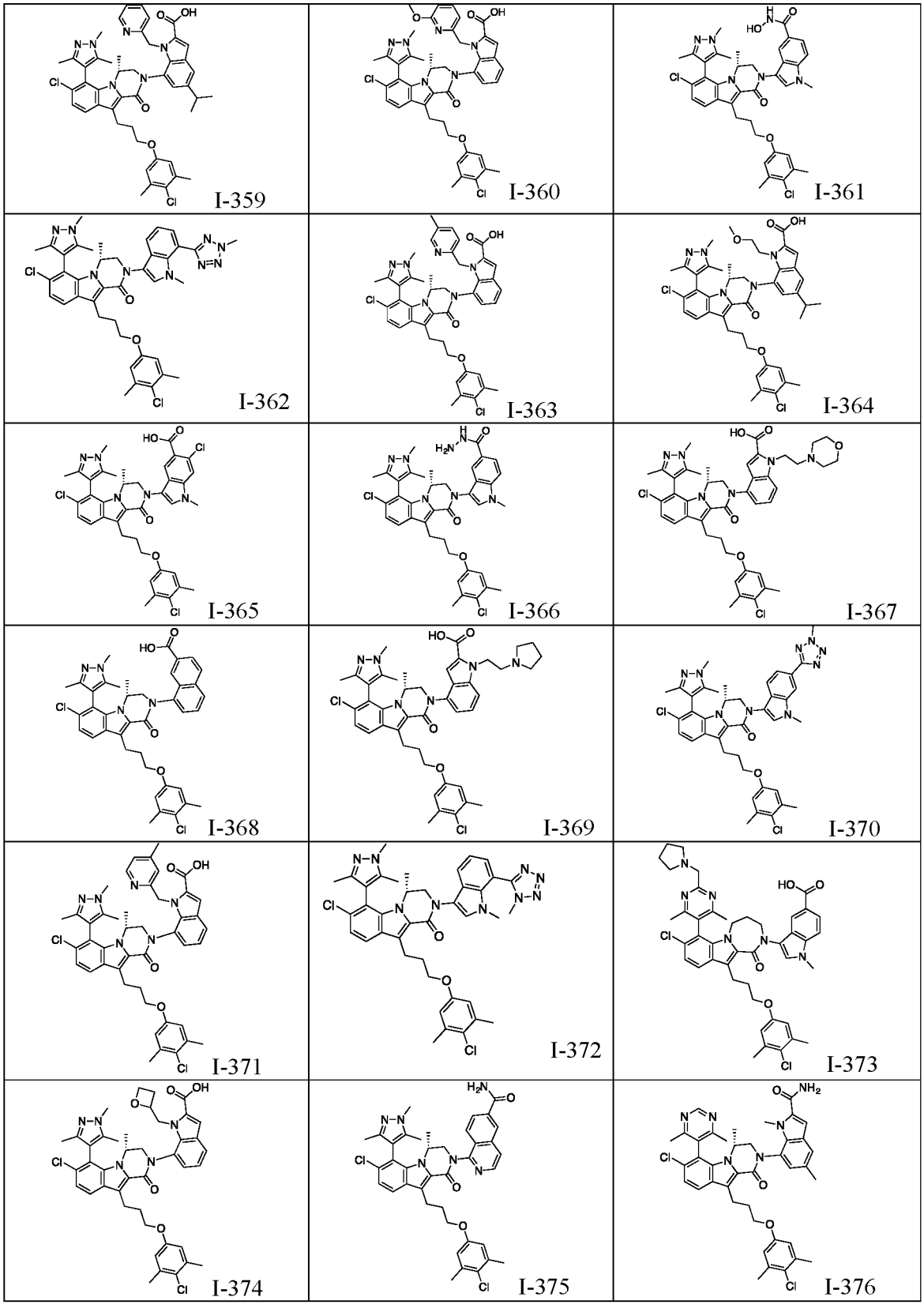

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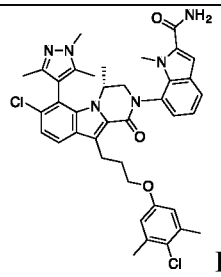
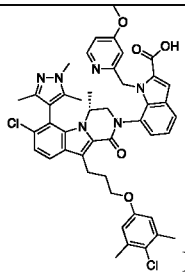
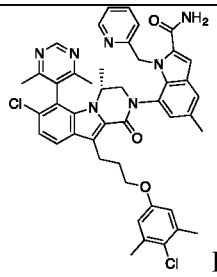
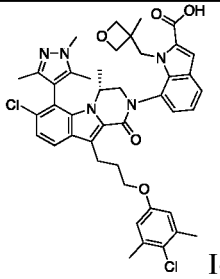
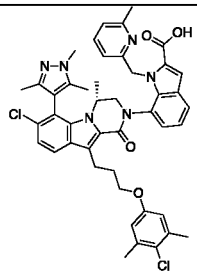
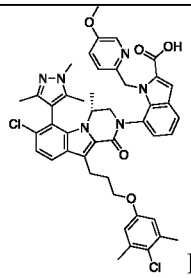
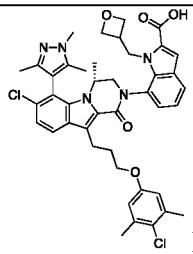
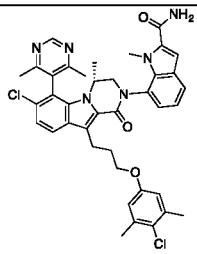
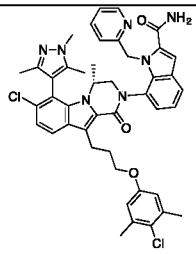
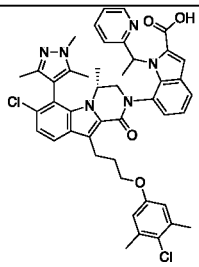
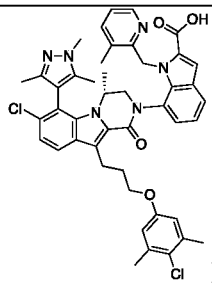
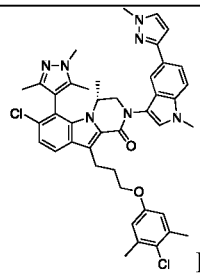
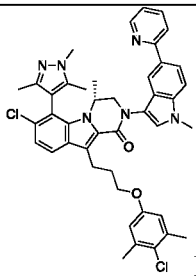
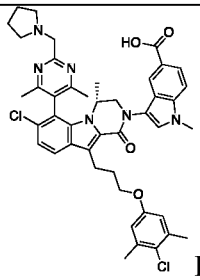
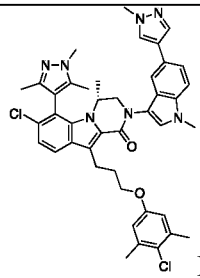
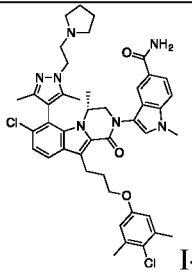
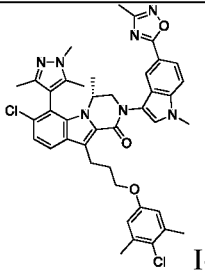
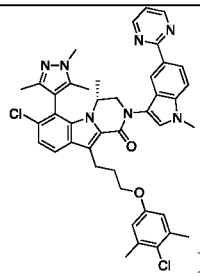

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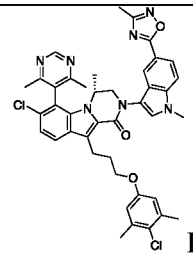
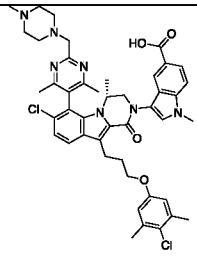
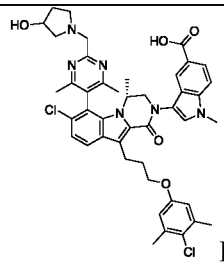
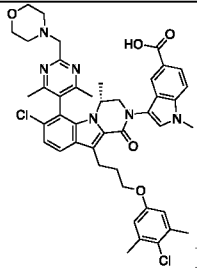
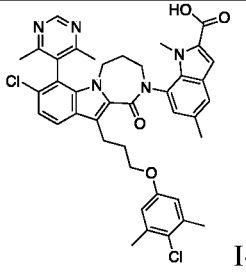
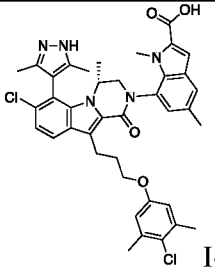
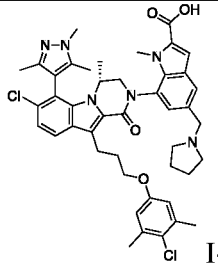
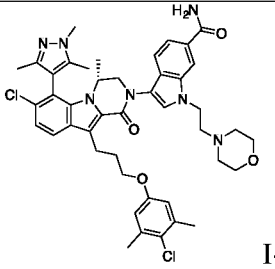
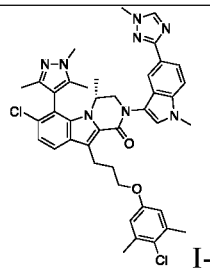
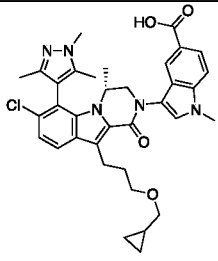
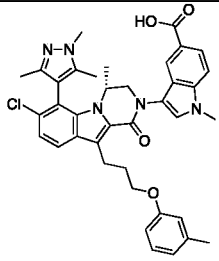
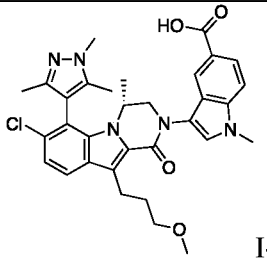
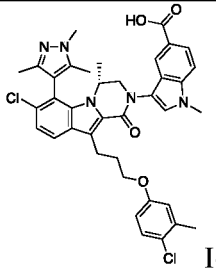
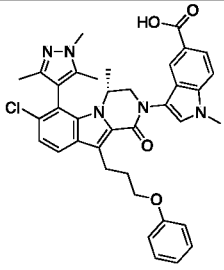
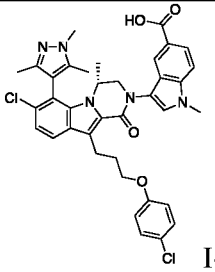
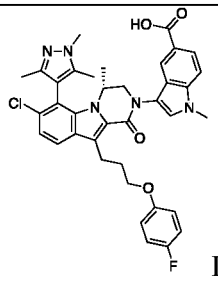
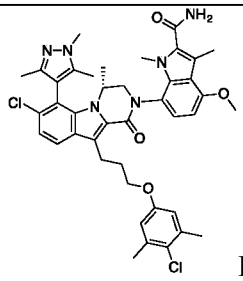
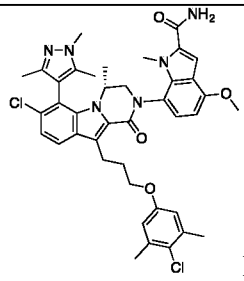

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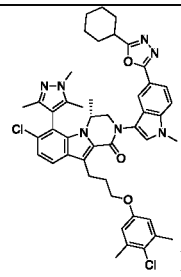
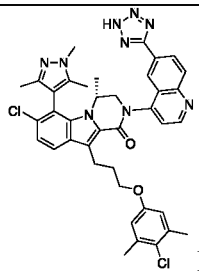
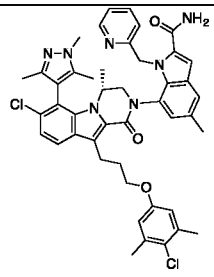
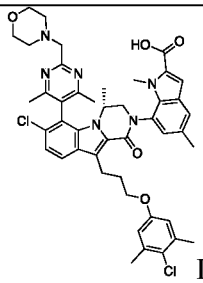
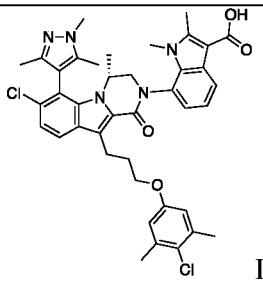
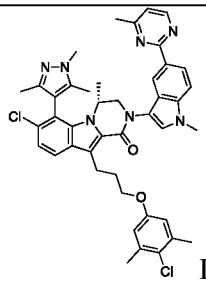
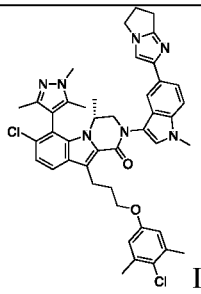
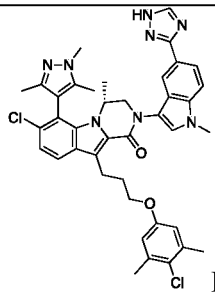
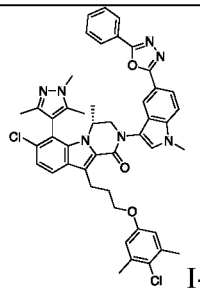
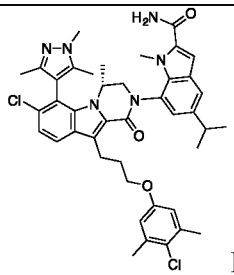
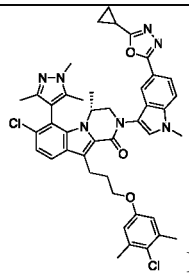
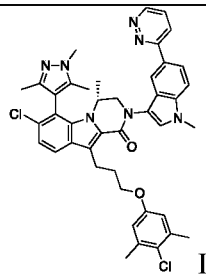
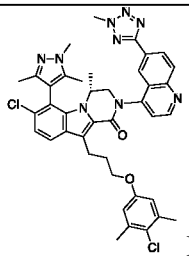
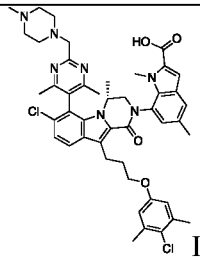
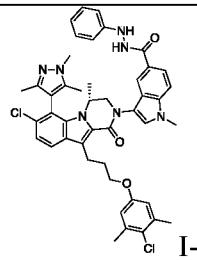
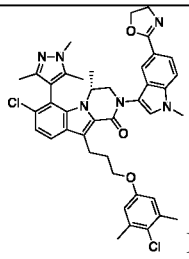
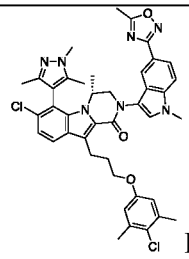
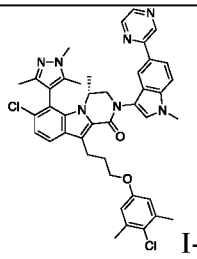

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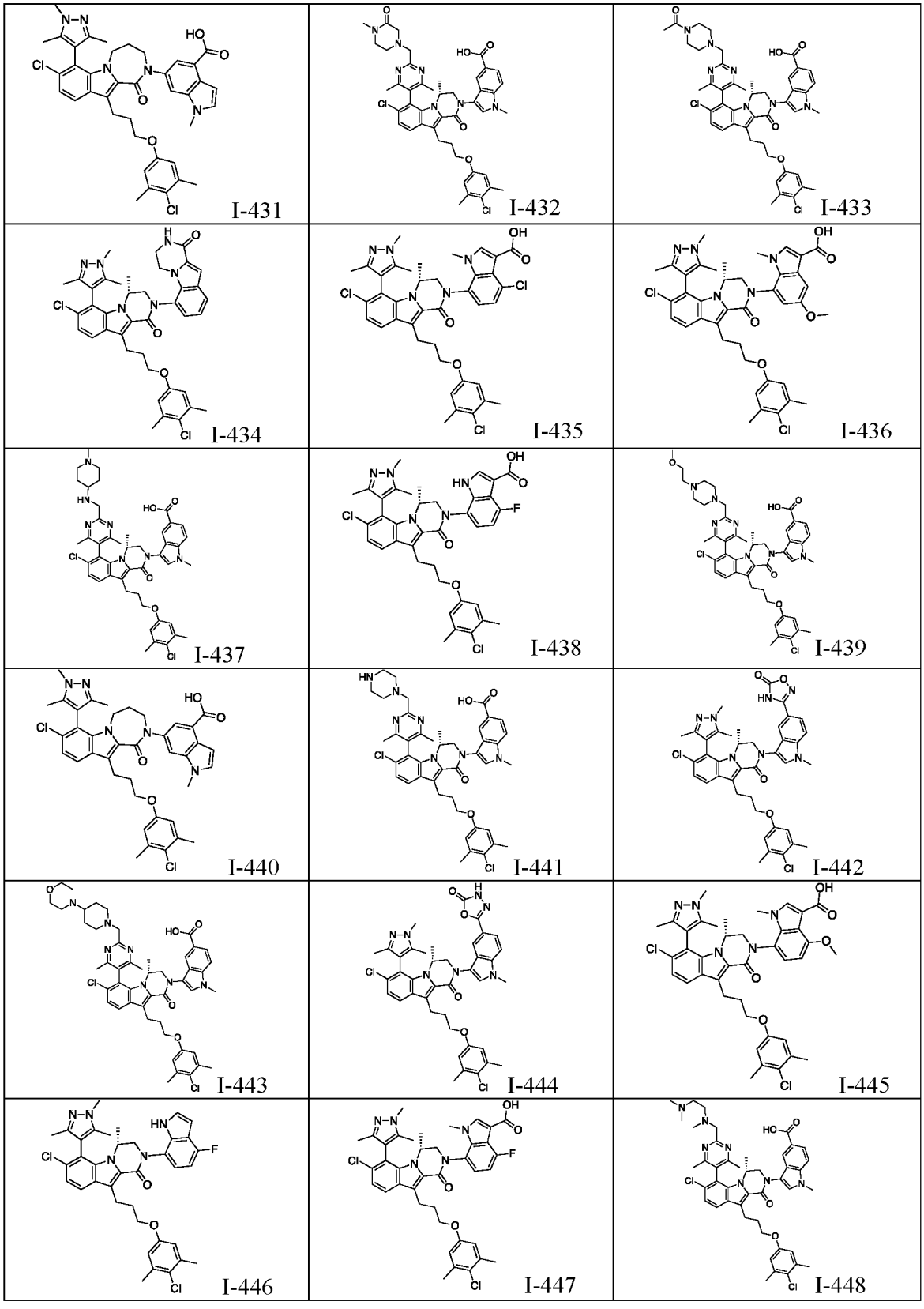
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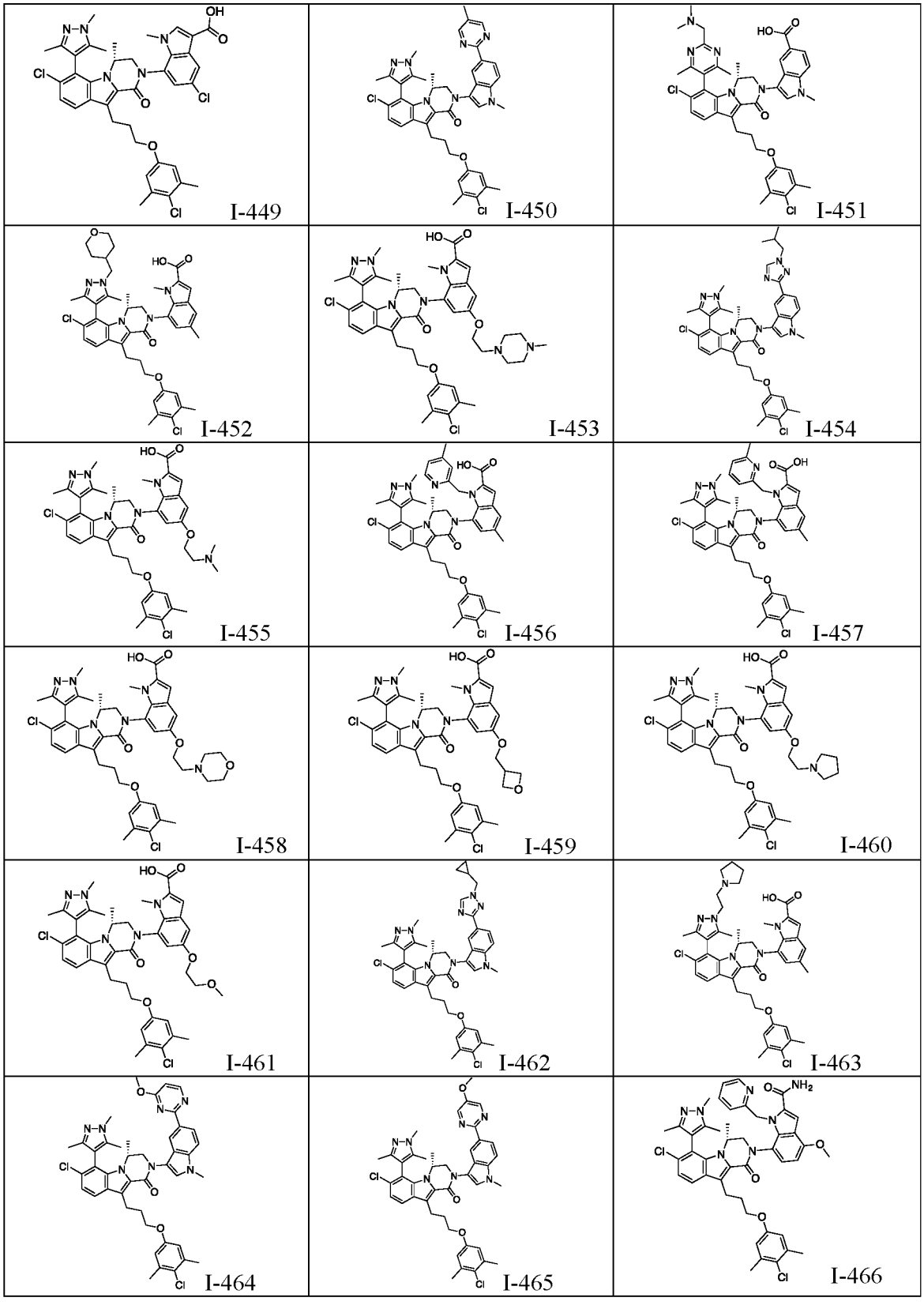

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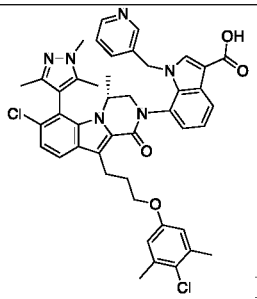
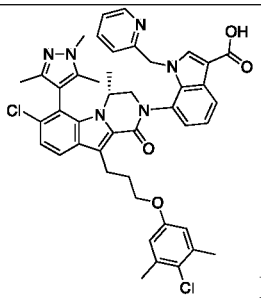
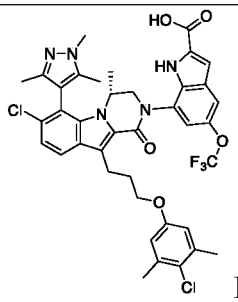
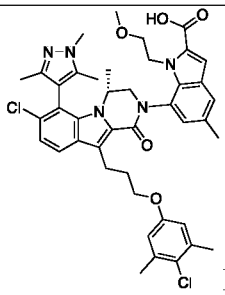
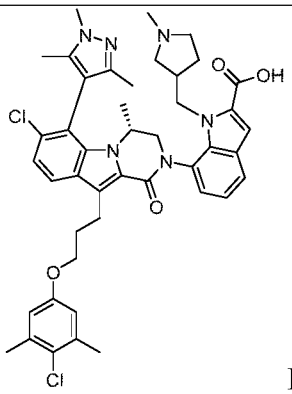
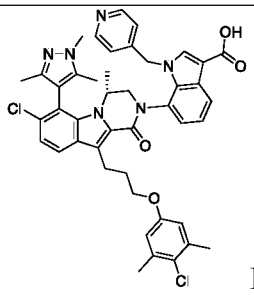
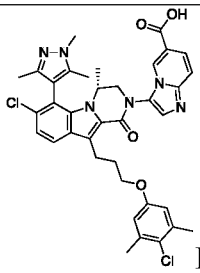
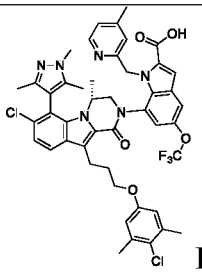
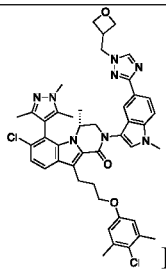
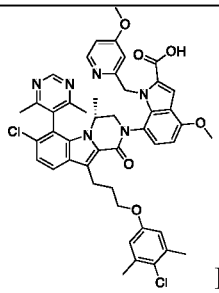
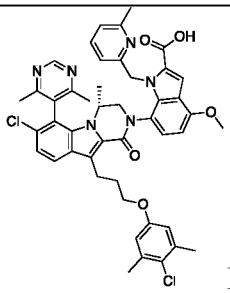
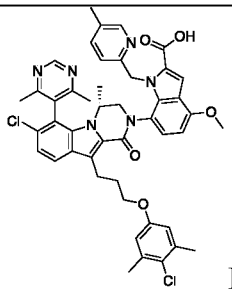
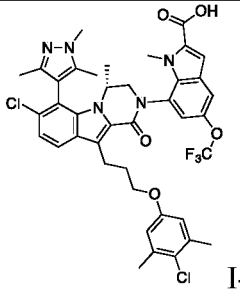
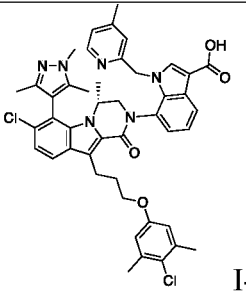
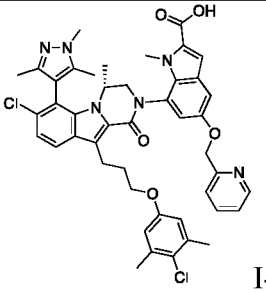
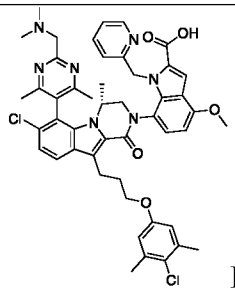
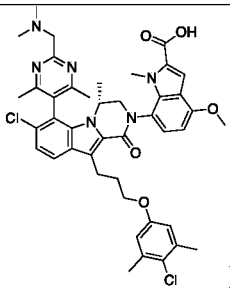
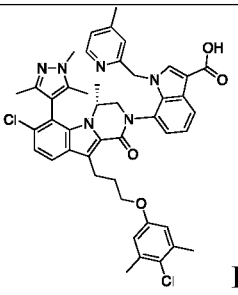
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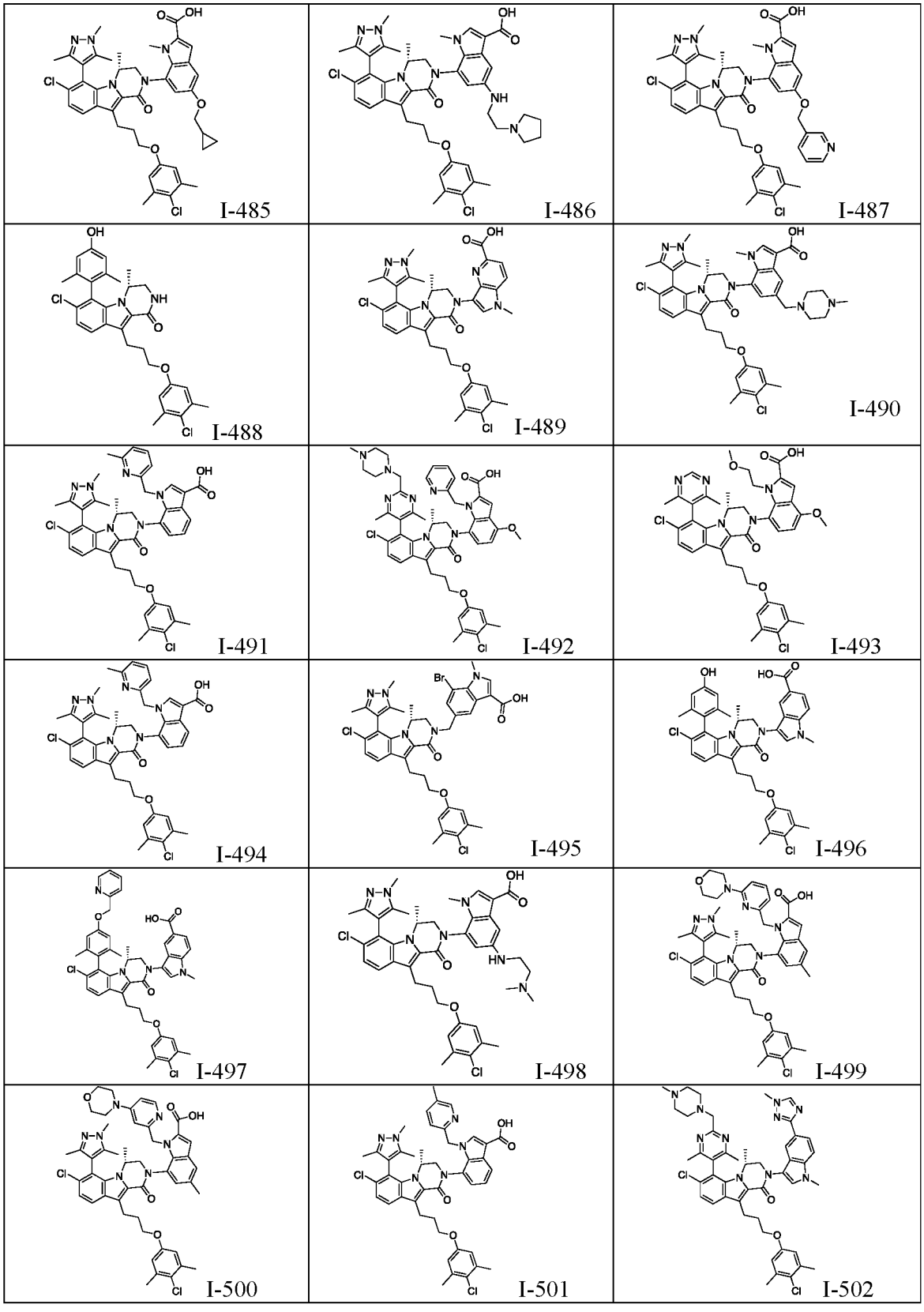
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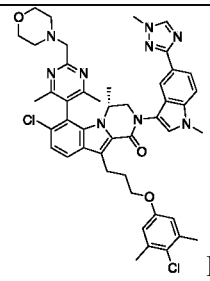
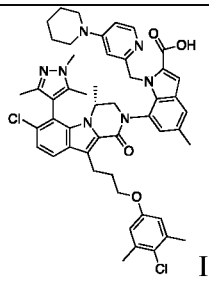
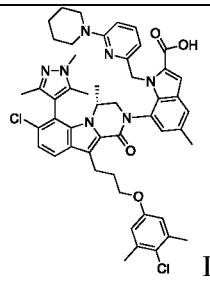
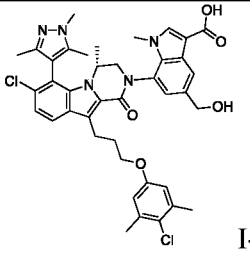
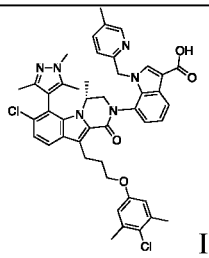
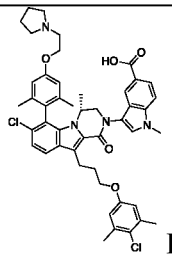
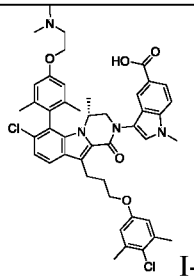
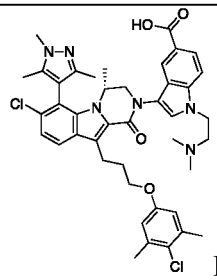
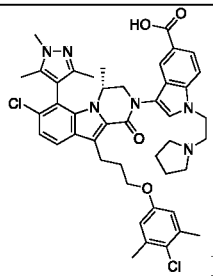
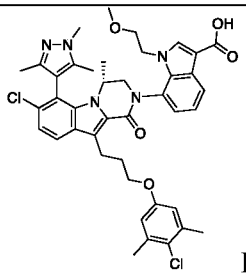
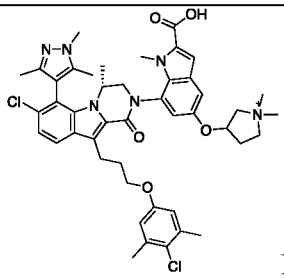
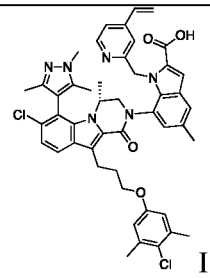
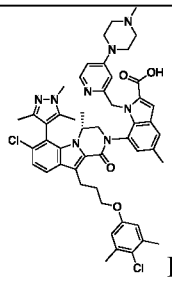
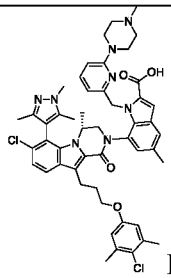
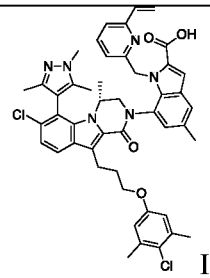
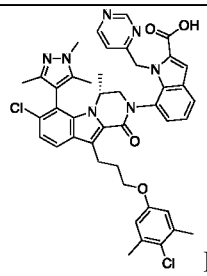
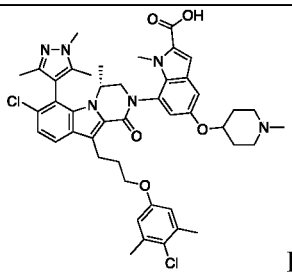
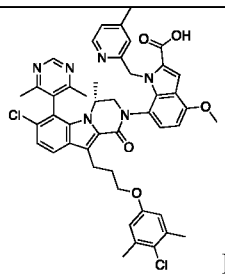
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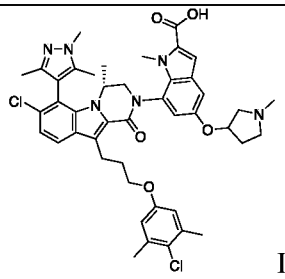
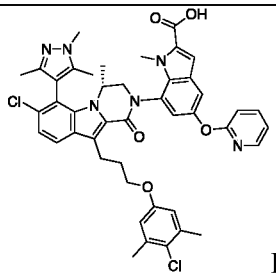
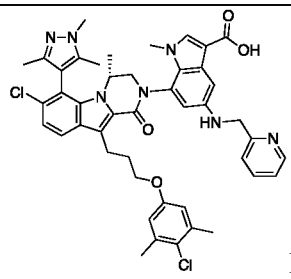
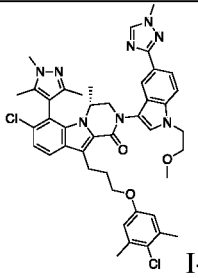
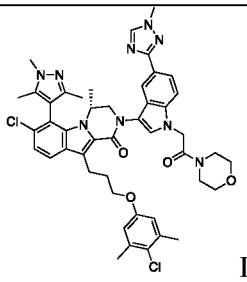
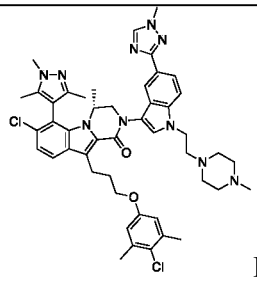
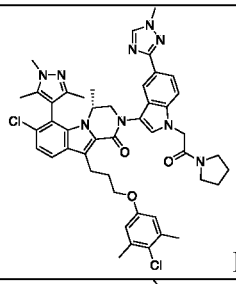
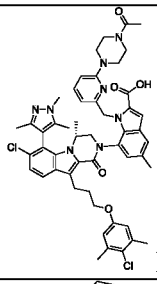
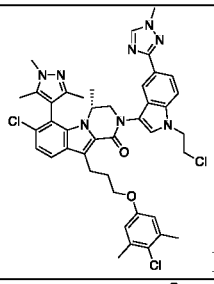
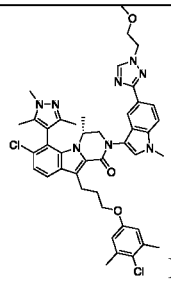
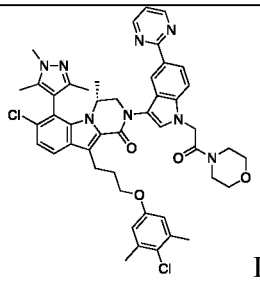
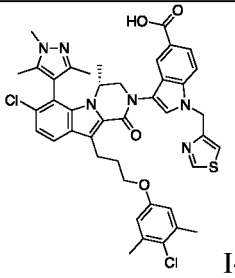
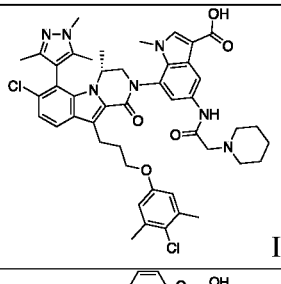
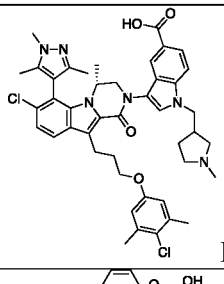
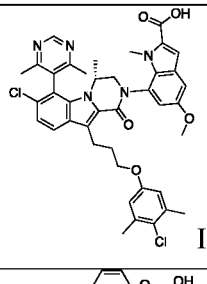
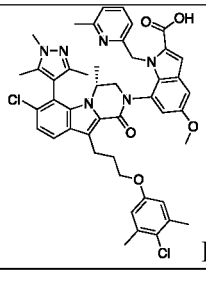
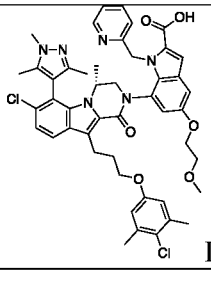
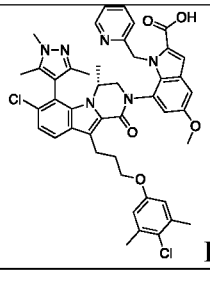

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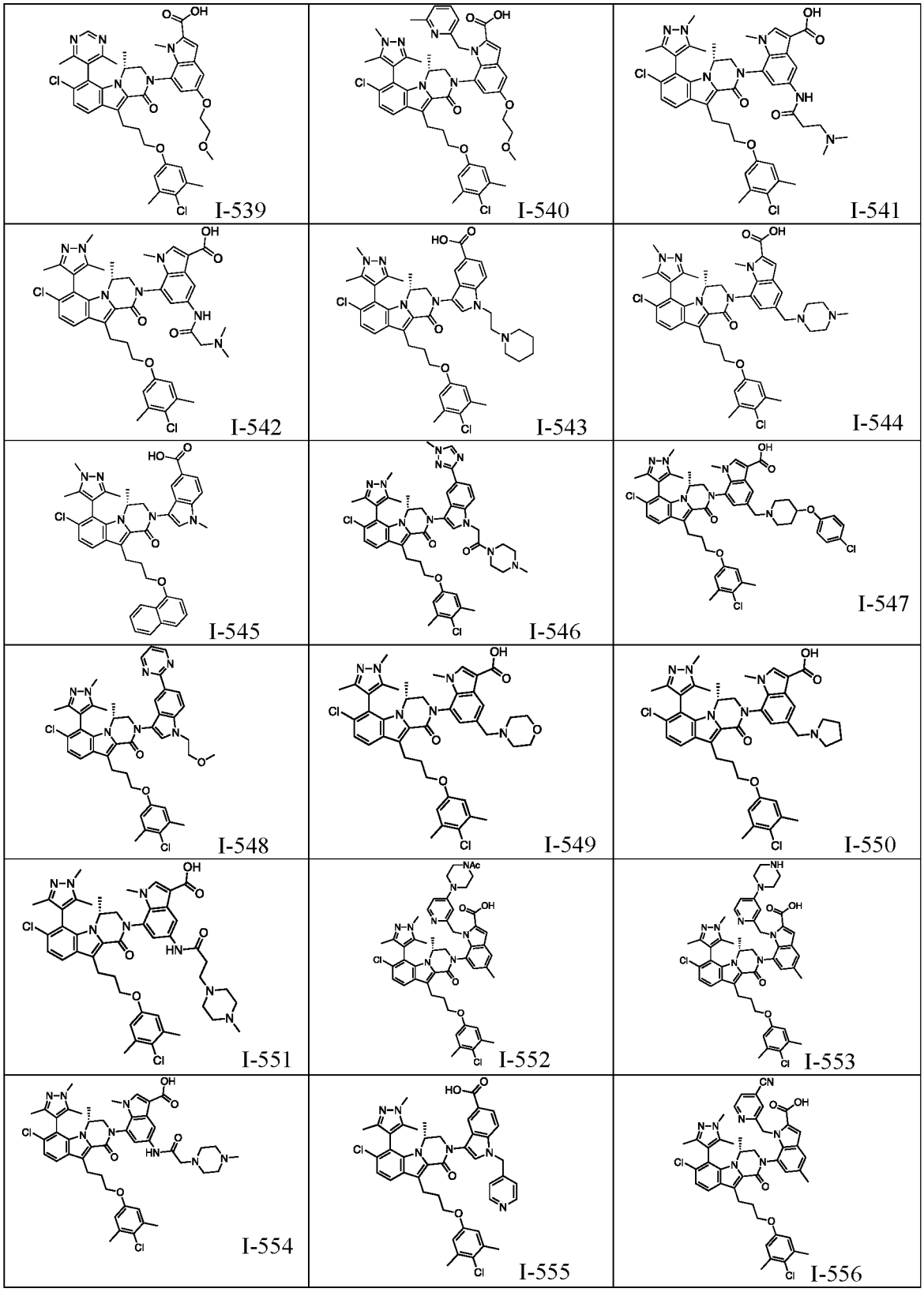

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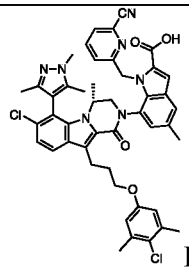
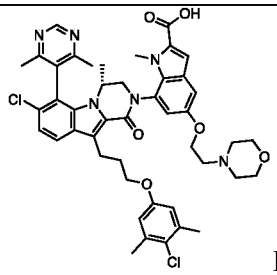
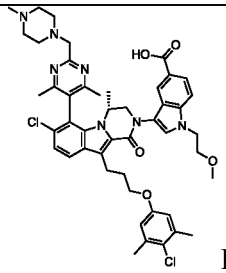
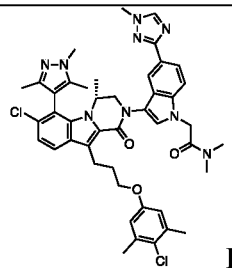
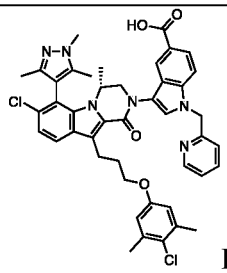
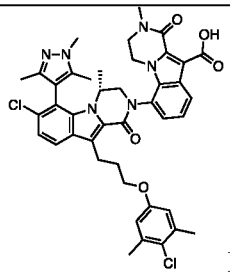
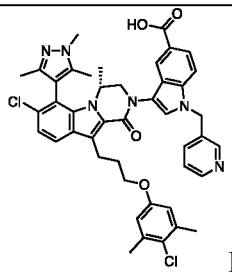
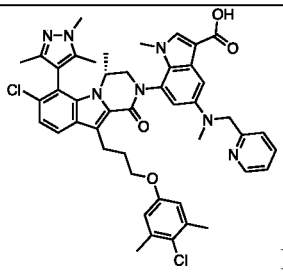
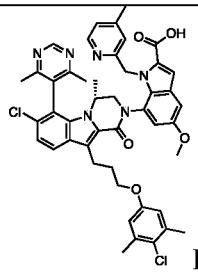
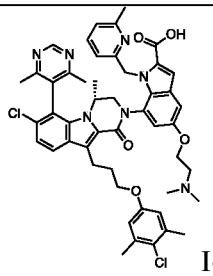
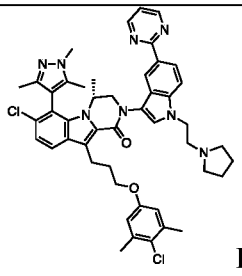
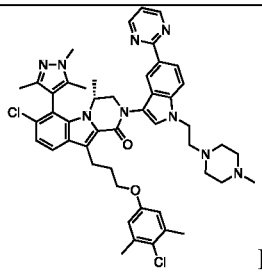
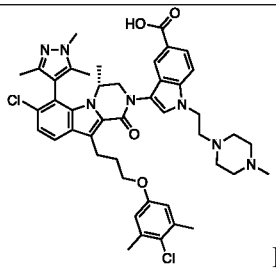
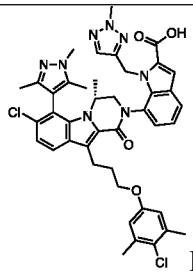
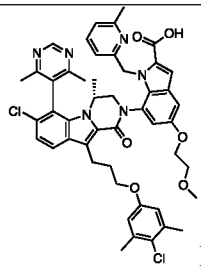
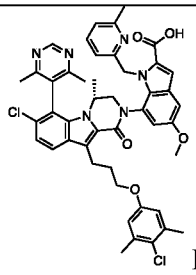
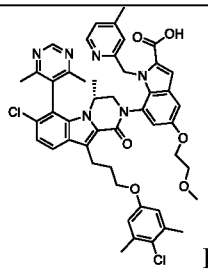
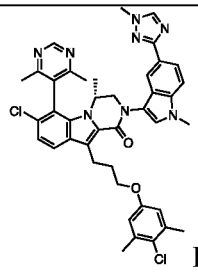
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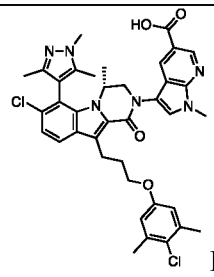
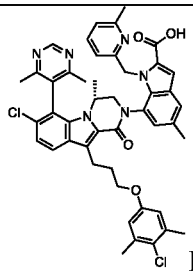
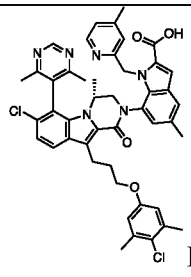
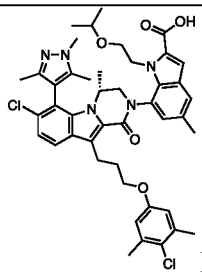
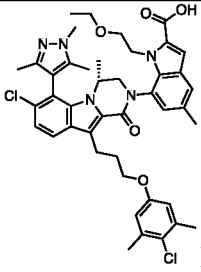
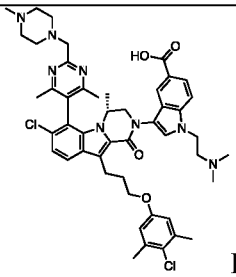
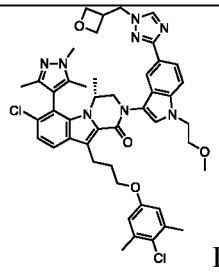
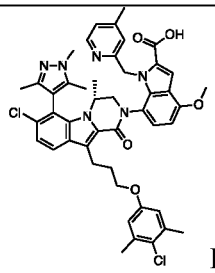
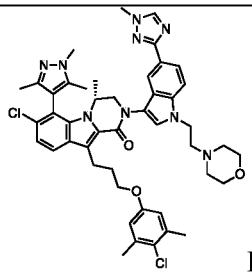
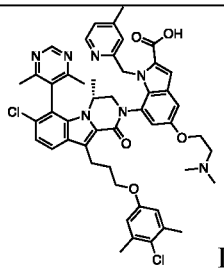
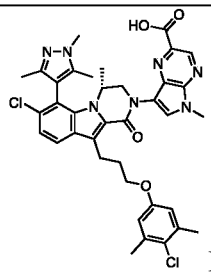
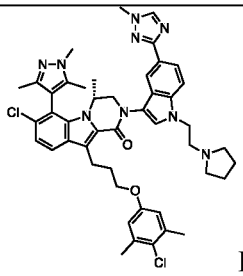
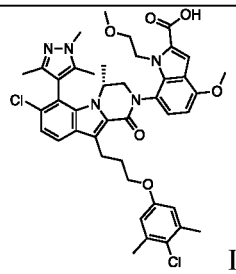
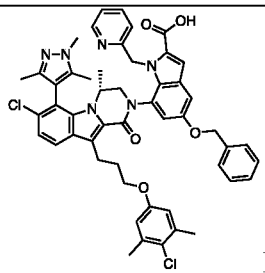
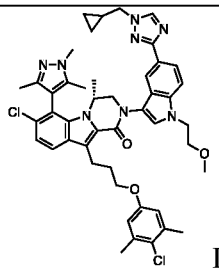
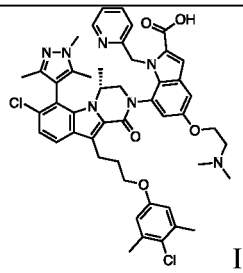
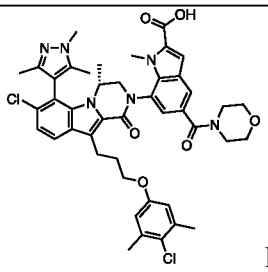
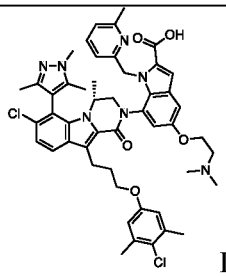

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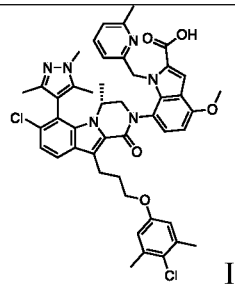
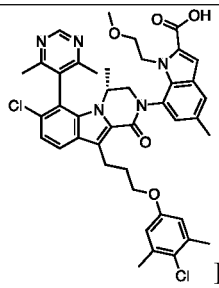
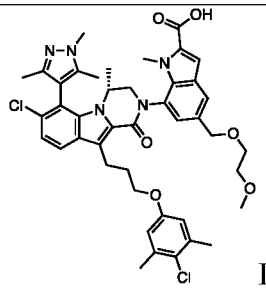
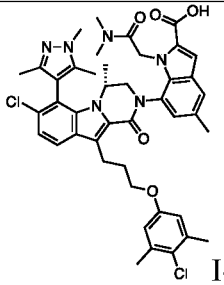
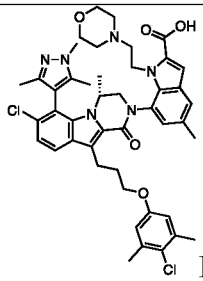
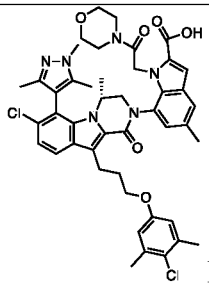
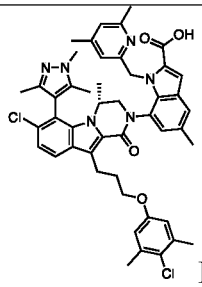
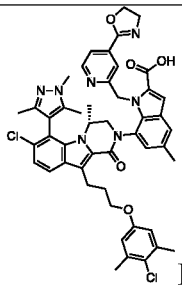
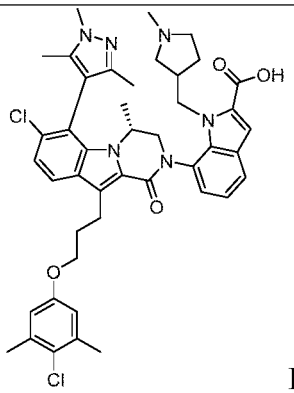
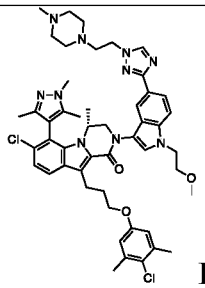
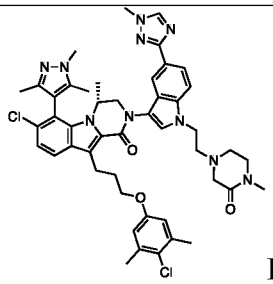
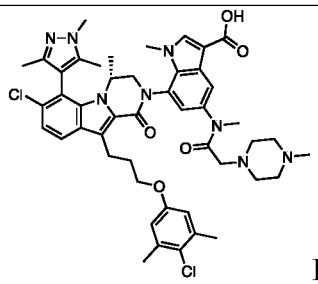
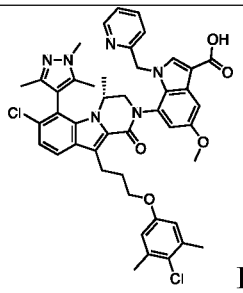
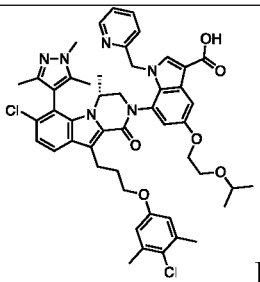
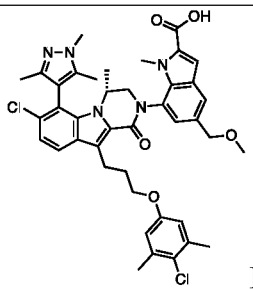
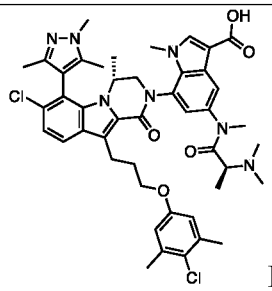
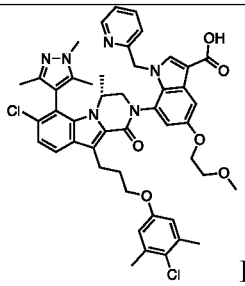
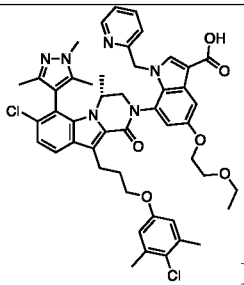
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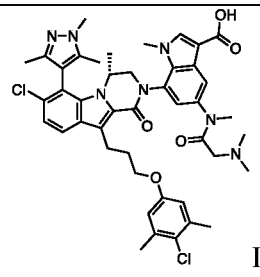
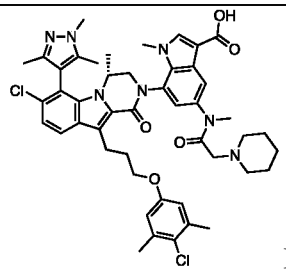
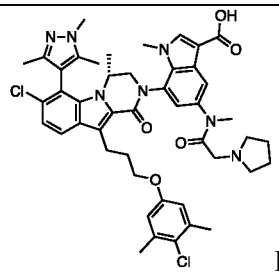
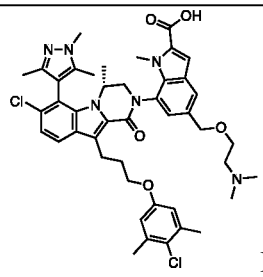
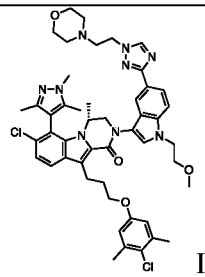
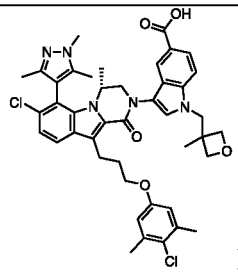
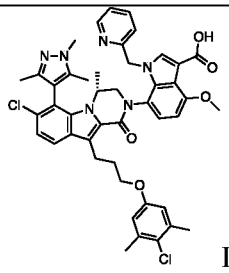
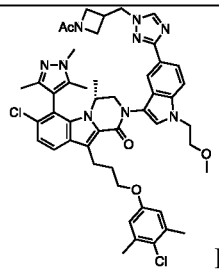
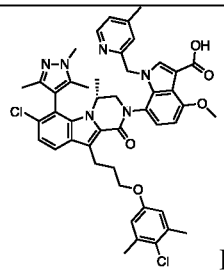
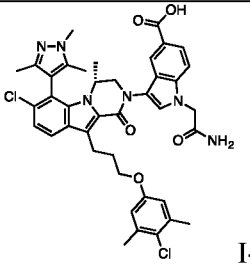
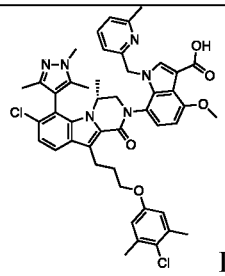
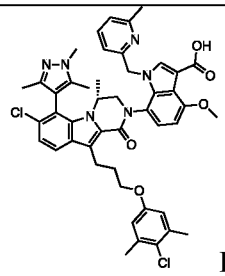
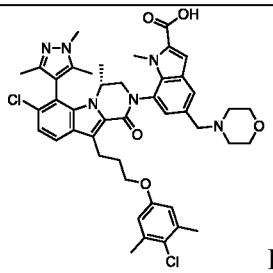
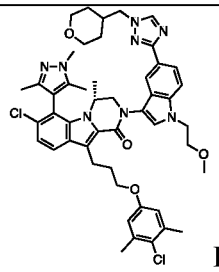
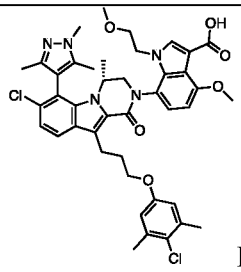
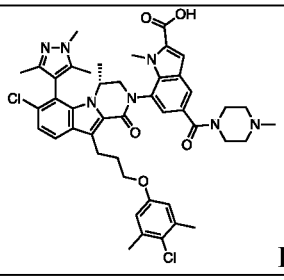
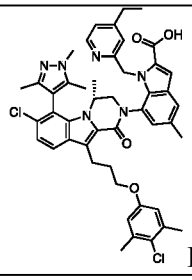
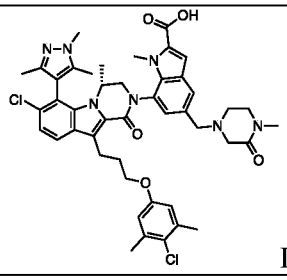
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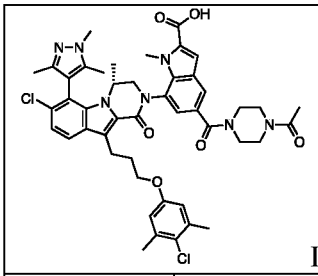
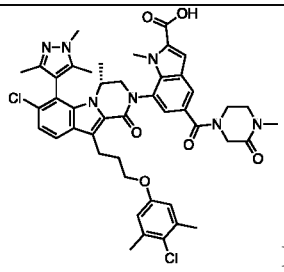
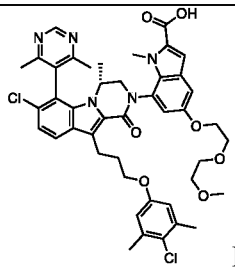
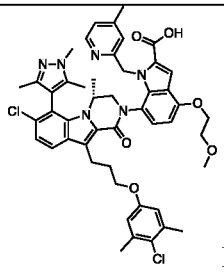
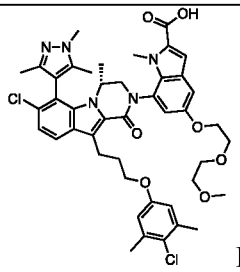
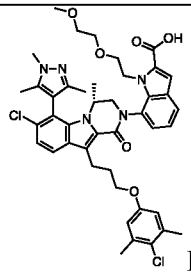
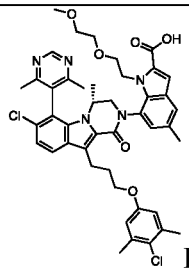
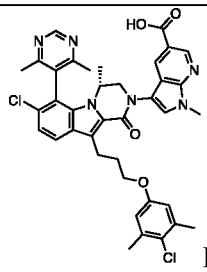
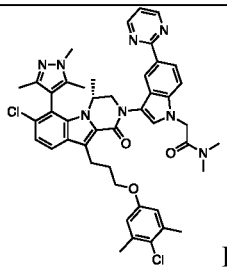
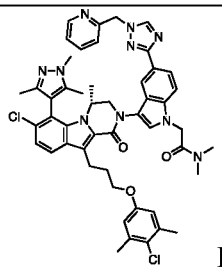
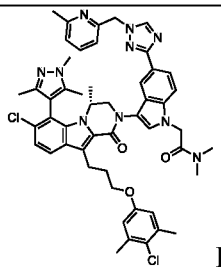
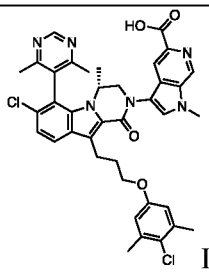
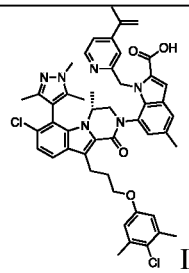
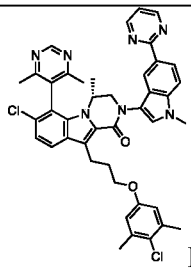
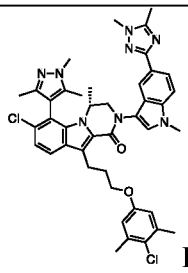
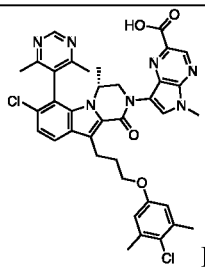
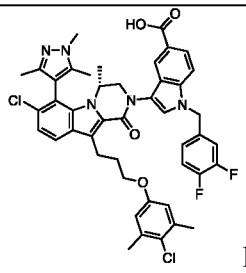
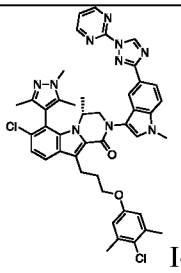

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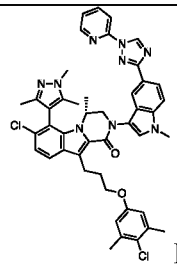
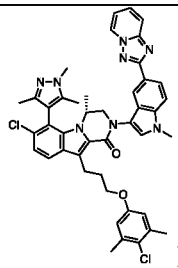
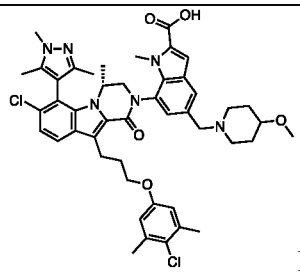
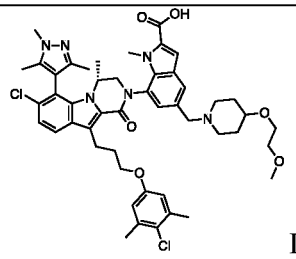
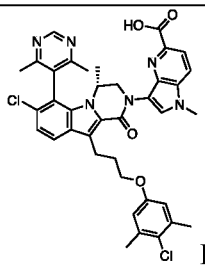
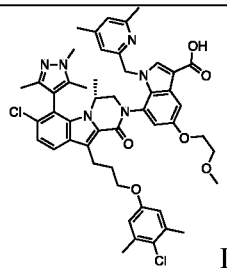
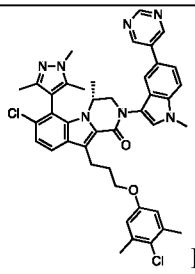
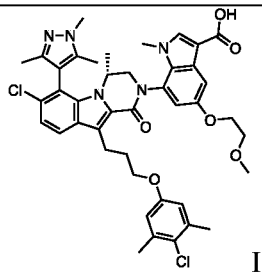
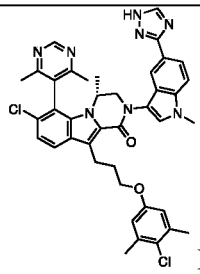
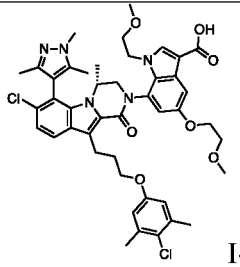
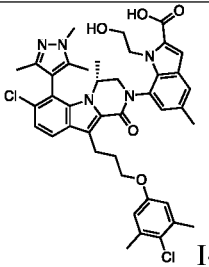
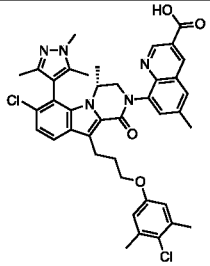
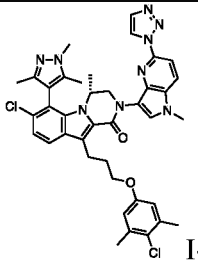
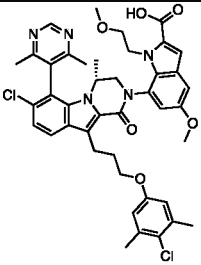
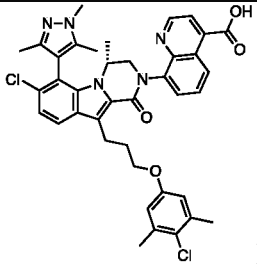
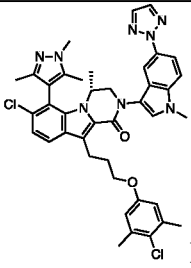
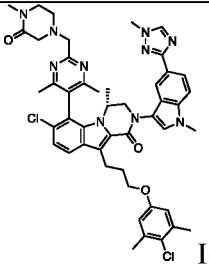
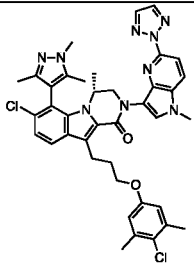
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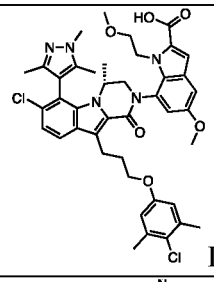
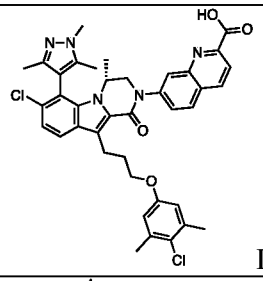
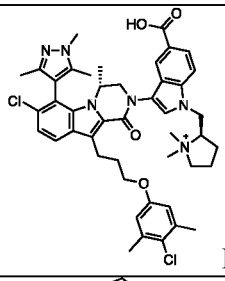
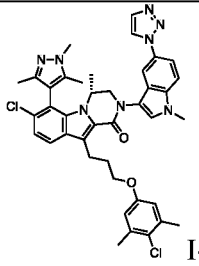
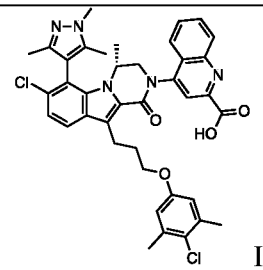
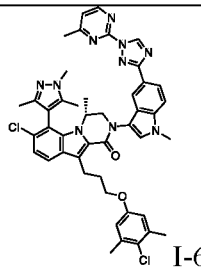
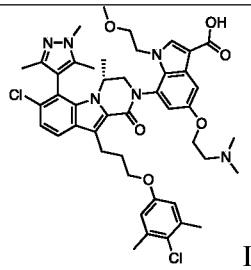
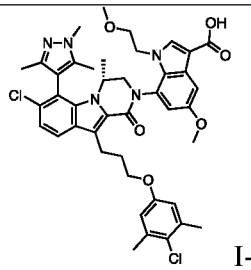
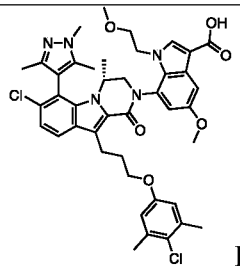
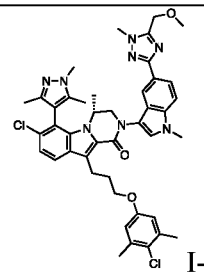
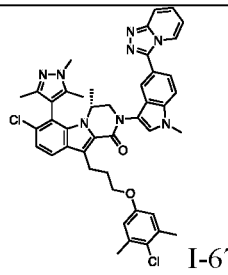
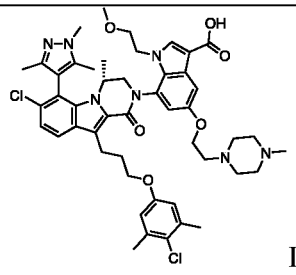
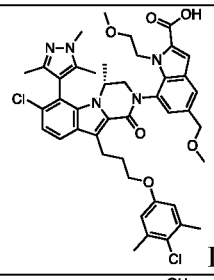
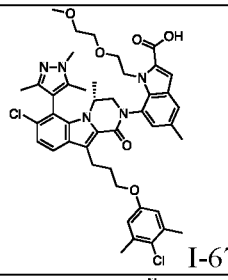
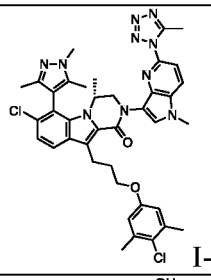
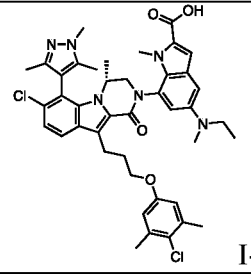
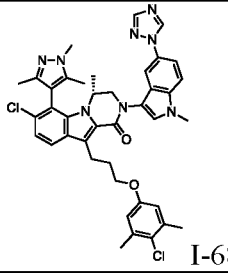
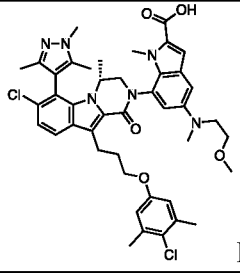
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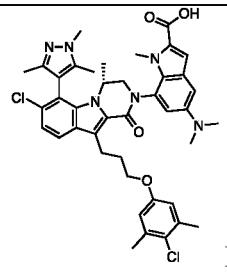
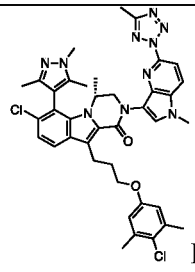
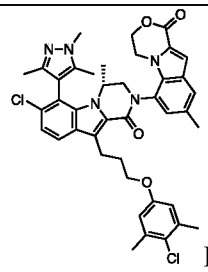
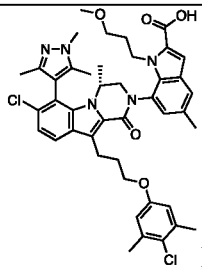
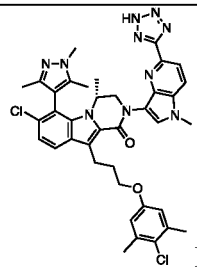
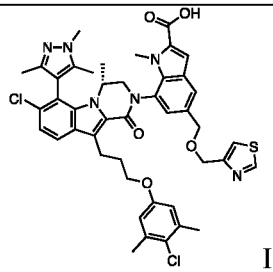
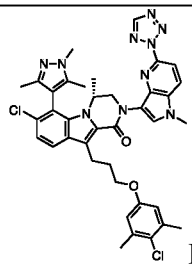
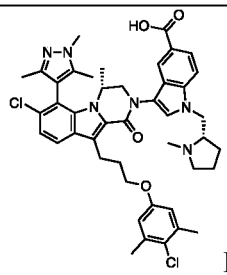
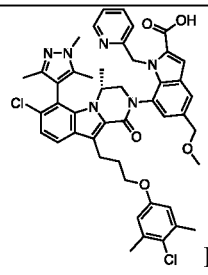
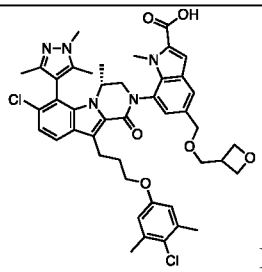
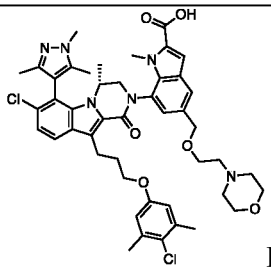
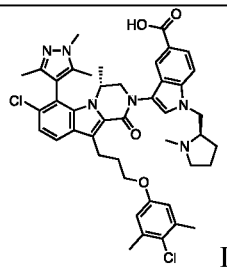
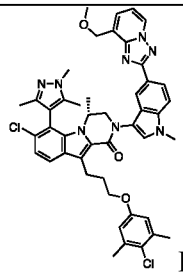
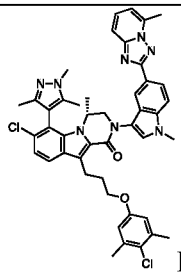
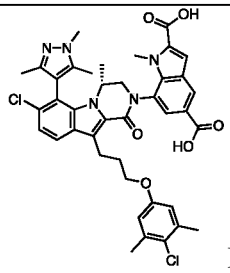
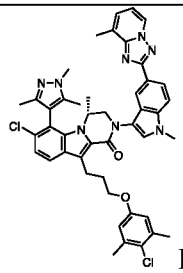
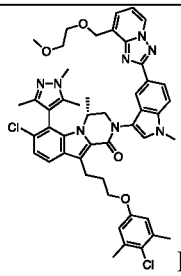
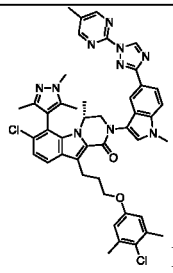
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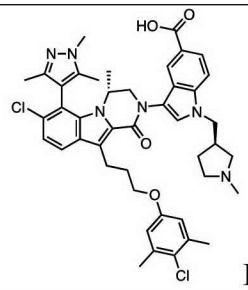
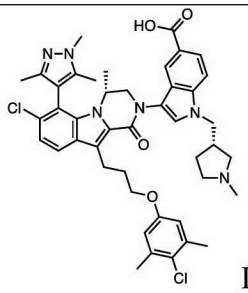
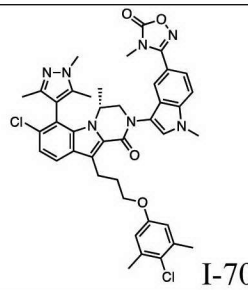
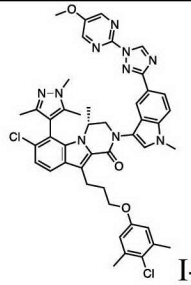
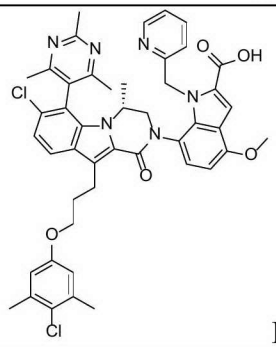
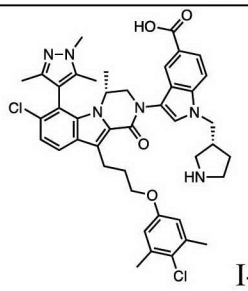
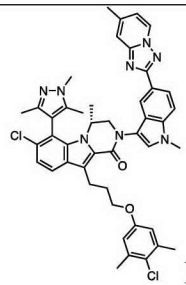
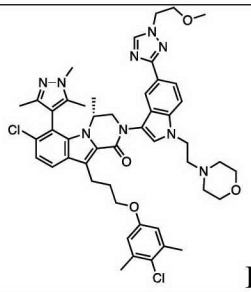
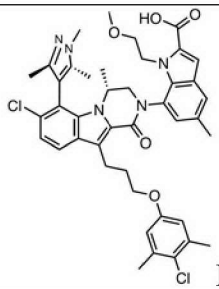
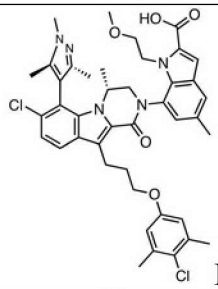
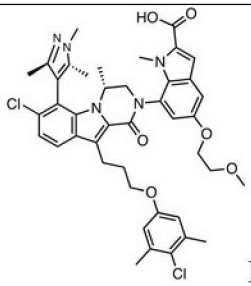
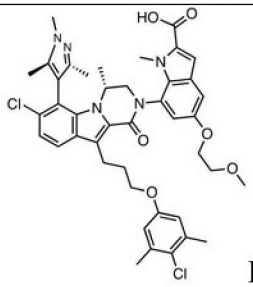
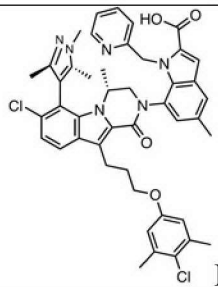
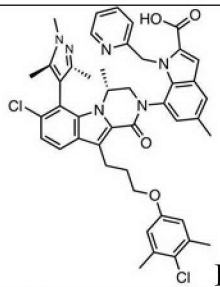
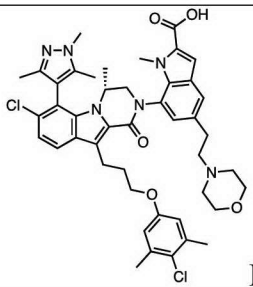
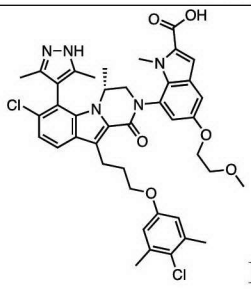
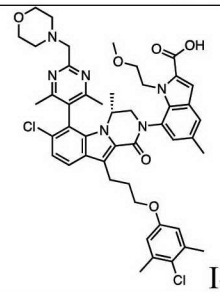
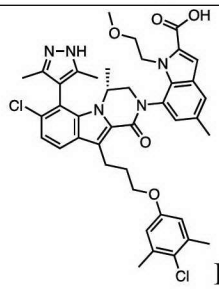
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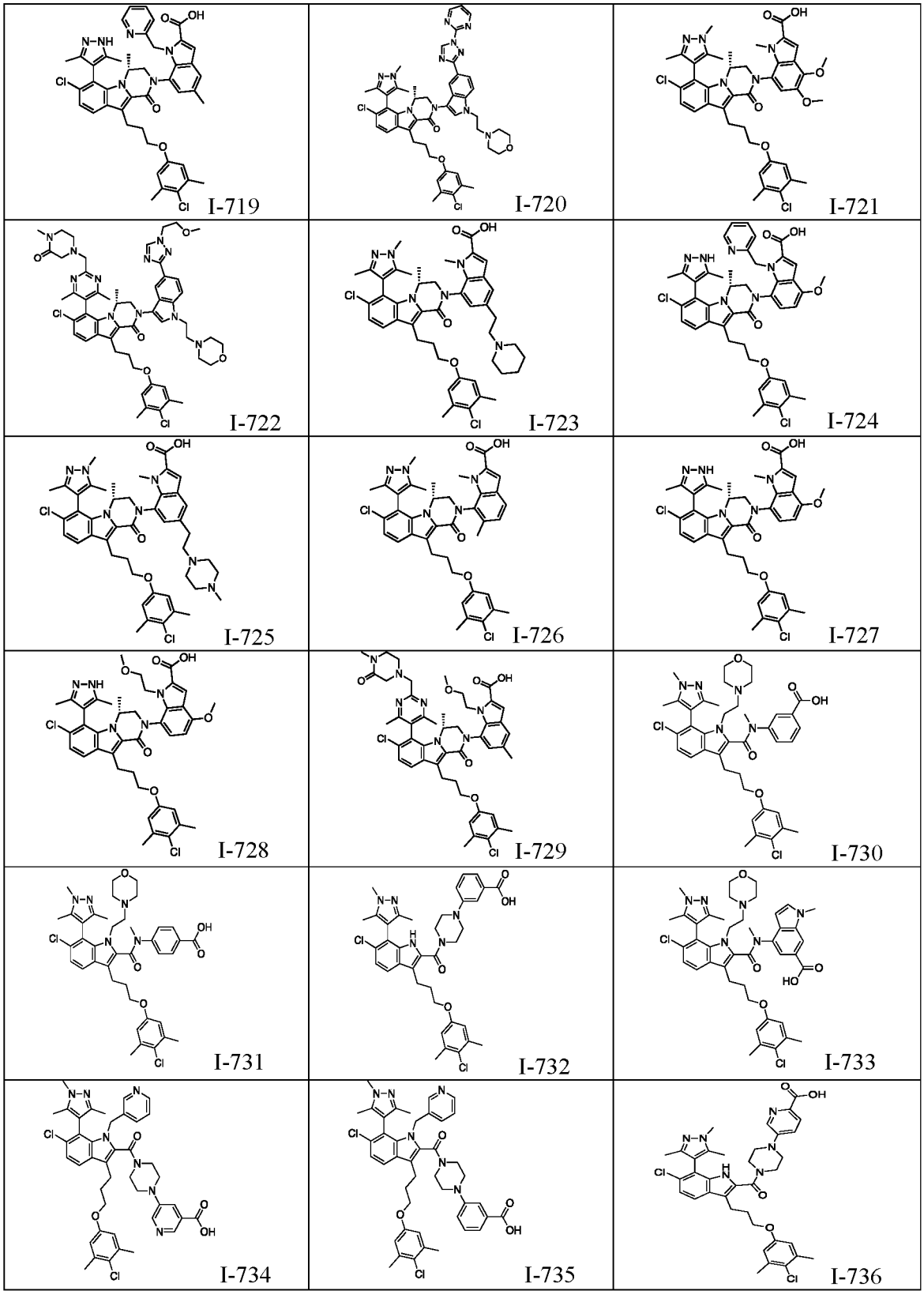
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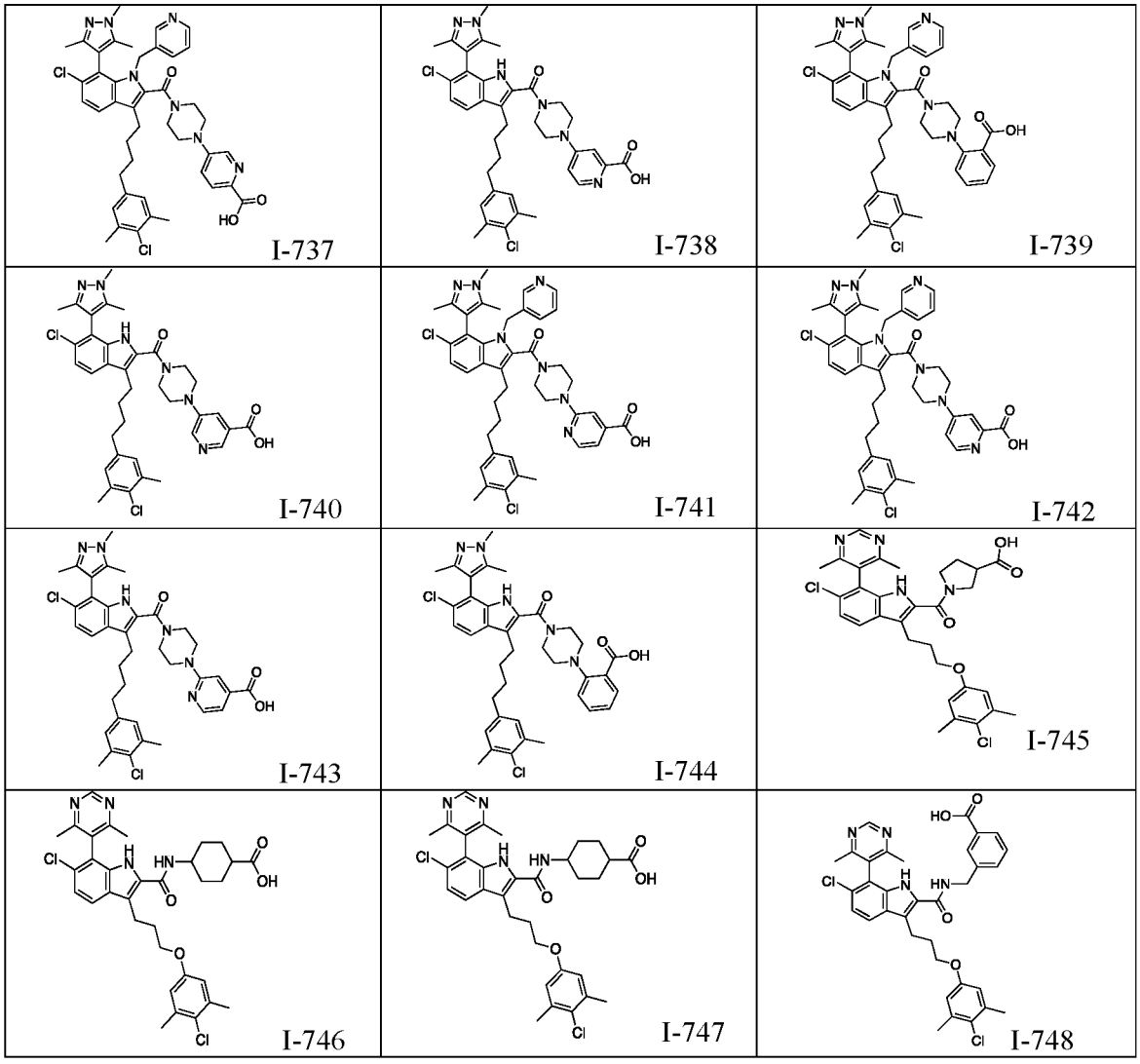
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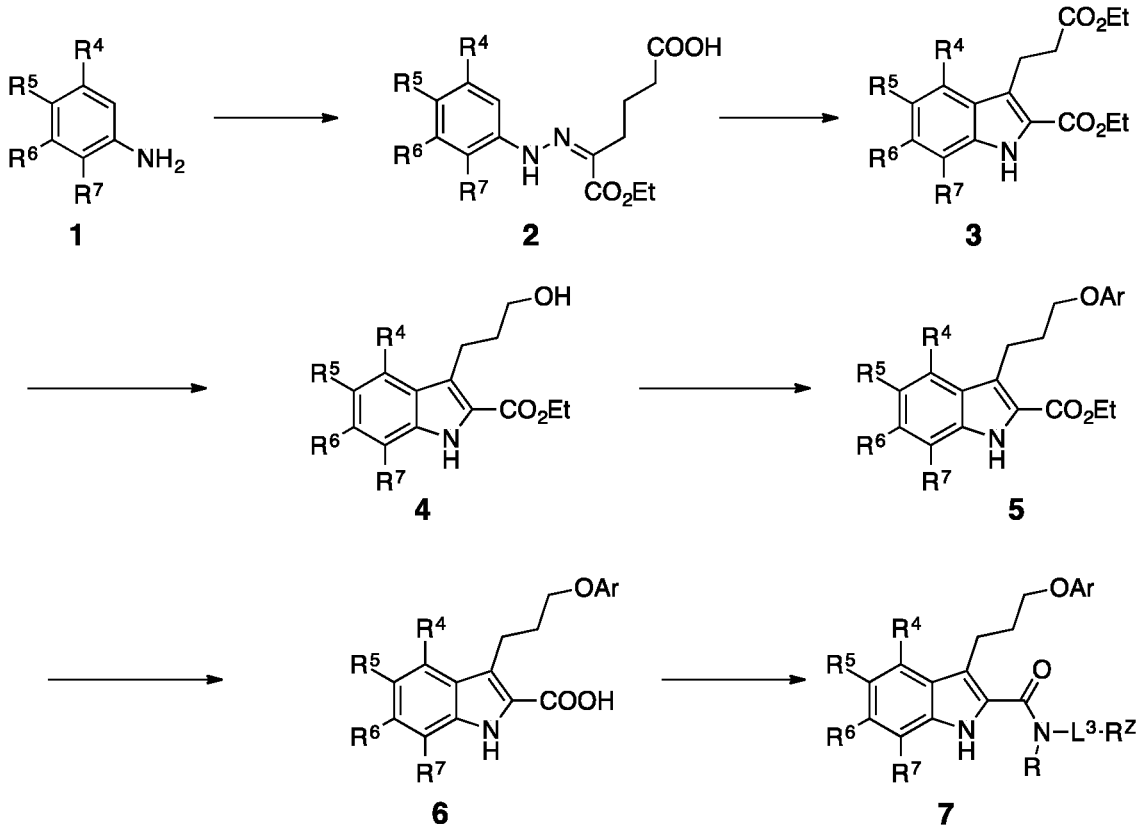
SYNTHESIS

[0063] The compounds of the present disclosure can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present disclosure can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety by reference as to the subject matter referenced herein.

[0064] The compounds of the disclosure may be prepared using the exemplary reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effective. Also, in the description of the synthetic methods described below, it is to be

understood that all proposed reaction conditions, including solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. One having ordinary skill in the art may adjust one or more of the conditions described herein. One skilled in the art of organic synthesis understands that the functionality present on various portions of the edict molecule must be compatible with the reagents and reactions proposed. Not all compounds of the disclosure falling into a given class may be compatible with some of the reaction conditions required in some of the methods described. Such restrictions to the substituents, which are compatible with the reaction conditions, will be readily apparent to one skilled in the art and alternate methods can be used.

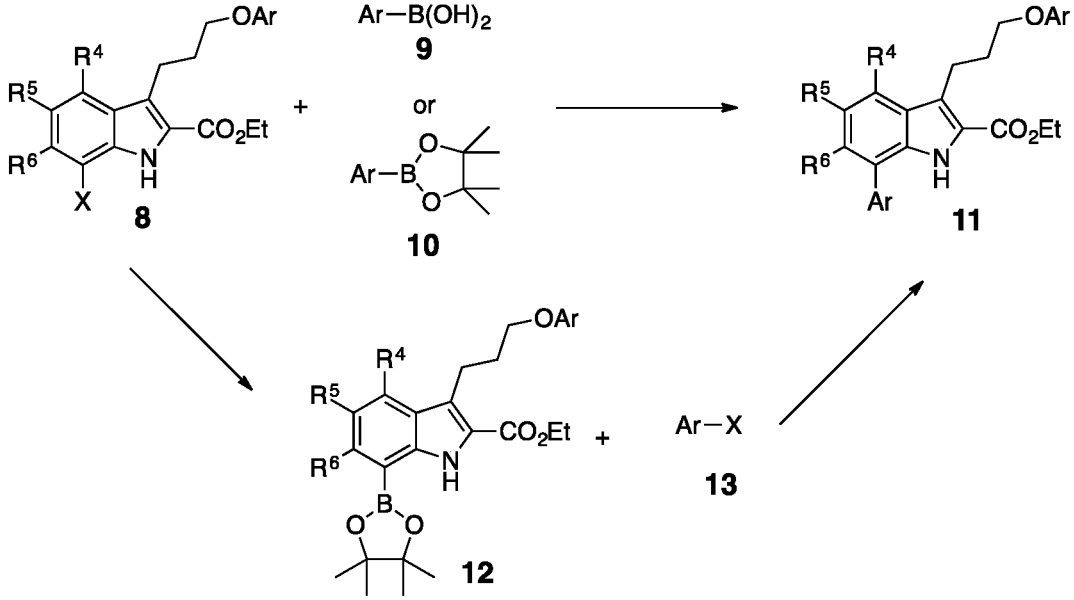
Scheme 1



[0065] In some embodiments, provided compounds of this invention may be prepared as shown in Scheme 1. Indole **3** can be assembled by using Japp-Klingemann reaction described by, but not limited to, F. G. Salituro, et al. *J. Med. Chem.* (1990) 33, 2944-2946 as follows. Aniline **1** is converted to the corresponding benzenediazonium intermediate followed by condensation with ethyl 2-oxocyclopentanecarboxylate to give hydrazone **2**. Intramolecular Fisher indole cyclization of the intermediate **2** is followed to give indole **3**.

The ethyl ester functional group at the flexible linker of indole **3** can be selectively reduced with excess BH_3, and the resulting alcohol **4** can be condensed with phenols or hydroxy-heterocycles via Mitsunobu reaction to give the ether **5** using, but not limited to, DEAD or Dt-BuAD. Indole acid **6** can be generated by saponification of compounds **5** with appropriate bases, such as Cs_2CO_3, K_2CO_3, LiOH or NaOH, at a number of conditions that are routine for those skilled in the art of organic synthesis. Indole amides **7** can be produced by coupling of compounds **6** with suitable amines using coupling reagents, but not limited to, PyBOP, DCC, EDC, HBTU, or TBTU at a number of conditions that are routine for those skilled in the art of organic synthesis.

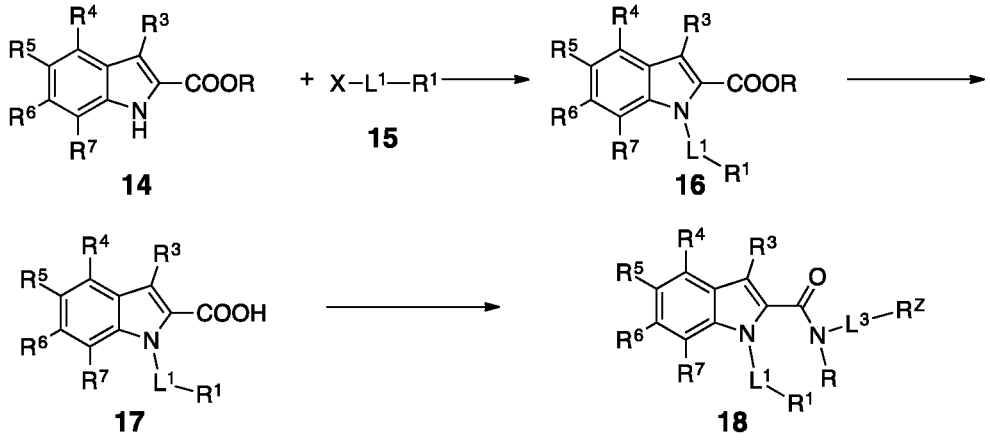
Scheme 2



[0066] In some embodiments, compounds of Formula **11** containing Ar or heteroaryl substituents as R^7 group may be synthesized by procedures illustrated in Scheme 2. Compounds of Formula **8**, wherein X = Cl, Br, I, triflates or diazoderivatives, can be prepared as previously described in Scheme 1. A variety of boronic acids **9** or borates **10**, which are commercially available or can be prepared, can be coupled with intermediates **8** *via e.g.*, Suzuki coupling protocol to afford biaryl adducts **11**(Miyaura, N., Suzuki, A., *Chem. Rev.* (1995), 2457). In some embodiments, one exemplary such procedure entails treatment of the aryl bromide or iodide **8** with an aryl boronic acid in the presence of a catalytic Pd species, such as $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, $Pd(OAc)_2$, $Pd_2(dba)_3$ and a suitable ligand such as PPh_3, $AsPh_3$, etc., or other such Pd catalyst, and a base such as Na_2CO_3, Cs_2CO_3, K_2CO_3, $Ba(OH)_2$ or Et_3N. Alternatively, biaryl adducts **11** can be prepared from Pinacolborates **12** which can be prepared from compounds **8** *via* Pd, such as $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, $Pd(OAc)_2$,

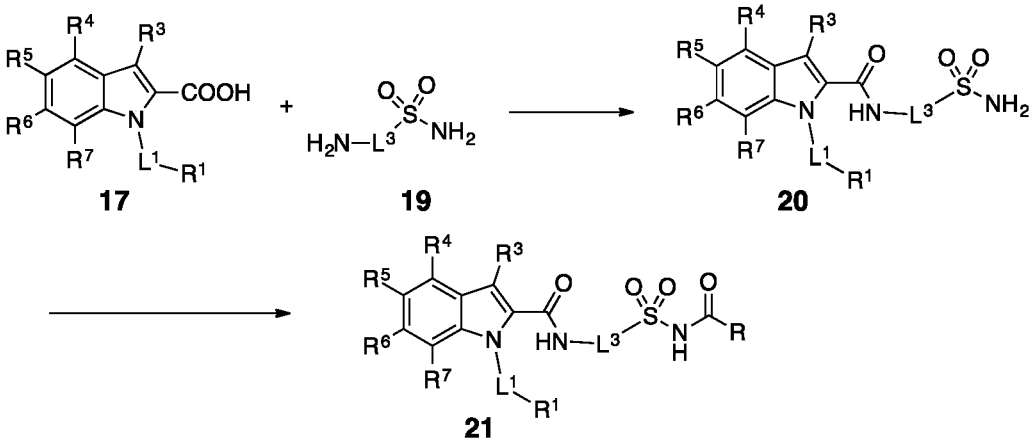
$Pd_2(dba)_3$, catalyzed coupling of bis(pinacolato)diboron. Intermediates **12** can be coupled with a variety of aryl-halides or heteroaryl-halides **13** using Suzuki coupling protocol described above to give compounds **11**. In some embodiments, a provided approach allows for great diversity in the subsequent coupling of indole boronic acids or borates with commercially available haloaromatic derivatives.

Scheme 3



[0067] In some embodiments, provided compounds of Formula **18** may be prepared by procedures outlined in Scheme 3. Compounds of Formula **14** can be reacted with compounds of Formula **15**, wherein X is Cl, Br, I, OMs, or OTs with a base such as NaH, K_2CO_3, Cs_2CO_3, Et_3N, or DIPEA in a suitable solvent such as DMF, THF, ether, DME, or the like, to give compounds of Formula **16**. Applying the same reaction sequence as described in Scheme 1, compounds of Formula **16** can undergo saponification followed by coupling reaction to give compounds of Formula **18**.

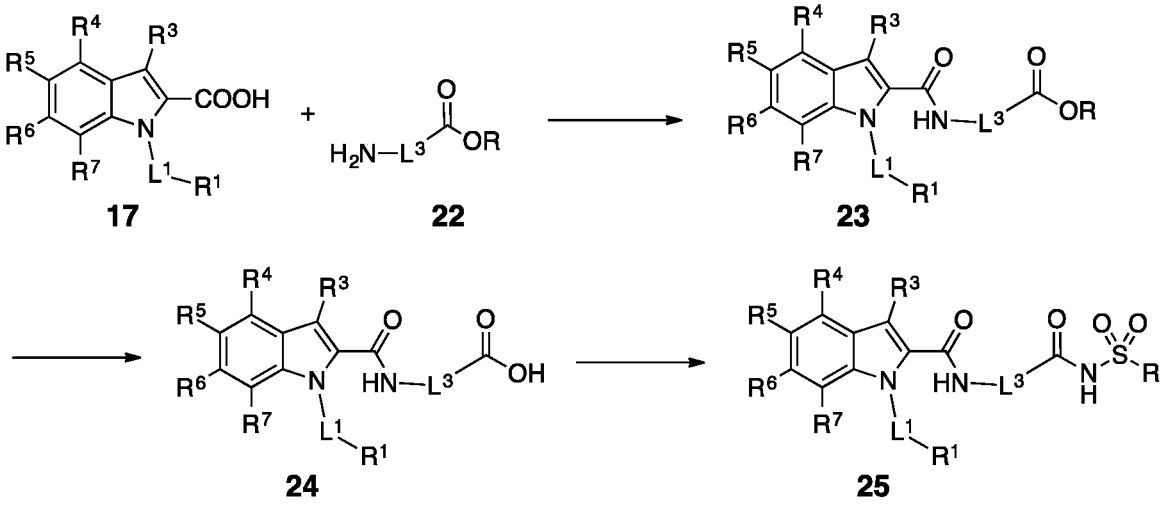
Scheme 4



[0068] In some embodiments, compounds of Formula **21** can be synthesized by procedures depicted in Scheme 4 *via* selective sequential coupling reactions in one-pot. An amino group

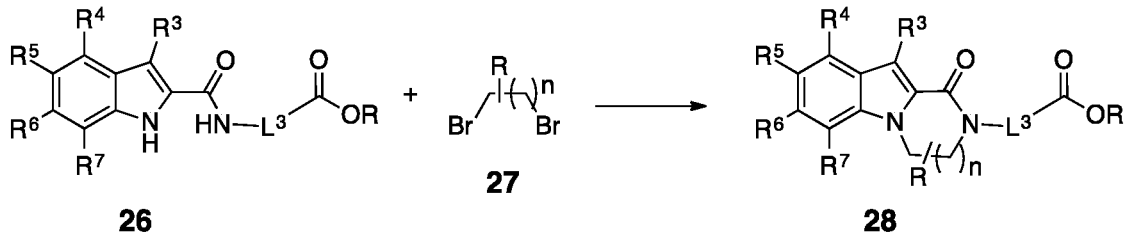
of compounds **19** can be coupled with compounds of Formula **17** as illustrated in Scheme 1 to afford intermediates **20**. In the same pot, suitable carboxylic acids can be coupled to the sulfonamide group of compounds of Formula **20** using coupling reagents, but not limited to, PyBOP, DCC, EDC, HBTU, or TBTU at a number of conditions that are routine for those skilled in the art of organic synthesis, to yield acylsulfonamides of Formula **21**.

Scheme 5



[0069] Alternatively, compounds of Formula **25** can be prepared by procedures illustrated in Scheme 5 by similar sequential coupling reactions. Compounds of Formula **17** can undergo coupling reactions with an amine functional group of compounds **22** as shown Scheme 1 to give intermediates **23**. An ester group of Formula **23** can be saponificated using aqueous based, such as Cs_2CO_3, K_2CO_3, LiOH or NaOH, at a number of conditions that are routine for those skilled in the art of organic synthesis to generated compounds of Formula **24**. Subsequent coupling reactions of acids **24** with suitable sulfonamides using coupling reagents at a number of conditions that are routine for those skilled in the art of organic synthesis to afford reverse acylsulfonamides of Formula **25**.

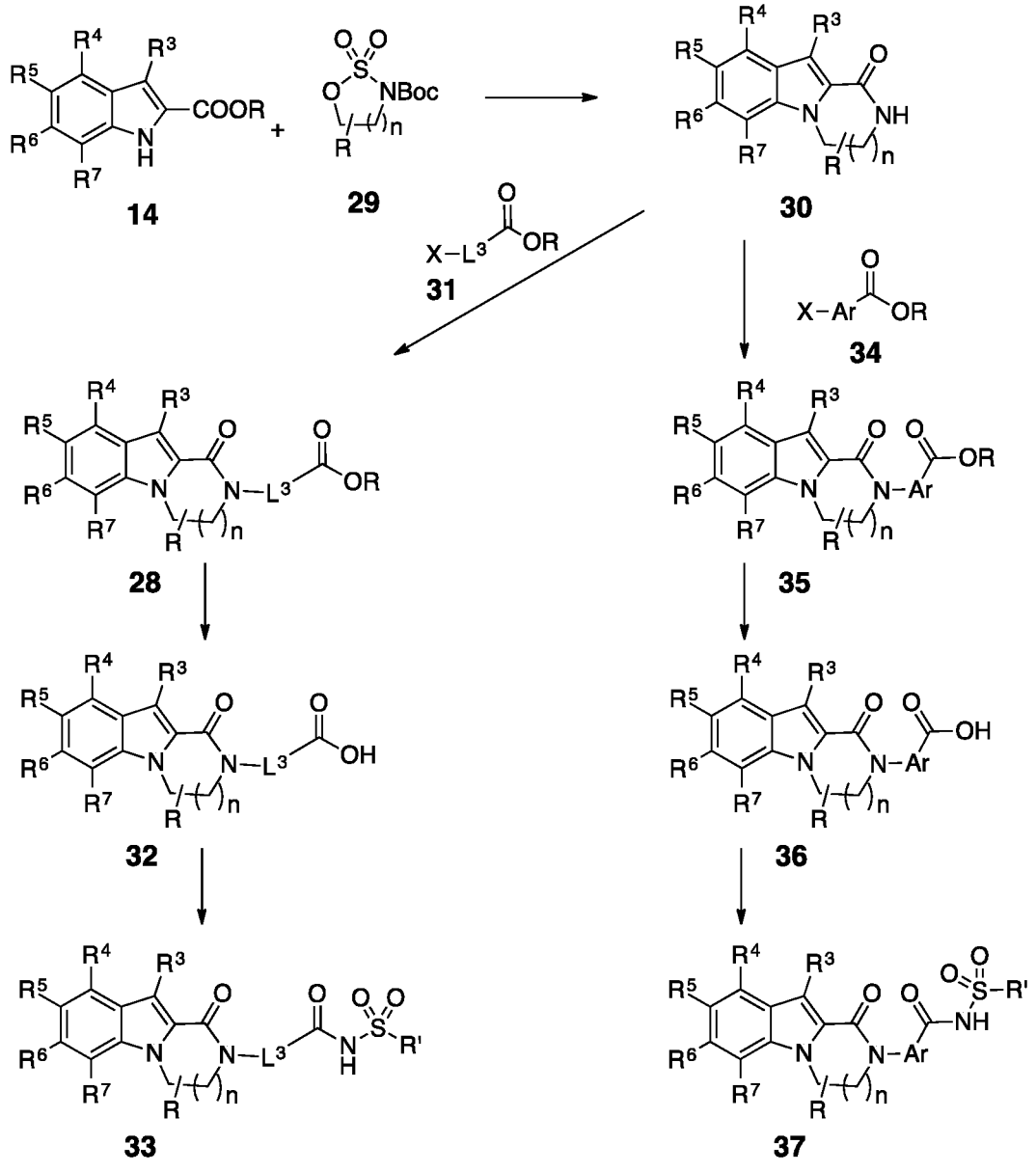
Scheme 6



[0070] Exemplary method for preparing compounds of Formula **28**, wherein the N1 position of indole and the amide NH is tethered to form rings, is described in Scheme 6 and proceeds

from compounds of Formula **26**. Optionally substituted di-bromo alkanes **27** can be used to react with indole amides **26**. The cyclization may be accomplished with a variety of bases, but not limited to, DBU, Et_3N, DIPEA, Cs_2CO_3, K_2CO_3, NaH, or *t*-BuONa in a suitable solvent such as DMF, toluene, THF, DME, CH_3CN, 1,4-dioxane or the like, to afford compounds of Formula **28** at a number of conditions that are routine for those skilled in the art of organic synthesis. Compounds of Formula **28** can be employed to subsequent reactions as depicted in above Schemes.

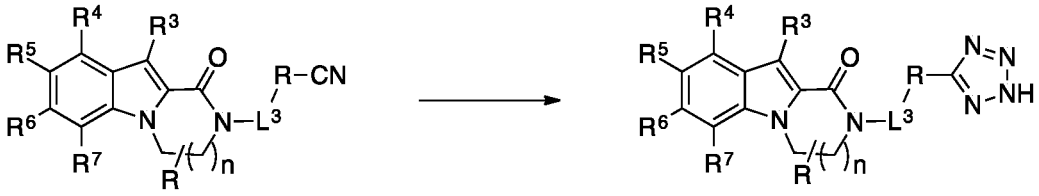
Scheme 7



[0071] An alternate route to substituted tricyclic indole amides is shown in Scheme 7 and described here. The tricyclic amide intermediates of Formula **30** can be prepared by

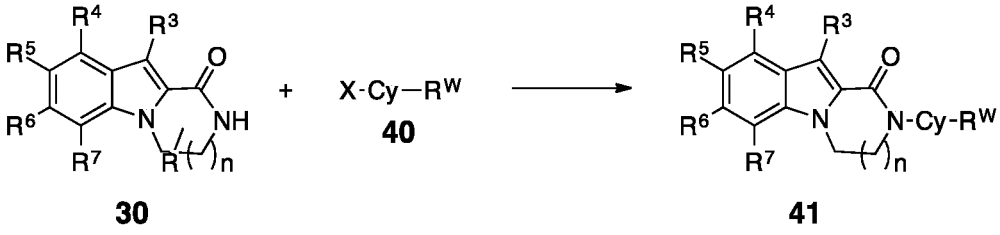
alkylation of the indole NH of ester **14** with optionally substituted cyclic sulfamidates **29** followed by cyclization upon removal of the Boc-protecting group (see, for example, Richter H. G. F. *Bioorg. Med. Chem. Lett.* **2010**, 5713). The size and stereochemistry of the newly formed cyclic amide can be controlled by size and preset stereo-configuration of the reagent **29**. The NH group of Formula **30** can undergo alkylation reactions with compounds of Formula **31**, wherein X is Cl, Br, I, OMs, or OTs with a base such as NaH, K_2CO_3, Cs_2CO_3, Et_3N, or DIPEA in a suitable solvent such as DMF, THF, ether, DME, or the like, to give compounds of Formula **28**. Corresponding compounds of Formulae **32** and **33** can be prepared from the ester **28** by saponification and coupling of sulfonamides to the carboxylic acid functional group of compounds **32** as described in Scheme 5. Alternatively, a variety of aryl or heteroaryl halides of Formula **34**, wherein X is Br, I, or OTf can be coupled to the NH group of Formula **30** in the presence of a catalytic Pd species, such as $Pd(OAc)_2$, $Pd_2(dba)_3$ and a suitable ligand such as Xantphos and a base such as Na_2CO_3, Cs_2CO_3, or K_2CO_3 to generate compounds of Formula **35**. Same saponification and coupling of sulfonamide coupling protocols described above can also be applied to prepare corresponding compounds of Formulae **36** and **37**.

Scheme 8



[0072] In some embodiments, compounds of Formula **39** containing tetrazole moiety can be generated by the procedure depicted in Scheme 8. A nitrile group of compounds **38** can undergo cyclization reation with NaN_3 in the presence salt such as NH_3Cl, $Et_3N{\cdot}HCl$ or catalytic amount of I_2, $AlCl_3$ or TMSCl in a suitable solvent such as DMF, $PhNO_2$ or NMP at a number of conditions that are routine for those skilled in the art of organic synthesis to give tetrazoles of Formula **39**.

Scheme 9



[0073] The NH group of Formula **30** can undergo cross-coupling reactions with a variety of aryl or heteroaryl halides of Formula **40**, wherein X is Br, I, or OTf in the presence of a catalytic Pd species, such as $Pd(OAc)_2$, $Pd_2(dba)_3$ and a suitable ligand such as Xantphos and a base such as Na_2CO_3, Cs_2CO_3, or K_2CO_3 to generate compounds of Formula **22**. Alternatively, compounds of Formula **30** can be produced using the Ullman coupling conditions in the presence of CuI and a suitable ligand such as (trans)-1,2-*N*,*N*'-dimethylaminocyclohexane or L-Proline and a base such as Cs_2CO_3, K_2CO_3 or K_2PO_4 in a suitable solvent such as toluene or DMF. The R^7 and R^W of Formula **21** and **22** can be further elaborated such as saponification, substitution, alkylation of NH or OH, halogenation, amidation and construction of heterocycles under a number of functional group modification conditions that are routine for those skilled in the art of organic synthesis.

ABBREVIATIONS

[0074] The following abbreviations are employed in the Examples and elsewhere herein:

Dt-BuAD = di-tert-butyl azodicarboxylate

DCM = dichloromethane

EDC = 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

TEA = triethylamine

DMAP = dimethylamino pyridine

HOBT = hydroxybenzotriazole

DBU = 1,8-Diazabicycloundec-7-ene

DMF = dimethylformamide

DMSO = dimethylsulfoxide

THF = tetrahydrofuran

K_2CO_3 = potassiumm carbonate

Cs_2CO_3 = cesium carbonate

DME = 1,2-dimethoxyethane

t-BuONa = sodium *tert*-butoxide

LDA = lithium di-isopropylamide

NaHMDS = sodium hexamethyldisilazide

LiHMDS = lithium hexamethyldisilazide

n-BuLi = n-butyl lithium

ether = diethyl ether

NaOH = sodium hydroxide

KOH = potassium hydroxide

EtOAc = ethyl acetate

Na_2CO_3 = sodium carbonate

Na_2SO_4 = sodium sulfate

$MgSO_4$ = magnesium sulfate

SiO_2 = silicon dioxide

CH_2Cl_2 = methylene chloride

MeOH = methanol

EtOH = ethanol

Hex = hexanes

HCl = hydrochloric acid

$Pd(dppf)Cl_2$ = [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II)

$Pd_2(dba)_3$ = tris(dibenzylideneacetone)dipalladium (0)

$Pd(PPh_3)_4$ = tetrakis(triphenylphosphine)palladium(0)

TFA = trifluoroacetic acid

Et_3N = triethylamine

DIPEA = N,N-diisopropylethylamine

$SnCl_2$ = tin(II) chloride

DEAD = diethyl azodicarboxylate

TBAD = dit-butyl azodicarboxylate

NaH = sodium hydride

$NaNO_2$ = sodium nitrite

CH_3COONa = sodium acetate

NaN_3 = sodium azid

MsCl = methanesulfonyl chloride

TBAI = tetrabutylammonium iodide

EtI = ethyl iodide

EtBr = ethyl bromide

TBAF = tetrabutyl ammonium fluoride

NMM = N-Methylmorpholine

NMO = N-Methylmorpholine N-oxide

DBU = 1,8-Diazabicyclo(5.4.0)undec-7-ene

PCC = Pyridinium chlorochromate

BOP = (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate

MsCl = mesyl chloride

PPA = polyphosphoric acid

min = minute(s)

h or hr = hour(s)

mL or ml = milliliter

g = gram(s)

mg = milligram(s)

mmol = millimole(s)

RT or rt = room temperature

LRMS = low resolution mass spectrometry

NMR = nuclear magnetic resonance

EXAMPLES

[0075] The following Examples are offered as illustrative as a partial scope and particular embodiments of the invention and are not meant to be limiting of the scope of the invention. Abbreviations and chemical symbols have their usual and customary meanings unless otherwise indicated. Unless otherwise indicated, the compounds described herein have been prepared, isolated and characterized using the Schemes and other methods disclosed herein or may be prepared using same.

General coupling procedure A:

[0076] A mixture of lactam (1.0 eq), bromide (2.0 eq), $Pd_2(dba)_3$ (0.1 eq), Xantphos (0.2 eq), and Cs_2CO_3 (2.5 eq) 1,4-Dioxane (1 mL) was sparged with Ar gas for 5 minutes. The reaction mixture was sealed and heated to 110 °C for 18 h. The reaction mixture was cooled to ambient temperature, poured to DCM/water (10 mL, 1:1). The organic layer was separated and the aqueous layer was extracted with DCM (2 x 5 mL). The combined organic solution was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by reverse phase HPLC or flash chromatography.

General coupling procedure B:

[0077] A mixture of lactam (1.0 eq), bromide (2.0 eq), CuI (0.5 eq), (trans)-1,2-*N*,*N*'-dimethylaminocyclohexane (1.0 eq), and K_2CO_3 (2.5 eq) in toluene (1 mL) was sparged with Ar gas for 5 min. The reaction mixture was sealed and heated to 110 °C for 18 h. Same work up and purification protocols described in general coupling procedure **A** were followed to obtaine a desire product.

General coupling procedure C:

[0078] A mixture of lactam (1.0 eq), bromide (2.0 eq), CuI (0.5 eq), (trans)-1,2-*N*,*N*'-dimethylaminocyclohexane (1.0 eq), and K_3PO_4 (2.5 eq) in DMF (1 mL) was sparged with Ar gas 5 minutes. The reaction mixture was sealed and heated to 120 °C for 18 h. Same work up and purification protocols described in general coupling procedure **A** were followed to obtaine a desire product.

General saponification procedure D:

[0079] To a solution of ester in a mixture of THF, MeOH, and H_2O (3 mL, 0.5 mL, 0.5 mL), was added LiOH (5 mg). The reaction was heated to 50 °C for 3 h then cooled to ambient temperature. The crude reaction mixture was concentrated *in vacuo*, and the residue was purified by reverse phase HPLC.

General peptide coupling procedure E:

[0080] To a solution of (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (10 mg, 0.014 mmol) and HATU (8 mg, 0.021 mmol) in DMF (1 mL) was added diisopropylethylamine (5 mg, 0.039 mmol), and the reaction was stirred at room temperature for 15 min. The appropriate amine was added, and the reaction was stirred at room temperature until complete by LCMS. Same work up and purification protocols described in general coupling procedure **A** were followed to obtaine a desire product.

General Procedure F: Headpiece Bromination & Alkylation

[0081] To a solution of indole or indazole (0.28 mmol) in DMF (2 mL) was added NBS (51 mg, 0.28 mmol) at 0 °C, and the reaction was stirred 1 h. The reaction as diluted into DCM/H_2O (20 mL, 1:1), the layers separated, and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were washed with 10% aqueous $Na_2S_2O_3$ (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was dissolved in DMF (2 mL), sodium hydride was added (14 mg, 0.34 mmol), and the reaction was allowed to stir 5 min at room temperature. Alkyl iodide (0.34 mmol) was added and the reaction was allowed to stir for 1 h. The reaction was diluted with DCM (10 mL), quenched with H_2O (10 mL), the layers separated and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic extracts were concentrated *in vacuo*. The crude residue was purified by flash chromatography.

General Procedure G: Headpiece Alkylation

[0082] To asolution of substituted indole/indazole or naphthoic acid/quinolone carboxylic acid (0.20 mmol) in DMF (2 mL) was added NaH (10 mg, 0.24 mmol) at room temperature

and stired for 5 min at room temperature. Alkyl iodide (0.24 mmol) was added, and the reaction was stirred for 1 h. The work up described in general coupling procedure **A** was followed. The crude residue was purified by flash chromatography.

General Procedure H: Alkylation of Indole Hydroxy Group

[0083] A mixture of hydroxyl-indole (1.0 eq), Cs_2CO_3 (3.0 eq) and the appropriate electrophile in DMF (0.05 M) was heated to 60 to 90 °C until complete by LCMS. The work up described in general coupling procedure **A** was followed. The crude residue was purified by flash chromatography.

General Procedure I: Alkylation of Indole Nitrogen After Coupling to Tricyclic Core

[0084] A mixture of NH-indole (1.0 eq), Cs_2CO_3 (3.0 eq) and the appropriate electrophile in DMF (0.05 M) was heated to 60 to 90 °C until complete by LCMS. The work up described in general coupling procedure **A** was followed. The crude residue was purified by flash chromatography.

General Procedure J: Mesylation and SN2 Displacement of 2-Hydroxymethyl Pyrimidine

[0085] To a solution of hydroxymethyl-pyrimidine (1.0 eq) in DCM (0.03 M) was added DIPEA (5.0 eq) followed by mesyl chloride (3.0 eq). The reaction mixture was stirred at RT for 2 h then concentrated *in vacuo*. The residue was dissolved in DMF (0.05 M), and DIPEA (5.0 eq) and the appropriate amine (5-10 eq) were added in sequence. The reaction mixture was stirred from 25 to 50 °C until complete by LCMS. The work up described in general coupling procedure **A** was followed. The crude reaction mixture was used for subsequent saponification without further purification.

Example 1

Ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate

Step A. Preparation of 5-(2-(2-bromo-3-chlorophenyl)hydrazono)-6-ethoxy-6-oxohexanoic acid

[0086] To a stirring mixture of 2-bromo-3-chloroaniline (20 mmol) in 1M HCl (25 mL) and water (5 mL) at 0 °C was added $NaNO_2$ (1.38 g, 20 mmol) in water (20 mL), CH_3COONa (9.23 g, 112 mmol) in water (25 mL) and ethyl 2-oxocyclopentane carboxylate (3.0 mL, 20 mmol) in sequence. The reaction mixture was stirred for 15 min at 0 °C then warmed to 20 °C over 2h and extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and

concentrated *in vacuo* to give the title compound as a red oil in 7.1 g (90% crude).

Step B. Preparation of ethyl 7-bromo-6-chloro-3-(3-ethoxy-3-oxopropyl)-1*H*-indole-2-carboxylate

[0087] To a solution of 5-(2-(2-bromo-3-chlorophenyl)hydrazono)-6-ethoxy-6-oxohexanoic acid (7.1 g, 18 mmol) in EtOH (30 mL) was added conc. H_2SO_4 (7.5 mL), slowly. The reaction mixture was refluxed for 1.5 h. The reaction was quenched by pouring into ice then extracted with CH_2Cl_2. The combined organic layer was washed with sat. $NaHCO_3$, water, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf Hex/EtOAc 25% gradient) to give the title compound as an off-white solid in 4.4 g (11 mmol). MS (ES) 402.0 (M+H).

Step C. Preparation of ethyl 7-bromo-6-chloro-3-(3-hydroxypropyl)-1*H*-indole-2-carboxylate

[0088] To a solution of ethyl 7-bromo-6-chloro-3-(3-ethoxy-3-oxopropyl)-1*H*-indole-2-carboxylate (1.9 g, 4.8 mmol) in THF (20 mmol) was added BH_3 in THF (20 mL, 20 mmol) at 20 °C. The reaction mixture was stirred for 15 h at 20 °C and quenched by addition of MeOH then concentrated *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf Hexane/EtOAc gradient 0-50%) to give the title compound as a white solid (1.4 g, 3.9 mmol). MS (ES) 360.1 (M+H).

Step D. Preparation of ethyl 7-bromo-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate

[0089] To a solution of ethyl 7-bromo-6-chloro-3-(3-hydroxypropyl)-1*H*-indole-2-carboxylate (101 mg, 0.28 mmol), PPh_3 (110 mg, 0.51 mmol) and 3,5-diMe-4-Cl-phenol (81 mg, 0.52 mmol) in THF (3.5 mL) was added Dt-BuAD (99 mg, 0.51 mmol) at 20 °C. The reaction mixture was stirred for 15 h at 20 °C then concentrated *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf Hexane/EtOAc gradient 0-10%) to give the title compound (105 mg, 0.21 mmol) as a colorless oil. MS (ES) 498.0 (M+H).

Step E. Preparation of ethyl 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate

[0090] To a solution of ethyl 7-bromo-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate (319 mg, 0.64 mmol) in dioxane (3.0 ml) and water (2.0 ml) at 20 was added 1,3,5-trimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (168 mg, 0.71mmol), $Pd(PPh_3)_4$ (37 mg, 0.032 mmol) and K_2CO_3 (267 mg, 1.94 mmol). The mixture was degased then heated to 125 °C in Biotage

Initiator for 40 min. The reaction was quenched by addition of water, extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf Hexane/EtOAc gradient 0-15%) to give the title compound (238 mg, 0.45 mmol) as a white solid. MS (ES) 528.2 (M+H).

Step F. Preparation of ethyl (*R*)-1-(1-((tert-butoxycarbonyl)amino)propan-2-yl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-indole-2-carboxylate

[0091] To a solution of ethyl 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-indole-2-carboxylate (360 mg, 0.68 mmol) in anhydrous DMF (2 mL) was added NaH (60%) (25 mg, 0.70 mmol) at 0 °C and stirred for 3 min. *tert*-Butyl (*S*)-5-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (0.70 mmol) was added. The reaction mixture was stirred in the ice bath for 20 min and then at RT for overnight. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with brine (2 X 30 mL), dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf, Hex/acetone = 80:20) to give the title compound (305 mg, 65%). MS (ES) 686.3 (M+H), Rf = 1.29.

Step G. Preparation of (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one

[0092] To a solution of ethyl (*R*)-1-(1-((tert-butoxycarbonyl)amino)propan-2-yl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-indole-2-carboxylate (218 mg, 0.32 mol) in anhydrous DCM (5.0 mL) at 0 °C was added TFA (1.5 mL) dropwise. The reaction mixture was warmed to RT and stirred for 2 h then concentrated *in vacuo*. The residue was dissolved in anhydrous ethanol (10 mL) then anhydrous K_2CO_3 (829 mg, 1.92 mmols) was added. The reaction mixture was stirred at RT for overnight then diluted with ethyl acetate (60 mL) and washed with brine (2X 30 mL). The organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, DCM/methanol = 0-10% gradient) to give the title compound (150 mg, 87%). MS (ES) 539.5 (M+H), Rf = 0.95.

Step H. Example 1

[0093] The title compound (210 mg, 52%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (300 mg, 0.55 mmol), ethyl 7-bromo-1*H*-indole-2-carboxylate (300 mg, 1.10 mmol), copper iodide (50 mg,

0.26 mmol), (*trans*)-N^1,N^2-dimethylcyclohexane-1,2-diamine (80 mg, 0.56 mmol), and K_2CO_3 (250 mg, 1.81 mmol). MS (ES) 726.3 (M+H).

Example 2

3-Bromo-6-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-a]indol-2(3*H*)-yl)-1-methyl-1*H*-indole-4-carboxylic acid

Step A. Preparation of ethyl 1-(3-((*tert*-butoxycarbonyl)amino)propyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate.

[0094] To a solution of ethyl 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-indole-2-carboxylate (360 mg, 0.683 mol) in anhydrous DMF (2 mL) was added NaH (60 %) (25 mg, 0.62 mol) at 0 °C and stirred for 3 min. *tert*-Butyl 2-oxo-1,3-oxazinane-3-carboxylate was added. The reaction mixture was stirred in the ice bath for 20 min then at RT overnight. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with brine (2 x 30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf, eluent 20% ethyl acetate in hexanes) to give the title compound (305 mg, 65%). ^{1}H NMR: δ 7.58 (d, *J* = 10.7 Hz, 1H), 7.23 (d, *J* = 10.7 Hz, 1H), 6.64 (s, 2H), 4.42-4.35 (m, 3H), 4.32-4.24 (m, 1H), 4.18-4.08 (m, 1H), 3.98 (t, *J* = 7.5 Hz, 2H), 3.88 (s, 3H), 3.24 (t, *J* = 9.0 Hz, 2H), 2.76 (q, *J* = 7.0 Hz, 2H), 2.34 (s, 6H), 2.13 (t, *J* = 7.0 Hz, 2H), 2.09 (s, 3H), 2.03 (s, 3H), 1.48 (t, *J* = 7.0 Hz, 2H), 1.43 (t, *J* = 9.0 Hz, 3H), 1.42 (s, 9H); ^{13}C NMR: (125 MHz in $CDCl_3$) δ 162.3, 156.7, 155.6, 146.4, 138.0, 137.2, 136.9, 134.2, 126.8, 126.1, 126.0, 125.0, 121.7, 120.9, 116.4, 114.4, 113.5, 78.9, 67.4, 60.7, 42.8, 37.9, 36.2, 31.2, 30.5, 28.3, 21.8, 20.9, 14.3, 12.3, 10.3; LCMS: R_T = 2.320 min; > 98% purity at 215 nm and 254 nm; MS (ES) 685.0 (M+H).

Step B. Preparation of 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-a]indol-1-one.

[0095] To a solution of ethyl 1-(3-((*tert*-butoxycarbonyl)amino)propyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (218 mg, 0.32 mol) in anhydrous CH_2Cl_2 at 0 °C was added TFA (1.5 mL) dropwise. The reaction mixture was warmed to RT, stirred for 2 h then concentrated *in vacuo*. The residue was dissolved in anhydrous ethanol (10 mL) then anhydrous K_2CO_3 (829 mg, 1.92 mmols) was added. The reaction mixture was stirred at RT for overnight. The reaction mixture was diluted with ethyl acetate (60 mL) and washed with brine (2 x 30 mL). The

organic layers were dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf, CH_2Cl_2/methanol = 0-10% gradient) to give the title compound (150 mg, 87%). ^{1}H NMR: (500 MHz in$CDCl_3$) δ□7.62 (d, *J* = 10.7 Hz, 2H), 7.25 (d, *J* = 10.7 Hz, 2H), 6.65 (s, 2H), 6.23 (t, *J* = 7.5 Hz, 1H), 4.06-3.93 (m, 4H), 3.90 (s, 3H), 3.22-3.15 (m, 4H), 2.35 (s, 6H), 2.20 (quint., *J* = 8.7 Hz, 2H), 2.06 (s, 3H), 2.04 (s, 3H), 1.82-1.66 (m, 2H); ^{13}C NMR: (125 MHz in $CDCl_3$) δ 166.4, 156.8, 145.8, 138.1, 136.9, 135.8, 132.9, 131.6, 126.7, 125.9, 121.7, 121.2, 120.8, 115.1, 114.5, 113.5, 67.4, 41.0, 38.5 36.1, 30.2, 30.1, 20.9, 20.4, 12.1, 10.0; LCMS: R_T = 1.896 min., > 98% purity at 215 nm and 254 nm; MS (ES) 539.0 (M+H).

Step C. Preparation of Methyl 3-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)benzoate

[0096] The title compound (66 mg, 76%) was prepared following General coupling procedure B using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (70 mg, 0.13 mmol, 1.0 eq), methyl 3-bromobenzoate (55 mg, 0.26 mmol, 2.0 eq), CuI (10 mg, 0.052 mmol, 0.40 eq), *rac*-*N*,*N*'-dimethylcyclohexane-1,2-diamine (15 mg, 0.105 mmol, 0.81 eq), and K_2CO_3 (55 mg, 0.40 mmol, 3.0 eq). ^{1}H NMR: (500 MHz in $CDCl_3$) δ 7.98-7.94 (m, H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.51-7.46 (m, 2H), 7.24 (d, *J* = 8.5 Hz, 1H), 6.61 (s, 2H), 4.16-4.06 (m, 2H), 3.96 (t, *J* = 6.0, 2H), 3.91 (s, 3H), 3.85 (s, 3H), 3.76-3.67 (m, 2H), 3.16 (oct, *J* = 7.5 Hz, 2H), 2.29 (s, 6H), 2.23 -2.16 (m, 2H), 2.06 (s, 3H), 2.05 (s, 3H), 1.92-1.80 (m, 2H); ^{13}C NMR: (125 MHz in $CDCl_3$) δ 166.2, 164.0, 156.8, 146.0, 142.3, 137.7, 136.9, 135.2, 133.0, 132.0, 131.4, 130.7, 129.3, 127.8, 126.7, 126.6, 125.9, 121.5, 121.2, 120.7, 115.5, 114.5, 113.2, 67.3, 52.2, 48.2, 40.7, 36.2, 30.2, 29.5, 20.8, 20.6, 12.3, 10.0; LCMS: R_T = 2.092 min, > 98% purity at 215 nm and 254 nm; MS (ES) 673.0 (M+H).

Step D. Example 2

[0097] To a solution of methyl 6-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-4,5-dihydro-1H-[1,4]diazepino[1,2-a]indol-2(3H)-yl)-1-methyl-1H-indole-4-carboxylate (40 mg, 0.055 mmol) in THF (0.5 mL) was added NBS (10 mg, 0.058 mmol) then stirred for 15 h at RT. LiOH (0.14 ml, 0.28 mmol, 2N) was added, and the mixtuer was heated to 70 °C for additional 6 h. The reaction was concentrated *in vacuo*, and the crude residue was dissolved in DMSO (1 mL) and filtered. The DMSO solution was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient from 30-90% CH_3CN, 0.1% TFA) to yield the title compound (28 mg, 65%) as an

off-white solid. MS (ES) 790.2 (M+H).

Example 3

3-Chloro-6-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-a]indol-2(3*H*)-yl)-1-methyl-1*H*-indole-4-carboxylic acid

[0098] The title compound was prepared (22 mg, 0.029 mmol) as a white solid according to procedures described in Example 2 Step D substituting NBS with NCS (7.4 mg, 0.055 mmol). MS (ES) 746.2 (M+H).

Example 4

6-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-1-methyl-benzotriazole-4-carboxylic acid

[0099] The title compound (6.2 mg, 16%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (30 mg, 0.056 mmol), methyl 6-bromo-1-methyl-1*H*-benzo[*d*][1,2,3]triazole-4-carboxylate (19 mg, 0.070 mmol), $Pd_2(dba)_3$ (8 mg, 0.0087 mmol), Xantphos (12 mg, 0.021 mmol), and Cs_2CO_3 (60 mg, 0.19 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.288 min, MS (ES) 714.1 (M+H).

Example 5

6-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-3-methyl-benzotriazole-4-carboxylic acid

[00100] The title compound (3.7 mg, 9.3%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (30 mg, 0.056 mmol), methyl 5-bromo-1-methyl-1*H*-benzo[*d*][1,2,3]triazole-7-carboxylate (25 mg, 0.092 mmol), $Pd_2(dba)_3$ (8 mg, 0.0087 mmol), Xantphos (12 mg, 0.021 mmol), and Cs_2CO_3 (60 mg, 0.19 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.360 min, MS (ES) 714.1 (M+H).

Example 6

7-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-1-methyl-indole-3-carbonitrile

[00101] The title compound (13 mg, 34%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (30 mg, 0.056 mmol), 7-bromo-1-methyl-1*H*-indole-3-carbonitrile (30 mg, 0.14 mmol), $Pd_2(dba)_3$ (8 mg, 0.0087 mmol), Xantphos (12 mg, 0.021 mmol), and Cs_2CO_3 (60 mg, 0.19 mmol). LCMS: R_T = 1.555 min, MS (ES) 693.1 (M+H).

Example 7

6-[8-chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-1-methyl-benzimidazole-4-carboxylic acid

Step A. Preparation of methyl 6-bromo-1-methyl-1*H*-benzo[*d*]imidazole-4-carboxylate

[00102] To a solution of 6-bromo-1*H*-benzo[*d*]imidazole-4-carboxylic acid (200 mg, 0.84 mmol) in THF (5 mL) and MeOH (1 mL) at 0 °C was added trimethylsilyldiazomethane in Et_2O (2.0 M, 0.63 mL, 1.3 mmol). The reaction was stirred for 1 h at 0 °C then warmed to RT. The reaction was quenched by addition of AcOH dropwise and concentrated *in vacuo*. The crude residue was diluted with DCM (20 mL) and washed with brine (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. To a solution of the crude residue in DMF (2 mL) was added NaH (30 mg, 1.25 mmol) at RT and stirred for 30 min. Methyl iodide (120 mg, 0.84 mmol) was added, and the reaction was stirred for 4 h at RT. The reaction mixture was cooled to -78 °C and quenched with MeOH. The mixture was diluted into DCM/H_2O (20 mL, 1:1), the organic layer separated and the aqueous layer was extracted with DCM (2 x 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by reverse phase preparative HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 20-80 % MeCN 0.1% TFA) to afford the title compound (83 mg, 37%).

Step B. Example 7

[00103] The title compound (3 mg, 8%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (30 mg, 0.056 mmol), methyl 6-bromo-1-methyl-1*H*-benzo[*d*]imidazole-4-carboxylate (35 mg, 0.13 mmol), $Pd_2(dba)_3$ (8 mg, 0.0087 mmol), Xantphos (12 mg, 0.021 mmol), and Cs_2CO_3 (60 mg, 0.19 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.048 min, MS (ES) 713.0 (M+H).

Example 8

2-(4-(*Tert*-butoxycarbonyl)piperazin-1-yl)-6-((8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)methyl)isonicotinic acid

[00104] The title compound (67 mg, 76%) was prepared following General coupling procedure A using methyl 2-chloro-6-((8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)methyl)isonicotinate (72 mg, 0.1 mmol), *tert*-butyl piperazine-1-carboxylate (22 mg, 0.12 mmol), $Pd_2(dba)_3$ (2 mg, 0.002 mmol), Xantphos (3.5 mg, 0.006 mmol), and Cs_2CO_3 (49 mg, 0.15 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.025 min, MS (ES) 858.3 (M+H).

Example 9

2-((8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)methyl)-6-(4-(furan-2-carbonyl)piperazin-1-yl)isonicotinic acid

Step A. Preparation of methyl 2-((8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)methyl)-6-(piperazin-1-yl)isonicotinate

[00105] To a solution of *tert*-butyl 4-(6-((8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)methyl)-4-(methoxycarbonyl)pyridin-2-yl)piperazine-1-carboxylate in CH_2Cl_2 (1 mL) was added TFA (0.5 mL) and the mixture was stirred at room temperature for 12 h. The reaction mixture was extracted in CH_2Cl_2 (3x15 mL), dried (anhyd. Na_2SO_4) and concentrated *in vacuo* to give the crude title compound. MS (ES) 772.2 (M+H).

Step B. Example 9

[00106] To a solution of methyl 2-((8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)methyl)-6-(piperazin-1-yl)isonicotinate (15 mg, 0.02 mmol), in CH_2Cl_2 (1 mL) at room temperature was added triethylamine (6 µL, 0.04 mmol) followed by furan-2-carbonyl chloride (4 µL, 0.04 mmol) and the mixture was stirred at room temperature for 1 h. The mixture was diluted with water (2 mL) and extracted in CH_2Cl_2 (3x5 mL), dried and concentrated *in vacuo*. The residue was dissolved in THF, MeOH, and H_2O (3 mL, 0.5 mL, 0.5 mL), and LiOH (5 mg) was added and the reaction was heated to 50 °C for 3 h. The crude was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN

gradient to 35-95 % MeCN 0.1% TFA) to afford the title compound (16 mg, 94%). LCMS: R_T = 1.785 min, MS (ES) 852.4 (M+H).

Example 10

2-((8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)methyl)-6-(piperazin-1-yl)isonicotinic acid

[00107] Title compound (54 mg, 63%) was prepared according to General saponification procedure D using methyl 2-((8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)methyl)-6-(piperazin-1-yl)isonicotinate (87 mg, 0.11 mmol). LCMS: R_T = 1.605 min, MS (ES) 758.3 (M+H).

Example 11

4-(8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1-(2-(dimethylamino)ethyl)-1*H*-indole-6-carboxylic acid

Step A. Preparation of methyl 4-amino-1-(2-(dimethylamino)ethyl)-1H-indole-6-carboxylate

[00108] To a solution of methyl 4-amino-1*H*-indole-6-carboxylate (100 mg, 0.526 mmol) in DMF (3 mL) was added NaH (63 mg, 1.6 mmol) and stirred at RT for 15 min. 2-Bromo-N,N-dimethylethan-1-amine (96 mg, 0.631 mmol) was added, and the resulting minture was stirred for 30 min then quenched by TFA (0.081 mL, 1.0 mmol). The reaction mixture was concentrated, and the residue was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 0-50 % MeCN 0.1% TFA) to give the title compound (50 mg, 36%) product. MS (ES) 262.3 (M+H).

Step B. Preparation of methyl 4-(6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1*H*-indole-2-carboxamido)-1-(2-(dimethylamino)ethyl)-1*H*-indole-6-carboxylate

[00109] To a solution of 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (70 mg, 0.14 mmol), methyl 4-amino-1-(2-(dimethylamino)ethyl)-1H-indole-6-carboxylate (40 mg, 0.15 mmol) and DMAP (34 mg, 0.28 mmol) in DCM (2 mL) was added EDC (54 mg, 0.28 mmol) and stirred at RT for 16 h. The reaction mixture was concentrated, and the residue was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 0-50 % MeCN 0.1% TFA) to give the title compound (24 mg, 23%). LCMS: R_T = 1.695 min, MS (ES) 742.8 (M+H).

Step C. Example 11

[00110] To a solution of methyl 4-(6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-indole-2-carboxamido)-1-(2-(dimethylamino)ethyl)-1H-indole-6-carboxylate (24 mg, 0.032 mmol) and 1,3-dibromopropane (9.8 µl, 0.097 mmol) in DMF (0.5 mL) was added Cs_2CO_3 (53 mg, 0.16 mmol) then stirred at rt for 20 h. The reaction mixture was filtered, and the filterate was concentrated. The residue was dissolved in THF (1 mL) and LiOH (0.2 mL, 2N) and stirred at 60 °C overnight. The reaction mixture was concentrated, and the residue was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 30-80 % MeCN 0.1% TFA) to give the title compound (9 mg, 36%). LCMS: R_T = 1.671 min, MS (ES) 768.7 (M+H).

Example 12

6-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-2-(2-morpholinoethyl)indazole-4-carboxylic acid

Step A. Preparaion of methyl 6-bromo-2-(2-morpholinoethyl)-2*H*-indazole-4-carboxylate

[00111] To a solution of methyl 6-bromo-1*H*-indazole-4-carboxylate (100 mg, 0.392 mmol) in DMF (5 mL) was added NaH (30 mg, 1.25 mmol) at RT. The reaction mixture was stirred for 30 min, followed by addition of 4-(2-bromoethyl)morpholine (120 mg, 0.619 mmol). After 4 h, the reaction was quenched with water then concentrated *in vacuo*. The residue was purified by reverse phase preparative HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 20-75 % MeCN 0.1% TFA) to separate the regioisomeric indazole intermediates. The desire region-isomer was dissolved in THF (5 mL) and MeOH (1 mL) and trimethylsilyldiazomethane (2.0 M in Et_2O, 0.25 mL, 0.50 mmol) was added. The reaction was stired for 30 min at RT then quenched by addition of AcOH dropwise and concentrated *in vacuo* to afford the title compound (21 mg, 15%).

Step B. Example 12

[00112] The title compound (4.6 mg, 10%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (30 mg, 0.056 mmol), methyl 6-bromo-2-(2-morpholinoethyl)-2*H*-indazole-4-carboxylate (20 mg, 0.054 mmol), $Pd_2(dba)_3$ (8 mg, 0.0087 mmol), Xantphos (12 mg, 0.021 mmol), and Cs_2CO_3 (60 mg, 0.19 mmol) followed by . saponification using General Procedure D. LCMS: R_T = 1.048 min, MS (ES) 812.1 (M+H).

Example 13

7-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-1-methyl-indazole-3-carboxylic acid

[00113] The title compound (2.7 mg, 7%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (30 mg, 0.056 mmol), methyl 7-bromo-1-methyl-1*H*-indazole-3-carboxylate (12 mg, 0.045 mmol), $Pd_2(dba)_3$ (8 mg, 0.0087 mmol), Xantphos (12 mg, 0.021 mmol), and Cs_2CO_3 (60 mg, 0.19 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.843 min, MS (ES) 712.7 (M+H).

Example 14

6-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-1-(2-morpholinoethyl)indazole-4-carboxylic acid

Step A. Preparation of methyl 6-bromo-1-(2-morpholinoethyl)-1*H*-indazole-4-carboxylate

[00114] The title compound (34 mg, 24%) was prepared following the same procedure as Example 12, Step A.

Step B. Example 14

[00115] The title compound (7.4 mg, 17%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (30 mg, 0.056 mmol), methyl 6-bromo-1-(2-morpholinoethyl)-1*H*-indazole-4-carboxylate (34 mg, 0.092 mmol), $Pd_2(dba)_3$ (8 mg, 0.0087 mmol), Xantphos (12 mg, 0.021 mmol), and Cs_2CO_3 (60 mg, 0.19 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.661 min, MS (ES) 811.8 (M+H).

Example 15

8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-2-[1-methyl-3-(2*H*-tetrazol-5-yl)indol-7-yl]-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-1-one

[00116] To a solution of 7-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1-methyl-1*H*-indole-3-carbonitrile (10 mg, 0.014 mmol) in DMF (1 mL) was added NaN_3 (10

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mg, 0.15 mmol) and ammonium chloride (10 mg, 0.19 mmol). The reaction was capped and heated to 130 °C for 72 h then cooled to RT. The work up described in general coupling procedure **A** was followed then purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient 35-95 % MeCN 0.1% TFA) to afford the title compound (2 mg, 19%). LCMS: R_T = 1.980 min, MS (ES) 735.9 (M+H).

Example 16

7-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-2-methyl-indazole-3-carboxylic acid

[00117] The title compound (6.1 mg, 16%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (30 mg, 0.056 mmol), methyl 7-bromo-2-methyl-2*H*-indazole-3-carboxylate (12 mg, 0.045 mmol), $Pd_2(dba)_3$ (8 mg, 0.0087 mmol), Xantphos (29 mg, 0.11 mmol), and Cs_2CO_3 (60 mg, 0.19 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.463 min, MS (ES) 713.0 (M+H).

Example 17

2-(4-acetylpiperazin-1-yl)-6-((8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-4,5-dihydro-1H-[1,4]diazepino[1,2-a]indol-2(3H)-yl)methyl)isonicotinic acid

[00118] To a solution of methyl 2-((8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)methyl)-6-(piperazin-1-yl)isonicotinate (15 mg, 0.02 mmol), in CH_2Cl_2 (1 mL) at RT was added triethylamine (6 µL, 0.04 mmol) followed by acetyl chloride (3 µL, 0.04 mmol) and the mixture was stirred at room temperature for 1 h. The mixture was diluted with water (2 mL) and extracted in CH_2Cl_2 (3x5 mL), dried and evaporated. The crude material was subjected to saponification conditions following General Procedure D followed by purification by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA) to afford the title compound (14 mg, 88%). LCMS: R_T = 1.721 min, MS (ES) 800.4 (M+H).

Example 18

5-[8-chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-2,3-dihydrobenzofuran-7-carboxylic acid

[00119] The title compound (2 mg, 5%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (30 mg, 0.056 mmol), methyl 5-bromo-2,3-dihydrobenzofuran-7-carboxylate (30 mg, 0.12 mmol), $Pd_2(dba)_3$ (8 mg, 0.0087 mmol), Xantphos (29 mg, 0.11 mmol), and Cs_2CO_3 (60 mg, 0.19 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.825 min, MS (ES) 700.8 (M+H).

Example 19

(*R*)-5-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-3-ethyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)quinoline-8-carboxylic acid

[00120] The title compound (53% yield) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-3-ethyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one and methyl 5-bromoquinoline-8-carboxylate followed by saponification using General Procedure D. MS (ES) 724.3 (M+H).

Example 20

(*R*)-6-((7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-3-ethyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)methyl)nicotinic acid

[00121] To a solution of (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-3-ethyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one (25 mg, 46 mmol) in anhydrous DMF (2 mL) was added NaH (60%) (3 mg, 78 mmol) at 0 °C under N_2 atmosphere and stirred for 10 min. Methyl 6-(bromomethyl)nicotinate (1.7 eq.) was added to the reaction mixture and stirred for 10 min at 0 °C and 1 h at RT. The reaction mixture was diluted with ethyl acetate (20 mL), washed with brine (2 X 10 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude material was subjected to saponification conditions following General Procedure D followed by purification by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 50-95 % MeCN 0.1% TFA) to give the title compound (68% yield). MS (ES) 688.3 (M+H) Rf = 0.79.

Example 21

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-3-ethyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)benzoic acid

[00122] The title compound (52% yield) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-3-ethyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one and methyl 3-bromobenzoate followed by saponification using General Procedure D. MS (ES) 673.2 (M+H).

Example 22

2-(5-(8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1-methyl-1*H*-indol-3-yl)acetic acid

[00123] The title compound (56 mg, 77%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (54 mg, 0.1 mmol), methyl 2-(5-bromo-1-methyl-1*H*-indol-3-yl)acetate (34 mg, 0.12 mmol), $Pd_2(dba)_3$ (2 mg, 0.002 mmol), Xantphos (3.5 mg, 0.006 mmol), and Cs_2CO_3 (49 mg, 0.15 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.756 min, MS (ES) 726.3 (M+H).

Example 23

(*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-3-ethyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)benzoic acid

[00124] The title compound (85% yield) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-3-ethyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one and methyl 4-bromobenzoate followed by saponification using General Procedure D. MS (ES) 673.2 (M+H); ^{1}H-NMR ($CDCl_3$) δ 8.14 (d, 2H, J = 8 Hz), 8.10 (m, 1H), 7.47 (d, 1H, J = 8 Hz) 7.75 (m, 1H), 7.32 -7.28 (m, 1H), 6.65 (s, 2H), 4.11 (tr, 2H, J = 8 Hz), 3.97 (multiple s, m, 5H), 3.52-3.34 (m, 2H), 2.33 (s, 6H), 2.30-2.09 (overlapped multiple s, tr, 10H), 1.64 (m, 2H), 0.57 (tr, 3H, J = 8 Hz).

Example 24

(*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-3-ethyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one

[00125] To a solution of ethyl 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethylpyrimidin-5-yl)-1H-indole-2-carboxylate (1.25 g, 2.37 mmol) in anhydrous acetonitrile (20 mL) was added cesium carbonate (1.5 g, 4.74 mmol) follow by *tert*-butyl (*R*)-

4-ethyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (3.8 mmols). The reaction mixture was stirred at 80 °C for overnight. Additional cesium carbonate (0.5 eq) and *tert*-butyl (*R*)-4-ethyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (0.5 eq) were added to the mixture and the reaction was heated for additional 6 h at 80 °C. The reaction mixture was cooled to abient temperature, diluted with ethyl acetate (100 mL). The solution was washed with brine (3 X 50 mL), dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in anhydrous DCM (30 mL) and cooled to 0 °C then TFA (10 eq) was added dropwise. The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated to driness then re-dissolved in anhydrous EtOH (20 mL). Anhydrous K_2CO_3 (15 eq.) was added and the reaction mixture was stirred at RT for 2 h then concentrated to 1/3 of original volume and diluted with ethyl acetate (100 mL). The solution was washed with brine (3 X 50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf, DCM/methanol = 0-5% gradient) to give the title compound (80% for 3 steps). MS (ES) 553.2 (M+H), Rf = 0.84; ^{1}H-NMR ($CDCl_3$) δ 7.66 (d, 1H, J = 8 Hz), 7.24 (d, 1H, J = 8 Hz), 6.65 (s, 2H), 5.77 (m, 1H), 4.03(tr, 2H, J = 8 Hz), 3.99 (s, 3H), 3.52-3.50 (m, 1H), 3.49-3.38 (m, 1H), 3.38-3.34 (m, 2H), 2.35 (s, 6H), 2.19 (tr, 2H, J = 8 Hz), 2.09 (2s, 6H), 1.59 (m, 2H), 1.26 (tr, 3H, J = 8 Hz).

Example 25

7-(8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-a]indol-2(3*H*)-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-5-carboxylic acid

[00126] The title compound was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one and methyl 7-bromo-2,3-dihydrobenzo[*b*][1,4]dioxine-5-carboxylate followed by saponification using General Procedure D. MS (ES) 717.2 (M+H).

Example 26

(*R*)-8-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylic acid

[00127] The title compound (45% yield) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one and methyl 8-

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bromo-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxylate followed by saponification using General Procedure D. MS (ES) 717.2 (M+H).

Example 27

2-((8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)methyl)-6-(4-((5-methylfuran-2-yl)sulfonyl)piperazin-1-yl)isonicotinic acid

[00128] To a solution of methyl 2-((8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)methyl)-6-(piperazin-1-yl)isonicotinate (15 mg, 0.02 mmol), in CH_2Cl_2 (1 mL) at RT was added Et_3N (6 µL, 0.04 mmol) followed by 5-methylfuran-2-sulfonyl chloride (6 µL, 0.04 mmol) and the mixture was stirred at room temperature for 1 h. The mixture was diluted with water (2 mL) and extracted in CH_2Cl_2 (3x5 mL), dried and concentrated. The crude material was subjected to saponification conditions following General Procedure D and purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA) to afford the title compound (13 mg, 69%). LCMS: R_T = 2.019 min, MS (ES) 902.3 (M+H).

Example 28

4-[8-chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-2-[2-(dimethylamino)ethyl]indazole-6-carboxylic acid

Step A. Preparation of methyl 4-bromo-2-(2-(dimethylamino)ethyl)-2*H*-indazole-6-carboxylate

[00129] The title compound (28 mg, 22%) was prepared following General Procedure G using methyl 4-bromo-1*H*-indazole-6-carboxylate (100 mg, 0.393 mmol), NaH (15 mg, 0.625 mmol), and 2-bromo-*N*,*N*-dimethylethan-1-amine (120 mg, 0.515 mmol).

Step B. Example 28

[00130] The title compound (22 mg, 51%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (30 mg, 0.056 mmol), methyl 4-bromo-2-(2-(dimethylamino)ethyl)-2*H*-indazole-6-carboxylate (20 mg, 0.061 mmol), $Pd_2(dba)_3$ (5 mg, 0.0054 mmol), Xantphos (8 mg, 0.013 mmol), and Cs_2CO_3 (60 mg, 0.19 mmol) followed by saponification using General Procedure D using LiOH (5 mg, 0.21 mmol). LCMS: R_T = 1.631 min, MS (ES) 770.2 (M+H); ^{1}H NMR (400 MHz,

DMSO-d_6) δ 8.71 (s, 1H), 8.24 (d, J = 1.2 Hz, 1H), 7.73 (d, J = 8.6 Hz, 1H), 7.48 (d, J = 1.1 Hz, 1H), 7.27 (d, J = 8.6 Hz, 1H), 6.73 (s, 2H), 4.98 (t, J = 6.7 Hz, 2H), 4.13 (t, J = 6.8 Hz, 2H), 3.98 (t, J = 6.4 Hz, 2H), 3.78 (s, 3H), 3.76-3.74 (m, 4H), 3.09 – 3.00 (m, 2H), 2.77 (s, 3H), 2.76 (s, 3H), 2.24 (s, 6H), 2.13 – 1.99 (m, 5H), 1.93 (s, 3H), 1.75 (quint, J = 8.0 Hz, 2H).

Example 29

(*R*)-6-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-3-ethyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-4-carboxylic acid

[00131] The title compound (45% yield) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-3-ethyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one and methyl 6-bromo-1-methyl-1*H*-indole-4-carboxylate followed by saponification using General Procedure D. MS (ES) 727.2 (M+H).

Example 30

6-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-1-[2-(dimethylamino)ethyl]indazole-4-carboxylic acid

Step A. Preparation of methyl 6-bromo-1-(2-(dimethylamino)ethyl)-1*H*-indazole-4-carboxylate

[00132] The title compound (39 mg, 30%) was prepared following the procedure described Example 12, Step A using methyl 6-bromo-1*H*-indazole-4-carboxylate (100 mg, 0.392 mmol), NaH (30 mg, 1.25 mmol), 2-bromo-*N*,*N*-dimethylethan-1-amine HBr salt (130 mg, 0.56 mmol), and trimethylsilyldiazomethane (2.0 M in Et_2O, 0.1 mL, 0.2 mmol).

Step B. Example 30

[00133] The title compound (17 mg, 40%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (30 mg, 0.056 mmol), methyl 6-bromo-1-(2-(dimethylamino)ethyl)-1*H*-indazole-4-carboxylate (20 mg, 0.061 mmol), $Pd_2(dba)_3$ (5 mg, 0.0054 mmol), Xantphos (8 mg, 0.013 mmol), and Cs_2CO_3 (60 mg, 0.19 mmol) followed by saponification using General Procedure D using LiOH (5 mg, 0.21 mmol). LCMS: R_T = 1.656 min, MS (ES) 770.3 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (d, J = 0.8 Hz, 1H), 8.25 (t, J = 1.3 Hz, 1H), 7.90 (d, J = 1.7 Hz, 1H), 7.73 (d, J = 8.6 Hz, 1H), 7.27 (d, J = 8.5 Hz, 1H), 6.74 (s, 2H), 4.97 (t, J = 6.7 Hz, 2H), 4.08 (t, J = 8.0 Hz, 2H), 3.98 (t, J = 6.3 Hz, 2H), 3.83 – 3.70 (m, 5H), 3.62-3.59 (m, 2H), 3.06 (t, J = 8.0

Hz, 2H), 2.78 (s, 3H), 2.77 (s, 3H), 2.22 (s, 6H), 2.15 – 2.00 (m, 5H), 1.96 – 1.83 (m, 5H).

Example 31

6-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1-(2-morpholinoethyl)-1*H*-indole-4-carboxylic acid

Step A. Preparation of methyl 6-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-4-carboxylate

[00134] To a solution of methyl 6-bromo-1*H*-indole-4-carboxylate (200 mg, 0.79 mmol) in DMF (5 mL) was added NaH (38 mg, 0.95 mmol) and stirred at rt for 15 min. (2-(Chloromethoxy)ethyl)trimethylsilane (197 mg, 1.2 mmol) was added, and the resulting minture was stirred for additional 30 min. The reaction was quenched by addition of MeOH (1 mL) then concentrated *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-25% gradient) to give the title compound (270 mg, 89%) as a colorless oil. LCMS: R_T = 1.939 min, MS (ES) 384.1 (M+H)

Step B. Preparation of methyl 6-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-a]indol-2(3*H*)-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-4-carboxylate

[00135] The title compound (187 mg, 80%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (150 mg, 0.278 mmol), methyl 6-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole-4-carboxylate (128 mg, 0.334 mmol), $Pd_2(dba)_3$ (5 mg, 0.0054 mmol), Xantphos (8 mg, 0.013 mmol), and Cs_2CO_3 (181 mg, 0.556 mmol). LCMS: R_T = 2.461 min, MS (ES) 842.3 (M+H).

Step C. Preparation of methyl 6-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-a]indol-2(3*H*)-yl)-1*H*-indole-4-carboxylate

[00136] A mixture of methyl 6-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-4,5-dihydro-1H-[1,4]diazepino[1,2-a]indol-2(3H)-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole-4-carboxylate (170 mg, 0.202 mmol), TBAF (2.0 ml, 2.0 mmol) was heated to 100 °C under microwave irradiation in Biotage Initiator for 20 min. The reaction was quenched by addition of H_2O (5 mL) then extracted with DCM (10 mL x 2). The combined organic solution was concentrated and purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA) to give the title compound (80 mg, 56%). LCMS: R_T = 2.065 min, MS (ES) 712.3

(M+H).

Step D. Example 31

[00137] To a solution of methyl 6-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-a]indol-2(3*H*)-yl)-1*H*-indole-4-carboxylate (20 mg, 0.028 mmol) in DMF (0.5 mL) was added NaH (4.5 mg, 0.11 mmol) then stirred for 20 min. 4-(2-Bromoethyl)morpholine (16 mg, 0.084 mmol) was added, and the resulting mixture was stirred at rt for 20 h. The reaction was quenched by MeOH (0.5 mL), acidified with TFA and purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 30-80% MeCN 0.1% TFA) to give the title compound (9.8 mg, 43%). LCMS: R_T = 1.670 min, MS (ES) 811.3 (M+H).

Example 32

4-(8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-a]indol-2(3*H*)-yl)-1-(methylsulfonyl)-1*H*-indole-6-carboxylic acid

Step A. Preparation of methyl 4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-6-carboxylate e

[00138] The title compounds were prepared according to procedures described in Example 31 Step A using methyl 4-bromo-1H-indole-6-carboxylate. MS (ES) 384.1 (M+H).

Step B. Preparation of methyl 4-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-a]indol-2(3*H*)-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-6-carboxylate

[00139] The title compound was prepared according to the procedure in Example 31 Step B substituting methyl 6-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-4-carboxylate with methyl 4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-6-carboxylate. MS (ES) 842.3 (M+H).

Step C. Preparation of methyl 4-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-a]indol-2(3*H*)-yl)-1*H*-indole-6-carboxylate

[00140] The title compound (50 mg, 59%) was prepared according to the procedure in Example 31 Step C using methyl 4-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-a]indol-2(3*H*)-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-6-carboxylate (100 mg, 0.12 mmol) and TBAF (0.593 mL, 0.593 mmol). LCMS: R_T = 2.056 min, MS (ES) 712.2 (M+H).

Step D. Example 32.

[00141] To a solution of methyl 4-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-a]indol-2(3*H*)-yl)-1*H*-indole-6-carboxylate (25 mg, 0.035 mmol) in DMF (1 mL) was added NaH (4.21 mg, 0.105 mmol) and stirred for 15 min. MsCl (8.20 µl, 0.11 mmol) was added and the resulting mixture was stirred overnight. The reaction mixture was concentrated and the residue was dissolved into THF (0.3 mL) and LiOH (0.2 mL, 2 N) then stirred at 60 °C for 4 h. The reaction mixture was concentrated, and the residue was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 40-90 % MeCN 0.1% TFA) to give the title compound (4 mg, 15%) as an off-white solid. LCMS: R_T = 1.979 min, MS (ES) 775.9 (M+H).

Example 33

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)benzo[*d*][1,3]dioxole-5-carboxylic acid

[00142] The title compound (42% yield) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one and methyl 7-bromobenzo[*d*][1,3]dioxole-5-carboxylate followed by saponification using General Procedure D. MS (ES) 703.2 (M+H).

Example 34

2-((8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)methyl)-6-(4-(dimethylcarbamoyl)piperazin-1-yl)isonicotinic acid

[00143] To a solution of methyl 2-((8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)methyl)-6-(piperazin-1-yl)isonicotinate (15 mg, 0.02 mmol), in CH_2Cl_2 (1 mL) at room temperature was added triethylamine (6 µL, 0.04 mmol) followed by dimethylcarbamic chloride (4 µL, 0.04 mmol) then the mixture was stirred at RT for 1 h. The mixture was diluted with water (2 mL) and extracted in CH_2Cl_2 (3x5 mL), dried and concentrated. The crude material was subjected to saponification conditions following General Procedure D and purified by reverse phase HPLC (Phenomenex Gemini C18,

H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA) to afford the title compound (11 mg, 66%). LCMS: R_T = 1.761 min, MS (ES) 829.3 (M+H).

Example 35

(*R*)-2-chloro-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)benzoic acid

[00144] The title compound (88% yield) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one and methyl 4-bromo-2-chlorobenzoate followed by saponification using General Procedure D. MS (ES) 693.2 (M+H).

Example 36

4-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-2-methyl-indazole-6-carboxylic acid

[00145] The title compound (26 mg, 65%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (30 mg, 0.056 mmol), methyl 4-bromo-2-methyl-2*H*-indazole-6-carboxylate (20 mg, 0.074 mmol), $Pd_2(dba)_3$ (5 mg, 0.0054 mmol), Xantphos (8 mg, 0.013 mmol), and Cs_2CO_3 (60 mg, 0.19 mmol) followed by saponification using General Procedure D using LiOH (5 mg, 0.21 mmol). LCMS: R_T = 1.873 min, MS (ES) 713.1 (M+H).

Example 37

5-(8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1*H*-1,2,4-triazole-3-carboxylic acid

[00146] To a solution of 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (50 mg, 0.1 mmol) in DMF (2 mL) were added methyl 5-amino-1*H*-1,2,4-triazole-3-carboxylate (15 mg, 0.1 mmol), HBTU (76 mg, 0.2 mmol), triethylamine (42 µL, 0.3 mmol), and the mixture was stirred at RT for 10 h. Water (5 mL) was added to the mixture and extracted with CH_2Cl_2 (3 x 5 mL). The organic layer was dried (anhyd. Na_2SO_4) and concentrated. To the solution crude in DMF (3 mL) were added 1,3-dibromopropane (42 µL, 0.4 mmol) and Cs_2CO_3 (130 mg, 0.4 mmol). The mixture was stirred at 40 °C for 6 h, filtered, diluted with water (5 mL) and extracted with

CH_2Cl_2 (3 x 5 mL). The organic layer was dried (anhyd. Na_2SO_4) and concentrated *in vacuo*. The crude material was subjected to saponification conditions following General Procedure D and purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA) to afford the title compound (34 mg, 52%). LCMS: R_T = 2.088 min, MS (ES) 650.2 (M+H).

Example 38

2-((8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)methyl)-6-(4-(phenethylsulfonyl)piperazin-1-yl)isonicotinic acid

[00147] To a solution of methyl 2-((8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)methyl)-6-(piperazin-1-yl)isonicotinate (15 mg, 0.02 mmol), in CH_2Cl_2 (1 mL) at room temperature was added triethylamine (6 µL, 0.04 mmol) followed by 2-phenylethane-1-sulfonyl chloride (8 mg, 0.04 mmol) and the mixture was stirred at RT for 1 h. The mixture was diluted with water (2 mL) and extracted with CH_2Cl_2 (3x5 mL), dried and concentrated. The crude material was subjected to saponification conditions following General Procedure D and purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA) to afford the title compound (17 mg, 92%). LCMS: R_T = 1.959 min, MS (ES) 926.3 (M+H).

Example 39

6-[8-chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-1-ethyl-indazole-4-carboxylic acid

Step A. Preparation of methyl 6-bromo-1-ethyl-1*H*-indazole-4-carboxylate

[00148] The title compound (44 mg, 39%) was prepared following the procedure described Example 12, Step A using methyl 6-bromo-1*H*-indazole-4-carboxylate (100 mg, 0.392 mmol) and ethyl bromide (85 mg, 0.78 mmoL).

Step B. Example 39

[00149] The title compound (6 mg, 18%) was prepared following General Procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (25 mg, 0.046 mmol), methyl 6-bromo-1-ethyl-1*H*-indazole-4-carboxylate (20 mg, 0.071 mmol), $Pd_2(dba)_3$ (4 mg, 0.0044

mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (60 mg, 0.19 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.977 min, MS (ES) 727.2 (M+H).

Example 40

4-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-1-[2-(dimethylamino)ethyl]indazole-6-carboxylic acid

Step A. Preparation of methyl 4-bromo-1-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxylate

[00150] The title compound (70 mg, 55%) was prepared following the procedure described Example 12, Step A using methyl 4-bromo-1*H*-indazole-6-carboxylate (100 mg, 0.393 mmol) and 2-bromo-*N*,*N*-dimethylethan-1-amine (120 mg, 0.515 mmol).

Step B. Example 40

[00151] The title compound (26 mg, 60%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (30 mg, 0.056 mmol), methyl 4-bromo-1-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxylate (20 mg, 0.061 mmol), $Pd_2(dba)_3$ (5 mg, 0.0054 mmol), Xantphos (8 mg, 0.013 mmol), and Cs_2CO_3 (60 mg, 0.19 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.666 min, MS (ES) 770.3 (M+H).

Example 41

(*R*)-5-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-3-ethyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-7-carboxylic acid

[00152] The title compound (48% yield) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-3-ethyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one and methyl 5-bromo-1-methyl-1*H*-indole-7-carboxylate followed by saponification using General Procedure D. MS (ES) 726.2 (M+H).

Example 42

6-[8-chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-2-[2-(dimethylamino)ethyl]indazole-4-carboxylic acid

Step A. Preparation of methyl 6-bromo-2-(2-(dimethylamino)ethyl)-2*H*-indazole-4-carboxylate

[00153] The title compound (13 mg, 10%) was prepared following the procedure described Example 12, Step A using methyl 6-bromo-1*H*-indazole-4-carboxylate (100 mg, 0.392 mmol), sodium hydride (30 mg, 1.25 mmol), 2-bromo-*N*,*N*-dimethylethan-1-amine HBr salt (130 mg, 0.56 mmol).

Step B. Example 42

[00154] The title compound (12 mg, 28%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (30 mg, 0.056 mmol), methyl 6-bromo-2-(2-(dimethylamino)ethyl)-2*H*-indazole-4-carboxylate (13 mg, 0.039 mmol), $Pd_2(dba)_3$ (5 mg, 0.0054 mmol), Xantphos (8 mg, 0.013 mmol), and Cs_2CO_3 (60 mg, 0.19 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.662 min, MS (ES) 770.2 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (s, 1H), 7.90 – 7.83 (m, 1H), 7.80 (d, *J* = 1.7 Hz, 1H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 6.73 (s, 2H), 5.03 (t, *J* = 6.6 Hz, 2H), 4.04 (t, *J* = 7.1 Hz, 2H), 3.96 (t, *J* = 6.3 Hz, 2H), 3.78 (s, 3H), 3.69 (dt, *J* = 25.3, 6.3 Hz, 4H), 3.06 (t, *J* = 7.4 Hz, 2H), 2.78 (s, 3H), 2.77 (s, 3H), 2.22 (s, 6H), 2.08 (q, *J* = 6.8 Hz, 2H), 2.02 (s, 3H), 1.91 (s, 3H), 1.79 (q, *J* = 7.9, 7.3 Hz, 2H).

Example 43

2-((8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)methyl)isonicotinic acid

[00155] To a solution of 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (54 mg, 0.1 mmol) in DMF (2 mL) was added NaH (5 mg, 0.12 mmol) and the mixture was stirred at RT for 10 min. Methyl 2-(bromomethyl)isonicotinate (28 mg, 0.12 mmol, 1.2 eqv.) was added to the mixture followed by TBAI (37 mg, 0.1 mmol) and stirred for additional 2 h. The mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was subjected to saponification conditions following General Procedure D using 2M LiOH (1 mL) and purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA) to afford the title compound (59 mg, 88%). LCMS: R_T = 1.849 min, MS (ES) 674.2 (M+H).

Example 44

6-[8-chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-1*H*-indazole-4-carboxylic acid

Step A. Preparation of methyl 6-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole-4-carboxylate

[00156] The title compound (154 mg, 93%) was prepared using the procedure described in Example 39 Step A using methyl 6-bromo-1*H*-indazole-4-carboxylate (110 mg, 0.43 mmol), (2-(chloromethoxy)ethyl)trimethylsilane (110 mg, 0.65 mmol), and sodium hydride (10 mg, 0.43 mmol) and purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient).

Step B. Preparation of methyl 6-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole-4-carboxylate

[00157] The title compound was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (30 mg, 0.056 mmol), methyl 6-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole-4-carboxylate (32 mg, 0.083 mmol), $Pd_2(dba)_3$ (8 mg, 0.0087 mmol), Xantphos (12 mg, 0.021 mmol), and Cs_2CO_3 (50 mg, 0.15 mmol).

Step C. Example 44

[00158] Methyl 6-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole-4-carboxylate was dissolved in TBAF (1.0 M in THF, 3 mL). The reaction was irradiated in the microwave at 100 °C for 1 h. Water (0.5 mL) and LiOH (5 mg, 0.21 mmol) were added, and the reaction was heated to 50 °C for additional 1 h. The work up described in general coupling procedure **A** was followed then purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient 35-95 % MeCN 0.1% TFA) to afford the title compound (8 mg, 20% two Steps). LCMS: R_T = 1.837 min, MS (ES) 699.3 (M+H).

Example 45

4-[8-chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-1-methyl-indazole-6-carboxylic acid

[00159] The title compound (21 mg, 52%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (30 mg, 0.056 mmol), methyl 4-bromo-1-methyl-1*H*-indazole-6-carboxylate (20 mg, 0.074 mmol), $Pd_2(dba)_3$ (5 mg, 0.0054 mmol), Xantphos (8 mg, 0.013 mmol), and Cs_2CO_3 (60 mg, 0.19 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.849 min, MS (ES) 713.2 (M+H), ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 1H), 8.06 (d, *J* = 1.0 Hz, 1H), 7.73 (d, *J* = 8.6 Hz, 1H), 7.58 (d, *J* = 1.1 Hz, 1H), 7.27 (d, *J* = 8.6 Hz, 1H), 6.72 (s, 2H), 4.15 (s, 3H), 4.12 (t, *J* = 6.0 Hz, 2H) 3.97 (t, *J* = 6.3 Hz, 2H), 3.78 (s, 3H), 3.76 (t, *J* = 3.8 Hz, 2H), 3.04 (d, *J* = 8.0 Hz, 2H), 2.23 (s, 6H), 2.13-2.00 (m, 5H), 1.93 (s, 3H), 1.75 (m, 2H).

Example 46

2-(6-(8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-3,4-dihydroquinolin-1(2*H*)-yl)acetic acid

[00160] To a solution of 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (50 mg, 0.1 mmol) in DMF (2 mL) were added *tert*-butyl 6-amino-3,4-dihydroquinoline-1(2*H*)-carboxylate (25 mg, 0.1 mmol), HBTU (76 mg, 0.2 mmol), triethylamine (42 µL, 0.3 mmol), and the mixture was stirred at RT for 10 h. Water (5 mL) was added to the mixture and it was extracted in CH_2Cl_2 (3 x 5 mL). The organic layer was dried over Na_2SO_4 and concentrated. To the solution of crude in DMF (3 mL) were added 1,3-dibromopropane (42 µL, 0.4 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and the mixture was stirred at 40 °C for 6 h. The mixture was filtered, diluted with water (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude residue was dissolved in CH_2Cl_2 (2 mL) and TFA (2 mL) was added. The mixture was stirred at room temperature for 6 h. Saturated aqueous $NaHCO_3$ (8 mL) was added to the mixture and extracted with DCM (3 x 5 mL). The organic layer was dried over Na_2SO_4, and concentrated. To a solution of crude in DMF (1 mL) was added NaH (5 mg, 0.12 mmol) and the mixture was stirred at room temperature for 10 min. Ethyl bromoacetate (14 µL, 0.12 mmol) was added to the mixture and stirred at RT for 2 h. The reaction mixture was quenched with water (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was subjected to saponification conditions following General Procedure D and purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA) to afford the title compound (15 mg, 21%). LCMS: R_T = 2.023 min, MS (ES) 728.2 (M+H).

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Example 47

2-((8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)methyl)-6-(4-(cyclopropylsulfonyl)piperazin-1-yl)isonicotinic acid

[00161] The title compound (10 mg, 58%) was prepared following the procedure described Example 38 using methyl 2-((8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)methyl)-6-(piperazin-1-yl)isonicotinate (15 mg, 0.02 mmol) and cyclopropanesulfonyl chloride (6 μL, 0.04 mmol) followed by saponification conditions following General Procedure D. LCMS: R_T = 1.931 min, MS (ES) 862.3 (M+H).

Example 48

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indazole-6-carboxylic acid

[00162] The title compound (40% yield) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one and methyl 3-bromo-1-methyl-1*H*-indazole-6-carboxylate followed by saponification using General Procedure D. MS (ES) 713.2 (M+H).

Example 49

3-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-4,5-dihydro-1H-[1,4]diazepino[1,2-a]indol-2(3H)-yl)-1-(2-morpholinoethyl)-1H-indazole-6-carboxylic acid

Step A. Preparation of methyl 3-bromo-1-(2-morpholinoethyl)-1*H*-indazole-6-carboxylate

[00163] To a solution of methyl 3-bromo-1H-indazole-6-carboxylate (0.27 mmol) in DMF (3 mL) was added sodium hydride (10 mg, 0.69 mmol), and the reaction was stirred 5 min at RT. 4-(2-Chloroethyl)morpholine (1.1 mmol) was added, and the reaction was stirred for additional 1 h. The reaction was diluted with EtOAc (10 mL), washed with H_2O (3 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-40% gradient) to afford the title compound (76 mg, 75 %).

Step B. Example 49

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[00164] A flame dried flask was charged with $Pd_2(dba)_3$ (1 mg, 0.5 mol%), Xantphos (2 mg, 1 mol%), cesium carbonate (27 mg, 0.084 mmol), 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indol-1-one (30 mg, 0.056 mmol), methyl 3-bromo-1-(2-morpholinoethyl)-1H-indazole-6-carboxylate (24 mg, 0.067 mmol), and 1,4-dioxane (1 mL). The reaction mixture was degassed for 10 min under argon and stirred for 16 h at 110°C then concentrated *in vacuo*. The residue was filtered through silica pad with DCM/MeOH (3/1) then concentrated *in vacuo*. To a solution of crude methyl 3-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-4,5-dihydro-1H-[1,4]diazepino[1,2-a]indol-2(3H)-yl)-1-(2-morpholinoethyl)-1H-indazole-6-carboxylate (0.056 mmol) in mixture of methanol and dioxane (1 mL / 2 mL) was added sodium hydroxide (0.2 mL, 2M solution). The reaction mixture was stirred for 3h at room temperature and then concentrated *in vacuo*. The residue was purified by reverse phase preparatory HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 5-95% CH_3CN 0.1% TFA) to afford the title compound (17 mg, 36 %). LCMS: R_T = 0.669 min (non polar method, >99%, ELSD); MS (ES) 812.2 [M+H]; ^{1}H NMR (DMSO, 400 MHz) δ (ppm) 8.41 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.69 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 1H), 6.71 (s, 2H), 4.92-4.79 (m, 2H), 4.05 (t, *J* = 6.0 Hz, 2H), 3.99-3.95 (m, 4H), 3.85 (t, *J* = 6.0 Hz, 2H), 3.76 (s, 3H), 3.71-3.55(m, 6H), 3.26-3.10 (m, 2H), 3.07 (t, *J* = 6.8 Hz, 2H), 2.21 (s, 6H), 2.12-2.01 (m, 2H), 2.02 (s, 3H), 1.92 (s, 3H), 1.85-1.62 (m, 2H).

Example 50

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-(2-morpholinoethyl)-1*H*-indazole-6-carboxylic acid

[00165] The title compound (40 mg, 87 %) was prepared according to procedures described in Example 49 Step B by substituting 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indol-1-one with (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino [1,2-a]indol-1(2*H*)-one (30 mg, 0.056 mmol). LCMS: R_T = 0.697 min (non polar method, >99%, ELSD); MS (ES) 812.3 [M+H]; ^{1}H NMR (DMSO, 400 MHz) δ (ppm) 8.41 (s, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.72 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 6.71 (s, 2H), 4.91-4.85 (m, 2H), 4.48-4.43 (m, 2H), 4.25-4.18 (m, 2H), 4.02-3.99

(m, 4H), 3.96-3.92 (m, 1H), 3.77 (s, 3H), 3.75-3.51 (m, 4H), 3.39-3.16 (m, 4H), 3.23 (s, 6H), 2.10 (s, 1.5H), 2.10 (s, 1.5H), 2.10-1.97 (m, 2H), 1.89 (s, 1.5H), 1.02 (d, J = 6.0 Hz, 3H).

Example 51

(*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-7-carboxylic acid

[00166] The title compound (84% yield) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one and methyl 4-bromo-1-methyl-1*H*-indole-7-carboxylate followed by saponification using General Procedure D. MS (ES) 712.3 (M+H); ^{1}H-NMR ($CDCl_3$) δ 7.89 (d, 1H, J = 8 Hz), 7.79 (d, 1H, J = 8 Hz), 7.34 (d, 1H, J = 8 Hz) 7.11 (m, 1H), 7.02 (m, 1H), 6.62 (s, 2H), 6.40 (m, 1H), 4.5 (m, 1H), 4.18 (tr, 2H, J = 8 Hz), 4.02 (s, 3H), 3.97 (s, 3H), 3.90-3.88 (m, 2H), 3.52-3.36 (m, 2H), 2.33 (s, 6H), 2.30-2.09 (overlapped multiple s, tr, 8H), 1.28 (two d, 3H, J = 8 Hz).

Example 52

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-4-carboxylic acid

[00167] The title compound (84% yield) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one and methyl 7-bromo-1-methyl-1*H*-indole-4-carboxylate followed by saponification using General Procedure D. MS (ES) 712.3 (M+H); ^{1}H-NMR ($CDCl_3$) δ 7.95 (d, 1H, J = 8 Hz), 7.75 (d, 1H, J = 8 Hz), 7.35 (d, 1H, J = 8 Hz) 7.13 (m, 1H), 7.02 (m, 1H), 6.99 (m, 1H), 6.62 (s, 2H), 4.02 (s, 3H), 4.00 (tr, 2H, J = 8 Hz), 3.78 (s, 3H), 3.90-3.88 (m, 1H), 3.52-3.35 (m, 2H), 2.33 (s, 6H), 2.30-2.18 (overlapped multiple s, tr, m, 10H), 1.28 (two d, 3H, J = 8 Hz).

Example 53

(*R*)-6-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indazole-4-carboxylic acid

[00168] The title compound (6.0 mg, 18%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 6-bromo-1-methyl-1*H*-indazole-4-carboxylate (20 mg, 0.074 mmol),

$Pd_2(dba)_3$ (4 mg, 0.0044 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (60 mg, 0.19 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.014 min, MS (ES) 713.2 (M+H).

Example 54

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-2-methyl-2*H*-indazole-3-carboxylic acid

[00169] The title compound (7.3 mg, 22%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 7-bromo-2-methyl-2*H*-indazole-3-carboxylate (20 mg, 0.074 mmol), $Pd_2(dba)_3$ (4 mg, 0.0044 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (60 mg, 0.19 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.066 min, MS (ES) 713.2 (M+H).

Example 55

7-(8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-tri methyl-1H-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-a]indol-2(3*H*)-yl)-1-methyl-1*H*-indole-4-carboxylic acid

[00170] The title compound (25mg, 62%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one and methyl 7-bromo-1-methyl-1*H*-indole-4-carboxylate followed by saponification using General Procedure D. MS (ES) 712.3 (M+H); ^{1}H NMR (DMSO, 400 MHz) δ (ppm) 7.73 (s, 1H), 7.70 (s, 1H), 7.44 (d, *J* = 2.8 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.10 (dd, *J* = 12.0, 8.0 Hz, 1H), 7.02 (d, *J* = 3.2 Hz, 1H), 6.73 (s, 2H), 4.20-4.08 (m, 2H), 4.00 (t, *J* = 6.0 Hz, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.75-3.68 (m, 1H), 3.53-3.45 (m, 1H), 3.16-3.08 (m, 1H), 2.99- 2.91 (m, 1H), 2.25 (s, 6H), 2.15-2.03 (m, 2H), 2.05 (s, 1.5H), 2.00 (s, 1.5H), 1.94 (s, 1.5H), 1.89 (s, 1.5H), 1.8-1.6 (m, 2H).

Example 56

(*R*)-6-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-(2-morpholinoethyl)-1*H*-indazole-4-carboxylic acid

Step A. Preparation of methyl 6-bromo-1-(2-morpholinoethyl)-1*H*-indazole-4-carboxylate

[00171] The title compound (74 mg, 26%) was prepared following General Procedure G using methyl 6-bromo-1*H*-indazole-4-carboxylate (200 mg, 0.784 mmol), NaH (36 mg, 1.5 mmol), and 4-(2-bromoethyl)morpholine (225 mg, 1.16 mmol).

Step B. Example 56

[00172] The title compound (7.1 mg, 19%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 6-bromo-1-(2-morpholinoethyl)-1*H*-indazole-4-carboxylate (30 mg, 0.081 mmol), $Pd_2(dba)_3$ (4 mg, 0.0044 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (60 mg, 0.19 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.783 min, MS (ES) 811.9 (M+H).

Example 57

(*R*)-6-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-2-(2-morpholinoethyl)-2*H*-indazole-4-carboxylic acid

Step A. Preparation of methyl 6-bromo-2-(2-morpholinoethyl)-2*H*-indazole-4-carboxylate

[00173] The title compound (42 mg, 15%) was prepared following General Procedure G using methyl 6-bromo-1*H*-indazole-4-carboxylate (200 mg, 0.784 mmol), NaH (36 mg, 1.5 mmol), and 4-(2-bromoethyl)morpholine (225 mg, 1.16 mmol).

Step B. Example 57

[00174] The title compound (5.4 mg, 14%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 6-bromo-2-(2-morpholinoethyl)-2*H*-indazole-4-carboxylate (30 mg, 0.081 mmol), $Pd_2(dba)_3$ (4 mg, 0.0044 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (60 mg, 0.19 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.726 min, MS (ES) 812.3 (M+H).

Example 58

6-(8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-1-oxo-4,5-dihydro-1*H*-[1,4]diazepino[1,2-a]indol-2(3*H*)-yl)-1-methyl-1*H*-indole-4-carboxylic acid

Step A. Preparation of 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole

[00175] To a solution of 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (6.456 g, 28.67 mmol) in DMF (57 ml) was added NaH (1.72 g, 43.0 mmol) and stirred for 15 min. (2-(Chloromethoxy)ethyl)trimethylsilane (6.59 ml, 37.28 mmol) was added to the reaction mixture and stirred at RT for additional 2 h. The reaction was diluted with DCM (50 mL) then quenched by H_2O (50 mL). The layers were separated and aqueous phase was extracted with DCM (2 x 50 mL). The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-10% gradient) to afford the title product (5.23 g, 52 %). LCMS: RT = 1.318 min, MS (ES) 353.2 (M+H).

Step B. Preparation of ethyl 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate

[00176] A solution of ethyl 7-bromo-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1H-indole-2-carboxylate (1.76 g, 3.55 mmol), 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole (1.50 g, 4.26 mmol), $Pd(PPh_3)_4$ (0.250 g, 0.178 mmol) and K_2CO_3 (1.47 g, 10.65 mmol) in 1,4-dioxane (12 mL) and water (4 mL) was irradiated at 140 °C for 45 min under microwave. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-70% gradient) to afford the title as a white solid (1.60 g, 70 %). LCMS: R_T = 1.30 min, MS (ES) 644.2 (M+H).

Step C. Preparation of ethyl 1-(3-((tert-butoxycarbonyl)amino)propyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate

[00177] To a solution of ethyl 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)-1H-indole-2-carboxylate (150 mg, 0.233 mmol) and tert-butyl 1,2,3-oxathiazinane-3-carboxylate 2,2-dioxide (66.2 mg, 0.279 mmol) in DMF (2 ml) was added NaH (12 mg, 0.30 mmol), and the resulting mixture was stirred at rt for 2 h. Satureated aq. NH_4Cl (20 mL) was added to quench the reaction. The mixture was extracted with DCM (20 mL x 3). The combined organics were concentrated, and the residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-30% gradient) to give the title product. LCMS: R_T = 2.232 min, MS (ES) 801.4 (M+H).

Step D. Preparation of ethyl 1-(3-aminopropyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate

[00178] To a stirred solution of ethyl 1-(3-((tert-butoxycarbonyl)amino)propyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)-1H-indole-2-carboxylate (115 mg, 0.143 mmol) in DCM (3 mL) was added TFA (0.055 mL, 0.717 mmol), and the resulting solution was stirred at 40 °C overnight. The reaction was quenched with saturated aq. $NaHCO_3$ (5 mL), the mixture was extracted with DCM (10 mL x 3). The combined organic solution was dried and concentrated to give the crude title compound, which was used for the next step without further purification. LCMS: R_T = 1.288 min, MS (ES) 701.4 (M+H).

Step E. Preparation of 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one

[00179] To a solution of ethyl 1-(3-aminopropyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (100 mg, 0.142 mmol) in MeOH (2 mL) was added K_2CO_3 (98 mg, 0.712 mmol), and the mixture was stirred for 2 h at 50 °C then filtered. The filtrate was concentrated and purified by flash chromatography (Combi-flash Rf, MeOH/DCM = 0-10% gradient) to give the title compound (74 mg, 79% two steps). LCMS: R_T = 1.617 min, MS (ES) 655.3 (M+H).

Step F. Preparation of methyl 6-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-1-oxo-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1-methyl-1*H*-indole-4-carboxylate

[00180] The title compound (38 mg, 34%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-a]indol-1-one (74 mg, 0.113 mmol), methyl 6-bromo-1-methyl-1*H*-indole-4-carboxylate (36.3 mg, 0.135 mmol), $Pd_2(dba)_3$ (2 mg, 0.0023 mmol), Xantphos (3.9 mg, 0.0068 mmol), and Cs_2CO_3 (74 mg, 0.23 mmol). LCMS: R_T = 1.807 min, MS (ES) 842.4 (M+H).

Step G. Example 58

[00181] A mixture of methyl 6-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-1-oxo-4,5-dihydro-1*H*-

[1,4]diazepino[1,2-a]indol-2(3*H*)-yl)-1-methyl-1H-indole-4-carboxylate (32 mg, 0.038 mmol) and TBAF (380 µl, 0.380 mmol) was heated to 100 °C under microwave irradiation in Biotage Initiator for 30 min. The reaction mixture was concentrated, and the residue was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 40-85 % MeCN 0.1% TFA) to give the title compound (16 mg, 60%). LCMS: R_T = 1.852 min, MS (ES) 698.2 (M+H).

Example 59

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indazole-3-carboxylic acid

[00182] The title compound (6.2 mg, 18%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 7-bromo-1-methyl-1*H*-indazole-3-carboxylate (20 mg, 0.074 mmol), $Pd_2(dba)_3$ (4 mg, 0.0044 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (60 mg, 0.19 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.984, 2.014 min, MS (ES) 713.2 (M+H); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.22 – 8.11 (m, 1H), 7.67 – 7.59 (m, 1H), 7.34 – 7.23 (m, 2H), 7.19 – 7.07 (m, 1H), 6.53 (s, 1.3H), 6.50 (s, 0.7H), 4.50-4.32 (m, 1H), 4.28 – 4.17 (m, 1H), 4.14 (d, *J* = 3.0 Hz, 1H), 4.06 (s, 1H), 4.01 (s, 1H), 3.96 – 3.82 (m, 5H), 3.58 – 3.20 (m, 3H), 2.24 (s, 6H), 2.19 - 2.15 (m, 3H), 2.14-2.07 (m, 2H), 2.03 (s, 0.7H), 2.02 (s, 0.3H), 1.98 (s, 2H), 1.25 (d, *J* = 6.4 Hz, 0.6H), 1.19 (d, *J* = 6.4 Hz, 1.4H), 1.14 (d, *J* = 6.4 Hz, 0.3H), 1.08 (d, *J* =6.4 Hz 0.7H).

Example 60

Methyl 8-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-a]indol-2(3*H*)-yl)-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylate

[00183] The title compound was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one, methyl 8-bromo-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxylate. MS (ES) 731.3 (M+H).

Example 61

5-[8-chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-4-methyl-2,3-dihydro-1,4-benzoxazine-7-carboxylic acid

Step A. Preparation of methyl 5-bromo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-7-carboxylate

[00184] To a solution of methyl 4-amino-3-bromo-5-hydroxybenzoate (250 mg, 1.02 mmol) in DMF (5 mL) was added dibromoethane (350 mg, 1.9 mmol) and K_2CO_3 (300 mg, 2.2 mmol). The reaction was heated to 80 °C for 20 h then cool to RT. The reaction was diluted with DCM/H_2O (40 mL, 1:1), the organic layer separated, and the aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (90 mg, 32%).

Step B. Preparation of methyl 5-bromo-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-7-carboxylate

[00185] The title compound (35 mg, 74%) was prepared following General Procedure G using methyl 5-bromo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-7-carboxylate (45 mg, 0.17 mmol), sodium hydride (9 mg, 0.38 mmol), and methyl iodide (40 mg, 0.28 mmol).

Step C Example 69

[00186] The title compound (2.3 mg, 7%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (25 mg, 0.046 mmol), methyl 5-bromo-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-7-carboxylate (25 mg, 0.087 mmol), $Pd_2(dba)_3$ (4 mg, 0.0044 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (60 mg, 0.19 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.953 min, MS (ES) 729.9 (M+H).

Example 62

3-[8-chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-4-(2-hydroxyethoxy)-5-methoxy-benzoic acid

Step A. Preparation of methyl 3-bromo-4-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)-5-methoxybenzoate

[00187] The title compound (43 mg, 27%) was prepared following the same procedure as described in Example 66 Step A using methyl 3-bromo-4-hydroxy-5-methoxybenzoate (100 mg, 0.381 mmol), Cs_2CO_3 (200 mg, 0.615 mmol) and (2-bromoethoxy)(*tert*-butyl)dimethylsilane (130 mg, 0.543 mmol).

Step B. Example 62

[00188] Crude Methyl 4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-5-methoxybenzoate was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (20 mg, 0.037 mmol), methyl 3-bromo-4-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)-5-methoxybenzoate (30 mg, 0.068 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (8 mg, 0.013 mmol), and Cs_2CO_3 (50 m, 0.153 mmol). To a solution of crude product in THF (3 mL) was added TBAF (1.0 M, 0.05 mL, 0.05 mmol). The reaction was stirred at 40 °C for 1 h then diluted into DCM/H_2O (10 mL, 1:1), extracted with DCM (2 x 5 mL) and concentrated *in vacuo*. The residue was then subjected to General Procedure D to afford the title compound (2 mg, 7%). LCMS: R_T = 1.858 min, MS (ES) 749.2 (M+H).

Example 63

(*R*)-5-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-naphthoic acid

[00189] The title compound (31 mg, 87%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 5-bromo-1-naphthoate (16 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.083 min, MS (ES) 709.2 (M+H).

Example 64

2-(1,2-benzoxazol-6-yl)-8-chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-1-one

[00190] The title compound (13 mg, 53%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (20 mg, 0.037 mmol), methyl 6-bromobenzo[*d*]isoxazole-3-carboxylate (20 mg, 0.078 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (8 mg, 0.013 mmol), and Cs_2CO_3 (50 m, 0.153 mmol). LCMS: R_T = 1.995 min, MS (ES) 656.2 (M+H).

Example 65

3-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-4-[2-(2-fluorophenoxy)ethoxy]-5-methoxy-benzoic acid

Step A. Preparation of methyl 3-bromo-4-(2-(2-fluorophenoxy)ethoxy)-5-methoxybenzoate

[00191] The title compound (101 mg, 66%) was prepared following the procedure described in Example 66 step 1 using methyl 3-bromo-4-hydroxy-5-methoxybenzoate (100 mg, 0.381 mmol), 1-(2-bromoethoxy)-2-fluorobenzene (120 mg, 0.547 mmol), and Cs_2CO_3 (200 mg, 0.615 mmol).

Step B. Example 65

[00192] The title compound (4 mg, 13%) was obtained following the procedures described in General Procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (20 mg, 0.037 mmol), methyl 3-bromo-4-(2-(2-fluorophenoxy)ethoxy)-5-methoxybenzoate (30 mg, 0.074 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (8 mg, 0.013 mmol), and Cs_2CO_3 (50 m, 0.153 mmol) followed by General Procedure D. LCMS: R_T = 2.051 min, MS (ES) 842.8 (M+H).

Example 66

3-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-5-methoxy-4-(2-phenylethoxy)benzoic acid

Step A. Preparation of methyl 3-bromo-5-methoxy-4-phenethoxybenzoate

[00193] To a solution of methyl 3-bromo-4-hydroxy-5-methoxybenzoate (100 mg, 0.381 mmol) in DMF (3 mL) was added Cs_2CO_3 (200 mg, 0.615 mmol) followed by (2-bromoethyl)benzene (100 mg, 0.541 mmol). The reaction was stirred at 50 °C until complete as determined by LCMS. The reaction was then cooled to RT, diluted into DCM/H_2O (20 mL, 1:1). The layers were separated and the aqueous layer was extracted with DCM (2 x 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (80 mg, 57%).

Step B. Example 66

[00194] The title compound (8 mg, 27%) was obtained following the procedures described in General Procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (20 mg, 0.037 mmol), methyl 3-bromo-5-methoxy-4-phenethoxybenzoate (25 mg, 0.068 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (8 mg, 0.013 mmol), and Cs_2CO_3 (50 m,

0.153 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.230 min, MS (ES) 809.2 (M+H).

Example 67

3-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-4-(3-hydroxypropoxy)-5-methoxy-benzoic acid

Step A. Preparation of methyl 3-bromo-4-(3-((*tert*-butyldimethylsilyl)oxy)propoxy)-5-methoxybenzoate

[00195] The title compound (107 mg, 64%) was prepared following the procedure described in Example 66 Step A substituting (2-bromoethyl)benzene with (3-bromopropoxy)(*tert*-butyl)dimethylsilane (130 mg, 0.514 mmol).

Step B. Example 67

[00196] The title compound (4 mg, 14%) was prepared following the same procedure as described in Example 62 Step B substituting methyl 3-bromo-4-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)-5-methoxybenzoate with methyl 3-bromo-4-(3-((*tert*-butyldimethylsilyl)oxy)propoxy)-5-methoxybenzoate (30 mg, 0.069 mmol). LCMS: R_T = 1.847 min, MS (ES) 763.3 (M+H).

Example 68

3-(8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1-methyl-1*H*-indole-6-carboxylic acid

[00197] The title compound (32 mg, 90%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (27 mg, 0.05 mmol), methyl 3-bromo-1-methyl-1*H*-indole-6-carboxylate (16 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.992 min, MS (ES) 712.3 (M+H).

Example 69

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylic acid

[00198] The title compound (22 mg, 31%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-

(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (54 mg, 0.1 mmol), methyl 7-bromo-1-methyl-1*H*-indole-3-carboxylate (32 mg, 0.12 mmol), $Pd_2(dba)_3$ (2 mg, 0.002 mmol), Xantphos (3.5 mg, 0.006 mmol), and Cs_2CO_3 (49 mg, 0.15 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.043 min, MS (ES) 712.2 (M+H).

Example 70

(*R*)-6-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-4-carboxylic acid

Step A. Preparation of (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one

[00199] The title compound was prepared following the procedure described Example 58 Step C to E using ethyl 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate, and *tert*-butyl (*S*)-5-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide. MS (ES) 656.2 (M+H).

Step B. Preparation of methyl (*R*)-6-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-4-carboxylate

[00200] The title compound (30 mg, 47%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one (50 mg, 0.076 mmol), methyl 6-bromo-1-methyl-1*H*-indole-4-carboxylate (25 mg, 0.092 mmol), $Pd_2(dba)_3$ (1.4 mg, 0.0015 mmol), Xantphos (2.7 mg, 0.0046 mmol), and Cs_2CO_3 (49 mg, 0.15 mmol). LCMS: R_T = 2.011 min, MS (ES) 842.3 (M+H).

Step C. Example 70

[00201] The title compound (16 mg, 66%) was prepared following the procedure described Example 58 Step G using methyl (*R*)-6-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-4-

carboxylate (30 mg, 0.036 mmol) and TBAF (356 µl, 0.356 mmol). LCMS: R_T = 1.893 min, MS (ES) 698.2 (M+H).

Example 71

(*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-6-carboxylic acid

[00202] The title compound (29 mg, 59% two steps) was prepared according to procedures described in Example 70 B to C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one (50 mg, 0.076 mmol) and methyl 4-bromo-1-methyl-1H-indole-6-carboxylate (25 mg, 0.092 mmol). LCMS: R_T = 1.895 min, MS (ES) 698.2 (M+H).

Example 72

4-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1H-pyrazol-4-yl)-1-oxo-4,5-dihydro-1H-[1,4]diazepino[1,2-a]indol-2(3H)-yl)-1-methyl-1H-indole-6-carboxylic acid

[00203] The title compound was prepared according to procedures described in Example 58 step F to G using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-a]indol-1-one and methyl 4-bromo-1-methyl-1H-indole-6-carboxylate. LCMS: R_T = 1.843 min, MS (ES) 698.2 (M+H).

Example 73

5-(8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-3-hydroxy-1,4-dihydropyrazine-2-carboxylic acid

[00204] The title compound (28 mg, 82%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (27 mg, 0.05 mmol), methyl 5-chloropyrazine-2-carboxylate (10 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.841 min, MS (ES) 679.2 (M+H).

Example 74

3-(8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1-methyl-1*H*-indole-7-carboxylic acid

Step A. Preparation of methyl 3-bromo-1-methyl-1*H*-indole-7-carboxylate

[00205] The title compound (73 mg, 96%) was prepared following General Procedure F using methyl-indole-7-carboxylate (50 mg, 0.28 mmol), NBS (51 mg, 0.28 mmol), NaH (14 mg, 0.34 mmol) and MeI (21 μL, 0.34 mmol). LCMS: R_T = 1.646 min, MS (ES) 268.1 (M+H).

Step B. Example 74

[00206] The title compound (23 mg, 65%) was prepared following General coupling procedure B using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (27 mg, 0.05 mmol), methyl 3-bromo-1-methyl-1*H*-indole-7-carboxylate (16 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.038 min, MS (ES) 712.2 (M+H).

Example 75

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-7-carboxylic acid

[00207] The title compound (31 mg, 87%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 3-bromo-1-methyl-1*H*-indole-7-carboxylate (16 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.092 min, MS (ES) 712.2 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (d, J = 8.6 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.49 (d, J = 2.8 Hz, 1H), 7.30 (d, J = 8.6 Hz, 1H), 7.09 (td, J = 7.7, 2.2 Hz, 1H), 6.72 (s, 2H), 4.48 (dd, J = 13.0, 3.8 Hz, 1H), 4.23 – 4.08 (m, 1H), 3.98 (dt, J = 6.4, 3.4 Hz, 2H), 3.84 (s, 3H), 3.78 (s, 1.5H), 3.77 (s, 1.5H), 3.40 – 3.15 (m, 3H), 2.25 (s, 6H), 2.12 (s, 1.5H), 2.08 (d, J = 12.0 Hz, 2H), 2.04 (s, 1.5H), 1.98 (s, 1.5H), 1.89 (s, 1.5H), 1.08 (d, J = 6.4 Hz, 3H).

Example 76

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00208] The title compound (28 mg, 79%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 3-bromo-1-methyl-1*H*-indole-5-carboxylate (16 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.003 min, MS (ES) 712.3 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (dd, *J* = 3.5, 1.5 Hz, 1H), 7.87 – 7.71 (m, 2H), 7.57 (dd, *J* = 9.4, 1.9 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 1H), 6.73 (s, 2H), 4.48 (dd, *J* = 13.0, 3.8 Hz, 1H), 4.24 – 4.09 (m, 1H) 3.99 (tt, *J* = 6.4, 3.2 Hz, 2H), 3.85 (s, 3H), 3.79 (s, 1.5H), 3.77 (s, 1.5H), 3.72 – 3.59 (m, 1H), 3.23 (dt, *J* = 13.4, 7.4 Hz, 2H), 2.24 (s, 6H), 2.12 (s, 1.5H), 2.07 (dd, *J* = 12.7, 6.0 Hz, 2H), 2.03 (s, 1.5H), 1.98 (s, 1.5H), 1.89 (s, 1.5H), 1.19 – 0.93 (m, 3H).

Example 77

(*P, R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (separated atropisomer A)

[00209] Example 91 was separated using reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA, 10 mins gradient) to give the title compound as the first eluting atropisomer (13 mg, 37%). LCMS: R_T = 1.970 min, MS (ES) 712.0 (M+H).

Example 78

(*M, R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (separated atropisomer B)

[00210] Example 91 was separated using reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA, 10 mins gradient) to give the title compound as a second eluting atropisomer (11 mg, 31%). LCMS: R_T = 1.989 min, MS (ES) 712.0 (M+H).

Example 79

(*R*)-6-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylic acid

[00211] The title compound (32 mg, 90%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 6-bromo-1-methyl-1*H*-indole-3-carboxylate (16 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.041 min, MS (ES) 712.3 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (d, *J* = 1.3 Hz, 1H), 8.00 (dd, *J* = 8.5, 2.7 Hz, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.56 (t, *J* = 2.5 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 1H), 7.21 (dt, *J* = 8.5, 2.2 Hz, 1H), 6.74 (s, 2H), 4.49 (dd, *J* = 13.0, 3.8 Hz, 1H), 4.21 – 4.09 (m, 1H), 3.99 (t, *J* = 6.6 Hz, 2H), 3.84 (s, 3H), 3.79 (s, 1.5H), 3.78 (s, 1.5H), 3.40 – 3.13 (m, 3H), 2.26 (s, 6H), 2.12 (s, 1.5H), 2.07 (d, *J* = 6.9 Hz, 2H), 2.03 (s, 1.5H), 1.98 (s, 1.5H), 1.89 (s, 1.5H), 1.05 (d, *J* = 6.4 Hz, 3H).

Example 80

3-(8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00212] The title compound (28 mg, 79%) was prepared following General coupling procedure B using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (27 mg, 0.05 mmol), methyl 3-bromo-1-methyl-1*H*-indole-5-carboxylate (16 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.942 min, MS (ES) 712.3 (M+H).

Example 81

6-(8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1-methyl-1*H*-indole-3-carboxylic acid

[00213] The title compound (20 mg, 70%) was prepared following General coupling procedure A using (8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (27 mg,

0.05 mmol), methyl 6-bromo-1-methyl-1*H*-indole-3-carboxylate (16 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.968 min, MS (ES) 712.3 (M+H).

Example 82

6-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-1-(2-methoxyethyl)indazole-4-carboxylic acid

Step A. Preparation of methyl 6-bromo-1-(2-methoxyethyl)-1*H*-indazole-4-carboxylate

[00214] To a solution of methyl 6-bromo-1*H*-indazole-4-carboxylate (200 mg, 0.79 mmol) in DMF (5 mL) was added NaH (40 mg, 1.63 mmol), and the reaction was stirred for 30 min at RT. 1-Bromo-2-methoxyethane (165 mg, 1.18 mmol) was added and the reaction was stirred overnight. The reaction was quenched with MeOH at -78 °C, then diluted with DCM/H_2O (60 mL, 1:1), the organic layer was separated, the aqueous layer was extracted with DCM (2 x 20 mL), the organic fractions combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (39 mg, 16%).

Step B. Example 82

[00215] The title compound (4 mg, 11%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (25 mg, 0.046 mmol), methyl 6-bromo-1-(2-methoxyethyl)-1*H*-indazole-4-carboxylate (20 mg, 0.064 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (50 mg, 0.153 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.948 min, MS (ES) 757.3 (M+H).

Example 83

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-ethyl-1*H*-indole-7-carboxylic acid

Step A. Preparation of methyl 3-bromo-1-ethyl-1*H*-indole-7-carboxylate

[00216] The title compound (70 mg, 62%) was prepared following General Procedure F using methyl-indole-7-carboxylate (70 mg, 0.40 mmol), NBS (71 mg, 0.40 mmol), NaH (20

mg, 0.48 mmol) and ethyl iodide (38 μL, 0.48 mmol). LCMS: R_T = 1.731 min, MS (ES) 282.1 (M+H).

Step B. Example 83

[00217] The title compound (34 mg, 96%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 3-bromo-1-ethyl-1*H*-indole-7-carboxylate (16 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.135 min, MS (ES) 726.3 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (d, *J* = 8.6 Hz, 1H), 7.65 – 7.44 (m, 3H), 7.30 (d, *J* = 8.6 Hz, 1H), 7.15 – 7.03 (m, 1H), 6.72 (s, 2H), 4.48 (dd, *J* = 13.0, 3.8 Hz, 1H), 4.43 – 4.26 (m, 2H), 4.24 – 4.09 (m, 2H), 3.99 (s, 3H), 3.78 (s, 1.5H), 3.77 (s, 1.5H), 3.68 – 3.57 (m, 2H), 3.41 – 3.14 (m, 2H), 2.25 (s, 6H), 2.12 (s, 1.5H), 2.11 – 2.04 (m, 2H), 2.04 (s, 1.5H), 1.98 (s, 1.5H), 1.89 (s, 1.5H), 1.26 (td, *J* = 7.1, 1.4 Hz, 3H), 1.08 (d, *J* = 6.4 Hz, 3H).

Example 84

(*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indazole-6-carboxylic acid

[00218] The title compound (13 mg, 39%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 4-bromo-1-methyl-1*H*-indazole-6-carboxylate (20 mg, 0.074 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (8 mg, 0.014 mmol), and Cs_2CO_3 (50 mg, 0.153 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.018 min, MS (ES) 713.2 (M+H).

Example 85

5-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-1-methyl-indazole-7-carboxylic acid

[00219] The title compound (4 mg, 12%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (25 mg, 0.046

mmol), methyl 5-bromo-1-methyl-1*H*-indazole-7-carboxylate (20 mg, 0.074 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (8 mg, 0.014 mmol), and Cs_2CO_3 (50 mg, 0.153 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.934 min, MS (ES) 713.2 (M+H).

Example 86

8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(2,6-dimethylphenyl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one

Step A. Preparation of ethyl 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(2,6-dimethylphenyl)-1*H*-indole-2-carboxylate

[00220] A mixture of ethyl 7-bromo-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate (25 mg, 0.050 mmoL), (2,6-dimethylphenyl)boronic acid (10 mg, 0.068 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), dicyclohexyl(2-(phenanthren-9-yl)phenyl)phosphane (6 mg, 0.014 mmol), and potassium phosphate (30 mg, 0.142 mmol) was purged with Ar for 5 min then toluene (1 mL) was added. The reaction was heated to 110 °C for 16 h then cooled to RT. The reaction was diluted into DCM/H_2O (10 mL, 1:1), the layers were separated, and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic extracts were dried by passage through a phase separator, concentrated *in vacuo*, and purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (22 mg, 88%).

Step B. Preparation of ethyl 1-(3-((*tert*-butoxycarbonyl)amino)propyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(2,6-dimethylphenyl)-1*H*-indole-2-carboxylate

[00221] To a solution of ethyl 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(2,6-dimethylphenyl)-1*H*-indole-2-carboxylate (96 mg, 0.18 mmol) and *tert*-butyl 1,2,3-oxathiazinane-3-carboxylate 2,2-dioxide (50 mg, 0.21 mmol) in DMF (4 mL) was added NaH (6 mg, 0.25 mmol), and the reaction was stirred for16 h at RT. The work up described in general coupling procedure **A** was followed and purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (72 mg, 57%).

Step C. Example 86

[00222] To a solution of ethyl 1-(3-((*tert*-butoxycarbonyl)amino)propyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(2,6-dimethylphenyl)-1*H*-indole-2-carboxylate (72 mg, 0.11 mmol) in dioxane (3 mL) was added HCl (4.0 M in dioxanes, 0.5 mL, 2.0 mmol). The reaction was stirred for 16 h at RT then concentrated *in vacuo*. The residue was dissolved in MeOH (5 mL), and K_2CO_3 (50 mg, 0.30 mmol) was added. The reaction was allowed to stir 20 h at 50 °C. The work up described in general coupling procedure **A** was

followed and purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (33 mg, 59%). LCMS: R_T = 2.317 min, MS (ES) 535.2 (M+H).

Example 87

(*R*)-6-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-ethyl-1*H*-indazole-4-carboxylic acid

[00223] The title compound (10 mg, 30%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 6-bromo-1-ethyl-1*H*-indazole-4-carboxylate (20 mg, 0.070 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (6 mg, 0.010 mmol), and cesium carbonate (50 mg, 0.153 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.036 min, MS (ES) 727.2 (M+H).

Example 88

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-6-carboxylic acid

[00224] The title compound (30 mg, 84%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 3-bromo-1-methyl-1*H*-indole-6-carboxylate (16 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.031 min, MS (ES) 712.3 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.70 – 7.60 (m, 2H), 7.48 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 1H), 6.72 (s, 2H), 4.48 (dd, *J* = 12.9, 3.8 Hz, 1H), 4.25 – 4.07 (m, 1H), 3.99 (td, *J* = 6.4, 2.0 Hz, 2H), 3.88 (s, 3H), 3.78 (s, 1.5H), 3.77 (s, 1.5H), 3.39 – 3.15 (m, 3H), 2.25 (s, 6H), 2.12 (s, 1.5H), 2.11 – 2.05 (m, 2H), 2.03 (s, 1.5H), 1.98 (s, 1.5H), 1.89 (s, 1.5H), 1.08 (d, *J* = 6.4 Hz, 3H).

Example 89

3-(8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1-(2-morpholinoethyl)-1*H*-indole-6-carboxylic acid

Step A. Preparation of methyl 3-bromo-1-(2-morpholinoethyl)-1*H*-indole-6-carboxylate

[00225] The title compound (36 mg, 49%) was prepared following General Procedure G using methyl 3-bromo-1*H*-indole-6-carboxylate (51 mg, 0.20 mmol), sodium hydride (10 mg, 0.24 mmol), 4-(2-chloroethyl)morpholine (36 mg, 0.24 mmol) and KI (40 mg, 0.24 mmol). LCMS: R_T = 1.515 min, MS (ES) 367.1 (M+H).

Step B. Example 89

[00226] The title compound (8 mg, 20%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 3-bromo-1-(2-morpholinoethyl)-1*H*-indole-6-carboxylate (19 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.719 and 1.745 min, MS (ES) 810.9 (M+H).

Example 90

(*R*)-5-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-4-ethyl-3-oxo-3,4-dihydro-2*H*-benzo[b][1,4]oxazine-7-carboxylic acid

Step A. Preparation of methyl 5-bromo-4-ethyl-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-7-carboxylate

[00227] To a solution of methyl 4-amino-3-bromo-5-hydroxybenzoate (250 mg, 1.02 mmol) in THF (10 mL) was added $NaHCO_3$ (150 mg, 1.8 mmol) and chloroacetyl chloride (170 mg, 1.5 mmol) at 0 °C. The reaction was stirred for 2 h and warm to RT. K_2CO_3 (150 mg, 1.1 mmol) was added, and the reaction was heated to 65 °C then cooled to RT. The mixture was diluted with DCM/H_2O (40 mL, 1:1) and extracted with DCM (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford methyl 5-bromo-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-7-carboxylate (86 mg, 30%). The product (40 mg, 0.14 mmol) was dissolved in DMF (3 mL), NaH (7 mg, 0.30 mmol) was added. The reaction was stirred at RT for 30 min, and EtBr (30 mg, 0.28 mmol) was added. The reaction was stirred for 3 h at RT then diluted with

DCM/H_2O (20 mL, 1:1). The organic layer was separated, and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic extracts were dried by passage through a phase separator and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (28 mg, 65%).

Step B. Example 90

[00228] The title compound (1 mg, 4%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (20 mg, 0.037 mmol), methyl 5-bromo-4-ethyl-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-7-carboxylate (20 mg, 0.063 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (35 mg, 0.107 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.034 min, MS (ES) 757.8 (M+H).

Example 91

6-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-7-(2,6-dimethylphenyl)-1-oxo-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-1-methyl-indole-4-carboxylic acid

[00229] The title compound (3 mg, 9%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(2,6-dimethylphenyl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (25 mg, 0.037 mmol), methyl 6-bromo-1-methyl-1*H*-indole-4-carboxylate (20 mg, 0.063 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (35 mg, 0.107 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.531 min, MS (ES) 708.3 (M+H).

Example 92

6-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-1-isopropyl-indazole-4-carboxylic acid

Step A. Preparation of methyl 6-bromo-1-isopropyl-1*H*-indazole-4-carboxylate

[00230] The title compound (43 mg, 18%) was prepared following the procedure described in Example 82 Step A substituting 1-bromo-2-methoxyethane with 2-bromopropane (190 mg, 1.54 mmol).

Step B. Example 92

[00231] The title compound (5 mg, 15%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-

1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (25 mg, 0.046 mmol), methyl 6-bromo-1-isopropyl-1*H*-indazole-4-carboxylate (20 mg, 0.067 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (50 mg, 0.153 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.048 min, MS (ES) 741.3 (M+H).

Example 93

(*R*)-6-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1H-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indazole-4-carboxylic acid

[00232] The title compound (19 mg, 38% two steps) was prepared according to procedures described in Example 70 B to C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one (50 mg, 0.076 mmol) and methyl 6-bromo-1-methyl-1H-indazole-4-carboxylate (23 mg, 0.084 mmol). LCMS: R_T = 1.859 min, MS (ES) 699.2 (M+H).

Example 94

(*R*)-6-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-(2-morpholinoethyl)-1*H*-indole-4-carboxylic acid

Step A. Preparation of methyl (*R*)-6-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-4-carboxylate

[00233] The title compound (138 mg, 88%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one (100 mg, 0.184 mmol), methyl 6-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole-4-carboxylate (78 mg, 0.20 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (121 mg, 0.37 mmol). MS (ES) 842.3 (M+H).

Step B. Preparation of methyl (*R*)-6-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1*H*-indole-4-carboxylate

[00234] A mixture of methyl (*R*)-6-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-

dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-4-carboxylate (138 mg, 0.164 mmol), TBAF (0.819 mL, 0.819 mmol) in THF (1 mL) was heated at 100 °C under microwave irradiation in Biotage Initiator for 20 min. The reaction was quenched with H_2O (5 mL) then extracted with DCM (10 mL x 2). The combined organic solution was concentrated and the residue was purified by flash chromatography (Combi-flash Rf, MeOH/DCM = 0-5% gradient) to give the title compound (80 mg, 69%) as a white solid. LCMS: R_T = 2.115 min, MS (ES) 712.2 (M+H).

Step C. Example 94

[00235] To a solution of methyl (*R*)-6-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1*H*-indole-4-carboxylate (40 mg, 0.056 mmol) in DMF (0.5 mL) was added NaH (4.5 mg, 0.11 mmol) and stirred for 20 min. 4-(2-Bromoethyl)morpholine (22 mg, 0.11 mmol) was added, and the resulting mixture was heated to 50 °C for 2 days. The reaction was quenched by MeOH (0.5 mL) and acidified with TFA then concentrated *in vacuo*. The residue was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 30-85 % MeCN 0.1% TFA) to give the title compound (14 mg, 30%). LCMS: R_T = 1.714 min, MS (ES) 811.3 (M+H).

Example 95

6-(8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-1-oxo-4,5-dihydro-1*H*-[1,4]diazepino[1,2-a]indol-2(3*H*)-yl)-1-methyl-1*H*-indazole-4-carboxylic acid

[00236] The title compound (25 mg, 56% two steps) was prepared according to procedures described in Example 70 B to C using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-a]indol-1-one (50 mg, 0.076 mmol) and methyl 6-bromo-1-methyl-1H-indazole-4-carboxylate (23 mg, 0.084 mmol). LCMS: R_T = 1.859 min, MS (ES) 699.2 (M+H).

Example 96

(*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-(2-morpholinoethyl)-1*H*-indole-6-carboxylic acid

[00237] The title compound (58% yield) was prepared according to procedures described in Example 94 Step A to C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one and

methyl 4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole-6-carboxylate. LCMS: R_T = 1.735 min, MS (ES) 811.3 (M+H).

Example 97

(*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-2-methyl-2*H*-indazole-6-carboxylic acid

[00238] The title compound (6 mg, 18%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 4-bromo-2-methyl-2*H*-indazole-6-carboxylate (20 mg, 0.074 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (8 mg, 0.014 mmol), and Cs_2CO_3 (50 mg, 0.153 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.949 min, MS (ES) 713.2 (M+H).

Example 98

(*R*)-5-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indazole-7-carboxylic acid

[00239] The title compound (3 mg, 9%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 5-bromo-1-methyl-1*H*-indazole-7-carboxylate (20 mg, 0.074 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (8 mg, 0.014 mmol), and Cs_2CO_3 (50 mg, 0.153 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.991 min, MS (ES) 713.2 (M+H).

Example 99

(*R*)-6-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-ethyl-1*H*-indole-4-carboxylic acid

[00240] The title compound (12 mg, 38%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one (40 mg, 0.074 mmol), methyl 6-bromo-1-ethyl-1*H*-indole-4-carboxylate (25 mg, 0.089 mmol), $Pd_2(dba)_3$ (1.4 mg, 0.0015 mmol), Xantphos (2.6 mg, 0.0045 mmol), and Cs_2CO_3 (48 mg, 0.15 mmol)

followed by saponification using General Procedure D. LCMS: R_T = 2.220 min, MS (ES) 740.3 (M+H).

Example 100

(*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1H-indole-6-carboxylic acid

[00241] The title compound was prepared along with Example 96 as a byproduct. MS (ES) 698.2 (M+H).

Example 101

(*R*)-6-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1*H*-indole-4-carboxylic acid

[00242] The title compound was prepared along with Example 94 as a byproduct. MS (ES) 698.2 (M+H).

Example 102

(*R*)-6-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)quinoline-2-carboxylic acid

[00243] The title compound (21 mg, 59%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 6-bromoquinoline-2-carboxylate (16 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.025 min, MS (ES) 710.2 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.14 (t, *J* = 8.6 Hz, 2H), 8.09 – 8.00 (m, 1H), 7.96 (ddd, *J* = 9.0, 2.4, 1.0 Hz, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 6.74 (s, 2H), 4.68 – 4.46 (m, 2H), 4.26 – 4.14 (m, 3H), 4.00 (s, 3H), 3.79 (s, 3H), 3.44 – 3.14 (m, 2H), 2.25 (s, 6H), 2.12 (s, 1.5H), 2.11 – 2.05 (m, 2H), 2.03 (s, 1.5H), 2.00 (s, 1.5H), 1.90 (s, 1.5H), 1.05 (d, *J* = 6.4 Hz, 3H).

Example 103

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-ethyl-1*H*-indole-3-carboxylic acid

Step A. Preparation of ethyl 7-bromo-1-ethyl-1*H*-indole-3-carboxylate

[00244] The title compound (58 mg, 68%) was prepared following General Procedure G using 7-bromo-1*H*-indole-3-carboxylic acid (70 mg, 0.29 mmol), NaH (26 mg, 0.64 mmol) and EtI (51 μL, 0.64 mmol). LCMS: R_T = 1.803 min, MS (ES) 296.1 (M+H).

Step B. Example 103

[00245] The title compound (8 mg, 22%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), ethyl 7-bromo-1-ethyl-1*H*-indole-3-carboxylate (14 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.042 min, MS (ES) 726.3 (M+H).

Example 104

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-ethyl-1*H*-indole-6-carboxylic acid

Step A. Preparation of methyl 3-bromo-1-ethyl-1*H*-indole-6-carboxylate

[00246] The title compound (76 mg, 95%) was prepared following General Procedure G using methyl 3-bromo-1*H*-indole-6-carboxylate (72 mg, 0.28 mmol), sodium hydride (14 mg, 0.34 mmol) and EtI (28 μL, 0.34 mmol). LCMS: R_T = 1.682 min, MS (ES) 282.1 (M+H).

Step B. Example 104

[00247] The title compound (35 mg, 96%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 3-bromo-1-ethyl-1*H*-indole-6-carboxylate (14 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.064 min, MS (ES) 726.3 (M+H).

Example 105

(*R*)-8-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)quinoline-3-carboxylic acid

[00248] The title compound (34 mg, 96%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-

(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 8-bromoquinoline-3-carboxylate (16 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.010 min, MS (ES) 710.2 (M+H).

Example 106

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-4-carboxylic acid

Step A. Preparation of methyl 3-bromo-1-methyl-1*H*-indole-7-carboxylate

[00249] The title compound (39 mg, 51%) was prepared following General Procedure F using methyl 1*H*-indole-4-carboxylate (50 mg, 0.28 mmol), NBS (51 mg, 0.28 mmol), NaH (14 mg, 0.34 mmol), and MeI (21 μL, 0.34 mmol). LCMS: R_T = 1.414 min, MS (ES) 268.1 (M+H).

Step B. Example 106

[00250] The title compound (16 mg, 45%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 3-bromo-1-methyl-1*H*-indole-4-carboxylate (14 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.936 and 1.963 min, MS (ES) 712.3 (M+H).

Example 107

6-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-7-(1,3,5-trimethylpyrazol-4-yl)-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-1-(2-hydroxyethyl)indazole-4-carboxylic acid

Step A. Preparation of methyl 6-bromo-1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1*H*-indazole-4-carboxylate

[00251] The title compound (73 mg, 23%) was prepared following the procedure describe in Example 82 Step A substituting 1-bromo-2-methoxyethane with (2-bromoethoxy)(*tert*-butyl)dimethylsilane (375 mg, 1.57 mmol).

Step B. Example 107

[00252] The title compound (3 mg, 9%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-

1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (25 mg, 0.046 mmol), methyl 6-bromo-1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1*H*-indazole-4-carboxylate (30 mg, 0.073 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (50 mg, 0.153 mmol). Following isolation of the coupling product, the crude residue was dissolved in THF (3 mL) and TBAF (1.0 M, 0.1 mL, 0.1 mmol) was added and the reaction was allowed to stir overnight at RT. The crude reaction mixture was concentrated and carried forward to saponification following General Procedure D. LCMS: R_T = 1.786 min, MS (ES) 742.9 (M+H).

Example 108

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylic acid

[00253] The title compound was prepared according to procedures described in Example 70 B to C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one and methyl 7-bromo-1-methyl-1H-indole-3-carboxylate. MS (ES) 699.2 (M+H).

Example 109

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-6-carboxylic acid

Step A. Preparation of methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-6-carboxylate

[00254] The title compound (88 mg, 69%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one (100 mg, 0.15 mmol), methyl 3-bromo-1-methyl-1H-indole-6-carboxylate (41 mg, 0.15 mmol), CuI (1.5 mg, 0.0078 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (2.2 mg, 0.015 mmol), and K_2CO_3 (42 mg, 0.31 mmol). MS (ES) 842.3 (M+H).

Step B. Example 109

[00255] The title compound was prepared according to procedures described in Example 70 C using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-

dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-6-carboxylate. LCMS: R_T = 1.900 min, MS (ES) 698.2 (M+H).

Example 110

(*R*)-6-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylic acid

[00256] The title compound (28 mg, 79%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 6-bromo-1-methyl-1*H*-indole-2-carboxylate (14 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.091 and 2.114 min, MS (ES) 712.3 (M+H).

Example 111

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)imidazo[1,5-a]pyridine-1-carboxylic acid

[00257] The title compound (89% yield) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one and methyl 3-bromoimidazo[1,5-a]pyridine-1-carboxylate followed by saponification using General Procedure D. MS (ES) 701.3 (M+H); ^{1}H NMR (DMSO, 400 MHz) δ (ppm) 8.08 (t, *J* = 10.0 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.29-7.26 (m, 1H), 6.93 (t, *J* = 6.8 Hz, 1H), 6.71 (s, 2H), 4.55-4.50 (m, 1H), 4.30-4.25 (m, 2H), 3.97 (t, *J* = 6.0 Hz, 2H), 3.77 (s, 3H), 3.33-3.15 (m, 2H), 2.23 (s, 6H), 2.11 (s, 1.5H), 2.09-2.01 (m, 2H), 2.02 (s, 1.5H), 1.97 (s, 1.5H), 1.88 (s, 1.5H), 1.09 (d, *J* = 5.6 Hz, 3H).

Example 112

(*R*)-2-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)imidazo[1,2-a]pyridine-8-carboxylic acid

[00258] The title compound (49% yield) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-

(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one and methyl 2-bromoimidazo[1,2-a]pyridine-8-carboxylate followed by saponification using General Procedure D. MS (ES) 701.4 (M+H).

Example 113

(*R*)-4-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylic acid

[00259] The title compound (26 mg, 73%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 4-bromo-1-methyl-1*H*-indole-2-carboxylate (14 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.076 min, MS (ES) 712.2 (M+H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 3.1 Hz, 0.5H), 7.72 (d, *J* = 3.1 Hz, 0.5H), 7.49 – 7.37 (m, 2H), 7.31 (dd, *J* = 9.7, 5.1 Hz, 2H), 7.13 – 7.05 (m, 1H), 6.70 – 6.55 (m, 2H), 4.57 – 4.40 (m, 1H), 4.37 – 4.17 (m, 2H), 4.10 (s, 3H), 3.97 (s, 1.5H), 3.96 (s, 1.5H), 3.62 (dd, *J* = 11.9, 4.2 Hz, 1H), 3.40 (ddt, *J* = 42.4, 13.8, 7.3 Hz, 3H), 2.32 (s, 6H), 2.26 (s, 1.5H), 2.25 (s, 1.5H), 2.22 (d, *J* = 7.0 Hz, 2H), 2.11 (s, 1.5H), 2.09 (s, 1.5H), 1.27 (d, *J* = 6.4 Hz, 1.5H), 1.20 (d, *J* = 6.5 Hz, 1.5H).

Example 114

(*R*)-5-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylic acid

[00260] The title compound (28 mg, 79%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 5-bromo-1-methyl-1*H*-indole-2-carboxylate (14 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.084 min, MS (ES) 712.3 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, *J* = 8.6 Hz, 1H), 7.66 – 7.54 (m, 2H), 7.36 – 7.26 (m, 2H), 7.23 (t, *J* = 0.9 Hz, 1H), 6.73 (s, 2H), 4.44 (dd, *J* = 13.0, 3.8 Hz, 1H), 4.05 (s, 3H), 3.98 (tt, *J* = 6.3, 2.9 Hz, 3H), 3.78 (s, 1.5H), 3.77 (s, 1.5H),

3.63 (t, *J* = 13.5 Hz, 1H), 3.22 (dt, *J* = 13.2, 7.2 Hz, 2H), 2.26 (s, 6H), 2.12 (s, 1.5H), 2.10 – 2.04 (m, 2H), 2.03 (s, 1.5H), 1.97 (s, 1.5H), 1.88 (s, 1.5H), 1.04 (d, *J* = 6.4 Hz, 3H).

Example 115

(*R*)-2-(benzo[d]isoxazol-6-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy) propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one

[00261] The title compound (41% yield) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one and 6-bromobenzo[*d*]isoxazole. MS (ES) 656.4 (M+H); ^{1}H NMR (DMSO, 400 MHz) δ (ppm) 7.73 (d, *J* = 8.8 Hz, 1H), 7.63 (dd, *J* = 8.4, 2.8 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 7.15 (s, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 6.72 (s, 2H), 4.45-4.41(m, 1H), 4.24-4.13 (m, 2H), 3.97 (t, *J* = 6.0 Hz, 2H), 3.76 (s, 3H), 3.32-3.15 (m, 2H), 2.24 (s, 6H), 2.08 (s, 1.5H), 2.07-2.02 (m, 2H), 1.98 (s, 1.5H), 1.94 (s, 1.5H), 1.85 (s, 1.5H), 0.94 (d, *J* = 6.4 Hz, 3H)

Example 116

(*R*)-5-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indazole-3-carboxylic acid

[00262] The title compound (25 mg, 70%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 5-bromo-1-methyl-1*H*-indazole-3-carboxylate (14 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.998 min, MS (ES) 713.2 (M+H).

Example 117

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-2-ethyl-2*H*-indazole-3-carboxylic acid

Step A. Preparation of methyl 7-bromo-2-ethyl-2*H*-indazole-3-carboxylate

[00263] The title compound (54 mg, 48%) was prepared following the procedure described in Example 82 Step A using methyl 7-bromo-1*H*-indazole-3-carboxylate (100 mg, 0.392 mmol), sodium hydride (18 mg, 0.75 mmol), and EtBr (80 mg, 0.74 mmol).

Step B. Example 117

[00264] The title compound (9.5 mg, 29%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 7-bromo-2-ethyl-2*H*-indazole-3-carboxylate (20 mg, 0.071 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (50 mg, 0.153 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.138 min, MS (ES) 727.3 (M+H); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 (ddd, *J* = 8.4, 3.9, 0.9 Hz, 1H), 7.73 (dd, *J* = 8.6, 2.9 Hz, 1H), 7.43 – 7.36 (m, 1H), 7.35 – 7.24 (m, 2H), 6.68 – 6.62 (m, 2H), 4.84 (q, *J* = 7.2 Hz, 2H), 4.64 – 4.49 (m, 1H), 4.36-4.20 (m, 1H), 4.04 (t, *J* = 6.4 Hz, 2H), 3.96 (d, *J* = 2.7 Hz, 3H), 3.79 (t, *J* = 13.5 Hz, 1H), 3.44 (ddt, *J* = 17.8, 11.7, 6.3 Hz, 2H), 2.33 (s, 6H), 2.28 – 2.19 (m, 5H), 2.12 (s, 1.5H), 2.09 (s, 1.5H), 1.49 (td, *J* = 7.2, 5.8 Hz, 3H), 1.34 (d, *J* = 6.3 Hz, 1.5H), 1.26 (d, *J* = 6.4 Hz, 1.5H).

Example 118

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-ethyl-1*H*-indazole-3-carboxylic acid

Step A. Preparation of methyl 7-bromo-1-ethyl-1*H*-indazole-3-carboxylate

[00265] The title compound (22 mg, 20%) was prepared in the same reaction as described in Example 117 Step A.

Step B. Example 118

[00266] The title compound (3 mg, 9%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 7-bromo-1-ethyl-1*H*-indazole-3-carboxylate (20 mg, 0.071 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (50 mg, 0.153 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.058 min, MS (ES) 727.2 (M+H).

Example 119

7-[8-chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-7-(4,6-dimethylpyrimidin-5-yl)-1-oxo-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-1-methyl-indole-3-carboxylic acid

[00267] The title compound (1 mg, 3%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethylpyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (25 mg,

0.046 mmol), methyl 7-bromo-1-methyl-1*H*-indole-3-carboxylate (20 mg, 0.074 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (50 mg, 0.153 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.032 min, MS (ES) 710.2 (M+H).

Example 120

8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethylpyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one

Step A. Preparation of ethyl 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethylpyrimidin-5-yl)-1*H*-indole-2-carboxylate

[00268] Ethyl 7-bromo-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1H-indole-2-carboxylate (1.647 g, 3.30 mmol) was combined with (4,6-dimethylpyrimidin-5-yl)boronic acid (1.2 g, 7.90 mmol), $Pd_2(dba)_3$ (0.30 g, 0.33 mmol), and dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine (SPhos) (0.406 g, 0.990 mmol) in 30 mL 1:1 THF/Toluene in a pressure tube. The mixture was treated with K_3PO_4 (1.16 mL, 11.6 mmol) and was stirred 10 minutes at RT under Ar flush. The reaction was heated to 110 °C and stirred for 24 h. The mixture was cooled, poured in 150 mL EtOAc and stirred with 50 mL saturated ammonium chlroide. The organic layer was dried over anhydrous $MgSO_4$ and was concentrated *in vacuo*. The crude material was purified by flash chromatography (EtOAc/DCM = 0-50% gradient) to give the title compound (970 mg, 56 %) as an amber foam. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.09 (s, 1H), 8.93 (s, 1H), 7.68 (dd, J = 8.6, 0.6 Hz, 1H), 7.25 (d, J = 8.7 Hz, 1H), 6.62 (s, 2H), 4.33 (q, J = 7.1 Hz, 2H), 3.97 (t, J = 6.1 Hz, 2H), 3.28 (dd, J = 8.1, 6.8 Hz, 2H), 2.32 (s, 6H), 2.20 (s, 6H), 2.21 - 2.10 (m, 2H), 1.36 - 1.20 (m, 3H); ^{13}C NMR (101 MHz, cdcl3) δ 165.98, 161.85, 157.76, 156.71, 137.03, 134.32, 130.42, 127.16, 127.11, 126.11, 124.93, 124.67, 121.97, 118.44, 114.45, 67.35, 61.10, 30.24, 22.26, 21.21, 20.96, 14.32.

Step B. Preparation of ethyl 1-(3-((*tert*-butoxycarbonyl)amino)propyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethylpyrimidin-5-yl)-1*H*-indole-2-carboxylate

[00269] To a solution of ethyl 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethylpyrimidin-5-yl)-1*H*-indole-2-carboxylate (500 mg, 0.952 mmol) and *tert*-butyl 1,2,3-oxathiazinane-3-carboxylate 2,2-dioxide (300 mg, 1.26 mmol) in DMF (20 mL) was added NaH (60 mg, 1.50 mmol), and the reaction was stirred at RT for 3 h. The reaction was diluted with DCM/H_2O (60 mL, 1:1), and the layers were separated. The aqueous layer was extracted with DCM (2 x 30 mL), and the combined organic extracts were dried over $MgSO_4$,

filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (525 mg, 81%).

Step C. Example 120

[00270] To a solution of ethyl 1-(3-((*tert*-butoxycarbonyl)amino)propyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethylpyrimidin-5-yl)-1*H*-indole-2-carboxylate in dioxane (20 mL) was added HCl in dioxane (4.0 M, 3.0 mL, 12 mmol), and the reaction was stirred for 72 h at RT. The reaction was concentrated *in vacuo*, and the crude residue was taken up in MeOH (30 mL). K_2CO_3 (300 mg, 2.17 mmol) was added, and the reaction was stirred for 6 h at 50 °C. The reaction was concentrated *in vacuo*, and the residue extracted with DCM (3 x 30 mL) and washed with H_2O (30 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was then purified by flash chromatography (Combi-flash Rf, CH_2Cl_2/methanol = 0-10% gradient) to afford the title compound (243 mg, 58%). LCMS: R_T = 1.947 min, MS (ES) 537.3 (M+H).

Example 121

(*R*)-6-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indazole-3-carboxylic acid

[00271] The title compound (19 mg, 53%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 6-bromo-1-methyl-1*H*-indazole-3-carboxylate (14 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 µL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.024 min, MS (ES) 713.2 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 – 7.98 (m, 1H), 7.82 – 7.69 (m, 1H), 7.63 (dd, *J* = 12.1, 7.1 Hz, 1H), 7.29 (dd, *J* = 8.6, 4.6 Hz, 2H), 6.74 (s, 2H), 4.74 – 4.45 (m, 1H), 4.45 – 4.32 (m, 1H), 4.25 – 4.08 (m, 2H), 4.01 (s, 3H), 4.00 – 3.95 (m, 1H), 3.79 (s, 1.5H), 3.78 (s, 1.5H), 3.74 -3.60 (m, 1H), 2.77 - 2.62 (m, 1H), 2.26 (s, 6H), 2.12 (s, 1.5H), 2.06 – 2.00 (m, 2H), 1.98 (s, 1.5H), 1.89 (s, 1.5H), 1.76 (s, 1.5H), 1.05 (d, *J* = 6.3 Hz, 3H).

Example 122

7-(8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-a]indol-2(3*H*)-yl)-1-ethyl-1*H*-indazole-5-carboxylic acid

Step A. Preparation of methyl 7-bromo-1-ethyl-1*H*-indazole-5-carboxylate

[00272] The title compound (42 mg, 37%) was prepared following the procedure described in Example 82 Step A using methyl 7-bromo-1*H*-indazole-5-carboxylate (100 mg, 0.392 mmol), NaH (18 mg, 0.75 mmol), and EtBr (80 mg, 0.74 mmol).

Step B. Example 137

[00273] The title compound (3 mg, 9%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (25 mg, 0.046 mmol), methyl 7-bromo-1-ethyl-1*H*-indazole-5-carboxylate (20 mg, 0.074 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (50 mg, 0.153 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.033 min, MS (ES) 727.2 (M+H).

Example 123

7-(8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-a]indol-2(3*H*)-yl)-1-methyl-1*H*-indazole-5-carboxylic acid

Step A. Preparation of methyl 7-bromo-1-methyl-1*H*-indazole-5-carboxylate

[00274] The title compound (64 mg, 61%) was prepared following the procedure described in Example 82 Step A using methyl 7-bromo-1-methyl-1*H*-indazole-5-carboxylate (100 mg, 0.392 mmol), NaH (18 mg, 0.75 mmol), and MeI (75 mg, 0.52 mmol).

Step B. Example 123

[00275] The title compound (5 mg, 15%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (25 mg, 0.046 mmol), methyl 7-bromo-1-methyl-1*H*-indazole-5-carboxylate (20 mg, 0.074 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (50 mg, 0.153 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.926 min, MS (ES) 712.9 (M+H).

Example 124

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7-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-4,5-dihydro-1H-[1,4]diazepino[1,2-a]indol-2(3H)-yl)-2-ethyl-2H-indazole-5-carboxylic acid

Step A. Preparation of methyl 7-bromo-2-ethyl-2*H*-indazole-5-carboxylate

[00276] The title compound (29 mg, 26%) was prepared in the same reaction as described in Example 122 Step A.

Step 2: Example 124

[00277] The title compound (3.9 mg, 12%) was prepared following General Procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (25 mg, 0.046 mmol), methyl 7-bromo-2-ethyl-2*H*-indazole-5-carboxylate (20 mg, 0.074 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (50 mg, 0.153 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.895 min, MS (ES) 726.9 (M+H).

Example 125

4-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indazole-3-carboxylic acid

[00278] The title compound (4 mg, 11%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.050 mmol), methyl 4-bromo-1-methyl-1*H*-indazole-3-carboxylate (20 mg, 0.074 mmol), $Pd_2(dba)_3$ (5 mg, 0.0055 mmol), Xantphos (7 mg, 0.012 mmol), and Cs_2CO_3 (50 mg, 0.153 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.944 min, MS (ES) 713.2 (M+H).

Example 126

4-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indazole-3-carboxylic acid (separated steroisomer A)

[00279] The title compound (8 mg, 20%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.052 mmol), methyl 4-bromo-1-methyl-1*H*-indazole-3-carboxylate (30 mg, 0.11 mmol), $Pd_2(dba)_3$ (5 mg, 0.0055 mmol), Xantphos (7 mg, 0.012 mmol), and Cs_2CO_3 (50 mg, 0.153 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.944 min, MS (ES)

713.2 (M+H). The title compound was separated using reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient from 30-90% CH_3CN, 0.1% TFA) during the final purification step to give as a separated atropisomer (1st fraction, absolute stereochemistry undeterminded). MS (ES) 713.2 (M+H).

Example 127

4-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indazole-3-carboxylic acid (separated steroisomer B)

[00280] The title compound was separated along with Example 141 as a separated atropisomer (2nd fraction). MS (ES) 713.2 (M+H).

Example 128

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylic acid

Step A. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylate

[00281] To a solution of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylate (20 mg, 0.028 mmol) in DMF (0.5 mL) was added NaH (1.4 mg, 0.034 mmol) and stirred for 15 min at RT. 4-(Bromomethyl)tetrahydro-2H-pyran (5.5 mg, 0.031 mmol) was added, and the resulting mixure was stirred overnight then concentrated *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-70% gradient) to give the title compound (20 mg, 88%) as white foam. LCMS: R_T = 2.107 min, MS (ES) 810.3 (M+H).

Step B. Example 128

[00282] The title compound (10 mg, 51%) was prepared following General Procedure D for saponification using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylate (20 mg, 0.025 mmol). LCMS: R_T = 2.124 min, MS (ES) 796.3 (M+H).

Example 129

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00283] The title compound was prepared following the procedure described in Example 109 Step A and B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one and methyl 3-bromo-1-methyl-1H-indole-5-carboxylate. LCMS: R_T = 1.872 min, MS (ES) 698.2 (M+H).

Example 130

6-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-7-(4,6-dimethylpyrimidin-5-yl)-1-oxo-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-1-methyl-indole-4-carboxylic acid

[00284] The title compound (2 mg, 6%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethylpyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (25 mg, 0.046 mmol), methyl 6-bromo-1-methyl-1*H*-indole-4-carboxylate (20 mg, 0.067 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (50 mg, 0.153 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.012 min, MS (ES) 710.2 (M+H).

Example 131

6-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-isopropyl-indazole-4-carboxylic acid

[00285] The title compound (8 mg, 23%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 6-bromo-1-isopropyl-1*H*-indazole-4-carboxylate (20 mg, 0.067 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (50 mg, 0.153 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.119 min, MS (ES) 741.3 (M+H).

Example 132

4-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-2-methyl-indazole-3-carboxylic acid

[00286] The title compound (12 mg, 34%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.050 mmol), methyl 4-bromo-2-methyl-2*H*-indazole-3-carboxylate (25 mg, 0.074 mmol), $Pd_2(dba)_3$ (5 mg, 0.0055 mmol), Xantphos (7 mg, 0.012 mmol), and Cs_2CO_3 (50 mg, 0.153 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.940, 1.971 min, MS (ES) 713.2 (M+H)

Example 133

4-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-2-methyl-indazole-3-carboxylic acid (separated steroisomer A)

[00287] The title compound was separated using reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient from 30-90% CH_3CN, 0.1% TFA) during the final purification step to give as a separated atropisomer (1st fraction, absolute stereochemistry undeterminded). LCMS: R_T = 1972 min, MS (ES) 713.2 (M+H).

Example 134

(*R*)-2-(4-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indol-1-yl)acetic acid

Step A. Preparation of *tert*-butyl (*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-1-carboxylate

[00288] The title compound (35 mg, 93%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), *tert*-butyl 4-bromo-1*H*-indole-1-carboxylate (18 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol). LCMS: R_T = 2.453 min, MS (ES) 754.30 (M+H).

Step B. Example 134

[00289] To a solution of *tert*-butyl (*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-1-carboxylate (35 mg, 0.046 mmol) in DCM (2 mL) was added TFA (2 mL), and the mixture was stirred at room temperature for 6 h. Saturated aqueous $NaHCO_3$ (8 mL) was added to the mixture and extracted in DCM (3 x 5

mL). The organic layer was dried (anhyd. Na_2SO_4), evaporated. The residue was dissolved in DMF (1 mL), and NaH (5 mg, 0.12 mmol, 1.2 eqv.) was added then stirred at RT for 10 min. Ethyl bromoacetate (14 μL, 0.12 mmol, 1.2 eqv.) was added to the mixture and stirred at RT for 2 h. The reaction was quenched with water (5 mL) and extracted with DCM (3x5 mL). The organic layer was dried (anhyd. Na_2SO_4) and concentrated. The residue was subjected to saponification using General Procedure D and purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA) to afford the title compound (16 mg, 45%). LCMS: R_T = 1.748 min, MS (ES) 712.2 (M+H).

Example 135

(*R*)-2-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-[1,2,4] triazolo[1,5-a]pyridine-7-carboxylic acid

[00290] The title compound (43% yield) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one and methyl 2-bromo-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylate followed by saponification using General Procedure D. MS (ES) 700.4 (M+H); ^{1}H NMR (DMSO, 400 MHz) δ (ppm) 9.00 (dd, *J* = 7.2, 3.6 Hz, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.58 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.29 (d, *J* = 8.8, 1.2 Hz, 1H), 6.73 (s, 2H), 4.37-4.19(m, 3H), 4.13-3.95 (m, 2H), 3.76 (d, *J* = 8.8 Hz, 3H), 3.36-3.15 (m, 2H), 2.24 (s, 6H), 2.09-2.05 (m, 2H), 2.08 (s, 1.5H), 1.99 (s, 1.5H), 1.97 (s, 1.5H), 1.87 (s, 1.5H), 0.95 (dd, *J* = 9.2, 6.8 Hz, 3H).

Example 136

2-(4-(8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-2-phenyl-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-a]indol-7-yl)-3,5-dimethyl-1*H*-pyrazol-1-yl)acetic acid

Step A. Preparation of 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-2-phenyl-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one

[00291] The title compound was prepared according to procedures described in Example 58 step F to G using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-a]indol-1-one and aniline. MS (ES) 601.2 (M+H)

Step B. Example 136

[00292] To a solution of 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-2-phenyl-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one

(0.05 mmol) in DMF (1 mL) was added NaH (0.08 mmol) at RT, and the reaction was stirred for 30 min. Methyl 2-chloroacetate (0.1 mmol) was added, and the reaction was stirred for 5 h at RT then diluted with DCM/H_2O (20 mL, 1:1). The organic layer was separated and the aqueous layer was extracted with DCM (2 x 5 mL). The combined organic extracts were concentrated *in vacuo*. The crude reaction product was then saponified and purified following the procedure described in General Procedure D to afford the title compound (71% yield). MS (ES) 659.2 (M+H).

Example 137

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((1-methylpiperidin-4-yl)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylic acid

Step A. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((1-methylpiperidin-4-yl)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylate

[00293] To a solution of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylate (20 mg, 0.028 mmol) and (1-methylpiperidin-4-yl)methanol (7.25 mg, 0.056 mmol) in Toluene (932 µl) was added 2-(tributyl-l5-phosphanylidene)acetonitrile (140 µl, 0.056 mmol) and stirred at 50 °C for 20 h. The reaction mixture was concentrated, and the residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-10% gradient) to give the title compound (15 mg, 65%). LCMS: R_T = 1.901 min, MS (ES) 823.3 (M+H).

Step B. Example 137

[00294] The title compound (5 mg, 34%) was prepared according to General Procedure G using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((1-methylpiperidin-4-yl)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1H-indole-3-carboxylate (15 mg, 0.018) and methyl 6-(bromomethyl)nicotinate. LCMS: R_T = 1.740 min, MS (ES) 809.4 (M+H).

Example 138

(*R*)-6-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)quinoline-8-carboxylic acid

[00295] The title compound (66% yield) was prepared following General coupling

procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one and methyl 6-bromoquinoline-8-carboxylate followed by saponification using General Procedure D. MS (ES) 710.2 (M+H); ^{1}H-NMR (MeOH-d_3) δ 9.12 (dd, 1H, J1= 2 Hz, ,J1= 5 Hz), 9.90 (dd, 1H, J1= 2 Hz, ,J1= 5 Hz), 8.81 (m, 1H), 8.33 (m, 1H) 7.93 (m, 1H), 7.78 (d, 1H, , J = 8 Hz), 7.32 (d, 1H, , J = 8 Hz), 6.63 (s, 2H), 4.46 (m, 2H), 4.35 (m, 1H), 4.01-3.96 (m, 2H), 3.87 (multiple s, 3H), 3.77-3.74 (m, 1H), 3.49-3.38 (m, 2H), 3.11-3.08 (m, 1H), 2.27 (s, 6H), 2.23-2.02 (multiple s and m, 8H), 1.18 and 1.16 (two d, 3H, J = 8 Hz).

Example 139

(*R*)-6-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)imidazo[1,2-a]pyridine-2-carboxylic acid

[00296] The title compound (78% yield) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one and methyl 6-bromoimidazo[1,2-*a*]pyridine-2-carboxylate followed by saponification using General Procedure D. MS (ES) 699.2 (M+H).

Example 140

(3*R*,4*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-3,4-dimethyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one

[00297] The title compound (74% yield) was prepared following same procedures described in Example 24 substituting *tert*-butyl (*R*)-4-ethyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide with *tert*-butyl (4*R*,5*S*)-4,5-dimethyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide. MS (ES) 553.4 (M+H); ^{1}H-NMR ($CDCl_3$) δ 7.70 (d, 1H, J = 8 Hz), 7.29 (d, 1H, J = 8 Hz), 6.64 (s, 2H), 5.82 (m, 1H), 4.05-3.90 (m, 6H), 3.52-3.50 (m, 1H), 3.47-3.31 (m, 3H), 2.35 (s, 6H), 2.17 (overlapped tr and multiple s, 8H), 1.21(d, 0.75H, J = 8 Hz), 1.19 (d, 0.75H, J = 8 Hz), 1.05 (d, 1.5H, J = 8 Hz), 1.03 (d, 1.5H, J = 8 Hz), 0.88 (d, 0.75H, J = 8 Hz), 0.82 (d, 0.75H, J = 8 Hz)

Example 141

3-((3*R*,4*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-3,4-dimethyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)benzoic acid

[00298] The title compound (62% yield) was prepared following General coupling procedure A using (3*R*,4*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-3,4-dimethyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one

and methyl 3-bromobenzoate followed by saponification using General Procedure D. MS (ES) 673.2 (M+H).

Example 142

4-((3*R*,4*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-3,4-dimethyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)benzoic acid

[00299] The title compound (73% yield) was prepared following General coupling procedure A using (3*R*,4*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-3,4-dimethyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one and methyl 4-bromobenzoate followed by saponification using General Procedure D. MS (ES) 673.3 (M+H).

Example 143

6-((3*R*,4*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-3,4-dimethyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-4-carboxylic acid

[00300] The title compound (8% yield) was prepared following General coupling procedure A using (3*R*,4*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-3,4-dimethyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one and methyl 6-bromo-1-methyl-1*H*-indole-4-carboxylate followed by saponification using General Procedure D. MS (ES) 726.3 (M+H).

Example 144

2-(4-(8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-2-(quinolin-8-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-7-yl)-3,5-dimethyl-1*H*-pyrazol-1-yl)acetic acid

[00301] The title compound (55% yield) was prepared according to procedures described in Example 136 step A and B by substituting aniline with 8-bromoquinoline. MS (ES) 710.2 (M+H)

Example 145

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1,7-dimethyl-1*H*-indole-5-carboxylic acid

Step A. Preparation of ethyl 1,7-dimethyl-1*H*-indole-5-carboxylate

[00302] A mixture of ethyl 7-bromo-1-methyl-1*H*-indole-5-carboxylate (200 mg, 0.71 mmol), methylboronic acid (57.9 mg, 0.97 mmol), dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphane (79 mg, 0.193 mmol), K_3PO_4 (253 mg, 1.29 mmol) and $PdOAc_2$

(22 mg, 0.097 mmol) was degased for 10 min under Ar. Toluene (1.5 ml) was added and the resulting mixure was heated at 100 °C for 3 h. The reaction mixture was concentrated, and the residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-20% gradient) to give the title compound (140 mg, 99%). LCMS: R_T = 1.558 min, MS (ES) 218.2 (M+H).

Step B. Preparation of ethyl 3-bromo-1,7-dimethyl-1*H*-indole-5-carboxylate

[00303] To a stirred solution of ethyl 1,7-dimethyl-1*H*-indole-5-carboxylate (140 mg, 0.64 mmol) in DMF (2 mL) was added NBS (115 mg, 0.64 mmol) at 0 °C. After 1 h, the reaction was quenched by addition of H_2O (10 mL). The mixture was extracted with DCM (10 mL X 2). The combined organic solution was washed with H_2O (20 mL), dried and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-10% gradient) to give the title compound (176 mg, 92%) as a yellow solid.

Step C. Example 145

[00304] The title compound (33 mg, 50%) was prepared following General coupling procedure B using R)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one (50 mg, 0.093 mmol), ethyl 3-bromo-1,7-dimethyl-1*H*-indole-5-carboxylate (33 mg, 0.11 mmol), CuI (0.9 mg, 0.005 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (1.3 mg, 0.0093 mmol), and K_2CO_3 (26 mg, 0.19 mmol) followed by saponification using General Procedure D. LCMS: RT = 2.018 min, MS (ES) 726.3 (M+H).

Example 146

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((1-methylpiperidin-4-yl)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00305] The title compound (14 mg, 60%) was prepared according to procedures described in Example 137 Step A and B using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (20 mg, 0.028 mmol) and (1-methylpiperidin-4-yl)methanol (18 mg, 0.14 mmol). MS (ES) 698.2 (M+H).

Example 147

5-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-7-(4,6-dimethylpyrimidin-5-yl)-1-oxo-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]quinoline-8-carboxylic acid

[00306] The title compound (12.7 mg, 38%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-

dimethylpyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (25 mg, 0.046 mmol), methyl 5-bromoquinoline-8-carboxylate (20 mg, 0.075 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (50 mg, 0.153 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.008 min, MS (ES) 708.3 (M+H); ^{1}H NMR (600 MHz, Chloroform-*d*) δ 9.20 (s, 1H), 9.00 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.87 (d, *J* = 7.8 Hz, 1H), 8.32 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.81 (d, *J* = 8.6 Hz, 1H), 7.64 (dd, *J* = 8.6, 4.3 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 8.6 Hz, 1H), 6.61 (s, 2H), 3.99 (h, *J* = 6.4 Hz, 5H), 3.77 (dt, *J* = 14.2, 5.7 Hz, 1H), 3.20 (dt, *J* = 12.5, 7.4 Hz, 2H), 2.42 (s, 3H), 2.39 (s, 3H), 2.33 (s, 6H), 2.21 (quint, *J* = 6.0 Hz, 2H), 1.95-1.92 (m, 1H), 1.83-1.78 (m, 1H).

Example 148

5-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2-yl]naphthalene-1-carboxylic acid

[00307] The title compound (8.3 mg, 25%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 5-bromo-1-naphthoate (20 mg, 0.075 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (20 mg, 0.14 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.107 min, MS (ES) 707.2 (M+H); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.14 (s, 1H), 9.05 (t, *J* = 9.7 Hz, 1H), 8.33 (dd, *J* = 7.3, 4.3 Hz, 1H), 8.17 (d, *J* = 10.0 Hz, 0.5H), 7.91 (d, *J* = 10.0 Hz, 0.5H), 7.81 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.63 (dt, *J* = 15.9, 8.0 Hz, 1H), 7.52 (q, *J* = 8.5 Hz, 1H), 7.44 (d, J = 10.0 Hz, 0.5H), 7.36 (dd, *J* = 11.5, 8.0 Hz, 1.5H), 6.60 (d, *J* = 9.0 Hz, 2H), 4.42 (dd, *J* = 12.9, 3.8 Hz, 1H), 4.01 (q, *J* = 6.0 Hz, 2H), 3.83-3.75 (m, 1H), 3.49 – 3.33 (m, 3H), 2.48 (s, 1.5H), 2.46 (s, 1.5H), 2.31 (s, 9H), 2.22 (h, *J* = 7.5 Hz, 2H), 1.31 (d, *J* = 3.9 Hz, 1.5H), 1.29 (d, *J* = 3.9 Hz, 1.5H).

Example 150

8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-2-(quinolin-8-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one

[00308] The title compound was prepared following the procedure described in Example 109 Step A and B using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one and 8-bromoquinoline. MS (ES) 698.2 (M+H).

Example 151

5-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-7-(4,6-dimethylpyrimidin-5-yl)-1-oxo-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]naphthalene-1-carboxylic acid

[00309] The title compound (6.3 mg, 19%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethylpyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (25 mg, 0.046 mmol), methyl 5-bromo-1-naphthoate (20 mg, 0.074 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (50 mg, 0.153 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.079 min, MS (ES) 707.2 (M+H).

Example 152

6-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indole-4-carboxylic acid

[00310] The title compound (8.1 mg, 25%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 6-bromo-1-methyl-1*H*-indole-4-carboxylate (20 mg, 0.075 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (20 mg, 0.14 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.075 min, MS (ES) 710.2 (M+H); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.15 (s, 1H), 7.82 – 7.72 (m, 2H), 7.64 (s, 1H), 7.33 (d, *J* = 8.6 Hz, 1H), 7.24 (d, *J* = 3.1 Hz, 1H), 7.14 (d, *J* = 3.2 Hz, 1H), 6.62 (s, 2H), 4.41 (dd, *J* = 13.0, 3.6 Hz, 1H), 4.00 (t, *J* = 6.2 Hz, 2H), 3.83 (s, 3H), 3.73 (d, *J* = 6.0 Hz, 1H), 3.60 (d, *J* = 12.7 Hz, 1H), 3.47-3.32 (m, 2H), 2.46 (s, 3H), 2.31 (s, 6H), 2.28 (s, 3H), 2.22 (q, *J* = 6.9 Hz, 2H), 1.20 (d, *J* = 6.4 Hz, 3H).

Example 153

3-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indole-6-carboxylic acid

[00311] The title compound (16.3 mg, 49%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 3-bromo-1-methyl-1*H*-indole-6-carboxylate (20 mg, 0.075 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (20 mg, 0.14 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.061 min, MS (ES) 710.2 (M+H); ^{1}H NMR (600 MHz, Chloroform-*d*) δ 9.25 (s, 1H), 7.79

(d, J = 8.6 Hz, 1H), 7.63 (d, J = 1.9 Hz, 1H), 7.58 – 7.51 (m, 1H), 7.34 (d, J = 8.6 Hz, 1H), 6.65 (s, 2H), 4.35 – 4.30 (m, 4H), 4.01 (t, J = 6.2 Hz, 2H), 3.88 (s, 2H), 3.66 (s, 2H), 3.18 (t, J = 7.5 Hz, 2H), 2.45 (s, 6H), 2.34 (s, 6H), 2.23 (dd, J = 10.0, 4.5 Hz, 2H), 1.73 (s, 2H).

Example 154

5-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-7-(4,6-dimethylpyrimidin-5-yl)-1-oxo-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-2,3-dihydro-1,4-benzodioxine-7-carboxylic acid

[00312] The title compound (5.7 mg, 17%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethylpyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (25 mg, 0.046 mmol), methyl 8-bromo-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxylate (20 mg, 0.074 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (50 mg, 0.153 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.975 min, MS (ES) 715.2 (M+H); ^{1}H NMR (600 MHz, Chloroform-*d*) δ 9.25 (s, 1H), 7.79 (d, J = 8.6 Hz, 1H), 7.63 (d, J = 1.9 Hz, 1H), 7.58 – 7.51 (m, 1H), 7.34 (d, J = 8.6 Hz, 1H), 6.65 (s, 2H), 4.35 – 4.30 (m, 4H), 4.01 (t, J = 6.2 Hz, 2H), 3.88 (s, 2H), 3.66 (s, 2H), 3.18 (t, J = 7.5 Hz, 2H), 2.45 (s, 6H), 2.34 (s, 6H), 2.23 (dd, J = 10.0, 4.5 Hz, 2H), 1.73 (s, 2H).

Example 155

6-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-7-(4,6-dimethylpyrimidin-5-yl)-1-oxo-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-1-methyl-indazole-4-carboxylic acid

[00313] The title compound (9 mg, 27%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethylpyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (25 mg, 0.046 mmol), methyl 6-bromo-1-methyl-1*H*-indazole-4-carboxylate (20 mg, 0.074 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (50 mg, 0.153 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.960 min, MS (ES) 711.3 (M+H); ^{1}H NMR (600 MHz, Chloroform-*d*) δ 9.22 (s, 1H), 8.51 (d, J = 0.9 Hz, 1H), 7.83 – 7.76 (m, 2H), 7.74 – 7.70 (m, 1H), 7.36 (d, J = 8.6 Hz, 1H), 6.65 (s, 2H), 4.11 (s, 3H), 4.02 (t, J = 6.1 Hz, 2H), 3.89 (t, J = 6.4 Hz, 2H), 3.83 (t, J = 6.0 Hz, 2H), 3.22 (dd, J = 8.3, 6.5 Hz, 2H), 2.40 (s, 6H), 2.32 (s, 6H), 2.20 (s, 2H), 1.90 – 1.85 (m, 2H).

Example 156

3-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-7-(4,6-dimethylpyrimidin-5-yl)-1-oxo-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-1-methyl-indole-5-carboxylic acid

[00314] The title compound (7.5 mg, 23%) was prepared following General coupling procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethylpyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (25 mg, 0.046 mmol), methyl 3-bromo-1-methyl-1*H*-indole-5-carboxylate (20 mg, 0.074 mmol), $Pd_2(dba)_3$ (4 mg, 0.0043 mmol), Xantphos (6 mg, 0.010 mmol), and Cs_2CO_3 (50 mg, 0.153 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.964 min, MS (ES) 710.2 (M+H); ^{1}H NMR (600 MHz, Chloroform-*d*) δ 9.21 (s, 1H), 8.25 (s, 1H), 8.02 (ddd, *J* = 8.8, 4.1, 1.5 Hz, 1H), 7.79 (dd, *J* = 8.6, 6.2 Hz, 1H), 7.37 (dd, *J* = 24.7, 8.6 Hz, 2H), 7.16 (s, 1H), 6.65 (d, *J* = 4.6 Hz, 2H), 4.01 (t, *J* = 6.1 Hz, 2H), 3.90 (s, 2H), 3.84 (s, 3H), 3.79 (t, *J* = 6.0 Hz, 2H), 3.21 (t, *J* = 9.0 Hz, 2H), 2.40 (s, 6H), 2.32 (s, 6H), 2.25 (quint, J = 6.0 Hz, 2H), 1.84-1.80 (m, 2H).

Example 157

(*R*)-2-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)quinoline-5-carboxylic acid

[00315] The title compound (22 mg, 62%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 2-chloroquinoline-5-carboxylate (16 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.323 min, MS (ES) 710.2 (M+H).

Example 158

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-propyl-1*H*-indole-5-carboxylic acid

Step A. Preparation of propyl 3-bromo-1-propyl-1*H*-indole-5-carboxylate

[00316] The title compound (56 mg, 61%) was prepared following General Procedure F using 1*H*-indole-5-carboxylic acid (46 mg, 0.28 mmol), NBS (51 mg, 0.28 mmol), NaH (25 mg, 0.62 mmol) and 1-iodopropane (61 μL, 0.48 mmol). LCMS: R_T = 1.761 min, MS (ES) 324.2 (M+H).

Step B. Example 158

[00317] The title compound (29 mg, 78%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), propyl 3-bromo-1-propyl-1*H*-indole-5-carboxylate (15 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.104 min, MS (ES) 740.2 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, *J* = 1.6 Hz, 1H), 7.84 – 7.69 (m, 2H), 7.62 (dd, *J* = 8.2, 1.7 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 1H), 6.73 (s, 2H), 4.48 (dt, *J* = 12.7, 3.2 Hz, 1H), 4.28 – 4.10 (m, 4H), 3.98 (s, 3H), 3.78 (s, 1.5H), 3.77 (s, 1.5H), 3.71 – 3.56 (m, 2H), 3.44 – 3.10 (m, 2H), 2.24 (s, 6H), 2.12 (s, 1.5H), 2.11 – 2.04 (m, 2H), 2.03 (s, 1.5H), 1.98 (s, 1.5H), 1.89 (s, 1.5H), 1.80 (h, *J* = 7.4 Hz, 2H), 1.09 (d, *J* = 6.4 Hz, 3H), 0.88 (td, *J* = 7.4, 2.7 Hz, 3H).

Example 159

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1,5-dimethyl-1*H*-indole-3-carboxylic acid (separated stereoisomer A)

Step A. Preparation of 7-bromo-5-methyl-1*H*-indole-3-carboxylic acid

To a stirred solution of 7-bromo-5-methyl-1*H*-indole (300 mg, 1.43 mmol) in DMF (1 mL) was added TFAA (0.24 mL, 1.71 mmol) dropwiseat at 0 °C. The reaction solution was warmed up to rt and stirred overnight. The reaction was quenched with H_2O (10 mL) then extracted with DCM (10 mL X 2). The combined organic solution was dried and concentrated *in vacuo*. The residue was dissolved in H_2O (1 mL) and NaOH (200 mg, 5.00 mmol) was added. The reaction mixture was refluxing for 3 h then neutralized with HCl (6 N). The resulting mixture was extracted with EtOAc (20 mL X 2). The combined organic solution was dried, concentrated and purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 20-80 % MeCN 0.1% TFA) to give the title compound (100 mg, 30%). LCMS: R_T = 1.252 min, MS (ES) 254.1 (M+H).

Step B. Preparation of methyl 7-bromo-1,5-dimethyl-1*H*-indole-3-carboxylate

[00318] To a stirred solution of 7-bromo-5-methyl-1*H*-indole-3-carboxylic acid (100 mg, 0.394 mmol) in DMF (1 mL) was added NaH (38 mg, 1.57 mmol) at 0°C. After 15 min, MeI (0.098 mL, 1.574 mmol) was added, and the resulting mixture was stirred for 1 h. The reaction was quenched with H_2O (3 mL) then extracted with DCM (10 mL X 2). The

combined organic solution was dried, concentrated to give the title compound. It was used for next step without further purification. MS (ES) 282.1 (M+H)

Step C. Example 159

[00319] The title compound (70 mg, 60%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one (200 mg, 0.37 mmol), methyl 7-bromo-1,5-dimethyl-1H-indole-3-carboxylate (115 mg, 0.41 mmol), $Pd_2(dba)_3$ (20 mg, 0.022 mmol), Xantphos (43 mg, 0.074 mmol), and Cs_2CO_3 (242 mg, 0.74 mmol) followed by saponification using General Procedure D. During the final purification step, the title compound was isolated as a separated atropisomer (1st fraction, absolute stereochemistry undeterminded). LCMS: RT = 2.044 min, MS (ES) 726.3 (M+H).

Example 160

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1,7-dimethyl-1*H*-indole-5-carboxylic acid

[00320] The title compound was prepared following the procedure described in Example 109 Step A and B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one and ethyl 3-bromo-1,7-dimethyl-1*H*-indole-5-carboxylate. MS (ES) 712.2 (M+H).

Example 161

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((1-methylpiperidin-4-yl)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,7-dimethyl-1*H*-indole-5-carboxylic acid

[00321] The title compound (25 mg, 74%) was prepared according to procedures described in Example 137 Step A and B using ethyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1,7-dimethyl-1*H*-indole-5-carboxylate (34 mg, 0.046 mmol) and (1-methylpiperidin-4-yl)methanol (30 mg, 0.23 mmol). LCMS: RT = 1.767 min, MS (ES) 823.3 (M+H).

Example 162

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1,5-dimethyl-1*H*-indole-3-carboxylic acid (separated stereoisomer B)

[00322] The title compound was isolated along with Example 159 as a separated atropisomer (2nd fraction, absolute stereochemistry undeterminded). LCMS: RT = 2.074 min, MS (ES) 726.3 (M+H).

Example 163

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indazole-5-carboxylic acid

[00323] The title compound (20 mg, 56%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 3-bromo-1-methyl-1*H*-indazole-5-carboxylate (17 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.994 min, MS (ES) 713.2 (M+H).

Example 164

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-ethyl-1*H*-indole-5-carboxylic acid

Step A. Preparation of ethyl 3-bromo-1-ethyl-1*H*-indole-5-carboxylate

[00324] The title compound (51 mg, 61%) was prepared following General Procedure F using 1*H*-indole-5-carboxylic acid (46 mg, 0.28 mmol), NBS (51 mg, 0.28 mmol), NaH (25 mg, 0.62 mmol) and EtI (53 μL, 0.62 mmol). LCMS: R_T = 1.756 min, MS (ES) 296.1 (M+H).

Step B. Example 164

[00325] The title compound (34 mg, 94%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), ethyl 3-bromo-1-ethyl-1*H*-indole-5-carboxylate (15 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.155 min, MS (ES) 726.3 (M+H).

Example 165

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indazole-7-carboxylic acid

[00326] The title compound (27 mg, 76%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 3-bromo-1-methyl-1*H*-indazole-7-carboxylate (15 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.058 min, MS (ES) 713.2 (M+H).

Example 166

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-isopropyl-1*H*-indole-5-carboxylic acid

Step A. Preparation of isopropyl 3-bromo-1-isopropyl-1*H*-indole-5-carboxylate

[00327] The title compound (28 mg, 30%)was prepared following General Procedure F using 1*H*-indole-5-carboxylic acid (46 mg, 0.28 mmol), NBS (51 mg, 0.28 mmol), NaH (25 mg, 0.62 mmol) and 2-iodopropane (61 μL, 0.62 mmol). LCMS: R_T = 1.765 min, MS (ES) 324.2 (M+H).

Step B. Example 166

[00328] The title compound (13 mg, 37%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), isopropyl 3-bromo-1-isopropyl-1*H*-indole-5-carboxylate (15 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.087 min, MS (ES) 740.2 (M+H).

Example 167

(*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-pyrrolo[2,3-b]pyridine-6-carboxylic acid

[00329] The title compound (87% yield) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-

(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one and methyl 4-bromo-1-methyl-1*H*-pyrrolo[2,3-b]pyridine-6-carboxylate followed by saponification using General Procedure D. MS (ES) 713.3 (M+H); ^{1}H NMR (DMSO, 400 MHz) δ (ppm) 7.83 (d, *J* = 4.8 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 3.2 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 6.70 (s, 2H), 6.44 (dd, *J* = 8.4, 3.2 Hz, 1H), 4.71-4.64(m, 1H), 4.20-4.10 (m, 2H), 3.99-3.95 (m, 2H), 3.89 (s, 3H), 3.73 (s, 3H), 3.33-3.20 (m, 2H), 2.23 (s, 6H), 2.09 (s, 1.5H), 2.09-2.03 (m, 2H), 2.00 (s, 1.5H), 1.98 (s, 1.5H), 1.89 (s, 1.5H), 1.00 (dd, *J* = 6.4, 3.6 Hz, 3H).

Example 168

7-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indole-3-carboxylic acid

[00330] The title compound (3.8 mg, 12%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 7-bromo-1-methyl-1*H*-indole-3-carboxylate (20 mg, 0.075 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (20 mg, 0.14 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.056 min, MS (ES) 710.1 (M+H); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.12 (s, 1H), 8.25 (d, *J* = 7.9 Hz, 0.7H), 8.21 (d, *J* = 7.9 Hz, 0.3H), 7.79 (s, 0.7H), 7.77 (s, 1.3H), 7.36 (d, *J* = 8.9 Hz, 1.3H), 7.32 (d, *J* = 7.8 Hz, 0.7H), 7.05 (d, *J* = 7.6 Hz, 1.3H), 7.00 (d, *J* = 7.6 Hz, 0.7H), 6.62 (s, 1.3H), 6.57 (s, 0.7H), 4.16 (dd, *J* = 13.5, 3.5 Hz, 1H), 4.08 – 3.96 (m, 2H), 3.93 (s, 1H), 3.84-3.71 (m, 3H) 3.54 (dd, *J* = 23.0, 13.2 Hz, 1H), 3.37 (dq, *J* = 14.4, 7.2 Hz, 2H), 2.44 (s, 3H), 2.34-2.28 (m, 6H), 2.26 (s, 3H), 2.23-2.16 (m, 2H), 1.30 (d, *J* = 6.5 Hz, 2H), 1.19 (d, *J* = 6.5 Hz, 1H).

Example 169

(*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-pyrrolo[2,3-b]pyridine-2-carboxylic acid

[00331] The title compound (90% yield) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one and methyl 4-bromo-1-methyl-1*H*-pyrrolo[2,3-b]pyridine-2-carboxylate followed by saponification using General Procedure D. MS (ES) 713.3 (M+H); ^{1}H NMR (DMSO, 400 MHz) δ (ppm) 8.47 (d, *J* = 4.8 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.15 (d, *J* = 5.2 Hz, 1H),

7.08 (s, 1H), 6.70 (s, 2H), 4.68-4.63(m, 1H), 4.18-4.09 (m, 2H), 4.06 (s, 3H), 4.02-3.95 (m, 2H), 3.76 (s, 3H), 3.37-3.16 (m, 2H), 2.25 (s, 3H), 2.22 (s, 6H), 2.06 (s, 1.5H), 2.03-1.99 (m, 2H), 1.98 (s, 1.5H), 1.89 (s, 1.5H), 0.99 (d, J = 6.4 Hz, 3H).

Example 170

2-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indole-4-carboxylic acid

Step A. Preparation of methyl 2-bromo-1*H*-indole-4-carboxylate

[00332] To a solution of methyl 2-oxoindoline-4-carboxylate (100 mg, 0.523 mmol) in DCE (5 mL) were added $POBr_3$ (880 mg, 3.05 mmol) and imidazole (140 mg, 2.06 mmol). The reaction was heated to 80 °C and stirred for 16 h. The reaction was cooled to RT, quenched with H_2O (20 mL) and extracted with DCM (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (27 mg, 20%).

Step B. Preparation of methyl 2-bromo-1-methyl-1*H*-indole-4-carboxylate

[00333] The title compound (21 mg, 75%) was prepared following General Procedure F using methyl 2-bromo-1*H*-indole-4-carboxylate, NaH (6 mg, 0.25 mmol) and MeI (30 mg, 0.211 mmol)..

Step C. Example 170

[00334] The title compound (9.7 mg, 29%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 2-bromo-1-methyl-1*H*-indole-4-carboxylate (20 mg, 0.075 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (20 mg, 0.14 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.116 min, MS (ES) 712.1 (M+H); ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.84 (dt, J = 7.7, 1.4 Hz, 1H), 7.56 (dd, J = 8.6, 5.8 Hz, 1H), 7.41 (t, J = 7.4 Hz, 1H), 7.22 – 7.14 (m, 2H), 6.88 (s, 1H), 6.46 (d, J = 1.5 Hz, 2H), 4.29-4.09 (m, 2H), 3.87-3.83 (m, 2H), 3.79 (s, 3H), 3.52 (s, 1.5H), 3.51 (s, 1.5H), 3.47 – 3.37 (m, 1H), 3.27 (dtd, J = 12.5, 7.3, 5.0 Hz, 1H), 3.19 (dt, J = 13.6, 7.4 Hz, 1H), 2.17 (s, 6H), 2.10 (s, 1.5H), 2.09 (s, 1.5H), 2.05-2.02 (m, 2H), 1.93 (s, 1.5H), 1.91 (s, 1.5H), 1.07 (br. s, 1.5H), 1.03 (br. S, 1.5H).

Example 171

(*R*)-5-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylic acid

[00335] The title compound (30 mg, 84%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 5-bromo-1-methyl-1*H*-indole-3-carboxylate (16 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.018 min, MS (ES) 712.2 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, *J* = 0.9 Hz, 1H), 7.94 (t, *J* = 2.1 Hz, 1H), 7.74 (d, *J* = 8.6 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 7.23 (td, *J* = 8.9, 2.1 Hz, 1H), 6.74 (s, 2H), 4.49 (dd, *J* = 12.9, 3.8 Hz, 1H), 4.21 – 4.10 (m, 1H), 4.01 – 3.94 (m, 3H), 3.88 (s, 3H), 3.78 (s, 1.5H), 3.77 (s, 1.5H), 3.23 (h, *J* = 6.9 Hz, 2H), 2.25 (s, 6H), 2.12 (s, 1.5H), 2.07 (q, *J* = 7.1, 6.5 Hz, 2H), 2.03 (s, 1.5H), 1.98 (s, 1.5H), 1.88 (s, 1.5H), 1.05 (dd, *J* = 6.5, 3.8 Hz, 3H).

Example 172

(*R*)-4-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)quinoline-6-carboxylic acid

[00336] The title compound (26 mg, 73%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 4-bromoquinoline-6-carboxylate (16 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.816 min, MS (ES) 710.2 (M+H).

Example 173

4-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-ethyl-indole-3-carboxylic acid

Step A. Preparation of methyl 4-bromo-1-ethyl-1*H*-indole-3-carboxylate

[00337] To a solution of 4-bromo-1*H*-indole-3-carboxylic acid (700 mg, 2.92 mmol) in THF (20 mL) and MeOH (1 mL) was added trimethylsilyldiazomethane (2.0 M solution in Et_2O, 1.6 mL, 3.2 mmol) was added at 0 °C, and the reaction mixture was stirred for 2 h then warmed to RT. The reaction was quenched with AcOH, concentrated *in vacuo*, and the crude

residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to give methyl 4-bromo-1*H*-indole-3-carboxylic acid (513 mg, 69% yield). The title compound (52 mg, 93%) was prepared following General Procedure F using methyl 4-bromo-1*H*-indole-3-carboxylic acid (50 mg, 0.20 mmol), NaH (9 mg, 0.375 mmol) and EtBr (40 mg, 0.367 mmol).

Step B. Example 173

[00338] The title compound (11.6 mg, 35%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 4-bromo-1-ethyl-1*H*-indole-3-carboxylate (20 mg, 0.071 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (20 mg, 0.14 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.996, 2.029 min, MS (ES) 726.1 (M+H).

Example 174

2-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indole-5-carboxylic acid

Step A. Preparation of methyl 2-bromo-1-methyl-1*H*-indole-5-carboxylate

[00339] The title compound (33 mg, 23%) was prepared following the procedures described in Example 170 Step A using methyl 2-oxoindoline-5-carboxylate (100 mg, 0.52 mmol), $POBr_3$ (400 mg, 1.4 mmol), imidazole (100 mg, 1.47 mmol), and Step B using NaH (6 mg, 0.25 mmol) and MeI (30 mg, 0.21 mmol).

Step B. Example 174

[00340] The title compound (8.9 mg, 27%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 2-bromo-1-methyl-1*H*-indole-5-carboxylate (20 mg, 0.074 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (20 mg, 0.14 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.097 min, MS (ES) 712.2 (M+H); ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.38 (s, 1H), 8.00 (ddd, *J* = 8.6, 3.0, 1.6 Hz, 1H), 7.72 (dd, *J* = 8.6, 4.6 Hz, 1H), 7.39 – 7.30 (m, 2H), 6.62 (s, 2H), 6.41 (d, *J* = 2.4 Hz, 1H), 4.44-4.24 (m, 2H), 4.03-4.00 (m, 2H), 3.96 (s, 3H), 3.69 (s, 1.5H), 3.68 (s 1.5H), 3.62 – 3.53 (m, 1H), 3.44 (dt, *J* = 14.1, 7.3 Hz, 1H), 3.35 (dt, *J* = 13.1,

7.5 Hz, 1H), 2.33 (d, *J* = 1.3 Hz, 6H), 2.26 (s, 1.5H), 2.24 (s, 1.5H), 2.23-2.18 (m, 2H), 2.09 (s, 1.5H), 2.08 (s, 1.5H), 1.23 (d, *J* = 6.2 Hz, 1.5H), 1.22 (d, *J* = 6.2 Hz, 1.5H).

Example 175

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indazole-4-carboxylic acid

[00341] The title compound (9 mg, 25%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 3-bromo-1-methyl-1*H*-indazole-4-carboxylate (17 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.948 min, MS (ES) 713.2 (M+H).

Example 176

3-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-7-(4,6-dimethylpyrimidin-5-yl)-1-oxo-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-1-methyl-indole-6-carboxylic acid

[00342] The title compound (5.4 mg, 20%) was prepared following General coupling procedure B using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethylpyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (20 mg, 0.037 mmol), methyl 3-bromo-1-methyl-1*H*-indole-6-carboxylate (20 mg, 0.074 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (40 mg, 0.29 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.020 min, MS (ES) 710.2 (M+H).

Example 177

3-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indole-5-carboxylic acid

[00343] The title compound (11.2 mg, 43%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (20 mg, 0.037 mmol), methyl 3-bromo-1-methyl-1*H*-indole-5-carboxylate (20 mg, 0.074 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (40 mg, 0.29 mmol) followed by saponification using General Procedure D. LCMS: R_T =

2.018 min, MS (ES) 710.2 (M+H); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.16 (s, 1H), 8.30 (s, 1H), 8.00 (d, *J* = 10.0 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.36 (d, *J* = 5.0 Hz, 1H), 7.35 (d, *J* = 10.0 Hz, 1H), 6.62 (s, 2H), 4.38 (dd, *J* = 13.1, 3.7 Hz, 1H), 4.00 (s, 2H), 3.83 (s, 3H), 3.74 (s, 1H), 3.62 (d, *J* = 12.7 Hz, 1H), 3.39 (m, 2H), 2.44 (s, 3H), 2.31 (s, 6H), 2.29 (s, 3H), 2.25-2.18 (m, 3H), 1.24 (d, *J* = 6.5 Hz, 3H).

Example 178

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of ethyl 7-bromo-1-methyl-1*H*-indole-2-carboxylate

[00344] The title compound (45 mg, 80%) was prepared following General Procedure G using ethyl 7-bromo-1*H*-indole-2-carboxylate (54 mg, 0.20 mmol), NaH (10 mg, 0.24 mmol) and MeI (15 μL, 0.24 mmol). LCMS: R_T = 1.882 min, MS (ES) 282.1 (M+H).

Step B. Example 178

[00345] The title compound (16 mg, 45%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), ethyl 7-bromo-1-methyl-1*H*-indole-2-carboxylate (14 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.059 min, MS (ES) 712.2 (M+H).

Example 179

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indazole-4-carboxylic acid (separated stereoisomer, 2nd eluting atropisomer)

[00346] The title compound (absoluted configuration unknown, 6 mg, 17%) was isolated from Example 175 using reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA, 10 mins gradient) as the second eluting stereoisomer. LCMS: R_T = 1.961 min, MS (ES) 713.2 (M+H).

Example 180

2-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indole-6-carboxylic acid

Step A. Preparation of methyl 2-bromo-1-methyl-1*H*-indole-6-carboxylate

[00347] The title compound (74 mg, 53%) was prepared following the procedures described in Example 170 Step A using methyl 2-oxoindoline-6-carboxylate (100 mg, 0.52 mmol), $POBr_3$ (400 mg, 1.39 mmol), and imidazole (100 mg, 1.47 mmol) and Step B using NaH (15 mg, 0.63 mmol) and MeI (60 mg, 0.42 mmol).

Step B. Example 180

[00348] The title compound (11.9 mg, 36%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 2-bromo-1-methyl-1*H*-indole-6-carboxylate (20 mg, 0.074 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (20 mg, 0.14 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.096 min, MS (ES) 712.2 (M+H); ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.96 (d, *J* = 3.0 Hz, 1H), 7.66 (dt, *J* = 8.3, 1.8 Hz, 1H), 7.52 (dd, *J* = 8.6, 4.6 Hz, 1H), 7.41 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.13 (dd, *J* = 8.6, 6.0 Hz, 1H), 6.42 (d, *J* = 2.2 Hz, 2H), 6.16 (s, 1H), 4.28 – 4.02 (m, 2H), 3.90 – 3.78 (m, 2H), 3.74 (s, 3H), 3.51 (s, 1.5H), 3.50 (s, 1.5H), 3.41-3.31 (m, 1H), 3.29 – 3.22 (m, 1H), 3.14 (m, 1H), 2.13 (s, 6H), 2.05 (s, 1.5H), 2.03 (s, 1.5H), 2.02 – 1.97 (m, 2H), 1.88 (d, *J* = 6.2 Hz, 3H), 1.03 (d, *J* = 3.9 Hz, 1.5H), 0.97 (d, *J* = 5.6 Hz, 1.5H).

Example 181

4-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-(2-methoxyethyl)indole-3-carboxylic acid

Step A. Preparation of methyl 4-bromo-1-(2-methoxyethyl)-1*H*-indole-3-carboxylate

[00349] The title compound (58 mg, 94%) was prepared following the procedure described in Example 173 Step A using methyl 4-bromo-1*H*-indole-3-carboxylate (50 mg, 0.20 mmol), NaH (9 mg, 0.38 mmol), and 1-bromo-2-methoxyethane (50 mg, 0.36 mmol).

Step B. Example 181

[00350] The title compound (13.7mg, 39%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 4-bromo-1-(2-methoxyethyl)-1*H*-indole-3-carboxylate (25 mg, 0.080 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (20 mg, 0.14 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.956, 1.908 min, MS (ES) 756.1 (M+H).

Example 182

4-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indole-3-carboxylic acid

Step A. Preparation of methyl 4-bromo-1-methyl-1*H*-indole-3-carboxylate

[00351] The title compound (51 mg, 97% yield) was prepared following the procedure described in Example 173 Step A using methyl 4-bromo-1*H*-indole-3-carboxylate (50 mg, 0.20 mmol), NaH (9 mg, 0.38 mmol), and MeI (50 mg, 0.35 mmol).

Step B. Example 182

[00352] The title compound (11 mg, 34%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 4-bromo-1-methyl-1*H*-indole-3-carboxylate (20 mg, 0.074 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (20 mg, 0.14 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.952, 1.988 min, MS (ES) 712.00 (M+H).

Example 183

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1,5-dimethyl-1*H*-indole-3-carboxylic acid

[00353] The title compound was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one and methyl 7-bromo-1,5-dimethyl-1H-indole-3-carboxylate followed by saponification using General Procedure D. MS (ES) 726.3 (M+H).

Example 184

(*R*)-5-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)quinoline-2-carboxylic acid

[00354] The title compound was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one and methyl 5-bromoquinoline-2-carboxylate followed by saponification using General Procedure D. MS (ES) 710.2 (M+H); ^{1}H NMR (MeOD, 400 MHz) δ (ppm) 8.56 (d, *J* = 8.4 Hz, 1H), 8.22 (d, *J* = 8.8 Hz, 1H), 8.08

(dd, J = 7.6, 1.2 Hz, 1H), 7.83 (s, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 6.70 (s, 2H), 4.33-4.29 (m, 1H), 3.97 (t, J = 6.0 Hz, 2H), 3.85 (s, 3H), 3.72-3.62 (m, 2H), 3.51-3.31 (m, 2H), 2.28 (s, 6H), 2.24 (s, 1.5H), 2.22-2.15 (m, 2H), 2.17 (s, 1.5H), 2.09 (s, 1.5H), 2.09 (s, 1.5H), 2.02 (s, 1.5H), 1.31 (s, 3H).

Example 185

(*R*)-6-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-2-naphthoic acid

[00355] The title compound (28 mg, 79%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 6-bromo-2-naphthoate (16 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.120 min, MS (ES) 709.0 (M+H).

Example 186

(*R*)-5-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-2-naphthoic acid (separated stereoisomer, 1st eluting atropisomer)

[00356] The title compound was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 5-bromo-2-naphthoate (16 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D and purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA) to afford the title compound as the first eluting stereoisomer (absoluted configuration unknown). LCMS: R_T = 2.047 min, MS (ES) 709.0 (M+H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 – 8.65 (m, 1H), 8.16 – 7.94 (m, 2H), 7.86 – 7.67 (m, 2H), 7.68 – 7.56 (m, 1H), 7.49 (td, J = 21.2, 7.8 Hz, 1H), 7.37 – 7.31 (m, 1H), 6.71 – 6.49 (m, 2H), 4.50 (qd, J = 12.8, 4.0 Hz, 1H), 4.42 – 4.20 (m, 1H), 4.07 – 3.96 (m, 2H), 3.93 (s, 0.75H), 3.92 (s, 1.5H), 3.91 (s, 0.75H), 3.54 – 3.35 (m, 3H), 2.32 (s, 6H), 2.29 - 2.24 (m, 2H), 2.21 (s, 0.75H), 2.20 (s, 1.5H), 2.19 (s, 0.75H), 2.11 (s, 0.75H), 2.10 (s, 0.75H), 2.09 (s, 1.5H), 1.40 – 1.21 (m, 3H).

Example 187

(*R*)-5-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-2-naphthoic acid (separated stereoisomer, 2nd eluting atropisomer)

[00357] The title compound was isolated along with Example 186 as the second eluting stereoisomer (absoluted configuration unknown). MS (ES) 709.0 (M+H).

Example 188

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-naphthoic acid

[00358] The title compound (29 mg, 82%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 3-bromo-1-naphthoate (16 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.123 and 2.140 min, MS (ES) 709.0 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.25 (t, *J* = 1.9 Hz, 1H), 8.12 (s, 1H), 8.05 – 7.94 (m, 1H), 7.77 (d, *J* = 8.6 Hz, 1H), 7.71 – 7.56 (m, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 7.11 (s, 0.5H), 6.98 (s, 0.5H), 6.74 (s, 2H), 4.68 – 4.48 (m, 1H), 4.27 – 4.13 (m, 1H), 4.08 – 3.92 (m, 2H), 3.79 (s, 3H), 3.29 (ddt, *J* = 41.8, 13.5, 6.4 Hz, 3H), 2.24 (s, 6H), 2.13 (s, 1.5H), 2.09 (s, 1.5H), 2.08 – 2.03 (m, 2H), 2.00 (s, 1.5H), 1.90 (s, 1.5H), 1.05 (dd, *J* = 6.5, 1.6 Hz, 3H).

Example 189

(*R*)-4-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-naphthoic acid

[00359] The title compound (21 mg, 59%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 4-bromo-1-naphthoate (16 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.091 min, MS (ES) 709.0 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (dd, *J* = 8.9, 3.3 Hz, 1H), 8.27 – 8.12 (m, 1H), 7.92 (t, *J* = 9.3 Hz, 1H), 7.82 – 7.76 (m, 1H), 7.75 – 7.47 (m, 3H), 7.40 – 7.27 (m, 1H), 6.70 (d, *J* = 4.6 Hz, 2H), 4.77 – 4.52 (m, 1H), 4.36 – 4.09 (m, 1H), 4.04 – 3.86 (m, 2H), 3.78 (s, 1.5H), 3.75 (s, 1.5H), 3.67 – 3.54 (m, 2H), 3.26 – 3.10 (m, 1H), 2.24 (s, 6H), 2.14 (s, 1.5H), 2.12 – 2.06 (m, 2H), 2.05 (s, 1.5H), 2.01 (s, 1.5H), 1.92 (s, 1.5H), 1.24 – 1.08 (m, 3H).

Example 190

(*R*)-1-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-2-naphthoic acid

[00360] The title compound (18 mg, 51%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 1-bromo-2-naphthoate (16 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.065 and 2.092 min, MS (ES) 709.0 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 – 8.05 (m, 2.5H), 8.01 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.91 – 7.85 (m, 0.5), 7.78 (dd, *J* = 8.6, 2.7 Hz, 1H), 7.74 – 7.60 (m, 1.5H), 7.58 (d, *J* = 7.6 Hz, 0.5H), 7.33 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.70 (d, *J* = 4.8 Hz, 2H), 4.40 (dq, *J* = 10.5, 6.2, 5.2 Hz, 1H), 4.29 – 4.14 (m, 1H), 3.95 (t, *J* = 6.5 Hz, 2H), 3.78 (s, 1.5H), 3.75 (s, 1.5H), 3.30 – 3.14 (m, 3H), 2.22 (s, 6H), 2.16 (s, 1H), 2.13 (s, 0.5H), 2.10 (s, 0.5H), 2.07 (s, 1H), 2.05 (s, 0.5H), 2.04 – 1.98 (m, 2H), 1.96 (s, 1H), 1.92 (s, 0.5H), 1.87 (s, 1H), 1.32 – 1.10 (m, 3H).

Example 191

(*R*)-8-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-naphthoic acid

[00361] The title compound (7 mg, 20%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 8-bromo-1-naphthoate (16 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.012 min, MS (ES) 709.0 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (dd, *J* = 7.5, 2.1 Hz, 1H), 8.04 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.74 (d, *J* = 8.6 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.63 – 7.53 (m, 2H), 7.52 – 7.42 (m, 1H), 7.30 (d, *J* = 8.6 Hz, 1H), 6.75 (s, 2H), 4.49 (dd, *J* = 13.8, 3.9 Hz, 1H), 4.29 – 4.10 (m, 1H), 3.95 (q, *J* = 6.4 Hz, 2H), 3.80 (s, 1.5H), 3.78 (s, 1.5H), 3.26 – 3.04 (m, 3H), 2.24 (s, 6H), 2.13 (s, 1.5H), 2.11 – 2.04 (m, 2H), 2.03 (s, 1.5H), 2.00 (s, 1.5H), 1.91 (s, 1.5H), 1.17 (d, *J* = 6.5 Hz, 3H).

Example 192

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-methyl-1*H*-indole-2-carboxylic acid

[00362] The title compound (11 mg, 30%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 7-bromo-4-methoxy-1-methyl-1*H*-indole-2-carboxylate (18 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.094 min, MS (ES) 742.0 (M+H).

Example 193

(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-2-[1-methyl-5-(trifluoromethyl)indol-3-yl]-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1-one (separated stereoisomer, 2nd eluting atropisomer)

Step A. Preparation of 3-bromo-1-methyl-5-(trifluoromethyl)-1*H*-indole

[00363] The title compound (61 mg, 51%) was prepared following General procedure F using 5-(trifluoromethyl)-1*H*-indole (80 mg, 0.43 mmol), NBS (100 mg, 0.561 mmol), NaH (18 mg, 0.75 mmol), and MeI (90 mg, 0.63 mmol).

Step B. Example 193

[00364] The title compound (7.6 mg, 29%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (20 mg, 0.037 mmol), 3-bromo-1-methyl-5-(trifluoromethyl)-1*H*-indole (20 mg, 0.072 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (20 mg, 0.14 mmol) followed by saponification using General Procedure D. The title compound was separated using reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient from 30-90% CH_3CN, 0.1% TFA) during the final purification step to give as a separated atropisomer (2nd fraction, absolute stereochemistry undeterminded). LCMS: R_T = 2.293. min, MS (ES) 736.0 (M+H).

Example 194

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)benzofuran-2-carboxylic acid

[00365] The title compound (19 mg, 54%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 7-bromobenzofuran-2-carboxylate (13 mg, 0.06 mmol), CuI (5 mg, 0.025

mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.103 min, MS (ES) 699.0 (M+H).

Example 195

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(3-oxo-2,3-dihydro-1*H*-inden-4-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00366] The title compound (8 mg, 24%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), 7-bromo-2,3-dihydro-1*H*-inden-1-one (11 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.069 min, MS (ES) 669.1 (M+H).

Example 196

(*R*)-5-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)benzofuran-2-carboxylic acid

[00367] The title compound (29 mg, 83%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 5-bromobenzofuran-2-carboxylate (14 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.130 min, MS (ES) 699.0 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (d, *J* = 2.2 Hz, 2H), 7.74 (d, *J* = 2.5 Hz, 1H), 7.68 (d, *J* = 1.0 Hz, 1H), 7.49 (ddd, *J* = 8.9, 3.6, 2.2 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 1H), 6.73 (s, 2H), 4.47 (d, *J* = 11.4 Hz, 2H), 4.19 – 4.11 (m, 1H), 3.99 (s, 3H), 3.78 (s, 1.5H), 3.77 (s, 1.5H), 3.74 – 3.61 (m, 2H), 3.22 (dt, *J* = 13.4, 7.4 Hz, 2H), 2.26 (s, 6H), 2.12 (s, 1.5H), 2.08 (d, *J* = 13.1 Hz, 2H), 2.03 (s, 1.5H), 1.97 (s, 1.5H), 1.88 (s, 1.5H), 1.04 (d, *J* = 6.4 Hz, 3H).

Example 197

(*R*)-4-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-isopropyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl 4-bromo-1-isopropyl-1*H*-indole-2-carboxylate

[00368] The title compound (35 mg, 59%) was prepared following General Procedure G using methyl 4-bromo-1*H*-indole-2-carboxylate (51 mg, 0.20 mmol), NaH (10 mg, 0.24 mmol) and 2-iodopropane (15 μL, 0.44 mmol). LCMS: R_T = 1.901 min, MS (ES) 296.0 (M+H).

[00369] Step B. Example 197

[00370] The title compound (21 mg, 57%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 4-bromo-1-isopropyl-1*H*-indole-2-carboxylate (15 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.192 and 1.257 min, MS (ES) 740.1 (M+H).

Example 198

(*R*)-4-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl 4-bromo-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-indole-2-carboxylate

[00371] The title compound (53 mg, 75%) was prepared following General Procedure G using methyl 4-bromo-1*H*-indole-2-carboxylate (51 mg, 0.20 mmol), NaH (10 mg, 0.24 mmol) and 4-(bromomethyl)tetrahydro-2*H*-pyran (32 μL, 0.24 mmol). LCMS: R_T = 1.776 min, MS (ES) 352.0 (M+H).

Step B. Example 198

[00372] The title compound (31 mg, 78%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 4-bromo-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-indole-2-carboxylate (21 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3

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(25 mg, 0.075 mmol) followed by saponification using Procedure D. LCMS: R_T = 2.079 min, MS (ES) 796.0 (M+H).

Example 199

(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-2-[1-methyl-6-(trifluoromethyl)indol-3-yl]-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1-one (separated stereoisomer, 2nd eluting atropisomer)

Step A. Preparation of 3-bromo-1-methyl-6-(trifluoromethyl)-1*H*-indole

[00373] The title compound (115 mg, 38%) was prepared following General procedure F using 6-(trifluoromethyl)-1*H*-indole (200 mg, 1.08 mmol), NBS (240 mg, 1.35 mmol), NaH (70 mg, 2.92 mmol), and MeI (220 mg, 1.55 mmol).

Step B. Example 199

[00374] The title compound (7.4 mg, 28%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (20 mg, 0.037 mmol), 3-bromo-1-methyl-6-(trifluoromethyl)-1*H*-indole (20 mg, 0.072 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (20 mg, 0.14 mmol) followed by saponification using General Procedure D. The title compound was separated using reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient from 30-90% CH_3CN, 0.1% TFA) during the final purification step to give as a separated atropisomer (2nd fraction, absolute stereochemistry undeterminded). LCMS: R_T = 2.312 min, MS (ES) 736.0 (M+H); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 (dd, *J* = 8.6, 3.5 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.41 – 7.34 (m, 1H), 7.34 – 7.28 (m, 2H), 6.61 (s, 2H), 4.41 (d, *J* = 11.9 Hz, 1H), 4.22 (s, 1H), 4.05 (s, 3H), 4.00 (tt, *J* = 6.2, 3.1 Hz, 2H), 3.88 (s, 2H), 3.85 (s, 1H), 3.64 (d, *J* = 12.6 Hz, 1H), 3.39 (m, 2H), 2.31 (d, *J* = 2.0 Hz, 6H), 2.27 (s, 3H), 2.22 (m, 5H), 1.23 (d, *J* = 5.5 Hz, 1H), 1.19 (d, *J* = 5.5 Hz, 2H).

Example 200

(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-2-[1-methyl-5-(trifluoromethyl)indol-3-yl]-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1-one (separated stereoisomer, 1st eluting atropisomer)

[00375] The title compound (6.9 mg, 26%) was separated as the 1st eluting atropisomer with Example 193. LCMS: R_T = 2.267 min, MS (ES) 736.0 (M+H).

Example 201

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(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,5-dimethyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl 7-bromo-1,5-dimethyl-1*H*-indole-2-carboxylate

[00376] The title compound (24 mg, 43%) was prepared following General Procedure G using 7-bromo-5-methyl-1*H*-indole-2-carboxylic acid (51 mg, 0.20 mmol), NaH (16 mg, 0.40 mmol) and MeI (26 μL, 0.40 mmol). LCMS: R_T = 1.761 min, MS (ES) 282.1 (M+H).

Step B. Example 201

[00377] The title compound (22 mg, 61%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 7-bromo-1,5-dimethyl-1*H*-indole-2-carboxylate (17 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.163 min, MS (ES) 726.1 (M+H).

Example 202

(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-2-[1-methyl-6-(trifluoromethyl)indol-3-yl]-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1-one (separated stereoisomer, 1st eluting atropisomer)

[00378] The title compound (6.5 mg, 24%) was separated as the 1st eluting atropisomer with Example 199. LCMS: R_T = 2.285 min, MS (ES) 736.0 (M+H); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.75 (d, *J* = 8.6 Hz, 1H), 7.64 (d, *J* = 9.1 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 8.3 Hz, 1H), 7.32 (dd, *J* = 8.8, 3.8 Hz, 2H), 6.61 (s, 2H), 4.40 (s, 1H), 4.09 (s, 4H), 4.03 – 3.93 (m, 2H), 3.89 (s, 2H), 3.86 (s, 1H), 3.66 (s, 1H), 3.52 – 3.27 (m, 2H), 2.35 (s, 3H), 2.32 (s, 6H), 2.23-2.11 (m, 5H), 1.26 (s, 3H).

Example 203

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-oxo-2,3-dihydro-1*H*-inden-4-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00379] The title compound (24 mg, 72%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), 4-bromo-2,3-dihydro-1*H*-inden-1-one (11 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol),

(*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.104 min, MS (ES) 669.1 (M+H).

Example 204

Methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (separated stereoisomer, 1st eluting atropisomer)

[00380] The title compound (12 mg, 33%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 3-bromo-1-methyl-1*H*-indole-5-carboxylate (16 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol). The title compound was isolated as the first eluting stereoisomer from reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA). LCMS: R_T = 2.146 min, MS (ES) 726.1 (M+H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 1.6, 0.6 Hz, 1H), 7.98 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.38 (dd, *J* = 8.8, 0.7 Hz, 1H), 7.34 – 7.30 (m, 2H), 6.64 (s, 2H), 4.47 (dd, *J* = 12.6, 3.8 Hz, 1H), 4.13 (s, 1H), 4.02 (t, *J* = 6.3 Hz, 2H), 3.96 (s, 3H), 3.92 (s, 3H), 3.85 (s, 3H), 3.71 (dd, *J* = 12.5, 1.7 Hz, 1H), 3.41 (ddt, *J* = 37.4, 13.2, 7.4 Hz, 2H), 2.33 (s, 6H), 2.26 (s, 3H), 2.25 – 2.17 (m, 2H), 2.09 (s, 3H), 1.27 (d, *J* = 6.5 Hz, 3H).

Example 205

Methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylate

[00381] The title compound (26 mg, 36%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (54 mg, 0.1 mmol), methyl 7-bromo-1-methyl-1*H*-indole-3-carboxylate (32 mg, 0.12 mmol), $Pd_2(dba)_3$ (2 mg, 0.002 mmol), Xantphos (3.5 mg, 0.006 mmol), and Cs_2CO_3 (49 mg, 0.15 mmol). LCMS: R_T = 2.162 and 2.193 min, MS (ES) 726.3 (M+H).

Example 206

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-6-carbonitrile

[00382] The title compound (34 mg, 98%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), 3-bromo-1-methyl-1*H*-indole-6-carbonitrile (14 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol). LCMS: R_T = 2.165 min, MS (ES) 693.1 (M+H).

Example 207

Methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (separated stereoisomer, 2nd eluting atropisomer)

[00383] The title compound (10 mg, 27%) was isolated as the second eluting stereoisomer along with Example 204 from reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA). LCMS: R_T = 2.167 min, MS (ES) 726.1 (M+H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 1.5 Hz, 1H), 7.98 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 7.33 – 7.28 (m, 2H), 6.64 (s, 2H), 4.43 (dd, *J* = 12.8, 3.8 Hz, 1H), 4.34 – 4.24 (m, 1H), 4.02 (tt, *J* = 6.2, 3.3 Hz, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 3.85 (s, 3H), 3.70 (dd, *J* = 12.8, 1.6 Hz, 1H), 3.54 – 3.23 (m, 2H), 2.33 (s, 6H), 2.24 (s, 3H), 2.23 – 2.15 (m, 2H), 2.09 (s, 3H), 1.24 (d, *J* = 6.5 Hz, 3H).

Example 208

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carbonitrile

[00384] The title compound (33 mg, 95%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), 3-bromo-1-methyl-1*H*-indole-5-carbonitrile (14 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol). LCMS: R_T = 1.214 min, MS (ES) 693.0 (M+H).

Example 209

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-7-carbonitrile

[00385] The title compound (26 mg, 75%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), 3-bromo-1-methyl-1*H*-indole-7-carbonitrile (14 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol). MS (ES) 693.2 (M+H).

Example 210

4-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indole-2-carboxylic acid

[00386] The title compound (2 mg, 8%) was prepared following General coupling procedure B using ((*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (20 mg, 0.037 mmol), methyl 4-bromo-1-methyl-1*H*-indole-2-carboxylate (20 mg, 0.074 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (20 mg, 0.14 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.071 min, MS (ES) 710.1 (M+H).

Example 211

4-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-2-(trifluoromethyl)indole-6-carboxylic acid

Step A. Preparation of methyl 4-bromo-1-methyl-2-(trifluoromethyl)-1*H*-indole-6-carboxylate

[00387] A mixture of methyl 4-bromo-1*H*-indole-6-carboxylate (125 mg, 0.49 mmol), 1-(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (100 mg, 0.54 mmol), and copper (I) acetate (5 mg, 0.04 mmol) were dissolved in MeOH (5 mL). The reaction mixture was purged with Ar for 5 min, sealed, and stirred at RT for 4 h. The reaction was then heated to 40 °C for 36 h. The reaction was cooled to RT, diluted with DCM/H_2O (20 mL, 1:1), the layers separated, and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The

crude reaction mixture was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford methyl 4-bromo-2-(trifluoromethyl)-1*H*-indole-6-carboxylate (44 mg, 28% yield). The resultant product was methylated following General coupling procedure G using NaH (6 mg, 0.25 mmol) and MeI (40 mg, 0.28 mmol) to afford the title compound (28 mg, 61% two steps).

Step B. Example 211

[00388] The title compound (3 mg, 8%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 4-bromo-1-methyl-2-(trifluoromethyl)-1*H*-indole-6-carboxylate (28 mg, 0.083 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (20 mg, 0.14 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.187 min, MS (ES) 780.0 (M+H).

Example 212

(*S*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1H-indole-5-carboxylic acid

[00389] The title compound (8% yield) was prepared following General coupling procedure A using (*S*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one and methyl 3-bromo-1-methyl-1*H*-indole-5-carboxylate followed by saponification using General Procedure D. MS (ES) 712.2 (M+H).

Example 213

5-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-7-(4,6-dimethylpyrimidin-5-yl)-1-oxo-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]naphthalene-2-carboxylic acid

[00390] The title compound (4.8 mg, 18%) was prepared following General coupling procedure B using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethylpyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (20 mg, 0.037 mmol), methyl 5-bromo-2-naphthoate (15 mg, 0.056 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (20 mg, 0.14 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.065 min, MS (ES) 707.0 (M+H).

Example 214

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylic acid (separated stereoisomer, 1st eluting atropisomer)

[00391] The title compound was isolated as a separated atropisomer (1st fraction, absolute stereochemistry undeterminded) from mixture of atropisomers. MS (ES) 712.2 (M+H).

Example 215

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylic acid (separated stereoisomer, 2nd eluting atropisomer)

[00392] The title compound was isolated as a separated atropisomer (2nd fraction, absolute stereochemistry undeterminded) from mixture of atropisomers. MS (ES) 712.2 (M+H).

Example 216

(*P,R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00393] The title compound was separated from diasteromeric (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one using reverse phase HPLC. Absolute stereochemistry was determined by single crystal X-ray structure. $[\alpha]_d^{25} = -138.7$.

Example 217

(*M,R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00394] The title compound was separated from diasteromeric (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one using reverse phase HPLC along with Example 216. Absolute stereochemistry was determined by single crystal X-ray structure. $[\alpha]_d^{25} = -182.4$.

Example 218

5-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2-yl]naphthalene-2-carboxylic acid

[00395] The title compound (5.8 mg, 22%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (20 mg, 0.037 mmol), methyl 5-bromo-2-naphthoate (15 mg, 0.057 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N,N'*-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (20 mg, 0.14

mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.037 min, MS (ES) 706.9 (M+H); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.10 (s, 1H), 8.63 (d, *J* = 1.6 Hz, 1H), 8.00 (dt, *J* = 8.9, 1.1 Hz, 1H), 7.89 (dt, *J* = 17.6, 8.8 Hz, 1.5H), 7.74 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 0.5 Hz), 7.52 (ddd, *J* = 13.5, 8.3, 7.3 Hz, 1H), 7.44 (dd, *J* = 7.3, 1.2 Hz, 0.5H), 7.34 (dd, *J* = 7.4, 1.1 Hz, 0.5H), 7.30 (s, 1H), 7.19 (s, 1H), 6.53 (s, 1H), 6.51 (s, 1H), 4.39 (dd, *J* = 26.2, 11.3 Hz, 1H), 3.92 (q, *J* = 5.9 Hz, 2H), 3.70 (s, 1H), 3.32 (dtt, *J* = 27.9, 13.5, 7.1 Hz, 3H), 2.43 (s, 1.5H), 2.42 (s, 1.5H), 2.27 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H), 2.13 (q, *J* = 6.9 Hz, 2H), 1.23 (d, *J* = 6.8 Hz, 1.5H), 1.21 (d, *J* = 6.8 Hz, 1.5H).

Example 219

7-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-7-(4,6-dimethylpyrimidin-5-yl)-1-oxo-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-1-methyl-indole-2-carboxylic acid

[00396] The title compound (2.5 mg, 9%) was prepared following General coupling procedure B using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethylpyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (20 mg, 0.037 mmol), ethyl 7-bromo-1-methyl-1*H*-indole-2-carboxylate (15 mg, 0.053 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (20 mg, 0.14 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.039 min, MS (ES) 710.1 (M+H).

Example 220

4-[8-Chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-7-(4,6-dimethylpyrimidin-5-yl)-1-oxo-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]quinoline-6-carboxylic acid

[00397] The title compound (4.5 mg, 17%) was prepared following General coupling procedure B using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethylpyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (20 mg, 0.037 mmol), methyl 4-bromoquinoline-6-carboxylate (10 mg, 0.037 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (20 mg, 0.14 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.786 min, MS (ES) 708.0 (M+H); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.19 (s, 1H), 9.11 (s, 1H), 8.65 (s, 1H), 8.41 (q, *J* = 8.8 Hz, 2H), 7.79 (d, *J* = 8.6 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 7.32 (d, *J* = 4.5 Hz, 1H), 6.62 (s, 2H), 4.11 – 3.96 (m, 4H), 3.90 (s, 2H), 3.22 (t, *J* = 7.4 Hz, 2H), 2.36 (s, 6H), 2.30 (s, 6H), 2.24 (quint, *J* = 7.1, 6.6 Hz, 2H), 1.86 (br s, 2H).

Example 221

3-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indole-5-carboxamide

[00398] The title compound (5.2 mg, 52%) was prepared following General Procedure E employing (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (10 mg, 0.014 mmol), HATU (10 mg, 0.026 mmol), DIPEA (10 mg, 0.078 mmol), and 7M ammonia in MeOH (0.05 mL, 0.35 mmol). LCMS: R_T = 1.924 min, MS (ES) 711.0 (M+H).

Example 222

(*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-6-(methylsulfonyl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 3-bromo-1-methyl-6-(methylsulfonyl)-1*H*-indole

[00399] To a solution of 6-(methylsulfonyl)-1*H*-indole (50 mg, 0.26 mmol) in DMF (3 mL) was added NaH (14 mg, 0.58 mmol) and stirred at RT for 30 min. MeI (70 mg, 0.49 mmol) was added and the reaction was stirred at RT for 3 h, diluted into DCM (10 mL), quenched with H_2O (10 mL). The layers were separated and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic extracts were dried and concentrated *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to give 1-methyl-6-(methylsulfonyl)-1*H*-indole. The product was dissolved in DMF (3 mL), cooled to 0 °C, and NBS (60 mg, 0.34 mmol) was added. After 30 min, the reaction was diluted into DCM (20 mL), washed with 10% aqueous $Na_2S_2O_3$, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (52 mg, 70%).

Step B. Example 222

[00400] The title compound (18.3 mg, 65%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (20 mg, 0.037 mmol), 3-bromo-1-methyl-6-(methylsulfonyl)-1*H*-indole (20 mg, 0.069 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (25 mg, 0.18 mmol). LCMS: R_T = 2.015, 2.034 min, MS (ES) 745.9 (M+H); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (t, *J* = 1.0 Hz, 1H), 7.75 – 7.60 (m, 3H), 7.39 (d, *J* = 6.0 Hz, 1H), 7.31 (dd, J = 8.0, 4.0 Hz, 1H), 6.62 (d, *J* = 1.6 Hz, 2H), 4.42 (dt, *J* = 12.2, 4.2 Hz, 1H), 4.35-

4.18 (m, 1H), 4.01 (td, *J* = 5.4, 4.5, 2.5 Hz, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 3.66 – 3.56 (m, 1H), 3.51 – 3.29 (m, 2H), 3.10 (s, 3H), 2.33 (s, 6H), 2.28 – 2.14 (m, 5H), 2.09 (s, 1.5H), 2.07 (s, 1.5H), 1.26 (d, *J* = 6.4 Hz, 1.5H), 1.19 (d, *J* = 6.4 Hz, 1.5H).

Example 223

(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-2-(1-methyl-5-nitro-indol-3-yl)-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1-one

[00401] The title compound (17.4 mg, 67%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (20 mg, 0.037 mmol), 3-bromo-1-methyl-5-nitro-1*H*-indole (20 mg, 0.078 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (25 mg, 0.18 mmol). LCMS: R_T = 2.136, 2.159 min, MS (ES) 712.9 (M+H); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.50 (dd, *J* = 6.2, 2.2 Hz, 1H), 8.18 (dd, *J* = 9.1, 2.2 Hz, 1H), 7.71 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.41 (d, J = 9.2 Hz, 1H), 7.37 (s, 0.5H), 7.32 – 7.29 (m, 1.5H), 6.66 – 6.61 (m, 2H), 4.49-4.23 (m, 2H), 4.06 – 3.98 (m, 2H), 3.92 (s, 3H), 3.87 (s, 3H), 3.65 (dd, *J* = 12.3, 7.2 Hz, 1H), 3.53 – 3.29 (m, 2H), 2.33 (s, 6H), 2.28 – 2.16 (m, 5H), 2.08 (d, *J* = 1.4 Hz, 3H), 1.26 (d, *J* = 6.4 Hz, 1.5H), 1.24 (d, *J* = 6.4 Hz, 1.5H).

Example 224

8-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2-yl]quinoline-5-carboxylic acid

[00402] The title compound (11.8 mg, 45%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (20 mg, 0.037 mmol), methyl 8-bromoquinoline-5-carboxylate (20 mg, 0.075 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (25 mg, 0.18 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.990 min, MS (ES) 707.8 (M+H).

Example 225

8-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2-yl]quinoline-4-carboxylic acid

[00403] The title compound (13.9 mg, 52%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-

dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (20 mg, 0.037 mmol), methyl 8-bromoquinoline-4-carboxylate (20 mg, 0.075 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (25 mg, 0.18 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.012 min, MS (ES) 707.8 (M+H).

Example 226

(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-2-(2-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-6-yl)-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1-one

Step A. Preparation of 6-bromo-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00404] The title compound (71 mg, 70%) was prepared following the procedure described in Example 86 Steps B and C using ethyl 7-bromo-1-methyl-1*H*-indole-2-carboxylate (100 mg, 0.56 mmol), *tert*-butyl 1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (180 mg, 0.81 mmol), NaH (24 mg, 1.0 mmol), HCl (4.0 M in dioxanes, 2 mL, 8.0 mmol), and K_2CO_3 (150 mg, 1.09 mmol).

Step B. Preparation of 6-bromo-2-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00405] The title compound (18 mg, 86%) was prepared following General Procedure G using 6-bromo-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (20 mg, 0.075 mmol), NaH (3 mg, 0.13 mmol), and MeI (20 mg, 0.14 mmol).

Step C. Example 226

[00406] The title compound (6.1 mg, 18%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), 6-bromo-2-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (18 mg, 0.064 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (20 mg, 0.15 mmol). MS (ES) 736.9 (M+H).

Example 227

8-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2-yl]quinoline-3-carboxylic acid

[00407] The title compound (15.4 mg, 58%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (20 mg, 0.037 mmol), methyl 8-bromoquinoline-3-carboxylate (20 mg, 0.075 mmol), CuI (5 mg, 0.026

mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (25 mg, 0.18 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.002 min, MS (ES) 707.9 (M+H); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.39 (d, *J* = 1.9 Hz, 1H), 9.22 (s, 1H), 8.88 (d, *J* = 2.0 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 1H), 7.88 – 7.77 (m, 2H), 7.72 (t, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.6 Hz, 1H), 6.62 (s, 2H), 4.71 (s, 1H), 4.00 (t, *J* = 6.1 Hz, 2H), 3.75 (s, 1H), 3.52 (s, 1H), 3.39 (m, 2H), 2.53 (s, 3H), 2.36 (s, 3H), 2.31 (s, 6H), 2.23 (quint, *J* = 7.0, 6.3 Hz, 2H), 1.33 (d, *J* = 5.9 Hz, 3H).

Example 228

3-(8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethyl-2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-1-oxo-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

Step A. Preparation of 4,6-dimethyl-2-(4-methylpiperazin-1-yl)pyrimidine

[00408] A mixture of 2-chloro-4,6-dimethylpyrimidine (1.0 g, 7.0 mmol), 1-methylpiperazine (750 mg, 7.5 mmol), and K_2CO_3 (1.5 g, 10.9 mmol) in MeCN (10 mL) was heated to 50 °C for 72 h. Reaction was diluted with DCM/H_2O (60 mL, 1:1), the organic layer was separated, and the aqueous layer was extracted with DCM (2 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the title compound (1.39 g, 96%).

Step B. Preparation of 5-bromo-4,6-dimethyl-2-(4-methylpiperazin-1-yl)pyrimidine

[00409] To a solution of 4,6-dimethyl-2-(4-methylpiperazin-1-yl)pyrimidine (1.39 g, 6.75 mmol) in $CHCl_3$ (10 mL) and NBS (1.25 g, 7.02 mmol) was added. The reaction was heated to 65 °C for 10 min then cooled to RT. The reaction mixture was diluted with DCM/H_2O (60 mL, 1:1) and extracted with DCM (2 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-10% gradient) to afford the title compound (1.66 g, 86%).

Step C. Preparation of (4,6-dimethyl-2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)boronic acid

[00410] To a solution of 5-bromo-4,6-dimethyl-2-(4-methylpiperazin-1-yl)pyrimidine (250 mg, 0.88 mmol) in toluene/THF (4 mL/1 mL) was added triisopropyl borate (250 mg, 1.33 mmol), and the reaction was cooled to -40 °C. *n*-Butyllitium (2.5 M, 0.48 mL, 1.20 mmol) was added over 1 h and stirred for 30 min, then warmed to -20 °C over 1 h. The reaction was quenched with 1M HCl, the organic layer was removed, and the aqueous layer was adjusted to pH 7 with 1M NaOH. The aqueous layer was extracted with 10% iPrOH in $CHCl_3$ (3 x 30

mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the title compound (140 mg, 56%).

Step D. Preparation of ethyl 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethyl-2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-1*H*-indole-2-carboxylate

[00411] A mixture of ethyl 7-bromo-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate (100 mg, 0.20 mmol), (4,6-dimethyl-2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)boronic acid (75 mg, 0.32 mmol), $Pd_2(dba)_3$ (20 mg, 0.022 mmol), S-Phos (25 mg, 0.061 mmol), and potassium phosphate (130 mg, 0.61 mmol) in THF (3 mL) and toluene (3 mL) was sparged with Ar for 5 min. The reaction was heated to 110 °C for 24 h then cooled to RT and diluted with DCM/H_2O (20 mL, 1:1). The layers were separated, and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to give the title compound (52 mg, 42%).

Step E. Preparation of 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethyl-2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one

[00412] The title compound (31 mg, 58%) was prepared following the procedures described in Example 120 Steps B and C using ethyl 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethyl-2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-1*H*-indole-2-carboxylate (52 mg, 0.083 mmol), *tert*-butyl 1,2,3-oxathiazinane-3-carboxylate 2,2-dioxide (30 mg, 0.13 mmol), NaH (8 mg, 0.20 mmol), HCl in dioxanes (4.0 M, 0.5 mL, 2.0 mmol), and K_2CO_3 (30 mg, 0.22 mmol).

Step F. Example 228

[00413] The title compound (13 mg, 33%) was prepared following General coupling procedure B using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethyl-2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (31 mg, 0.049 mmol), methyl 3-bromo-1-methyl-1*H*-indole-5-carboxylate (30 mg, 0.11 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (25 mg, 0.18 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.760 min, MS (ES) 808.0 (M+H); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.28 (s, 1H), 8.00 (d, *J* = 8.8 Hz, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 7.18 (s, 1H), 6.64 (s, 2H), 5.04 (d, J = 11.2 Hz, 2H), 4.11 (t, *J* = 6.4 Hz, 2H), 4.00 (t, *J* = 6.1 Hz, 2H), 3.83 (s, 3H), 3.77 (t, *J* = 6.2 Hz, 4H), 3.56 (s, 2H), 3.21 (t, *J* =

7.4 Hz, 2H), 2.92 (s, 5H), 2.31 (s, 6H), 2.28 – 2.19 (m, 2H), 2.12 (s, 6H), 1.91 (d, *J* = 6.0 Hz, 2H).

Example 229

(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-2-(2-isopentyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-6-yl)-4-methyl-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1-one

Step A. Preparation of 6-bromo-2-isopentyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00414] The title compound (15 mg, 59%) was prepared following General Procedure G using 6-bromo-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (20 mg, 0.075 mmol), NaH (3 mg, 0.13 mmol), and isovaleryl bromide (25 mg, 0.17 mmol).

Step B. Example 229

[00415] The title compound (4.7 mg, 13%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), 6-bromo-2-isopentyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (15 mg, 0.045 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (25 mg, 0.18 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.177 min, MS (ES) 793.0 (M+H).

Example 230

(*R*)-4-Chloro-8-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)quinoline-2-carboxylic acid

[00416] The title compound (11 mg, 30%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 8-bromo-4-chloroquinoline-2-carboxylate (19 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.089 min, MS (ES) 743.9 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (dt, *J* = 7.8, 1.5 Hz, 1H), 8.26 (d, *J* = 1.8 Hz, 1H), 8.04 – 7.90 (m, 2H), 7.77 (d, *J* = 8.6 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 6.72 (s, 2H), 4.77 – 4.55 (m, 1H), 4.27 – 4.12 (m, 1H), 3.96 (t, *J* = 6.5 Hz, 2H), 3.78 (s, 1.5H), 3.76 (s, 1.5H), 3.35 – 3.12 (m, 3H), 2.23 (s, 6H), 2.13 (s, 1.5H), 2.11 – 2.04 (m, 2H), 2.02 (s, 1.5H), 1.98 (s, 1.5H), 1.89 (s, 1.5H), 1.37 – 1.16 (m, 3H).

Example 231

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-5-carboxylic acid

Step A. Preparation of methyl 3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-5-carboxylate

[00417] The title compound (96 mg, 88%) was prepared following General Procedure F using methyl 1*H*-indole-5-carboxylate (50 mg, 0.28 mmol), NBS (51 mg, 0.28 mmol), NaH (14 mg, 0.34 mmol) and (2-(chloromethoxy)ethyl)trimethylsilane (60 μL, 0.34 mmol). LCMS: R_T = 1.979 min, MS (ES) 384.0 (M+H).

Step B. Example 231

[00418] The title compound (30 mg, 72%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-5-carboxylate (23 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.257 min, MS (ES) 828.0 (M+H).

Example 232

(*R*)-5-Chloro-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)benzofuran-2-carboxylic acid (separated stereoisomer, 1st eluting atropisomer)

[00419] The title compound (11 mg, 30%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 7-bromo-5-chlorobenzofuran-2-carboxylate (19 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D The title compound was isolated as a separated atropisomer (1st fraction, absolute stereochemistry undeterminded) by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA). LCMS: R_T = 2.138 min, MS (ES) 732.9 (M+H).

Example 233

7-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1H-indole-2-carboxylic acid (separated stereoisomer, 1st eluting atropisomer)

Step A. Preparation of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate

[00420] The title compound (210 mg, 52%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (300 mg, 0.55 mmol), ethyl 7-bromo-1*H*-indole-2-carboxylate (300 mg, 1.10 mmol), CuI (50 mg, 0.26 mmol), (*trans*)-N^1,N^2-dimethylcyclohexane-1,2-diamine (80 mg, 0.56 mmol), and K_2CO_3 (250 mg, 1.81 mmol).

Step B. Example 233

[00421] The title compound (6.8 mg, 35%) was obtained following General Procedure D using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (20 mg, 0.0 27 mmol) and isolated as a separated atropisomer (1st fraction, absolute stereochemistry undeterminded) by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient from 30-90% CH_3CN, 0.1% TFA). LCMS: R_T = 1.954 min, MS (ES) 697.9 (M+H).

Example 234

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-1*H*-indol-7-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(1*H*-indol-7-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00422] The title compound was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), 7-bromo-1*H*-indole (12 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol).

Step B. Example 234

[00423] The title compound (17 mg, 51%) was prepared following General procedure G using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(1*H*-indol-7-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one, NaH (5 mg, 0.12 mmol) and MeI (8 μL, 0.12 mmol). LCMS: R_T = 2.169 and 2.194 min, MS (ES) 667.9 (M+H).

Example 235

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1*H*-tetrazol-5-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (separated stereoisomer, 2nd eluting atropisomer)

[00424] To a solution of (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carbonitrile (69 mg, 0.1 mmol) in DMF (2 mL) were added sodium azide (33 mg, 0.5 mmol), ammonium chloride (27 mg, 0.5 mmol) and the mixture was heated at 120 °C for 12 h then cooled to ambient temperature. The reaction mixture was quenched with H_2O (5 mL), extracted with CH_2Cl_2 (3x15 mL), dried (anhyd. Na_2SO_4), and concentrated. The residue was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA) to afford the title compound (25 mg, 34%) as the second eluting atropisomer (absolute configuration undetermined). LCMS: R_T = 2.007 min, MS (ES) 736.0 (M+H).

Example 236

(*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-6-(2*H*-tetrazol-5-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00425] The title compound (13 mg, 80%) was prepared according to the procedure for Example 235 using (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-6-carbonitrile (15 mg, 0.022 mmol). LCMS: R_T = 2.045 min, MS (ES) 736.0 (M+H).

Example 237

(*R*)-2-(Benzofuran-3-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (separated stereoisomer, 1st eluting atropisomer)

[00426] The title compound (9 mg, 27%) was prepared following General coupling procedure B as the first eluting atropisomer (absolute configuration undetermined) using (*R*)-

7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), 3-bromobenzofuran (13 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol). LCMS: R_T = 2.260 min, MS (ES) 655.0 (M+H).

Example 238

7-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indole-2-carboxylic acid

[00427] The title compound (23 mg, 58%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.056 mmol), ethyl 7-bromo-1-methyl-1*H*-indole-2-carboxylate (30 mg, 0.11 mmol), $Pd_2(dba)_3$ (10 mg, 0.011 mmol), Xantphos (15 mg, 0.026 mmol), and Cs_2CO_3 (80 mg, 0.246 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.957 min, MS (ES) 709.9 (M+H).

Example 239

(*R*)-8-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxyquinoline-2-carboxylic acid

[00428] The title compound (16 mg, 44%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 8-bromo-4-chloroquinoline-2-carboxylate (19 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.019 and 2.034 min, MS (ES) 739.9 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.83 (ddd, *J* = 7.4, 3.1, 1.5 Hz, 1H), 7.78 – 7.68 (m, 2H), 7.59 (d, *J* = 1.6 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 1H), 6.73 (s, 2H), 4.88 – 4.49 (m, 1H), 4.31 – 4.18 (m, 1H), 4.15 (s, 3H), 3.97 (t, *J* = 6.4 Hz, 2H), 3.78 (s, 1.5H), 3.75 (s, 1.5H), 3.34 – 3.15(m, 3H), 2.24 (s, 6H), 2.13 (s, 1.5H), 2.11 – 2.04 (m, 2H), 2.02 (s, 1.5H), 1.98 (s, 1.5H), 1.89 (s, 1.5H), 1.36 – 1.15 (m, 3H).

Example 240

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-(tetrahydro-2*H*-pyran-4-yl)ethyl)-1*H*-indole-5-carboxylic acid

[00429] To a solution of methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-5-carboxylate (15 mg, 0.019 mmol) in DCM (1 mL) was added TFA (1 mL), and the mixture was stirred at RT for 6 h. Saturated aqueous $NaHCO_3$ (8 mL) was added to the mixture and extracted with DCM (3 x 5 mL). The organic layer was dried (anhyd. Na_2SO_4) and concentrated *in vacuo*. The crude product was alkylated following General procedure G using NaH (5 mg, 0.12 mmol) and 4-(2-bromoethyl)tetrahydro-2*H*-pyran (6 mg, 0.031 mmol) followed by saponification using General Procedure D to afford the title compound (8 mg, 52%). LCMS: R_T = 2.168 min, MS (ES) 810.3 (M+H).

Example 241

1-Benzyl-7-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]indole-2-carboxylic acid

[00430] To a solution of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (10 mg, 0.014 mmol) in DMF (1 mL) was added NaH (2 mg, 0.08 mmol), and the reaction was stirred at RT for 30 min. Benzyl bromide (5 mg, 0.029 mmol) was added, and the reaction was stirred for 16 h at RT then diluted with DCM/H_2O (20 mL, 1:1). The mixture was extracted with DCM (2 x 5 mL), dried by passing through a phase separator and concentrated *in vacuo*. The crude reaction product was then saponified and purified following General Procedure D to afford the title compound (6.9 mg, 64% yield). LCMS: R_T = 2.084 min, MS (ES) 787.8 (M+H).

Example 242

7-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1H-indole-2-carboxylic acid (separated stereoisomer, 2nd eluting atropisomer)

[00431] The title compound (8.1, 42% yield) was prepared in the same procedure as described in Example 233 as the 2nd fraction. LCMS: R_T = 1.953 min, MS (ES) 697.9 (M+H).

Example 243

Methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-5-carboxylate

[00432] The title compound (37 mg, 88%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-5-carboxylate (23 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol). LCMS: R_T = 2.451 min, MS (ES) 841.9 (M+H).

Example 244

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-7-cyano-1-methyl-1*H*-indole-5-carboxylic acid

Step A. Preparation of ethyl 3-bromo-7-cyano-1-methyl-1*H*-indole-5-carboxylate

[00433] To a solution of ethyl 7-bromo-1*H*-indole-5-carboxylate (97 mg, 0.36 mmol) in DMF (2 mL) was added NaH (17 mg, 0.43 mmol) and the mixture was stirred at RT for 10 min. Methyl iodide (27 μL, 0.43 mmol) was added to the mixture and stirred at ambient temperature for 2 h. The mixture was diluted with water (5 mL) and was extracted in CH_2Cl_2 (3 x 5 mL). The organic layer was dried (anhyd. Na_2SO_4) and concentrated. The crude was subjected to General Procedure B using sodium cyanide (22 mg, 0.43 mmol), CuI (7 mg, 0.04 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (57 μL, 0.36 mmol), and K_2CO_3 (120 mg, 0.72 mmol) and purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-20% gradient). To a solution of resulted ethyl 7-cyano-1-methyl-1*H*-indole-5-carboxylatehe in DMF (2 mL) was added and NBS (51 mg, 0.28 mmol) at 0 °C and stirred for 1 h. Same work up and purification protocols described in general coupling procedure **A** were followed to afford the title compound (52 mg, 47%). LCMS: R_T = 1.672 min, MS (ES) 307.0 (M+H).

Step B. Example 244

[00434] The title compound (25 mg, 68%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), ethyl 3-bromo-7-cyano-1-methyl-1*H*-indole-5-carboxylate (19 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and

K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.006 min, MS (ES) 736.9 (M+H).

Example 245

7-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-(3-pyridylmethyl)indole-2-carboxylic acid

[00435] The title compound (7.3 mg, 84%) was prepared following the procedure described Example 241 using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (8 mg, 0.011 mmol), NaH (2 mg, 0.05 mmol) and 3-chloromethylpyridine HCl salt (5 mg, 0.031 mmol). LCMS: R_T = 1.760, 1.786 min, MS (ES) 789.0 (M+H).

Example 246

(*R*)-2-(Benzofuran-3-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (separated stereoisomer, 2nd eluting atropisomer)

[00436] The title compound (11 mg, 33%) was prepared following General coupling procedure B as the second eluting atropisomer (absolute configuration undetermined) along with Example 237. LCMS: R_T = 2.238 min, MS (ES) 655.0 (M+H).

Example 247

7-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-(2-pyridylmethyl)indole-2-carboxylic acid

[00437] The title compound (4 mg, 37%) was prepared following the procedure described Example 241 using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (10 mg, 0.014 mmol) NaH (2 mg, 0.05 mmol) and 2-bromomethylpyridine HBr salt (5 mg, 0.020 mmol). LCMS: R_T = 1.839 min (major), 1.867 min (minor), MS (ES) 789.0 (M+H).

Example 248

7-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-(4-pyridylmethyl)indole-2-carboxylic acid

[00438] The title compound (5.7 mg, 53%) was prepared following the same procedure as described for Example 247, substituting 3-bromomethylpryidine HBr with 4-bromomethylpyridine HBr salt (5 mg, 0.020 mmol). LCMS: R_T = 1.817 min, MS (ES) 788.8 (M+H).

Example 249

7-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-(2-pyridylmethyl)indole-2-carboxylic acid (separated stereoisomer, 1st eluting atropisomer)

[00439] The title compound (2.1 mg, 19%) was separated from Example 247 by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient 35-95 % MeCN 0.1% TFA) as the 1st eluting atropisomer (absolute stereochemistry undetermined). LCMS: R_T = 1.839 min, MS (ES) 789.0 (M+H).

Example 250

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,7-dimethyl-1*H*-indole-6-carboxylic acid

Step A. Preparation of methyl 3-bromo-1,7-dimethyl-1*H*-indole-6-carboxylate

[00440] The title compound (65 mg, 81%) was prepared following General Procedure F using methyl 7-methyl-1*H*-indole-6-carboxylate (50 mg, 0.28 mmol), NBS (51 mg, 0.28 mmol), NaH (14 mg, 0.34 mmol) and MeI (22 μL, 0.34 mmol). LCMS: R_T = 1.602 min, MS (ES) 282.1 (M+H).

Step B. Example 250

[00441] The title compound (27 mg, 74%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 3-bromo-1,7-dimethyl-1*H*-indole-6-carboxylate (15 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 μL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.043 min, MS (ES) 726.0 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, *J* = 8.6 Hz, 1H), 7.49 (d, *J* = 3.3 Hz, 1H), 7.39 (dd, *J* = 8.4, 2.7 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 7.21 (dd, *J* = 8.4, 4.7 Hz, 1H), 6.72 (s, 2H), 4.44 (dd, *J* = 13.0, 3.9 Hz, 2H), 4.11 (s, 3H), 3.98 (tt, *J* = 6.4, 2.7 Hz, 2H), 3.78 (s, 1.5H), 3.77 (s, 1.5H), 3.58 (t, *J* = 11.2 Hz, 1H), 3.39 – 3.16

(m, 2H), 2.95 (s, 3H), 2.25 (s, 6H), 2.12 (s, 1.5H), 2.11 – 2.04 (m, 2H), 2.04 (s, 1.5H), 1.97 (s, 1.5H), 1.88 (s, 1.5H), 1.07 (d, J = 6.5 Hz, 3H).

Example 251

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1*H*-tetrazol-5-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (separated stereoisomer, 1st eluting atropisomer)

[00442] The title compound (28 mg, 38%) was isolated along with Example 235 as the first eluting atropisomer (absolute configuration undetermined). LCMS: R_T = 1.981 min, MS (ES) 736.0 (M+H).

Example 252

4-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indole-3-carboxylic acid

[00443] The title compound (11.5 mg, 42%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (20 mg, 0.037 mmol), methyl 4-bromo-1-methyl-1*H*-indole-3-carboxylate (20 mg, 0.075 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-N^1,N^2-dimethylcyclohexane-1,2-diamine (8 mg, 0.056 mmol), and K_2CO_3 (25 mg, 0.18 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.954 min, MS (ES) 709.9 (M+H); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.13 (s, 1H), 7.81 (d, J = 8.6 Hz, 1H), 7.45 – 7.30 (m, 3H), 7.16 (dd, J = 5.4, 3.0 Hz, 1H), 7.06 (d, J = 4.4 Hz, 1H), 6.56 (s, 2H), 4.38 (dd, J = 12.3, 4.0 Hz, 1H), 3.92 (qd, J = 7.8, 6.3, 4.7 Hz, 2H), 3.80 (s, 3H), 3.71 (s, 1H), 3.49 – 3.17 (m, 3H), 2.52 (s, 3H), 2.33 (d, J = 8.0 Hz, 1H), 2.29 – 2.19 (m, 8H), 2.17 – 2.04 (m, 2H), 1.28 (d, J = 6.4 Hz, 3H).

Example 253

(*R*)-4-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)quinoline-8-carboxylic acid

[00444] The title compound (20 mg, 56%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), methyl 4-bromoquinoline-8-carboxylate (16 mg, 0.06 mmol), $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Xantphos (2 mg, 0.003 mmol), and Cs_2CO_3 (25 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.030 min, MS (ES) 709.9 (M+H);

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (d, J = 5.0 Hz, 1H), 8.70 – 8.48 (m, 1H), 8.19 (dt, J = 8.5, 1.8 Hz, 1H), 7.83 (ddd, J = 15.6, 8.6, 4.4 Hz, 3H), 7.34 (d, J = 8.6 Hz, 1H), 6.70 (d, J = 5.4 Hz, 2H), 4.92 – 4.62 (m, 1H), 4.40 – 4.12 (m, 2H), 3.97 (t, J = 6.4 Hz, 2H), 3.79 (s, 3H), 3.39 - 3.13 (m, 2H), 2.23 (s, 6H), 2.14 (s, 1.5H), 2.04 (s, 3H), 2.02 – 1.97 (m, 2H), 1.92 (s, 1.5H), 1.15 (dd, J = 6.5, 3.1 Hz, 3H).

Example 254

7-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-(cyclopropylmethyl)indole-2-carboxylic acid

[00445] The title compound (7.6 mg, 92%) was prepared following the procedure described Example 241 using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (8 mg, 0.011 mmol), NaH (2 mg, 0.08 mmol) and bromomethylcyclopropane (5 mg, 0.075 mmol). LCMS: R_T = 2.096 min, MS (ES) 751.9 (M+H).

Example 255

8-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2-yl]naphthalene-1-carboxylic acid

[00446] The title compound (1.3 mg, 5%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (20 mg, 0.037 mmol), methyl 8-bromo-1-naphthoate (20 mg, 0.075 mmol), copper iodide (5 mg, 0.026 mmol), (*trans*)-N^1,N^2-dimethylcyclohexane-1,2-diamine (8 mg, 0.056 mmol), and K_2CO_3 (25 mg, 0.18 mmol) followed by saponification and purification following General Procedure D. LCMS: R_T = 1.976 min, MS (ES) 706.9 (M+H).

Example 256

7-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-(2-methoxyethyl)indole-2-carboxylic acid

[00447] The title compound (2.6 mg, 25% yield) was prepared following the same procedure as described in Example 245 substituting 3-chloromethylpyridine HCl with 1-bromo-2-methoxyethane (5 mg, 0.036 mmol). LCMS: R_T = 2.016 min, MS (ES) 755.8 (M+H).

Example 257

***N*-[3-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indol-5-yl]acetamide**

Step A. Prepaation of *N*-(3-bromo-1-methyl-1*H*-indol-5-yl)acetamide

[00448] To a solution of 1-methyl-1*H*-indol-5-amine (60 mg, 0.41 mmol) in DCM (3 mL) was added DIPEA (100 mg, 0.78 mmol) followed by acetyl chloride (40 mg, 0.513 mmol) at RT, and the reaction was stirred for 10 min. The reaction was quenched by the addition of MeOH, diluted into DCM/H_2O (20 mL, 1:1), the layers were separated, and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic extracts were dried concentrated *in vacuo*. The crude residue was dissolved in DMF (3 mL), and NBS (75 mg, 0.42 mmol) was added. The reaction was stirred for 1 h at RT and determined to be complete by LCMS. The reaction was diluted into DCM (20 mL) and washed with 10% aqueous $Na_2S_2O_3$ solution. The organic layer was dried, concentrated, and purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (40 mg, 36%).

Step B. Example 257

[00449] The title compound (15.2 mg, 75%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (15 mg, 0.028 mmol), *N*-(3-bromo-1-methyl-1*H*-indol-5-yl)acetamide (20 mg, 0.075 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), and K_2CO_3 (30 mg, 0.22 mmol). MS (ES) 724.9 (M+H).

Example 258

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-7-(1*H*-tetrazol-5-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00450] The title compound (15 mg, 93%) was prepared according to the procedure for Example 235 using (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-7-carbonitrile (15 mg, 0.022 mmol) and sodium azide (7 mg, 0.11 mmol). LCMS: R_T = 2.004 and 2.028 min, MS (ES) 736.0 (M+H).

Example 259

(*R*)-5-Chloro-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)benzofuran-2-carboxylic acid (separated stereoisomer, 2nd eluting atropisomer)

[00451] The title compound (12 mg, 33%) was isolated along with Example 232 as the 2nd eluting atropisomer (absolute configuration undetermined). LCMS: R_T = 2.245 min, MS (ES) 732.9 (M+H).

Example 260

(*R*)-2-(5-Acetyl-1-methyl-1*H*-indol-3-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00452] The title compound (21 mg, 59%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol), 1-(3-bromo-1-methyl-1*H*-indol-5-yl)ethan-1-one (13 mg, 0.06 mmol), CuI (5 mg, 0.025 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 µL, 0.05 mmol), and K_2CO_3 (25 mg, 0.075 mmol). LCMS: R_T = 2.078 and 2.099 min, MS (ES) 710.0 (M+H).

Example 261

3-((4*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl -1-((1-methylpyrrolidin-3-yl)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydro pyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

Step A. Preparation of methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate

[00453] To solution of methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (100mg, 0.12 mmol) in THF (2 mL) was added TBAF (0.59 mL, 0.59 mmol). The reaction mixture was heated to 100 °C for 20 min under microwave. The solvent was removed *in vacuo* and residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-10% gradient) to afford the title compound as brown oil (75 mg, 88 %). LCMS: R_T = 0.984 min, MS (ES) 712.2 (M+H).

Step B. Example 261

[00454] To a solution of methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (41 mg, 0.057 mmol) in DMF (1.5 mL) was added NaH (5 mg, 0.11 mmol). After 15 min, 3-(bromomethyl)-1-methylpyrrolidine (20 mg, 0.11 mmol) was added to reaction mixture and stirred overnight. The solvent was concentrated *in vacuo* and residue was filtered through silica pad with DCM/MeOH (3/1) then solvent was removed *in vacuo*. The residue was re-dissolved in mixture of methanol and dioxane (1 mL / 2 mL), and sodium hydroxide (0.2 mL, 2M solution) was added. The reaction mixture was stirred for 3h at room temperature and then concentrated *in vacuo*. The residue was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA) to afford the title compound (18 mg, 49 %). LCMS: R_T = non polar method: 0.712 min, MS (ES) 795.3 (M+H).

Example 262

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((tetrahydro-2H-pyran-4-yl)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydro pyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00455] The title compound (15 mg, 41 %) was prepared according to the procedure used in Example 261 Step B by substituting 3-(bromomethyl)-1-methylpyrrolidine for 4-(bromomethyl)tetrahydro-2H-pyran. LCMS: R_T = non polar method: 0.976 min, MS (ES) 796.3 (M+H).

Example 263

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00456] The title compound (13 mg, 40 %) was prepared according to the procedure used in Example 261 Step B by substituting 3-(bromomethyl)-1-methylpyrrolidine for 1-(2-bromoethyl)pyrrolidine. LCMS: R_T = non polar method: 0.766 min, MS (ES) 795.3 (M+H); ^{1}H NMR (MeOD, 400 MHz) δ (ppm) 8.27 (s, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.39 (d, *J* = 3.6 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 6.64 (s, 2H), 4.62-4.47 (m, 3H), 4.32-4.30 (m, 1H), 4.02- 3.95 (m, 2H), 3.89 (s, 2H), 3.78-3.68 (m, 4H), 3.52-3.30 (m, 2H), 3.20-3.13 (m, 2H), 2.68 (s, 2H), 2.29 (s, 6H), 2.25-2.03 (m, 4H), 2.20 (s, 3H), 2.04 (s, 3H), 1.25 (t, *J* = 6.0 Hz, 3H).

Example 264

1-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]isoquinoline-6-carboxylic acid

[00457] The title compound (14 mg, 53%) was prepared following General coupling procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (20 mg, 0.037 mmol), methyl 1-chloroisoquinoline-6-carboxylate (20 mg, 0.90 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-N^1,N^2-dimethylcyclohexane-1,2-diamine (8 mg, 0.056 mmol), and K_3PO_4 (30 mg, 0.14 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.299 min, MS (ES) 709.9 (M+H).

Example 265

(*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(piperazin-1-ylsulfonyl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of *tert*-butyl 4-((3-bromo-1-methyl-1*H*-indol-5-yl)sulfonyl)piperazine-1-carboxylate

[00458] To a solution of *tert*-butyl 4-((1-methyl-1*H*-indol-5-yl)sulfonyl)piperazine-1-carboxylate (65 mg, 0.17 mmol) in DMF (2 mL) was added NBS (35 mg, 0.20 mmol), and the reaction was stirred at RT until complete as determined by LCMS. The reaction was diluted into DCM (20 mL), washed with 10% aqueous $Na_2S_2O_3$ (10 mL), dried, and concentrated *in vacuo* to afford the title compound (66 mg, 85%).

Step B. Preparation of *tert*-butyl (*R*)-4-((3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indol-5-yl)sulfonyl)piperazine-1-carboxylate

[00459] The title compound (25 mg, 49% crude) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (20 mg, 0.037 mmol), *tert*-butyl 4-((3-bromo-1-methyl-1*H*-indol-5-yl)sulfonyl)piperazine-1-carboxylate (30 mg, 0.066 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-N^1,N^2-dimethylcyclohexane-1,2-diamine (8 mg, 0.056 mmol), and K_2CO_3.

Step C. Example 265

[00460] To a solution of the crude reaction product from Step B in dioxane (2 mL) was added HCl in dioxane (4.0 M, 0.5 mL, 2.0 mmol), and the reaction was stirred for 16 h at RT.

The reaction mixture was concentrated *in vacuo*, and half of the material was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient 35-95 % MeCN 0.1% TFA) to afford the title compound (7.3 mg, 48% yield two steps). LCMS: R_T = 1.848 min, MS (ES) 816.0 (M+H).

Example 266

4-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indole-2-carboxamide

[00461] The title compound (4.8 mg, 48%) was prepared following General Procedure E employing (*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylic acid (10 mg, 0.014 mmol), HATU (10 mg, 0.026 mmol), DIPEA (10 mg, 0.078 mmol), and ammonia in MeOH (7.0 M, 0.05 mL, 0.35 mmol). LCMS: R_T = 2.061 min, MS (ES) 711.0 (M+H).

Example 267

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-*N*,1-dimethyl-1*H*-indole-5-sulfonamide

Step A. Preparation of 3-bromo-*N*,1-dimethyl-1*H*-indole-5-sulfonamide.

[00462] To a solution of 1-methyl-1*H*-indole-5-sulfonyl chloride (40 mg, 0.17 mmol) in DCM (2 mL) was added DIPEA (40 mg, 0.31 mmol). Methylamine hydrochloride (30 mg, 0.45 mmol) was added, and the reaction was stirred at RT until complete by LCMS then concentrated *in vacuo*. The crude residue was then brominated following the procedure described in Example 265 Step A using NBS (35 mg, 0.20 mmol) to afford the title compound (37 mg, 71%).

Step B. Example 267

[00463] The title compound (9 mg, 32%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (20 mg, 0.037 mmol), 3-bromo-*N*,1-dimethyl-1*H*-indole-5-sulfonamide (25 mg, 0.083 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-N^1,N^2-dimethylcyclohexane-1,2-diamine (8 mg, 0.056 mmol), and K_2CO_3 (25 mg, 0.18 mmol). LCMS: R_T = 2.059 min, MS (ES) 760.9 (M+H); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09 (d, *J* = 11.2 Hz, 1H), 7.73 (ddd, *J* = 9.3, 7.6, 1.8 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 1H), 7.40 – 7.28 (m, 2H), 6.63 (s, 2H), 4.51 (dd, *J* = 40.0, 11.5 Hz, 1H), 4.20

(d, J = 21.5 Hz, 1H), 4.08 (s, 1.5H), 4.05 (s, 1.5H), 3.99 (t, J = 6.2 Hz, 2H), 3.86 (s, 3H), 3.70 (t, J = 12.6 Hz, 1H), 3.51 – 3.28 (m, 2H), 2.62 (s, 1.5H), 2.60 (s, 1.5H), 2.34 (s, 1.5H), 2.32 (s, 6H), 2.28 (s, 1.5H), 2.24 – 2.09 (m, 5H), 1.23 (d, J = 5.9 Hz, 3H).

Example 268

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-methoxyethyl)-1*H*-indole-5-carboxylic acid

Step A. Preparation of methyl 3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-5-carboxylate

[00464] The title compound (107 mg, 71%) was prepared following General Procedure G using methyl 3-bromo-1*H*-indole-5-carboxylate (100 mg, 0.39 mmol), NaH (24 mg, 0.59 mmol), and (2-(chloromethoxy)ethyl)trimethylsilane (0.11 mL, 98.5 mg, 0.59 mmol).

Step B. Preparation of methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-5-carboxylate

[00465] The title compound (93 mg, 82%) was prepared following General Procedure B using methyl 3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-5-carboxylate (78 mg, 0.20 mmol), (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (61 mg, 0.11 mmol), (1*R*,2*R*)-N^1,N^2-dimethylcyclohexane-1,2-diamine (14 mg, 0.098 mmol), CuI (9.4 mg, 0.049 mmol) and K_2CO_3 (54.7 mg, 0.40 mmol). MS (ES) 842.3 (M+H).

Step C. Preparation of methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-5-carboxylate

[00466] To a solution of methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-5-carboxylate (110 mg, 0.13 mmol) in THF (0.5 mL) was added TBAF (1.18 mL, 1.17 mmol, 1.0 M in THF), and the reaction mixture was stirred as 40 °C for 24 h. The reaction was cooled to RT, quenched with saturated NH_4Cl aq. solution and extracted with EtOAc (3 x 5 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf,

Hex/EtOAc = 0-100% gradient followed by DCM/MeOH = 0-10% gradient) to afford the title compound (40 mg, 43%). MS (ES) 712.3 (M+H).

Step D. Example 268

[00467] The title compound (5.1 mg, 21%, 2 steps) was prepared following General Procedure G using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-5-carboxylate (23 mg, 0.032 mmol), NaH (1.9 mg, 0.048 mmol), 1-bromo-2-methoxyethane (30 mg, 0.275 mmol) followed by saponification and purification following General Procedure D. LCMS: R_T = 1.947 min, MS (ES) 756.3 (M+H).

Example 269

3-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indole-5-carboxamide

[00468] The title compound (5.6 mg, 55%) was prepared following General Procedure E using ((*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (10 mg, 0.014 mmol), HATU (10 mg, 0.026 mmol), DIPEA (10 mg, 0.078 mmol), and ammonia in MeOH (7.0 M, 0.05 mL, 0.35 mmol). LCMS: R_T = 2.015 min, MS (ES) 708.9 (M+H).

Example 270

7-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indole-2-carboxamide

[00469] The title compound (6.8 mg, 68%) was prepared following General Procedure E using (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylic acid (10 mg, 0.014 mmol), HATU (10 mg, 0.026 mmol), DIPEA (10 mg, 0.078 mmol), and ammonia in MeOH (7.0 M, 0.05 mL, 0.35 mmol). LCMS: R_T = 2.001 min, MS (ES) 711.0 (M+H).

Example 271

(*R*)-7-(10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4,7-dimethyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylic acid (partially separated the 1st eluting atropisomer)

Step A. Preparation of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate

[00470] The title compound (14 mg, 13%) was prepared following General Procedure B using ethyl 7-bromo-1*H*-indole-2-carboxylate (80 mg, 0.30 mmol), (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (80 mg, 0.15 mmol), (1*R*,2*R*)-N^1,N^2-dimethylcyclohexane-1,2-diamine (47 μL, 42.4 mg, 0.30 mmol), CuI (28.4 mg, 0.15 mmol) and K_2CO_3 (61.8 mg, 0.45 mmol). MS (ES) 704.3 (M+H).

Step B. Example 271

[00471] The title compound was prepared following General Procedure G using ethyl (*R*)-7-(10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4,7-dimethyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (14 mg, 0.019 mmol), NaH (4.6 mg, 0.11 mmol), 2-(bromomethyl)pyridine hydrobromide (14.4 mg, 0.058 mmol) followed by saponification using General Procedure D. The title compound was isolated as a partially separated the first eluting isomer (2.2 mg, 15%, absolute configuration undetermined). LCMS: R_T = 1.877 min, MS (ES) 767.3 (M+H).

Example 272

7-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1,5-dimethyl-indole-2-carboxylic acid

[00472] The title compound (14.9 mg, 37%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.056 mmol), methyl 7-bromo-1,5-dimethyl-1*H*-indole-2-carboxylate (25 mg, 0.089 mmol), $Pd_2(dba)_3$ (6 mg, 0.0065 mmol), Xantphos (8 mg, 0.013 mmol), and Cs_2CO_3 (60 mg, 0.19 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.092, 2.119 min, MS (ES) 723.9 (M+H); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.19 (s, 1H), 7.82 (dd, *J* = 8.7, 1.1 Hz, 1H), 7.48 (s, 0.7H), 7.44 (s, 0.3H) 7.39 - 7.34 (m, 2H), 6.95 (d, *J* = 1.5 Hz, 1H), 6.63 (s, 1.3H),6.61 (s, 0.7H), 4.20 (d, *J* = 21.5 Hz, 2H), 4.06 – 3.93 (m, 4H), 3.85 – 3.71 (m, 1H),3.53 (dd, *J* = 12.6, 5.4 Hz, 1H), 3.45 – 3.32 (m, 2H), 2.52 (s, 1H), 2.50 (s, 2H), 2.43 (s, 2H), 2.40 (s, 1H), 2.34 (s, 1H), 2.33 (s, 2H), 2.32 (s, 6H), 2.25 – 2.18 (m, 2H),1.32 (d, *J* = 6.4 Hz, 2H), 1.22 (d, *J* = 6.5 Hz, 1H).

Example 273

3-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indazole-4-carboxylic acid

[00473] The title compound (13.2 mg, 39%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 3-bromo-1-methyl-1*H*-indazole-4-carboxylate (20 mg, 0.075 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-N^1,N^2-dimethylcyclohexane-1,2-diamine (8 mg, 0.056 mmol), and K_2CO_3 (30 mg, 0.22 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.935 min, MS (ES) 711.0 (M+H); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.17 (s, 1H), 7.75 (d, *J* = 8.7 Hz, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.34 (dd, *J* = 7.8, 5.4 Hz, 3H), 6.51 (s, 2H), 4.36 (s, 1H), 4.07 (s, 3H), 3.92 (s, 2H), 3.74 (s, 2H), 3.36 (s, 1H), 3.21 (dt, *J* = 13.7, 7.4 Hz, 1H), 2.49 (s, 3H), 2.26 (s, 6H), 2.24 – 2.10 (m, 5H), 1.27 (d, *J* = 5.7 Hz, 3H).

Example 274

(*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-((4-methylpiperazin-1-yl)sulfonyl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 3-bromo-1-methyl-5-((4-methylpiperazin-1-yl)sulfonyl)-1*H*-indole

[00474] The title compound (49 mg, 75%) was prepared following the procedure described in Example 265 Step A using 1-methyl-5-((4-methylpiperazin-1-yl)sulfonyl)-1*H*-indole (80 mg, 0.17 mmol) and NBS (35 mg, 0.20 mmol).

Step B. Example 274

[00475] The title compound (22.6 mg, 73%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (20 mg, 0.037 mmol), 3-bromo-1-methyl-5-((4-methylpiperazin-1-yl)sulfonyl)-1*H*-indole (30 mg, 0.081 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-N^1,N^2-dimethylcyclohexane-1,2-diamine (8 mg, 0.056 mmol), and K_2CO_3 (25 mg, 0.18 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.868 min, MS (ES) 829.9 (M+H); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.97 (d, *J* = 1.6 Hz, 0.5 H), 7.90 (d, *J* = 2.0 Hz, 0.5H) 7.75 (dd, *J* = 8.6, 5.5 Hz, 1H), 7.63 (ddd, *J* = 13.7, 8.7, 1.7 Hz, 1H), 7.51 (s, 0.5H), 7.49 (s, 0.5H), 7.37 (s, 1H), 7.32 (dd, *J* = 8.6, 1.9 Hz, 1H), 6.65 (s, 1H), 6.64 (s, 1H), 4.50 (dd, *J* = 12.8, 4.0 Hz, 0.5H),

4.28 (d, J = 12.4 Hz, 1.5H), 4.11 – 3.96 (m, 5H), 3.94 – 3.70 (m, 7H), 3.64 – 3.27 (m, 3H), 3.15 – 2.87 (m, 4H), 2.82 (s, 1.5H), 2.79 (s, 1.5H), 2.34 (s, 3H), 2.33 (s, 3H), 2.32 (s, 1.5H), 2.28 (s, 1.5H), 2.25 - 2.19 (m, 2H), 2.14 (d, J = 2.6 Hz, 3H), 1.32 (d, J = 6.1 Hz, 1.5H), 1.18 (d, J = 6.3 Hz, 1.5H).

Example 275

3-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1,2-dimethyl-indole-5-carboxylic acid

Step A. Preparation of methyl 3-bromo-1,2-dimethyl-1*H*-indole-5-carboxylate

[00476] The title compound (98 mg, 81%) was prepared following General Procedure F using 2-methyl-1*H*-indole-5-carboxylic acid (75 mg, 0.43 mmol), NBS (90 mg, 0.51 mmol), NaH (42 mg, 1.75 mmol), and MeI (200 mg, 1.41 mmol).

Step B. Example 275

[00477] The title compound (12.5 mg, 35%) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol), methyl 3-bromo-1,2-dimethyl-1*H*-indole-5-carboxylate (30 mg, 0.11 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-N^1,N^2-dimethylcyclohexane-1,2-diamine (8 mg, 0.056 mmol), and K_2CO_3 (30 mg, 0.22 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.109 min, MS (ES) 726.0 (M+H).

Example 276

(*R*)-7-(10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4,7-dimethyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylic acid (partially separated the 2nd eluting atropisomer)

[00478] The title compound was isolated by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA, 10 mins gradient) as a partially separated the 2nd eluting isomer (absolute configuration undetermined). LCMS: R_T = 1.897 min, MS (ES) 767.3 (M+H).

Example 277

3-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indole-6-carboxamide

[00479] The title compound (3.2 mg, 32%) was prepared following General Procedure E employing (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-

(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-6-carboxylic acid (10 mg, 0.014 mmol), HATU (10 mg, 0.026 mmol), DIPEA (10 mg, 0.078 mmol), and ammonia in MeOH (7.0 M, 0.05 mL, 0.35 mmol). LCMS: R_T = 2.011 min, MS (ES) 711.0 (M+H).

Example 278

(*R*)-2-(5-((4-acetylpiperazin-1-yl)sulfonyl)-1-methyl-1*H*-indol-3-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00480] To a solution of (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(piperazin-1-ylsulfonyl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (15 mg, 0.018 mmol) in DCM (3 mL) was added DIPEA (10 mg, 0.078 mmol) followed by acetyl chloride (5 mg, 0.037 mmol). The reaction was stirred at RT for 10 min. The reaction was quenched with MeOH, diluted with DCM/H_2O (10 mL, 1:1) and extracted with DCM (2 x 5 mL). The combined organic extracts were dried, concentrated *in vacuo*, and purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient 35-95 % MeCN 0.1% TFA) to afford the title compound (12.1 mg, 77%). LCMS: R_T = 2.245, 2.262 min, MS (ES) 858.0 (M+H).

Example 279

7-(8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethylpyrimidin-5-yl)-1-oxo-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylic acid

Step A. Preparation of ethyl 7-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethylpyrimidin-5-yl)-1-oxo-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1*H*-indole-2-carboxylate

[00481] The title compound (21 mg, 20% yield) was prepared following General Procedure B using ethyl 7-bromo-1*H*-indole-2-carboxylate (79.8 mg, 0.30 mmol), 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethylpyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (80 mg, 0.15 mmol), (1*R*,2*R*)-N^1,N^2-dimethylcyclohexane-1,2-diamine (47 µL, 42.4 mg, 0.30 mmol), CuI (28.4 mg, 0.15 mmol) and K_2CO_3 (61.8 mg, 0.45 mmol). MS (ES) 724.3 (M+H).

Step B. Example 279

[00482] The title compound (5.7 mg, 32%, 2 steps) was prepared following General Procedure G using ethyl 7-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-

dimethylpyrimidin-5-yl)-1-oxo-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1*H*-indole-2-carboxylate (17 mg, 0.023 mmol), NaH (2.8 mg, 0.069 mmol), 2-(bromomethyl)pyridine hydrobromide (8.9 mg, 0.035 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.845 min, MS (ES) 787.1 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.59 (s, 1H), 8.01-7.97 (m, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.6 Hz, 1H), 7.59 (s, 1H), 7.39-7.34 (m, 1H), 7.30-7.23 (m, 2H), 7.06 (d, *J* = 7.3 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.59 (s, 2H), 6.41 (d, *J* = 17.8 Hz, 1H), 6.12 (d, *J* = 17.0 Hz, 1H), 4.09-3.97 (m, 2H), 3.84-3.79 (m, 1H), 3.70-3.59 (m, 2H), 3.38-3.36 (m, 1H), 2.89-2.84 (m, 1H), 2.42 (s, 3H), 2.32 (s, 6H), 2.28 (s, 3H), 2.16-2.12 (m, 1H), 2.05-1.94 (m, 2H), 1.88-1.83 (m, 1H), 1.64-1.57 (m, 1H).

Example 280

3-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-*N*-(2-pyridyl)indole-5-carboxamide

[00483] The title compound (3.5 mg, 31%) was prepared following General Procedure E employing (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (10 mg, 0.014 mmol), HATU (10 mg, 0.026 mmol), DIPEA (20 mg, 0.155 mmol), and 2-aminopyridine (5 mg, 0.053 mmol). The reaction was stirred for 16 h at room temperature followed by 8 h at 50 °C. LCMS: R_T = 1.994 min, MS (ES) 787.9 (M+H).

Example 281

3-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-*N*-(2-pyridylmethyl)indole-5-carboxamide

[00484] The title compound (6.6 mg, 58%) was prepared following General Procedure E employing (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (10 mg, 0.014 mmol), HATU (10 mg, 0.026 mmol), DIPEA (20 mg, 0.155 mmol), and pyridin-2-ylmethanamine (5 mg, 0.046 mmol). After 16 hr the reaction was complete. LCMS: R_T = 1.861 min, MS (ES) 802.0 (M+H).

Example 282

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3-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-*N*,1-dimethyl-*N*-(3-pyridylmethyl)indole-5-carboxamide

[00485] The title compound (8.5 mg, 75%) was prepared following General Procedure E employing (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (10 mg, 0.014 mmol), HATU (10 mg, 0.026 mmol), DIPEA (20 mg, 0.155 mmol), and *N*-methyl-1-(pyridin-3-yl)methanamine (5 mg, 0.041 mmol). After 16 h the reaction was complete. LCMS: R_T = 1.860 min, MS (ES) 816.0 (M+H).

Example 283

3-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-*N*-(4-pyridyl)indole-5-carboxamide

[00486] The title compound (6.6 mg, 58%) was prepared following General Procedure E employing (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (10 mg, 0.014 mmol), HATU (10 mg, 0.026 mmol), DIPEA (20 mg, 0.155 mmol), and 4-aminopyridine (5 mg, 0.053 mmol). The reaction was stirred for 16 h at room temperature followed by 8 h at 50 °C. LCMS: R_T = 1.875 min, MS (ES) 787.9 (M+H).

Example 284

3-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-*N*-(4-pyridylmethyl)indole-5-carboxamide

[00487] The title compound (8.3 mg, 73%) was prepared following General Procedure E employing (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (10 mg, 0.014 mmol), HATU (10 mg, 0.026 mmol), DIPEA (20 mg, 0.155 mmol), and pyridin-4-ylmethanamine (5 mg, 0.046 mmol). After 16 h the reaction was be complete. LCMS: R_T = 1.825 min, MS (ES) 802.0 (M+H).

Example 285

(R)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-N,1-dimethyl-1H-indole-5-carboxamide

[00488] The title compound (6.3 mg, 57%) was prepared following General Procedure E employing (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (10 mg, 0.014 mmol), HATU (10 mg, 0.026 mmol), DIPEA (20 mg, 0.155 mmol), and aniline (5 mg, 0.053 mmol). The reaction was stirred for 16 h at room temperature followed by 8 h at 50 °C. LCMS: R_T = 2.234 min, MS (ES) 787.0 (M+H).

Example 286

3-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-*N*-(3-pyridylmethyl)indole-5-carboxamide

[00489] The title compound (6.8 mg, 67%) was prepared following General Procedure E employing (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (10 mg, 0.014 mmol), HATU (10 mg, 0.026 mmol), DIPEA (20 mg, 0.155 mmol), and methylamine hydrochloride (5 mg, 0.074 mmol). After 16 h the reaction was complete. LCMS: R_T = 2.029 min, MS (ES) 725.0 (M+H).

Example 287

3-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-*N*-(3-pyridylmethyl)indole-5-carboxamide

[00490] The title compound (8.8 mg, 78%) was prepared following General Procedure E employing (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (10 mg, 0.014 mmol), HATU (10 mg, 0.026 mmol), DIPEA (20 mg, 0.155 mmol), and pyridin-3-ylmethanamine (5 mg, 0.046 mmol). After 16 h the reaction was complete. LCMS: R_T = 1.841 min, MS (ES) 802.0 (M+H).

Example 288

(*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00491] The title compound (14.6 mg, 78%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (15 mg, 0.028 mmol), 3-bromo-1-methyl-1*H*-indole (11.7 mg, 0.056 mmol), (1*R*,2*R*)-N^1,N^2-

dimethylcyclohexane-1,2-diamine (8.9 μL, 8.0 mg, 0.056 mmol), CuI (5.3 mg, 0.028 mmol) and K_2CO_3 (11.6 mg, 0.084 mmol). LCMS: R_T = 2.151 min, MS (ES) 667.9 (M+H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.40 (dd, *J* = 7.9, 3.8 Hz, 1H), 7.28-7.26 (m, 1H), 7.22-7.21 (m, 1H), 7.18-7.16 (m, 1H), 7.10 (d, *J* = 5.3 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.54 (s, 2H), 4.31-4.26 (m, 1H), 4.24-4.10 (m, 1H), 3.95-3.90 (m, 2H), 3.80 (d, *J* = 3.2 Hz, 3H), 3.73 (s, 3H), 3.56 (ddd, *J* = 12.5, 7.9, 1.5 Hz, 1H), 3.40-3.33 (m, 1H), 3.31-3.24 (m 1H), 2.24 (s, 6H), 2.12 (s, 3H), 1.95 (d, *J* = 2.9 Hz, 3H), 1.19-1.15 (m, 2H), 1.10 (d, *J* = 6.4 Hz, 3H).

Example 289

3-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-*N*,*N*,1-trimethyl-indole-5-carboxamide

[00492] The title compound (8.0 mg, 76%) was prepared following General Procedure E employing (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (10 mg, 0.014 mmol), HATU (10 mg, 0.026 mmol), DIPEA (20 mg, 0.155 mmol), and dimethylamine hydrochloride (5 mg, 0.061 mmol). After 16 h the reaction was complete. LCMS: R_T = 2.085 min, MS (ES) 739.0 (M+H).

Example 290

(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-2-[1-methyl-5-(pyrrolidine-1-carbonyl)indol-3-yl]-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1-one

[00493] The title compound (7.8, 72%) was prepared following General Procedure E employing (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (10 mg, 0.014 mmol), HATU (10 mg, 0.026 mmol), DIPEA (20 mg, 0.155 mmol), and pyrrolidine (5 mg, 0.070 mmol). After 16 hr the reaction was complete. LCMS: R_T = 2.193 min, MS (ES) 765.0 (M+H); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.69 (m, 2H), 7.48 – 7.28 (m, 4H), 6.62 (d, *J* = 1.8 Hz, 2H), 4.53-4.36 (m, 1H), 4.15-4.09 (m, 4H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.88 – 3.79 (m, 3H), 3.74-3.49 (s, 4H), 3.37 (ddt, *J* = 34.7, 13.6, 7.1 Hz, 2H), 2.34 (s, 1.5H), 2.32 (s, 3H), 2.31 (s, 3H), 2.28 (s, 1.5H), 2.22-2.13 (m, 6H), 2.05-1.81 (br. s, 4H), 1.24 (m, 3H).

Example 291

3-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-*N*-(3-pyridyl)indole-5-carboxamide

[00494] The title compound (6.7 mg, 60%) was prepared following General Procedure E employing (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (10 mg, 0.014 mmol), HATU (10 mg, 0.026 mmol), DIPEA (20 mg, 0.155 mmol), and 3-aminopyridine (5 mg, 0.053 mmol). The reaction was stirred for 16 h at room temperature followed by 8 h at 50 °C. LCMS: R_T = 1.882 min, MS (ES) 787.9 (M+H).

Example 292

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-(2-morpholinoethyl)-1*H*-indole-6-carboxylic acid (separated the 2nd eluting atropisomer)

Step A. Preparation of methyl 3-bromo-1-(2-morpholinoethyl)-1*H*-indole-6-carboxylate

[00495] The title compound (27 mg, 19%) was prepared following General Procedure G using methyl 3-bromo-1*H*-indole-6-carboxylate (100 mg, 0.39 mmol), NaH (94.6 mg, 2.36 mmol) and 4-(2-chloroethyl)morpholine hydrochloride (220 mg, 1.2 mmol). MS (ES) 367.0 (M+H).

Step B. Example 292

[00496] The title compound (2.5 mg, 6%, 2 steps) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.056 mmol), methyl 3-bromo-1-(2-morpholinoethyl)-1*H*-indole-6-carboxylate (27 mg, 0.074 mmol), (1*R*,2*R*)-N^1,N^2-dimethylcyclohexane-1,2-diamine (7.0 µL, 6.4 mg, 0.044 mmol), CuI (4.3 mg, 0.022 mmol) and K_2CO_3 (27.0 mg, 0.21 mmol) followed by saponification using General Procedure D. The title compound was isolated as the 2nd eluting isomer from the final purification by reverse phase HPLC (absolute configuration undetermined). LCMS: R_T = 1.837 min, MS (ES) 811.3 (M+H).

Example 293

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-(2-morpholinoethyl)-1*H*-indole-6-carboxylic acid (separated the 1st eluting atropisomer)

[00497] The title compound (11.5 mg, 25%, 2 steps) was isolated as the 1st eluting isomer from the final reverse phase HPLC along with Example 292. LCMS: R_T = 1.815 min, MS (ES) 811.3 (M+H).

Example 294

3-[7-[2-(benzyloxymethyl)-4,6-dimethyl-pyrimidin-5-yl]-8-chloro-11-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-oxo-4,5-dihydro-3*H*-[1,4]diazepino[1,2-a]indol-2-yl]-1-methyl-indole-5-carboxylic acid

Step A. Preparation of ethyl 7-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-1-(3-((*tert*-butoxycarbonyl)amino)propyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate

[00498] A mixture of ethyl 7-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate (180 mg, 0.278 mmol), *tert*-butyl 1,2,3-oxathiazinane-3-carboxylate 2,2-dioxide (100 mg, 0.42 mmol), and Cs_2CO_3 (200 mg, 0.61 mmol) in MeCN (10 mL) was heated to 80 °C for 16 h. After which time, an additional portion of *tert*-butyl 1,2,3-oxathiazinane-3-carboxylate 2,2-dioxide (30 mg, 0.0.13 mmol) was added. The reaction was heated an additional 6 h, cooled to RT then diluted with EtOAc/H_2O (40 mL, 1:1). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (194 mg, 87%).

Step B. Preparation of 7-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one

[00499] To a solution of ethyl 7-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-1-(3-((*tert*-butoxycarbonyl)amino)propyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate (194 mg, 0.24 mmol) in 1,4-dioxane (20 mL) was added a solution of 4M HCl in dioxanes (1 mL, 4 mmol). The reaction was stirred overnight then concentrated *in vacuo*. The crude residue taken up in MeOH (10 mL) then K_2CO_3 (300 mg, 2.17 mmol) was added. The reaction was heated to 50 °C for 5 h, concentrated then dissolved in DCM/H_2O (60 mL, 1:1). The organic layer was separated, and the aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by flash

chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (117 mg, 74% 2 steps).

Step C. Preparation of methyl 3-(7-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate

[00500] The title compound (78 mg, 53%) was prepared following General coupling procedure B using 7-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (115 mg, 0.17 mmol), methyl 3-bromo-1-methyl-1*H*-indole-5-carboxylate (100 mg, 0.37 mmol), CuI (10 mg, 0.052 mmol), (*trans*)-1,2-*N,N'*-dimethylaminocyclohexane (15 mg, 0.10 mmol), and K_2CO_3 (75 mg, 0.54 mmol).

Step D. Example 294

[00501] The title compound (4 mg, 80%) was prepared following General Procedure D using methyl 3-(7-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (5 mg, 0.0059 mmol) and LiOH (2 mg, 0.083 mmol). LCMS: R_T = 2.155 min, MS (ES) 829.9 (M+H).

Example 295

7-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-5-methyl-1-(2-pyridylmethyl)indole-2-carboxylic acid

Step A. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate

[00502] The title compound was prepared following General Procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg. 0.055 mmol), methyl 7-bromo-5-methyl-1*H*-indole-2-carboxylate (30 mg, 0.112 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N,N'*-dimethylaminocyclohexane (8 mg, 0.056 mmol), K_3PO_4 (40 mg, 0.19 mmol).

Step B. Example 295

[00503] The title compound (9.3 mg, 21%, 2 steps) was prepared following the same procedure as described for Example 247 using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-

dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate NaH (6 mg, 0.25 mmol) and 2-(Bromomethyl)pyridine HBr salt (30 mg, 0.119 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.096, 2.121 min, MS (ES) 802.9 (M+H).

Example 296

7-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2-yl]-5-methyl-1-(2-pyridylmethyl)indole-2-carboxylic acid

Step A. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate

[00504] The title compound was prepared following General Procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg. 0.056 mmol), methyl 7-bromo-5-methyl-1*H*-indole-2-carboxylate (30 mg, 0.112 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N,N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), K_3PO_4 (40 mg, 0.19 mmol).

Step B. Example 296

[00505] The title compound (5.7 mg, 13%, 2 steps) was prepared following the same procedure as described for Example 247 using methyl methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate, NaH (6 mg, 0.25 mmol) and 2-(Bromomethyl)pyridine HBr salt (30 mg, 0.119 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.956 min, MS (ES) 801.0 (M+H).

Example 297

(*P, R*)-6-(benzyloxy)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylic acid

[00506] The title compound was prepared following General coupling procedure B using (*P,R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one, methyl 6-(benzyloxy)-4-bromo-1-methyl-1*H*-indole-2-carboxylate, CuI , (*trans*)-1,2-*N,N*'-dimethylaminocyclohexane, and K_2CO_3 followed by saponification and purification following General Procedure D. LCMS: R_T = 2.337 min, MS (ES) 818.2 (M+H).

Example 298

7-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-(thiazol-2-ylmethyl)indole-2-carboxylic acid

[00507] To a solution of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (20 mg, 0.028 mmol) in DMF (2 mL) was added Cs_2CO_3 (40 mg, 0.123 mmol), KI (20 mg, 0.12 mmol), and 2-(chloromethyl)thiazole (25 mg, 0.19 mmol), and the reaction was heated to 90 °C for 4 h. The reaction was then cooled to RT and diluted with DCM/H_2O (20 mL, 1:1). The organic layer was separated, and the aqueous layer was extracted with DCM (2 x 5 mL). The combined organic extracts were dried and concentrated *in vacuo*. The crude product was saponified and purified following the procedure described in General Procedure D to afford the title compound (2.2 mg, 10%, 2 steps). LCMS: R_T = 2.067 min, MS (ES) 795.0 (M+H).

Example 299

(*P*, *R*)-7-(benzyloxy)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylic acid

[00508] The title compound was prepared following General coupling procedure B using (*P,R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one, methyl 7-(benzyloxy)-4-bromo-1-methyl-1*H*-indole-2-carboxylate, CuI , (*trans*)-1,2-*N,N'*-dimethylaminocyclohexane, and K_2CO_3 followed by saponification and purification following General Procedure D. LCMS: R_T = 2.329 min, MS (ES) 817.9 (M+H).

Example 300

7-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indole-2-carbonitrile

[00509] The title compound (11.7 mg, 32%) was prepared following General Procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg. 0.046 mmol), 7-bromo-1-methyl-1*H*-indole-2-carbonitrile (17 mg, 0.068 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N,N'*-dimethylaminocyclohexane (8 mg, 0.056 mmol), K_3PO_4 (30 mg, 0.14 mmol). LCMS: R_T = 2.221 min, MS (ES) 693.0 (M+H).

Example 301

4-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indole-2-carbonitrile

Step A. Preparation of 4-bromo-1-methyl-1*H*-indole-2-carboxamide

[00510] The title compound (47 mg, 47%) was prepared following General Procedure E using 4-bromo-1-methyl-1*H*-indole-2-carboxylic acid (100 mg, 0.39 mmol), HATU (200 mg, 0.526 mmol), DIPEA (200 mg, 1.55 mmol), and ammonia in methanol (7.0 M, 0.25 mL, 1.75 mmol).

Step B. Preparation of 4-bromo-1-methyl-1*H*-indole-2-carbonitrile

[00511] A solution of 4-bromo-1-methyl-1*H*-indole-2-carboxamide (47 mg, 0.17 mmol) in $POCl_3$ (2mL) was heated to 100 °C for 2 h. The reaction was cooled to RT and poured into ice/aqueous $NaHCO_3$. The aqueous layer was extracted with DCM (3 x 10 mL), the combined organic reactions were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100%) to afford the title compound (32 mg, 73% yield).

Step C. Example 301

[00512] The title compound (25 mg, 65%) was prepared following General Procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg. 0.056 mmol), 4-bromo-1-methyl-1*H*-indole-2-carbonitrile (26 mg, 0.11 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (8 mg, 0.056 mmol), K_3PO_4 (50 mg, 0.24 mmol). LCMS: R_T = 2.276 min, MS (ES) 693.0 (M+H); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.53 – 7.43 (m, 1H), 7.40 – 7.27 (m, 2H), 7.13 – 7.02 (m, 2H), 6.65 – 6.60 (m, 2H), 4.48 (d, *J* = 11.6 Hz, 1H), 4.32-4.14 (m, 2H), 4.05 – 4.00 (m, 4H), 3.95 (s, 3H), 3.59 (d, *J* = 12.4 Hz, 1H), 3.46 (dt, *J* = 14.2, 7.5 Hz, 1H), 3.33 (dt, *J* = 14.0, 7.5 Hz, 1H), 2.33 (s, 5H), 2.29 (s, 1.5H), 2.26 (1.5H), 2.22-2.17 (m, 3H), 2.15 (s, 1.5H), 2.10 (s, 1.5H), 1.24 (d, *J* = 4.8 Hz, 1.5H), 1.18 (d, *J* = 6.4 Hz, 1.5H).

Example 302

7-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2-yl]-4-methoxy-1-(2-pyridylmethyl)indole-2-carboxylic acid

Step A. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1*H*-indole-2-carboxylate

[00513] The title compound (15 mg, 36%) was prepared following General Procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg. 0.056 mmol), methyl 7-bromo-4-methoxy-1*H*-indole-2-carboxylate (30 mg, 0.11 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N,N'*-dimethylaminocyclohexane (8 mg, 0.056 mmol), K_3PO_4 (40 mg, 0.19 mmol).

Step B. Example 302

[00514] The title compound (7.2 mg, 43%) was prepared following the procedure described Example 247 using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1*H*-indole-2-carboxylate, NaH (6 mg, 0.25 mmol) and 2-(bromomethyl)pyridine HBr salt (30 mg, 0.12 mmol). LCMS: R_T = 2.061 min, MS (ES) 816.9 (M+H).

Example 303

(*P, R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-6-hydroxy-1-methyl-1H-indole-2-carboxylic acid

[00515] To a solution of (*P, R*)-6-(benzyloxy)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylic acid (6 mg, 0.0072 mmol) in MeOH (3 mL) was added Pd/C (10% wt, 2 mg, 0.0018 mmol). The reaction was flushed with hydrogen then stired under H_2 for 6 h at RT. The reaction was filtered, concentrated *in vacuo*, and purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient 35-95 % MeCN 0.1% TFA) to afford the title compound (4 mg, 72% yield). LCMS: R_T = 2.007 min, MS (ES) 727.9 (M+H).

Example 304

7-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-(thiazol-4-ylmethyl)indole-2-carboxylic acid

[00516] The title compound (6.3 mg, 58%) was prepared following the procedure described Example 247 using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (10 mg, 0.014 mmol), NaH (5 mg, 0.12 mmol) and 4-(chloromethyl)thiazole (10 mg, 0.075 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.099, 2.129 min, MS (ES) 794.9 (M+H).

Example 305

(*M, R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-6-hydroxy-1-methyl-1H-indole-2-carboxylic acid (singlr atropisomer)

[00517] The title compound (3.3 mg, 59%) was prepared following the same procedure as Example 303 using (*M, R*)-6-(benzyloxy)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylic acid (6 mg, 0.0072 mmol) and Pd/C (10% wt, 2 mg, 0.0019 mmol). LCMS: R_T = 2.020 min, MS (ES) 727.9 (M+H).

Example 306

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-6-carboxylic acid

[00518] The title compound was prepared according to the procedure used in Example 261 Step B by substituting 3-(bromomethyl)-1-methylpyrrolidine with 1-(2-bromoethyl)pyrrolidine. LCMS: R_T = non polar method: 0.976 min, MS (ES) 795.3 (M+H).

Example 307

(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-2-[1-methyl-2-(2H-tetrazol-5-yl)indol-4-yl]-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1-one

[00519] The title compound (4 mg, 21%) was prepared according to the procedure for Example 235 using (*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carbonitrile (18 mg, 0.026 mmol) and sodium azide (10 mg, 0.15 mmol). LCMS: R_T = 2.145, 2.172 min, MS (ES) 736.0 (M+H).

Example 308

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-6-carboxylic acid

[00520] The title compound was prepared according to the procedure used in Example 261 Step B by substituting 3-(bromomethyl)-1-methylpyrrolidine with 4-(bromomethyl)tetrahydro-2*H*-pyran. MS (ES) 796.3 (M+H); ^{1}H-NMR (MeOH-d_3) δ 8.19 (d, 1H, J = 8 Hz), 7.79-7.75 (m, 2H), 7.487.47 (m, 2H) 7.31 (d, 1H, J = 8 Hz), 6.62 (s, 2H),

4.50-4.47 (m, 1H), 4.30-4.28 (m, 1H) 4.06 (tr, 2H, J = 8 Hz), 3.99 (s, 3H), 3.92 (s, 3H), 3.36-3.60 (m, 2H), 3.50-3.40 (m, 4H), 2.33 (s, 6H), 2.29- 2.16 (multiples s (3H), tr (2H), total 5H), 2.08 (s, 1.5H), 2.01 (s, 1.5H), 1.54-1.46 (m, 2H), 1.45 -1.40 (m, 2H), 1.31 (m, 1H), 1.23-1.19 (multiple d, 3H).

Example 309

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(1-(2-(dimethylamino)ethyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-6-carboxylic acid

[00521] The title compound was prepared according to the procedure used in Example 261 Step B by substituting 3-(bromomethyl)-1-methylpyrrolidine with 2-bromo-*N*,*N*-dimethylethan-1-amine. MS (ES) 769.3 (M+H)

Example 310

(*M, R*)-6-(benzyloxy)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-methyl-1H-indole-2-carboxylic acid

[00522] The title compound (5.5 mg, 92%) was prepared following General Procedure D using methyl (*M, R*)-6-benzyloxy-4-[7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indole-2-carboxylate (6 mg, 0.0072 mmol). LCMS: R_T = 2.349 min, MS (ES) 817.9 (M+H).

Example 311

7-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-(pyrimidin-5-ylmethyl)indole-2-carboxylic acid

[00523] The title compound (2 mg, 31%) was prepared according to the procedure used in Example 298 using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (6 mg, 0.0083 mmol), Cs_2CO_3 cesium carbonate (20 mg, 0.061 mmol), KI (10 mg, 0.0.060 mmol), and 5-(chloromethyl)pyrimidine (20 mg, 0.15 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.006 min, MS (ES) 790.0 (M+H).

Example 312

(*M, R*)-7-(benzyloxy)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1H-indole-2-carboxylic acid

[00524] The title compound (4 mg, 81%) was prepared following General Procedure D using methyl (*M, R*)-7-benzyloxy-4-[7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-methyl-indole-2-carboxylate (5 mg, 0.0060 mmol). LCMS: R_T = 2.192 min, MS (ES) 817.9 (M+H).

Example 313

7-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-4-methoxy-1-(2-pyridylmethyl)indole-2-carboxylic acid

Step A. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1*H*-indole-2-carboxylate

[00525] The title compound was prepared following General Procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg. 0.056 mmol), methyl 7-bromo-4-methoxy-1*H*-indole-2-carboxylate (30 mg, 0.11 mmol), CuI (5 mg, 0.026 mmol), (*trans*)-1,2-*N,N'*-dimethylaminocyclohexane (8 mg, 0.056 mmol), K_3PO_4 (40 mg, 0.19 mmol).

Step B. Example 313

[00526] The title compound (12.8 mg, 28% 3 steps) was prepared following the procedure described Example 241 using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1*H*-indole-2-carboxylate (from Step A), NaH (6 mg, 0.25 mmol) and 2-(bromomethyl)pyridine HBr salt (30 mg, 0.12 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.941, 1.965 min, MS (ES) 819.0 (M+H).

Example 314

7-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-[(5-methyl-1,2,4-oxadiazol-3-yl)methyl]indole-2-carboxylic acid

[00527] The title compound (4.2 mg, 19%) was prepared following the procedure described Example 298 using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (20 mg, 0.028 mmol), Cs_2CO_3 (40 mg, 0.123 mmol), KI (20 mg, 0.12 mmol), and 3-(chloromethyl)-5-methyl-1,2,4-oxadiazole (25 mg, 0.186 mmol) followed by saponification using General Procedure D to afford the title compound. LCMS: R_T = 2.063 min, MS (ES) 793.9 (M+H).

Example 315

7-[(4*R*)-7-chloro-10-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-4-methyl-1-oxo-6-(1,3,5-trimethylpyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2-yl]-1-[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]indole-2-carboxylic acid

[00528] The title compound (4.9 mg, 45%) was prepared following the procedure described Example 241 using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (10 mg, 0.014 mmol), NaH (3 mg, 0.12 mmol), and 2-(chloromethyl)-5-methyl-1,3,4-oxadiazole (10 mg, 0.076 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.072 min, MS (ES) 793.9 (M+H).

Example 316

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,3-dimethyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl 7-bromo-3-methyl-1*H*-indole-2-carboxylate

[00529] To a solution of (2-bromophenyl)hydrazine hydrochloride (223 mg, 1.0 mmol) in MeOH (5 mL) was added ethyl pyruvate (0.1 mL, 116 mg 1.0 mmol) followed by conc. HCl (5 mL). The reaction mixture was stirred at 70 °C for 4 h then cooled to RT, quenched with sat. $NaHCO_3$ aq. solution and extracted with DCM (3 x 5 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (227 mg, 85% yield). LCMS: R_T = 1.618 min, MS (ES) 268.0 (M+H).

Step B. Preparation of methyl 7-bromo-1,3-dimethyl-1*H*-indole-2-carboxylate

[00530] The title compound (38 mg, 37% yield) was prepared following General Procedure G using methyl 7-bromo-3-methyl-1*H*-indole-2-carboxylate (100 mg, 0.37 mmol). LCMS: R_T = 1.828 min, MS (ES) 282.0 (M+H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.9 Hz,

1H), 7.42 (d, *J* = 7.5 Hz, 1H), 6.87 (t, *J* = 7.8 Hz, 1H), 4.25 (s, 3H), 3.87 (s, 3H), 2.44 (s, 3H).

Step C. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,3-dimethyl-1*H*-indole-2-carboxylate

[00531] The title compound (20 mg, 33 %) was prepared following General Procedure B, using methyl 7-bromo-1,3-dimethyl-1*H*-indole-2-carboxylate (35 mg, 0.124 mmol) and (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (44.6 mg, 0.083 mmol). LCMS: R_T = 2.244, 2.267 min, MS (ES) 739.9 (M+H).

Step D. Example 316

[00532] The title compound (3.1 mg, 15%) was prepared following General procedure D using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,3-dimethyl-1*H*-indole-2-carboxylate (20 mg, 0.027 mmol). LCMS: R_T = 2.096 min, MS (ES) 726.0 (M+H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 1H), 7.74-7.68 (m, 1H), 7.36-7.33 (m, 1H), 7.23-7.10 (m, 2H), 6.64-6.59 (m, 2H), 4.52-4.46 (m, 1H), 4.30-4.25 (m, 2H), 4.13-4.11 (m, 4H), 4.01-3.97 (m, 4H), 3.42-3.36 (m, 2H), 2.63-2.61 (m, 3H), 2.39-2.32 (m, 9H), 2.24-2.15 (m, 5H), 1.31-1.28 (m, 3H).

Example 317

(*R*)-4-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1,6-dimethyl-1*H*-indole-2-carboxylic acid

[00533] The title compound was prepared according to General Procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one and methyl 4-bromo-1,6-dimethyl-1H-indole-2-carboxylate followed by saponification using General Procedure D. LCMS: R_T = 2.71 min, MS (ES) 726.2 (M+H) (LC method III). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 (d, *J* = 8.8 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 1H), 7.26 (s, 1H), 7.22 (s, 1H), 6.92 (s, 1H), 6.60 (s, 2H), 4.40 (dd, *J* = 12.4, 3.6 Hz, 1H), 4.19 (d, *J* = 4.8 Hz, 1H), 4.03 – 3.96 (m, 5H), 3.90 (s, 3H), 3.58 (d, *J* = 12.4 Hz, 1H), 3.49 – 3.31 (m, 2H), 2.51 (s, 3H), 2.30 (s, 6H), 2.21 – 2.17 (m, 5H), 2.04 (s, 3H), 1.24 (d, *J* = 6.4 Hz, 3H).

Example 318

(*R*)-4-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylic acid.

Step A. Preparation of methyl (*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylate

[00534] The title compound was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one and methyl 4-bromo-1-methyl-1*H*-indole-2-carboxylate. MS (ES) 842.3 (M+H).

Step B. Preparation of methyl (*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylate

[00535] The title compound (77 mg, 90 %) was prepared following the procedure described Example 261 Step A using methyl (*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylate (100mg, 0.12 mmol) and TBAF (0.59 mL, 0.59 mmol). MS (ES) 712.2 (M+H).

Step C. Example 318

[00536] The title compound (17 mg, 38% 2 steps) was prepared following the procedure described Example 261 Step B using methyl (*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylate (41 mg, 0.057 mmol), NaH (5 mg, 0.113 mmol) and 1-(2-bromoethyl)pyrrolidine (20 mg, 0.113 mmol) followed by saponification using General Procedure D. LCMS: R_T = 0.863 min (LC method IV), MS (ES) 795.8 (M+H); ^{1}H NMR (DMSO, 400 MHz) δ (ppm) 7.79 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.38 (t, *J* = 8.4 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.06 (s, 2H), 6.70 (s, 2H), 4.59-4.40 (m, 2H), 4.20-4.11 (m, 1H), 4.04 (s, 3H), 3.97-3.93 (m, 2H), 3.65-3.60 (m, 2H), 3.55-3.50 (m, 2H), 3.12-2.90 (m, 2H), 2.53 (s, 3H), 2.22 (s, 6H), 2.18 (s, 2H), 2.05 (d, *J* = 4.0 Hz, 3H), 2.03-1.90 (m, 2H), 2.05 (s, 3H), 1.85-1.82 (m, 2H), 1.08-1.05 (m, 4H).

Example 319

4-((M, *R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-7-((1-methylpyrrolidin-3-yl)methoxy)-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl (*M*, *R*)-7-(benzyloxy)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylate

[00537] The title compound was prepared according to General Procedure B using (*M*, *R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one and methyl 7-(benzyloxy)-4-bromo-1-methyl-1*H*-indole-2-carboxylate. LCMS: R_T = 1.772 min, MS (ES) 831.8 (M+H) (LC method II).

Step B. Preparation of methyl (*M*, *R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-7-hydroxy-1-methyl-1*H*-indole-2-carboxylate

[00538] To a solution of methyl (*R*)-7-(benzyloxy)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylate (25 mg, 0.030 mmol) in MeOH (5 mL) was added Pd/C (10 wt.%, 5 mg, 0.0046 mmol), and the reaction was stirred for 18 h under H_2 atmosphere at RT. The reaction mixture was filtered through celite and concentrated to afford the title compound (21 mg, 94%). LCMS: R_T = 2.090 min, MS (ES) 742.0 (M+H).

Step C. Example 319

[00539] The title compound (4.0 mg, 36%) was prepared according to General Procedure H using methyl (*M*, *R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-7-hydroxy-1-methyl-1*H*-indole-2-carboxylate (10 mg, 0.014 mmol) and 3-(bromomethyl)-1-methylpyrrolidine (10 mg, 0.056 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.825 min, MS (ES) 825.0 (M+H).

Example 320

7-((*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-((1-methylpyrrolidin-3-yl)methyl)-1*H*-indole-2-carboxylic acid

[00540] The title compound (3.0 mg, 27%) was prepared according to General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-

(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (10 mg, 0.014 mmol) and 3-(bromomethyl)-1-methylpyrrolidine (10 mg, 0.056 mmol) followed by saponification using General Procedure K. LCMS: R_T = 1.876 min, MS (ES) 795.0 (M+H).

Example 321

(*M*, *R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-hydroxy-1-methyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl (*M*, *R*)-4-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylate

[00541] The title compound was prepared according to General Procedure B using (*M*, *R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one and methyl 4-(benzyloxy)-7-bromo-1-methyl-1*H*-indole-2-carboxylate. MS (ES) 832.2 (M+H).

Step B. Preparation of methyl (*M*, *R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-hydroxy-1-methyl-1*H*-indole-2-carboxylate

[00542] The title compound (17 mg, 45%) was prepared following the procedure described Example 319 Step B using methyl (*M*, *R*)-4-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylate (42 mg, 0.051 mmol) and Pd/C (10 wt.%, 20 mg, 0.019 mmol). LCMS: R_T = 1.944 min, MS (ES) 727.9 (M+H).

Step C. Example 321

[00543] The title compound (4.4 mg, 64%) was prepared according to General Procedure D using methyl (*M*, *R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-hydroxy-1-methyl-1*H*-indole-2-carboxylate (7 mg, 0.0094 mmol). LCMS: R_T = 1.946 min, MS (ES) 727.9 (M+H).

Example 322

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-(dimethylamino)ethyl)-1*H*-indole-2-carboxylic acid

[00544] The title compound (2.9 mg, 27%) was prepared according to General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (10 mg, 0.014 mmol) and 2-bromo-*N*,*N*-dimethylethan-1-amine (10 mg, 0.066 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.861, 1.882 min, MS (ES) 769.0 (M+H).

Example 323

(*M*, *R*)-4-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-7-(2-methoxyethoxy)-1-methyl-1*H*-indole-2-carboxylic acid

[00545] The title compound (4.3 mg, 41%) was prepared according to General Procedure H using methyl (*M*, *R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-7-hydroxy-1-methyl-1*H*-indole-2-carboxylate (10 mg, 0.014 mmol) and 1-bromo-2-methoxyethane (10 mg, 0.072 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.044 min, MS (ES) 786.0 (M+H).

Example 324

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate

[00546] The title compound (44 mg, 61%) was prepared according to General Procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (54 mg, 0.1 mmol) and methyl 7-bromo-5-methyl-1*H*-indole-2-carboxylate (80 mg, 0.3 mmol). LCMS: R_T = 2.221 min, MS (ES) 726.0 (M+H).

Step B. Example 324

[00547] The title compound (6 mg, 53%) was prepared according to General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (10 mg, 0.014 mmol) and 4-(bromomethyl)tetrahydro-2*H*-pyran (5 mg, 0.028 mmol) followed by saponification using General Procedure D. LCMS: R_T =

2.217 MS (ES) 809.8 (M+H); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.76 (d, J = 8.6 Hz, 1H), 7.48 (s, 0.75H), 7.44 (s, 0.25H), 7.34 - 7.28 (m, 1H), 7.26 - 7.23 (m, 1H), 6.98 (d, J = 8.7 Hz, 1H), 6.69 (s, 1.5H), 6.68 (s, 0.5H), 4.33 - 4.26 (m, 2H), 4.25 - 4.18 (m, 2H), 3.78 (s, 1.5H), 3.76 (s, 0.5H), 3.75 (s, 1H), 3.63 - 3.60 (m, 1H), 3.33 - 3.13 (m, 3H), 3.06 - 2.91 (m, 3H), 2.37 (s, 2H), 2.35 (s, 1H), 2.23 (s, 6H), 2.14 (s, 0.5H), 2.13 (s, 1H), 2.08 (s, 1.5H), 2.06 - 1.96 (m, 4H), 1.93 (s, 1H), 1.90 (s, 0.5H), 1.83 (s, 1.5H), 1.17 - 1.08 (m, 3H), 1.05 - 0.96 (m, 2H), 0.93 - 0.75 (m, 3H).

Example 325

(*M*, *R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-(2-methoxyethoxy)-1-methyl-1*H*-indole-2-carboxylic acid

[00548] The title compound (3.6 mg, 33%) was prepared according to General Procedure H using methyl (*M*, *R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-hydroxy-1-methyl-1*H*-indole-2-carboxylate (10 mg, 0.013 mmol) and 1-bromo-2-methoxyethane (10 mg, 0.072 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.047 min, MS (ES) 786.0 (M+H).

Example 326

7-((*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((tetrahydrofuran-2-yl)methyl)-1*H*-indole-2-carboxylic acid

[00549] The title compound (2.7 mg, 25%) was prepared according to General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (10 mg, 0.014 mmol) and 2-(bromomethyl)tetrahydrofuran (10 mg, 0.061 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.105 min, MS (ES) 781.9 (M+H).

Example 327

(*P*, *R*)-7-(Benzyloxy)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylic acid

[00550] The title compound was prepared according to General Procedure B using (*P*, *R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one and methyl 7-(benzyloxy)-4-bromo-1-methyl-1H-indole-2-

carboxylate followed by saponification using General Procedure D. LCMS: R_T = 2.99 min, MS (ES) 818.0 (M+H) (LC method III). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 (d, *J* = 8.8 Hz, 1H), 7.47 – 7.22 (m, 7H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.60 (s, 2H), 5.20 (s, 2H), 4.48 – 4.26 (m, 5H), 3.97 – 3.94 (m, 5H), 3.78 – 3.27 (m, 3H), 2.29 (s, 6H), 2.20 – 2.16 (m, 5H), 2.03 (s, 3H), 1.13 (d, *J* = 6.4 Hz, 3H).

Example 328

(*M*, *R*)-4-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-6-(2-methoxyethoxy)-1-methyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl (*M*, *R*)-6-(benzyloxy)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylate

[00551] The title compound was prepared according to General Procedure B using (*M, R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one and methyl 6-(benzyloxy)-4-bromo-1-methyl-1H-indole-2-carboxylate followed by saponification using General Procedure K. LCMS: R_T = 1.823 min, MS (ES) 831.8 (M+H) (LC methodII).

Step B. Preparation of methyl (*M*, *R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-6-hydroxy-1-methyl-1*H*-indole-2-carboxylate

[00552] The title compound (34 mg, 77%) was prepared following the procedure described Example 319 Step B using methyl (*M, R*)-6-(benzyloxy)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylate (50 mg, 0.060 mmol) and Pd/C (10 wt.%, 7 mg, 0.0065 mmol). LCMS: R_T = 2.067 min, MS (ES) 742.0 (M+H).

Step C. Example 328

[00553] The title compound (5.1 mg, 60%) was prepared according to General Procedure H using methyl (*M, R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-6-hydroxy-1-methyl-1*H*-indole-2-carboxylate (8 mg, 0.011 mmol) and 1-bromo-2-methoxyethane (10 mg, 0.072 mmol) followed by saponification using General Procedure K. LCMS: R_T = 2.029 min, MS (ES) 786.0 (M+H).

Example 329

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(pyrimidin-2-ylmethyl)-1*H*-indole-2-carboxylic acid

[00554] The title compound (3.6 mg, 17%) was prepared according to General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (10 mg, 0.014 mmol) and 2-(chloromethyl)pyrimidine (20 mg, 0.16 mmol), followed by saponification using General Procedure D. LCMS: R_T = 2.026 min, MS (ES) 790.0 (M+H).

Example 330

7-((*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1-((1-methylpyrrolidin-3-yl)methyl)-1*H*-indole-2-carboxylic acid

[00555] The title compound (7 mg, 62%) was prepared according to General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (10 mg, 0.014 mmol) and 3-(bromomethyl)-1-methylpyrrolidine hydrobromide (7 mg, 0.028 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.962 MS (ES) 808.9 (M+H); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.69 (bs, 1H), 7.90 - 7.73 (m, 1H), 7.60 - 7.47 (m, 1H), 7.41 - 7.29 (m, 2H), 7.28 - 7.16 (m, 0.5H), 7.09 - 6.98 (m, 0.5H), 6.71 (s, 2H), 4.58 - 4.49 (m, 3H), 4.42 - 4.09 (m, 3H), 4.08 - 4.01 (m, 1H), 3.99 (s, 3H), 3.77 (s, 1.5H), 3.75 (s, 1.5H), 3.30 - 3.13 (m, 3H), 2.75 - 2.62 (m, 3H), 2.37 (s, 1.5H), 2.35 (s, 1.5H), 2.24 (s, 6H), 2.12 (s, 1.5H), 2.07 (s, 1.5H), 2.06 - 2.04 (m, 2H), 2.04 - 2.03 (m, 1H), 2.03 - 2.01 (m, 2H), 1.99 (s, 1.5H), 1.91 (s, 1.5H), 1.17 - 1.05 (m, 3H).

Example 331

4-((*M*, *R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-6-((1-methylpyrrolidin-3-yl)methoxy)-1*H*-indole-2-carboxylic acid

[00556] The title compound (4.1 mg, 46%) was prepared according to General Procedure H using methyl (*M*, *R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-6-hydroxy-1-methyl-1*H*-indole-2-carboxylate (8 mg, 0.011 mmol) and 3-(bromomethyl)-1-methylpyrrolidine (10 mg, 0.056 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.795 min, MS (ES) 825.0 (M+H).

Example 332

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1,5-dimethyl-1*H*-indole-2-carboxamide

[00557] The title compound (7 mg, 70%) was prepared according to General Procedure E using (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,5-dimethyl-1*H*-indole-2-carboxylic acid (10 mg, 0.014 mmol) and ammonia in MeOH (7.0 M, 0.25 mL). LCMS: R_T = 2.017, 2.043 min, MS (ES) 724.9 (M+H).

Example 333

(*M, R*)-5-(Benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylic acid

[00558] The title compound was prepared according to General Procedure B using (*M*, *R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one and methyl 5-(benzyloxy)-7-bromo-1-methyl-1*H*-indole-2-carboxylate followed by saponification using General Procedure D. LCMS: R_T = 2.430, 2.457 min, MS (ES) 817.8 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 (d, *J* = 8.8 Hz, 1H), 7.32 – 7.30 (m, 7H), 7.14 (s, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 6.61 (s, 1.5H), 6.59 (s, 0.5H), 5.07 (s, 2H), 4.24 – 4.17 (m, 3H), 4.03 – 3.88 (m, 7H), 3.41 – 3.29 (m, 3H), 2.29 (s, 6H), 2.22 – 2.18 (m, 5H), 2.03 (s, 3H), 1.25 (d, *J* = 6.0 Hz, 2H), 1.18 (d, *J* = 6.0 Hz, 1H).

Example 334

(*M, R*)-4-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-6-methoxy-1-methyl-1*H*-indole-2-carboxylic acid

[00559] The title compound (4.8 mg, 48%) was prepared according to General Procedure H using methyl (*M*, *R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-6-hydroxy-1-methyl-1*H*-indole-2-carboxylate (10 mg, 0.0138 mmol) and MeI (5 mg, 0.035 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.034 min, MS (ES) 742.0 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.6 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 7.23 (s, 1H), 6.80 – 6.72 (m, 2H), 6.63 (s, 2H), 4.46 – 4.36 (m, 1H), 4.18 (s,

1H), 4.05 (s, 3H), 4.02-3.94 (m, 5H), 3.93 (s, 3H), 3.59 (d, *J* = 12.4 Hz, 1H), 3.48-3.30 (m, 2H), 2.32 (s, 6H), 2.27 – 2.17 (m, 5H), 2.08 (s, 3H), 1.25 (d, *J* = 6.2 Hz, 3H).

Example 335

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-*N*-hydroxy-1-methyl-1*H*-indole-6-carboximidamide

[00560] To a solution of (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-6-carbonitrile (15 mg, 0.02 mmol) in EtOH (1 mL) at RT was added $NH_2OH.HCl$ (6 mg, 0.088 mmol) followed by K_2CO_3 (9 mg, 0.066 mmol). The mixture was heated at 80 °C for 8 h then concentrated *in vacuo*. The crude material was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA) to afford the title compound (12 mg, 75%). LCMS: R_T = 1.791 min, MS (ES) 726.0 (M+H).

Example 336

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,3,5-trimethyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl 7-bromo-1,3,5-trimethyl-1*H*-indole-2-carboxylate

[00561] The title compound (52 mg, 88%) was prepared following General Procedure G using 7-bromo-5-methyl-1*H*-indole-2-carboxylic acid (51 mg, 0.20 mmol) and MeI (39 μL, 0.80 mmol). LCMS: R_T = 1.783 min, MS (ES) 296.2 (M+H).

Step B. Example 336

[00562] The title compound (11 mg, 30%) was prepared according to General Procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol) and methyl 7-bromo-1,3,5-trimethyl-1*H*-indole-2-carboxylate (18 mg, 0.06 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.137 MS (ES) 739.9 (M+H); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.83 - 7.68 (m, 1H), 7.48 (s, 0.5H), 7.43 (s, 0.5H), 7.33 - 7.24 (m, 1H), 7.16 (s, 0.5H), 6.94 (s, 0.25H), 6.93 (s, 0.25H), 6.69 (s, 1H), 6.68 (s, 1H), 4.36 - 4.27 (m, 1H), 4.26 - 4.09 (m, 1H), 4.02 - 3.93 (m, 2H), 3.91 (s, 1.5H), 3.92 (s, 1.5H), 3.80 (s, 0.75H), 3.77 (s, 0.75H), 3.76 (0.75H), 3.75 (s, 0.75H), 3.71 - 3.61 (m, 2H), 3.21 - 3.11 (m, 1H), 2.39 (s, 1.5H), 2.36 (s, 1.5H), 2.22 (s, 6H), 2.10 (s, 1.5H), 2.08 (s, 1.5H), 2.06 - 2.03 (m,

2H), 1.96 (s, 1.5H), 1.94 (s, 1.5H), 1.91 (s, 3H), 1.87 (s, 1.5H), 1.15 (d, J = 6.2 Hz, 1.5H), 1.04 (d, J = 6.2 Hz, 1.5H).

Example 337

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of (*R*)-*N*'-acetyl-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carbohydrazide

[00563] The title compound (32 mg, 74%) was prepared according to General Procedure E using (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (40 mg, 0.056 mmol) and acetohydrazide (15 mg, 0.20 mmol). LCMS: R_T = 2.098 min, MS (ES) 768.0 (M+H).

Step B. Example 337

[00564] (*R*)-*N*'-acetyl-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carbohydrazide (10 mg, 0.013 mmol) was dissolved in $POCl_3$ (1 mL) and heated to 95 °C for 1 h. The reaction mixture was cooled to RT, poured into ice/aqueous $NaHCO_3$ (50 mL), and the mixture was then stirred for 15 min. The aqueous layer was extracted with DCM (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The crude reaction mixture was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient 35-95 % MeCN 0.1% TFA) to afford the title compound (5.3 mg, 54%). LCMS: R_T = 2.051 min, MS (ES) 750.0 (M+H).

Example 338

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(pyridin-2-ylmethyl)-1*H*-indole-6-carboxylic acid

Step A. Preparation of methyl 3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-5-carboxylate

[00565] The title compound (107 mg, 71%) was prepared following General Procedure G using methyl 3-bromo-1*H*-indole-5-carboxylate (100 mg, 0.39 mmol) and (2-(chloromethoxy)ethyl)trimethylsilane (0.11 mL, 98.5 mg, 0.59 mmol). LCMS: R_T = 1.977 min, MS (ES) 384.0 (M+H).

Step B. Preparation of methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-5-carboxylate

[00566] The title compound (93 mg, 82%) was prepared following General Procedure B using methyl 3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-5-carboxylate (78 mg, 0.20 mmol) and (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (60.8 mg, 0.11 mmol). LCMS: R_T = 2.393 min, MS (ES) 842.0 (M+H).

Step C. Preparation of methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-5-carboxylate

[00567] To a solution of methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-5-carboxylate (110 mg, 0.13 mmol) in THF (0.5 mL) was added TBAF (1.18 mL, 1.17 mmol, 1.0 M in THF), and the reaction mixture was stirred at 40 °C for 24 h. The reaction was quenched with sat. NH_4Cl aq. solution and extracted with EtOAc (3 x 5 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-10% gradient) to afford the title compound (40 mg, 43%). LCMS: R_T = 2.077 min, MS (ES) 711.9 (M+H).

Step D. Example 338

[00568] The title compound (7 mg, 81%, 2 steps) was prepared following General Procedure G, using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-5-carboxylate (8 mg, 0.011 mmol) and 2-(bromomethyl)pyridine hydrobromide (4.2 mg, 0.017 mmol) followed by General Procedure D. LCMS: R_T = 1.887 min, MS (ES) 789.0 (M+H). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.52 (s, 2H), 8.11 (s, 2H), 7.85 (s, 2H), 7.82 (t, *J* = 7.3 Hz, 2H), 7.74 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.37-7.34 (m, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 7.16 (t, *J* = 7.1 Hz, 2H), 6.71 (s, 4H), 5.63 (s, 4H), 4.50-4.47 (m, 2H), 4.16-4.13 (m, 2H), 3.97 (m, 4H), 3.77-3.76 (m, 6H), 3.70 (d, *J* = 13.0 Hz, 1H), 3.66 (d, *J* = 13.1 Hz, 1H), 3.32-3.29 (m, 2H), 3.25-3.20 (m, 2H),

2.23 (s, 12H), 2.11 (s, 3H), 2.07-2.04 (m, 4H), 2.02 (s, 3H), 1.96 (s, 3H), 1.87 (s, 3H), 1.07 (d, J = 6.2 Hz, 6H).

Example 339

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,3,5-trimethyl-1*H*-indole-2-carboxylic acid

[00569] The title compound (13 mg, 35%) was prepared according to General Procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol) and methyl 7-bromo-1,3,5-trimethyl-1*H*-indole-2-carboxylate (18 mg, 0.06 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.191 MS (ES) 738.0 (M+H).

Example 340

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-(dimethylamino)ethyl)-1*H*-indole-6-carboxylic acid

[00570] The title compound (4.3 mg, 37%) was prepared following General Procedure G using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-5-carboxylate and 2-bromo-*N*,*N*-dimethylethan-1-amine hydrobromide (5.4 mg, 0.023 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.824 min, MS (ES) 769.0 (M+H).

Example 341

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-2-(1,3,4-oxadiazol-2-yl)-1*H*-indol-7-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00571] A solution of (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylic acid (10 mg, 0.014 mmol) and *N*-isocyano-1,1,1-triphenyl-λ^5-phosphanimine (20 mg, 0.066 mmol) in DCM (2 mL) was stirred at 40 °C for 7 days. The reaction mixture was then diluted with DCM (10 mL), washed with H_2O (5 mL), dried by passage through a phase separator, and concentrated. The crude reaction mixture was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient 35-95 % MeCN 0.1% TFA) to afford the title compound (4.4 mg, 43%). LCMS: R_T = 2.083 min, MS (ES) 736.0 (M+H).

Example 342

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methoxy-1-methyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-methyl-1*H*-indole-2-carboxylate

[00572] The title compound (252 mg, 94%) was prepared following the procedure described Example 319 Step B using ethyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylate (300 mg, 0.35 mmol) and Pd/C (10 wt.%, 40 mg, 0.037 mmol). LCMS: R_T = 2.093 min, MS (ES) 755.8 (M+H).

Step B. Example 342

[00573] The title compound (13.6 mg, 69%) was prepared according to General Procedure H using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-methyl-1*H*-indole-2-carboxylate (20 mg, 0.026 mmol) and MeI (10 mg, 0.070 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.028 min, MS (ES) 742.0 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.73 (d, *J* = 8.6 Hz, 1H), 7.40 – 7.29 (m, 2H), 7.10 (d, *J* = 2.3 Hz, 0.66H), 7.06 (d, *J* = 2.3 Hz, 0.34H), 6.88-6.83 (m, 1H), 6.63 (s, 1.3H), 6.61 (s, 0.7H), 4.47-4.18 (m, 2H), 4.06 – 3.95 (m, 7H), 3.91 (s, 0.7H), 3.90 (s, 0.3H), 3.87 (s, 2H), 3.86 (s, 1H), 3.58 (d, *J* = 12.2 Hz, 0.3H),3.53 (d, *J* = 12.2 Hz, 0.7H), 3.45 – 3.30 (m, 2H), 2.32 (s, 6H), 2.28 (s, 3H), 2.22-2.15 (m, 2H), 2.10 (s, 1H), 2.08 (s, 2H), 1.30 (d, *J* = 6.5 Hz, 2H), 1.22 (d, *J* = 6.6 Hz, 1H).

Example 343

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-6-(1,3,4-oxadiazol-2-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00574] The title compound (2.8 mg, 26%) was prepared following the procedure described Example 341 using (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-6-carboxylic acid (10 mg, 0.014 mmol) and *N*-isocyano-1,1,1-triphenyl-λ^5-phosphanimine (20 mg, 0.066 mmol). LCMS: R_T = 2.115 min, MS (ES) 736.0 (M+H).

Example 344

(*M*, *R*)-4-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-7-methoxy-1-methyl-1*H*-indole-2-carboxylic acid

[00575] The title compound (7.1 mg, 71%) was prepared according to General Procedure H using methyl (*M*, *R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-7-hydroxy-1-methyl-1*H*-indole-2-carboxylate (10 mg, 0.014 mmol) and MeI (5 mg, 0.035 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.044 min, MS (ES) 742.0 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 8.6 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 7.21 (s, 1H), 6.95 (d, *J* = 8.1 Hz, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 6.62 (s, 2H), 4.37 (s, 4H), 4.17 (s, 1H), 4.04 – 3.94 (m, 8H), 3.54 (d, *J* = 12.5 Hz, 1H), 3.46-3.27 (m, 2H), 2.32 (s, 6H), 2.26 (s, 3H), 2.24 – 2.14 (m, 2H), 2.08 (s, 3H), 1.27 (d, *J* = 6.4 Hz, 3H).

Example 345

(*P*, *R*)-5-(Benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylic acid

[00576] The title compound was prepared according to General Procedure B using (*P*, *R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one and methyl 5-(benzyloxy)-7-bromo-1-methyl-1H-indole-2-carboxylate followed by saponification using General Procedure D. LCMS: R_T = 2.430, 2.457 min, MS (ES) 817.8 (M+H).

Example 346

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1,3,4-oxadiazol-2-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00577] The title compound (2.2 mg, 21%) was prepared following the procedure described Example 341 using (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (10 mg, 0.014 mmol) and *N*-isocyano-1,1,1-triphenyl-λ^5-phosphanimine (20 mg, 0.066 mmol). LCMS: R_T = 2.043 min, MS (ES) 736.0 (M+H).

Example 347

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-2-(1,3,4-oxadiazol-2-yl)-1*H*-indol-4-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00578] The title compound (1.8 mg, 17%) was prepared following the procedure described Example 341 using (*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylic acid (10 mg, 0.014 mmol) and *N*-isocyano-1,1,1-triphenyl-λ^5-phosphanimine (20 mg, 0.066 mmol). LCMS: R_T = 2.089 min, MS (ES) 735.9 (M+H).

Example 348

(*P*, *R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-6-fluoro-1-methyl-1*H*-indole-5-carboxylic acid

[00579] The title compound was prepared according to General Procedure B using (*P*, *R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one and methyl 3-bromo-6-fluoro-1-methyl-1H-indole-5-carboxylate followed by saponification using General Procedure D. LCMS: R_T = 2.176 min, MS (ES) 729.9 (M+H).

Example 349

(*M*, *R*)-8-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-2-naphthoic acid

[00580] The title compound was prepared according to General Procedure B using (*M*, *R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one and methyl 8-bromo-2-naphthoate followed by saponification using General Procedure D. LCMS: R_T = 2.233 min, MS (ES) 708.9 (M+H).

Example 350

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(2-methyl-2*H*-tetrazol-5-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00581] The title compound (12 mg, 60%) was prepared following General Procedure G using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1*H*-tetrazol-5-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (20 mg, 0.03 mmol) and MeI (4 μL, 0.05 mmol) and

isolated as the first eluting isomer by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 40-90 % MeCN 0.1% TFA). LCMS: R_T = 2.033 min, MS (ES) 750.0 (M+H).

Example 351

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1,3-dimethyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1*H*-indole-2-carboxylate

[00582] The title compound (35 mg, 94%) was prepared according to General Procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol) and methyl 7-bromo-4-methoxy-1*H*-indole-2-carboxylate (43 mg, 0.15 mmol). LCMS: R_T = 2.116 min, MS (ES) 742.0 (M+H).**51.**

[00583] The title compound (6 mg, 53% yield) was prepared according to General Procedure G using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1*H*-indole-2-carboxylate (15 mg, 0.02 mmol) and MeI (5 μL, 0.08 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.766 MS (ES) 756.0 (M+H).

Example 352

(*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl 4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-2-carboxylate

[00584] The title compound (115 mg, 76%) was prepared following General Procedure G using methyl 4-bromo-1*H*-indole-2-carboxylate (100 mg, 0.39 mmol) and (2-(chloromethoxy)ethyl)trimethylsilane (0.11 mL, 98.5 mg, 0.59 mmol).

Step B. Preparation of methyl (*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-2-

carboxylate

[00585] The title compound (125 mg, 99%) was prepared following General Procedure B using methyl 4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-2-carboxylate (96 mg, 0.25 mmol) and (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (85 mg, 0.139 mmol). LCMS: R_T = 2.466 min, MS (ES) 842.0 (M+H).

Step C. Preparation of methyl (*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate

[00586] To a solution of methyl (*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-2-carboxylate (125 mg, 0.148 mmol) in THF (0.5 mL) was added TBAF (3.7 mL, 3.7 mmol, 1.0 M in THF), and the reaction mixture was irradiated under microwave for 10 h at 120 °C. The reaction was cooled to RT, quenched with sat. NH_4Cl aq. solution and extracted with EtOAc (3 x 5 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was redissolved in THF (6 mL) and MeOH (0.6 mL) then trimethylsilyl diazomethane (0.114 mL, 0.228 mmol, 2.0 M in Et_2O) was added. After 1 h of stirring at RT, the reaction was quenched with glacial acetic acid then concentrated. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-10% gradient) (57 mg, 54% yield, 2 steps). LCMS: R_T = 2.090 min, MS (ES) 712.0 (M+H).

Step D. Example 352

[00587] The title compound (8 mg, 53%, 2 steps) was prepared following General Procedure G using methyl (*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (13 mg, 0.019 mmol) and 2-(bromomethyl)pyridine hydrobromide (6.2 mg, 0.025 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.869 min, MS (ES) 788.9 (M+H).

Example 353

(*R*)-4-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-methoxyethyl)-1*H*-indole-2-carboxylic acid

[00588] The title compound (11 mg, 75%, 2 steps) was prepared following General Procedure G using methyl (*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-

methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (13 mg, 0.019 mmol) and 1-bromo-2-methoxyethane (3 μL, 4.4 mg, 0.032 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.040 min, MS (ES) 756.0 (M+H).

Example 354

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-methoxyethyl)-1*H*-indole-2-carboxamide

[00589] The title compound (4.5 mg, 45%) was prepared according to General Procedure E using (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-methoxyethyl)-1*H*-indole-2-carboxylic acid (10 mg, 0.013 mmol) and ammonia in MeOH (7.0 M, 0.25 mL). LCMS: R_T = 2.012 min, MS (ES) 754.9 (M+H).

Example 355

(*M*, *R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-6-fluoro-1-methyl-1*H*-indole-5-carboxylic acid

[00590] The title compound was prepared according to General Procedure B using (*M*, *R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one and methyl 3-bromo-6-fluoro-1-methyl-1H-indole-5-carboxylate followed by saponification using General Procedure D. LCMS: R_T = 2.74 min, MS (ES) 730.0 (M+H) (LC method III).

Example 356

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-isopropyl-1-methyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-isopropyl-1*H*-indole-2-carboxylate

[00591] The title compound (22 mg, 58%) was prepared according to General Procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol)

and methyl 7-bromo-5-isopropyl-1*H*-indole-2-carboxylate (45 mg, 0.15 mmol). LCMS: R_T = 2.295 min, MS (ES) 754.0 (M+H).

Step B. Example 356

[00592] The title compound (12 mg, 80%) was prepared according to General Procedure G using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-isopropyl-1*H*-indole-2-carboxylate (15 mg, 0.02 mmol) and MeI (5 μL, 0.08 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.186 MS (ES) 754.0 (M+H).

Example 357

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxamide

[00593] To a solution of (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylic acid (20 mg, 0.028 mmol) in DCM (1 mL) was added DMF (1 μL) and oxalyl chloride (3.8 μL), sequentially. The reaction mixture was stirred for 30 min at RT then concentrated. The residue was dissolved in dry DCM (1 mL) and amonia (10 μL, 0. 5M in 1,4-dioxane) was added. The reaction mixture was stirred at RT for 15 min then concentrated. The residue was purified by HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient from 50% to 100% CH_3CN for 5 min, 0.1% TFA) to give the title compound (16 mg, 80%). MS (ES) 712.1 (M+H), Rf = 0.88

Example 358

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1-methyl-1*H*-tetrazol-5-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00594] The title compound (4 mg, 20%) was isolated as the second eluting isomer along with Example 350. LCMS: R_T = 2.110 min, MS (ES) 749.9 (M+H).

Example 359

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-isopropyl-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylic acid

[00595] The title compound (16 mg, 96%) was prepared according to General Procedure G using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-

6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-isopropyl-1*H*-indole-2-carboxylate (15 mg, 0.02 mmol) and 2-(bromomethyl)pyridine hydrobromide (7.6 mg, 0.03 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.971 MS (ES) 831.0 (M+H).

Example 360

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((6-methoxypyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

[00596] The title compound (7.2 mg, 64% yield) was prepared according to General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (10 mg, 0.014 mmol) and 2-(chloromethyl)-6-methoxypyridine (10 mg, 0.064 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.105 min, MS (ES) 819.0 (M+H).

Example 361

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-*N*-hydroxy-1-methyl-1*H*-indole-5-carboxamide

[00597] To a solution of (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (115 mg, 0.16 mmol) in DCM (3 mL) was added NMM (18 mg, 0.18 mmol), hydroxylamine hydrochloride (13 mg, 0.18 mmol) and DMAP (2 mg, 0.02 mmol). The reaction mixture was stirred at RT for 12h then quenched with water (5 mL). The mixture was extracted with DCM (3x5 mL). The organic layer was dried and concentrated. The residue was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA) to afford the title compound (49 mg, 42%). LCMS: R_T = 1.897 min, MS (ES) 726.9 (M+H).

Example 362

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-7-(2-methyl-2*H*-tetrazol-5-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00598] The title compound (11 mg, 54%) was prepared following General Procedure G using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-7-(1*H*-tetrazol-5-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-

dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (20 mg, 0.03 mmol) and methyl iodide (4 μL, 0.05 mmol) and isolated as the first eluting isomer. LCMS: R_T = 2.074 min, MS (ES) 750.0 (M+H).

Example 363

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((5-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

[00599] The title compound (8.9 mg, 80%) was prepared according to General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (10 mg, 0.014 mmol) and 2-(chloromethyl)-5-methylpyridine (10 mg, 0.070 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.885 min, MS (ES) 802.9 (M+H).

Example 364

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-isopropyl-1-(2-methoxyethyl)-1*H*-indole-2-carboxylic acid

[00600] The title compound (12 mg, 75%) was prepared according to General Procedure G using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-isopropyl-1*H*-indole-2-carboxylate (15 mg, 0.02 mmol) and 1-bromo-2-methoxyethane (4.2 mg, 0.03 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.208 MS (ES) 798.0 (M+H).

Example 365

(*R*)-6-Chloro-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00601] The title compound was prepared according to General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one and methyl 3-bromo-6-chloro-1-methyl-1H-indole-5-carboxylate followed by saponification using General Procedure D. LCMS: R_T = 2.81 min, MS (ES) 745.9 (M+H). (LC method III).

Example 366

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carbohydrazide

[00602] To a solution of methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (15 mg, 0.02 mmol) in DMF (1 mL) was added hydrazine hydrate (0.5 mL, 2.4 mmol, 50% solution), and the mixture was heated at 60 °C for 6 h. The reaction was quenched with water (5 mL) and extracted with CH_2Cl_2 (3x5 mL). The organic layer was dried (anhyd. Na_2SO_4) and concentrated. The residue was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA) to afford the title compound (13 mg, 89%). LCMS: R_T = 1.768 min, MS (ES) 726.0 (M+H).

Example 367

(*R*)-4-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylic acid

[00603] The title compound (2.5 mg, 16%, 2 steps) was prepared following General Procedure G using methyl (*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (13 mg, 0.019 mmol) and 4-(2-chloroethyl)morpholine hydrochloride (5.1 mg, 0.027 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.843 min, MS (ES) 811.0 (M+H).

Example 368

(*P*, *R*)-8-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-2-naphthoic acid

[00604] The title compound was prepared according to General Procedure I using (*P*, *R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one and methyl 8-bromo-2-naphthoate followed by saponification using General Procedure D. LCMS: R_T = 2.237 min, MS (ES) 708.9(M+H).

Example 369

(*R*)-4-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-indole-2-carboxylic acid

[00605] The title compound (3 mg, 20%, 2 steps) was prepared following General Procedure G using methyl (*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (13 mg, 0.019 mmol) and 1-(2-bromoethyl)pyrrolidine hydrobromide (10.2 mg, 0.039 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.855 min, MS (ES) 795.0 (M+H).

Example 370

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-6-(2-methyl-2*H*-tetrazol-5-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00606] The title compound (14 mg, 69%) was prepared following General Procedure G using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-6-(1*H*-tetrazol-5-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (20 mg, 0.03 mmol) and MeI (4 μL, 0.05 mmol). LCMS: R_T = 2.125 min, MS (ES) 750.0 (M+H).

Example 371

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((4-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

[00607] The title compound (6.6 mg, 60% yield) was prepared according to General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (10 mg, 0.014 mmol) and 2-(chloromethyl)-4-methylpyridine (10 mg, 0.070 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.842, 1.862 min, MS (ES) 802.9 (M+H).

Example 372

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-7-(1-methyl-1*H*-tetrazol-5-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00608] The title compound (6 mg, 30%) was isolated as the second eluting isomer along with Example 362. LCMS: R_T = 2.119 min, MS (ES) 749.9 (M+H).

Example 373

3-(8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethyl-2-(pyrrolidin-1-ylmethyl)pyrimidin-5-yl)-1-oxo-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

Step A. Preparation of 2-((benzyloxy)methyl)-4,6-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine

[00609] A mixture of 2-((benzyloxy)methyl)-5-bromo-4,6-dimethylpyrimidine (800 mg, 2.26 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (864 mg, 3.4 mmol), Pd(dppf)Cl_2 (165 mg, 0.23 mmol) and KOAc (353 mg, 4.5 mmol) in 1,4-dioxane (20 mL) was sparged for 1 min with N_2 gas. The reaction mixture was stirred at 100 °C for 15 h. The reaction mixture was cooled to RT, quenched with H_2O and extracted with EtOAc. The combined organic solution was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-25% gradient) to afford the title compound (560 mg, 70%).

Step B. Preparation of 2-((benzyloxy)methyl)-4,6-dimethyl-5-(trifluoro-l4-boranyl)pyrimidine potassium salt

[00610] To a solution of 2-((benzyloxy)methyl)-4,6-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (2.2 g, 6.2 mmol) in MeOH (30 mL) was added aqueous KH_2F (4.5 M, 15 mL). The mixture was stirred at RT for 15 min then concentrated *in vacuo*. The residue was dissolved in hot acetone then filtered. The filtrate was concentrated *in vacuo*, and the residue was recrystallized in hot acetone and Et_2O to afford the title compound as a white solid (1.6g, 77%).

Step C. Preparation of (2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)boronic acid

[00611] To a solution of 2-((benzyloxy)methyl)-4,6-dimethyl-5-(trifluoro-l4-boranyl)pyrimidine potassium salt (1.4 g, 4.2 mmol) in MeCN (20 mL) was added H_2O (13 μM, 12.6 mmol) and TMSCl (1.35 g, 12.6 mmol). The reaction mixture was stirred at room temperature for 1 h then concentrated *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-10% gradient) to afford the title compound (790 mg, 69%).

Step D. Preparation of ethyl 7-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate

[00612] A mixture of ethyl 7-bromo-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-

1*H*-indole-2-carboxylate (260 mg, 0.52 mmol), (2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)boronic acid (214 mg, 0.78 mmol), dicyclohexyl(2-(phenanthren-9-yl)phenyl)phosphane (25 mg, 0.055 mmol), $Pd_2(dba)_3$ (19 mg, 0.018 mmol), and K_2CO_3 (136 mg, 1.0 mmol) in PhMe (2.0 mL)/THF(2.0 mL)/H_2O (0.2 mL) was degassed and heated at 110 °C for 24 h. The reaction mixture was quenched with H_2O and extracted with EtOAc. The combined organic layer was dried, filtered and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (210 mg, 62%). MS (ES) 646.2 (M+H)

Step E. Preparation of ethyl 7-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-1-(3-((*tert*-butoxycarbonyl)amino)propyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate

[00613] To a solution of ethyl 7-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate (180 mg, 0.28 mmol) and *tert*-butyl 1,2,3-oxathiazinane-3-carboxylate 2,2-dioxide (150 mg, 0.63 mmol) in MeCN (10 mL) was added Cs_2CO_3 (200 mg, 0.62 mmol). The reaction was heated at 80 °C for 24 h, then cooled to RT. The reaction mixture was diluted with DCM/H_2O (50 mL, 1:1) then layers were separated. The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (194 mg, 87%). LCMS: R_T = 1.724 min, MS (ES) 803.0 (M+H) (LC method II).

Step F. Preparation of 7-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one

[00614] To a solution of ethyl 7-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-1-(3-((*tert*-butoxycarbonyl)amino)propyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate (194 mg, 0.24 mmol) 1,4-dioxane (10 mL) was added HCl in dioxanes (4.0 M, 1.0 mL, 4.0 mmol), and the reaction mixture was stirred at RT overnight. The reaction was concentrated, and the residue was dissolved in MeOH (20 mL). K_2CO_3 (300 mg, 2.2 mmol) was added, and the reaction mixture was stirred at 50 °C for 5 h. The reaction mixture was concentrated, and the residue was dissolved in DCM/H_2O (40 mL, 1:1). The layers were separated, and the aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford

the title compound (117 mg, 74%). LCMS: R_T = 2.219 min, MS (ES) 657.0 (M+H).

Step G. preparation of methyl 3-(7-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate

[00615] The title compound (78 mg, 53%) was prepared according to General Procedure B using 7-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-8-chloro-11-(3-(4-chloro-3,5 dimethylphenoxy)propyl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (115 mg, 0.17 mmol) and methyl 3-bromo-1-methyl-1*H*-indole-5-carboxylate (100 mg, 0.37 mmol). LCMS: R_T = 2.439 min, MS (ES) 843.9 (M+H).

Step H. Preparation of methyl 3-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-1-oxo-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate

[00616] To a solution of methyl 3-(7-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (78 mg, 0.092 mmol) in a mixture of EtOH/MeOH/EtOAc (2 mL/1 mL/1 mL) was added HCl in dioxanes (4.0 M, 0.25 mL, 1.0 mmol) followed by Pd/C (10 wt.%, 20 mg, 0.018 mmol). The reaction mixture was stirred under H_2 atmosphere at RT for 96 h. The reaction mixture was filtered through celite, rinsed with DCM and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (34 mg, 49%). LCMS: R_T = 2.023 min, MS (ES) 753.9.0 (M+H).

Step I. Example 373

[00617] The title compound (5.2 mg, 15%) was prepared according to General Procedure J using methyl 3-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-1-oxo-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (34 mg, 0.045 mmol) and pyrrolidine (15 mg, 0.21 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.778 min, MS (ES) 793.0 (M+H).

Example 374

7-((*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-(oxetan-2-ylmethyl)-1*H*-indole-2-carboxylic acid

[00618] The title compound (2 mg, 18%) was prepared according to General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-

(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (10 mg, 0.014 mmol) and 2-(bromomethyl)oxetane (10 mg, 0.066 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.034 min, MS (ES) 767.9 (M+H).

Example 375

(*R*)-1-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)isoquinoline-6-carboxamide

[00619] The title compound (4.3 mg, 72% yield) was prepared according to General Procedure L using (*R*)-1-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)isoquinoline-6-carboxylic acid (6 mg, 0.0085 mmol) and ammonia in MeOH (7.0 M, 0.25 mL). LCMS: R_T = 1.940 min, MS (ES) 708.9 (M+H).

Example 376

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,5-dimethyl-1*H*-indole-2-carboxamide

[00620] The title compound (2.4 mg, 48%) was prepared according to General Procedure E using (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,5-dimethyl-1*H*-indole-2-carboxylic acid (5 mg, 0.0069 mmol) and ammonia in MeOH (7.0 M, 0.25 mL). LCMS: R_T = 2.064 min, MS (ES) 723.0 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.19 (s, 1H), 7.82 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.52 – 7.34 (m, 3H), 7.02-6.90 (m, 1H), 6.64 (s, 1.5H), 6.61 (s, 0.5H), 4.30 - 4.10 (m, 2H), 4.07 - 03.93 (m, 4H), 3.85 - 3.70 (m, 1H), 3.58 - 3.48 (m, 1H), 3.42 – 3.33 (m, 2H), 2.54 (s, 0.75H), 2.52 (s, 2.25H), 2.47 (s, 0.75H), 2.44 (s, 2.25H), 2.40-2.35 (m, 2H), 2.34 (s, 6H), 2.24 - 2.17 (m, 3H), 1.36 - 1.20 (m, 3H).

Example 377

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxamide

The title compound was prepared according to General Procedure E using (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-

pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylic acid and ammonia in MeOH. LCMS: R_T = 2.004 min, MS (ES) 711.2 (M+H).

Example 378

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((4-methoxypyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

[00621] The title compound (7.8 mg, 69%) was prepared according to General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (10 mg, 0.014 mmol) and 2-(chloromethyl)-4-methoxypyridine hydrochloride salt (5 mg, 0.026 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.835, 1.858 min, MS (ES) 819.0 (M+H).

Example 379

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxamide

[00622] To a solution of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylate (10 mg, 0.012 mmol) in DMF (0.5 mL) was added NH_4OH (1 mL). The reaction mixture was stirred at 90 °C for 72 h. The crude reaction mixture was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient 35-95 % MeCN 0.1% TFA) to afford the title compound (2.0 mg, 20%). LCMS: R_T = 1.869 min, MS (ES) 799.9 (M+H).

Example 380

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indazole-3-carboxylic acid

[00623] The title compound (7.4 mg, 69%) was prepared according to General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (10 mg, 0.014 mmol) and 3-(bromomethyl)-3-methyloxetane (10 mg, 0.061 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.035 min, MS (ES) 781.9 (M+H).

Example 381

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((6-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

[00624] The title compound (7.9 mg, 72%) was prepared according to General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (10 mg, 0.014 mmol) and 2-(chloromethyl)-6-methylpyridine (5 mg, 0.035 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.850 min, MS (ES) 802.9 (M+H).

Example 382

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((5-methoxypyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

[00625] The title compound (10.2 mg, 90%) was prepared according to General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (10 mg, 0.014 mmol) and 2-(chloromethyl)-5-methoxypyridine hydrochloride salt (10 mg, 0.053 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.911 min, MS (ES) 819.0 (M+H).

Example 383

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(oxetan-3-ylmethyl)-1*H*-indole-2-carboxylic acid

[00626] The title compound (3.3 mg, 91%) was prepared according to General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (10 mg, 0.014 mmol) and 3-(bromomethyl)oxetane (10 mg, 0.066 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.009 min, MS (ES) 768.0 (M+H).

Example 384

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxamide

[00627] The title compound (7.2 mg, 72%) was prepared according to General Procedure E using (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylic acid (10 mg, 0.0069 mmol) and ammonia in MeOH (7.0 M, 0.25 mL). LCMS: R_T = 2.018 min, MS (ES) 708.9 (M+H).

Example 385

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxamide

[00628] The title compound (2.5 mg, 17%) was prepared following the procedure described Example 379 using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylate (15 mg, 0.019 mmol) and NH_4OH (1 mL). LCMS: R_T = 1.809, 1.831 min, MS (ES) 787.9 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.18 (s, 1H), 7.82 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 0.75H), 7.62 (d, *J* = 7.9 Hz, 0.25H), 7.38 (d, *J* = 8.6 Hz, 0.25H), 7.37 (d, *J* = 8.6 Hz, 0.75H), 7.25 – 6.95 (m, 3H), 6.64 (s, 1.5H), 6.60 (s, 0.5H), 4.46 – 4.13 (m, 2H), 4.05 – 3.97 (m, 4H), 3.85 - 3.71 (m, 1H), 3.55 – 3.32 (m, 3H), 2.51 (s, 0.75H), 2.49 (s, 2.25H), 2.33 (s, 9H), 2.25 – 2.17 (m, 2H), 1.31 (d, *J* = 6.5 Hz, 2.25H), 1.22 (d, J = 6.5 Hz, 0.75H).

Example 386

7-((*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(1-(pyridin-2-yl)ethyl)-1*H*-indole-2-carboxylic acid

[00629] The title compound (3.7 mg, 33%) was prepared according to General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (10 mg, 0.014 mmol) and 2-(1-chloroethyl)pyridine hydrochloride (10 mg, 0.056 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.862 min, MS (ES) 802.9 (M+H).

Example 387

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((3-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

[00630] The title compound (2.3 mg, 21%) was prepared according to General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (10 mg, 0.014 mmol) and 2-(chloromethyl)-3-methylpyridine hydrochloride (10 mg, 0.056 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.850 min, MS (ES) 802.9 (M+H).

Example 388

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1-methyl-1*H*-pyrazol-3-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 1-methyl-5-(1-methyl-1*H*-pyrazol-3-yl)-1*H*-indole

[00631] 3-Bromo-1-methyl-1*H*-pyrazole (100 mg, 0.62 mmol), $PdCl_2$(dppf)•DCM (25 mg, 0.03 mmol), K_2CO_3 (745 μL, 1.86 mmol, 2.5 M aq. solution) were added to a solution of 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (196 mg, 0.76 mmol) in MeCN (2.5 mL). The reaction mixture was degassed using Ar then stirred at 95 °C for 13 hr. The reaction mixture was cooled to RT, filtered through Celite pad and extracted with DCM (3 x 5 mL). The combined organic layers were dried and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-25% gradient) to provide the title compound (120 mg, 91%). LCMS: R_T = 1.237 min, MS (ES) 212.2 (M+H).

Step B. Preparation of 3-iodo-1-methyl-5-(1-methyl-1*H*-pyrazol-3-yl)-1*H*-indole

[00632] NIS (134 mg, 0.60 mmol) was added to a solution of 1-methyl-5-(1-methyl-1*H*-pyrazol-3-yl)-1*H*-indole (120 mg, 0.57 mmol) in DMF (5.7 mL) at 0 °C. The reaction was warmed to RT and stirred for 2 h. The reaction was quenched with water and extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with water, dried and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-50% gradient) to afford the title compound (95 mg, 50%). LCMS: R_T = 1.491 min, MS (ES) 337.9 (M+H).

Step B. Example 388

[00633] The title compound (23 mg, 66%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol) and 3-iodo-1-methyl-5-(1-methyl-1*H*-pyrazol-3-yl)-1*H*-indole (30 mg, 0.089 mmol). LCMS: R_T = 2.057 min, MS (ES) 748.9 (M+H).

Example 389

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(pyridin-2-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 1-methyl-5-(pyridin-2-yl)-1*H*-indole

[00634] The title compound (110 mg, 83%) was prepared following the procedure described Example 388, Step A using 2-bromopyridine (60 μL, 0.63 mmol) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (200 mg, 0.78 mmol). LCMS: R_T = 0.973 min, MS (ES) 209.1 (M+H).

Step B. Preparation of 3-iodo-1-methyl-5-(pyridin-2-yl)-1*H*-indole

[00635] The title compound (160 mg, 91%) was prepared following the procedure described Example 388, Step B using 1-methyl-5-(pyridin-2-yl)-1*H*-indole (110 mg, 0.53 mmol). LCMS: R_T = 1.146 min, MS (ES) 334.9 (M+H).

Step B. Example 389

[00636] The title compound (37 mg, 88%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.056 mmol) and 3-iodo-1-methyl-5-(pyridin-2-yl)-1*H*-indole (36 mg, 0.11 mmol). LCMS: R_T = 1.895 min, MS (ES) 745.0 (M+H).

Example 390

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethyl-2-(pyrrolidin-1-ylmethyl)pyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

Step A. Preparation of ethyl (*R*)-7-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-1-(1-((*tert*-butoxycarbonyl)amino)propan-2-yl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate

[00637] The title compound (259 mg, 84%) was prepared following the procedure described Example 373, Step E using of ethyl 7-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate (250 mg, 0.39 mmol), *tert*-butyl (*S*)-5-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (150 mg, 0.63 mmol) and Cs_2CO_3 (250 mg, 0.77 mmol). LCMS: R_T = 1.737 min, MS (ES) 803.0 (M+H).

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Step B. Preparation of (*R*)-6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00638] The title compound (143 mg, 68%) was prepared following the procedure described Example 373, Step F using ethyl (*R*)-7-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-1-(1-((*tert*-butoxycarbonyl)amino)propan-2-yl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy) propyl)-1*H*-indole-2-carboxylate (259 mg, 0.32 mmol), HCl in dioxanes (4.0 M, 1.0 mL, 4.0 mmol) and K_2CO_3 (250 mg, 1.8 mmol). LCMS: R_T = 1.270 min, MS (ES) 657.0 (M+H).

Step C. Preparation of methyl (*R*)-3-(6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate

[00639] The title compound (123 mg, 67%) was prepared according to General Procedure B using (*R*)-6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (143 mg, 0.22 mmol) and methyl 3-bromo-1-methyl-1*H*-indole-5-carboxylate (120 mg, 0.45 mmol). LCMS: R_T = 2.336 min, MS (ES) 843.9 (M+H).

Step D. Preparation of methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate

[00640] To a solution of methyl (*R*)-3-(6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (123 mg, 0.15 mmol) in MeOH (5 mL) and EtOAc (1 mL) was added HCl in dioxane (4.0 M, 0.25 mL, 1.0 mmol) followed by Pd/C (10 wt.%, 10 mg, 0.0093 mmol). The reaction mixture was stirred under H_2 atmosphere at 35 °C for 24 h. The reaction was filtered through celite, rinsed with DCM, and concentrated to afford the title compound (92 mg, 84%). LCMS: R_T = 2.066 min, MS (ES) 754.0 (M+H).

Step E. Example 390

[00641] The title compound (8.2 mg, 60%) was prepared according to General Procedure J using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (13 mg, 0.017 mmol) and pyrrolidine (50 mg, 0.70 mmol) followed by saponification using General Procedure D. LCMS: R_T =

1.841 min, MS (ES) 793.0 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.27 (s, 1H), 7.95 (dd, *J* = 8.8, 1.5 Hz, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.32 (dd, *J* = 8.7, 4.7 Hz, 2H), 6.64 (s, 2H), 4.61 (s, 2H), 4.43 – 4.11 (m, 3H), 4.01 (t, *J* = 6.2 Hz, 2H), 3.82 (s, 3H), 3.81-3.78 (m, 1H), 3.67 (d, *J* = 13.0 Hz, 1H), 3.50 – 3.26 (m, 2H), 3.23 – 3.08 (m, 2H), 2.41 (s, 3H), 2.33 (s, 6H), 2.28 – 2.14 (m, 9H), 1.23 (d, *J* = 6.3 Hz, 3H).

Example 391

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of (*R*)-2-(5-bromo-1-methyl-1*H*-indol-3-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00642] The title compound (50 mg, 72%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (50 mg, 0.090 mmol) and 5-bromo-3-iodo-1-methyl-1*H*-indole (60 mg, 0.18 mmol). LCMS: R_T = 2.277 min, MS (ES) 746.8 (M+H).

Step B. Example 391

[00643] 1-Methylpyrazole-4-boronic acid pinacol ester (20 mg, 0.094 mmol), $PdCl_2$(dppf)•DCM (2 mg, 0.002 mmol), K_2CO_3 (56 μL, 0.14 mmol, 2.5 M aq. solution) were added to a solution of (*R*)-2-(5-bromo-1-methyl-1*H*-indol-3-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl) -4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (35 mg, 0.047 mmol) in MeCN (1 mL). The reaction mixture was degassed using Ar and stirred at 95 °C for 1 h. The cooled reaction mixture was filtered through Celite followed by silica gel and the filterate was concentrated. The residue was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/MeCN gradient to 30-95% MeCN 0.1% TFA) to afford the title compound (25 mg, 71%). LCMS: R_T = 2.071 min, MS (ES) 748.0 (M+H).

Example 392

(R)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-(2-(pyrrolidin-1-yl)ethyl)-1H-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-methyl-1H-indole-5-carboxamide

[00644] To a solution of (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino [1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (9 mg, 0.0113 mmol) in DCM (1 mL) was added oxalyl chloride (2.2 μL, 0.026 mmol), followed by catalytic amount of DMF. The reaction mixture was stirred for 1 h at RT then concentrated *in vacuo*. The residue was re-dissolved in dry DCM (1 mL), and ammonia (10 uL, 0. 5M in 1-4-dioxane) was added. The reaction mixture was stirred at RT for 15 min and concentrated. The residue was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 25-95 % MeCN 0.1% TFA) to give the title compound (3.2 mg, 36%). LCMS: R_T = 0.783 min (LC method IV), MS (ES) 794.1 (M+H).

Example 393

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(3-methyl-1,2,4-oxadiazol-5-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of (*R*)-*N*-((3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carbonyl)oxy)acetimidamide

[00645] The title compound was prepared according to General Procedure E using (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (25 mg, 0.035 mmol) and *N*-hydroxyacetimidamide (10 mg, 0.135 mmol). The crude product was carried forward to Step B without further purification. LCMS: R_T = 1.916 min, MS (ES) 768.0 (M+H).

Step B. Example 393

[00646] To a solution of (*R*)-*N*-((3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carbonyl)oxy)acetimidamide from Step A in EtOH/H_2O (3:1, 4 mL) was added sodium acetate (10 mg, 0.121 mmol), and the mixture was stirred at 70 °C for 16 h. The reaction was cooled to RT and diluted into DCM/H_2O (10 mL, 1:1). The layers were separated, and the aqueous layer was extracted with DCM (2 x5 mL). The combined organic layer was dried and concentrated. The residue was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient 35-95 % MeCN 0.1% TFA) to afford the title compound (8.1 mg, 31%). LCMS: R_T = 2.138 min, MS (ES) 749.8 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.30 (d, *J* = 2.0 Hz, 1H),

8.04 (d, *J* = 8.7 Hz, 1H), 7.78 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.50 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.38 – 7.24 (m, 2H), 6.63 (s, 2H), 4.56-4.36 (m, 1H), 4.27-4.13 (m, 1H), 4.08 – 3.96 (m, 5H), 3.86 (s, 3H), 3.70 (d, *J* = 12.3 Hz, 1H), 3.50-3.30 (m, 2H), 2.49 (s, 1.5H), 2.47 (s, 1.5H), 2.34 (s, 1.5H), 2.32 (s, 6H), 2.31 (s, 1.5H), 2.24-2.18 (m, 5H), 1.30 – 1.23 (m, 3H).

Example 394

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(pyrimidin-2-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 1-methyl-5-(pyrimidin-2-yl)-1*H*-indole

[00647] The title compound (61 mg, 58%) was prepared following the procedure described Example 388, Step A using 2-bromopyrimidine (80 mg, 0.50 mmol) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (159 mg, 0.62 mmol). LCMS: R_T = 1.103 min, MS (ES) 210.1 (M+H).

Step B. Preparation of 3-iodo-1-methyl-5-(pyrimidin-2-yl)-1*H*-indole

[00648] The title compound (82 mg, 84%) was prepared following the procedure described Example 388, Step B using 1-methyl-5-(pyrimidin-2-yl)-1*H*-indole (61 mg, 0.29 mmol). LCMS: R_T = 1.456 min, MS (ES) 335.9 (M+H).

Step C. Example 394

[00649] The title compound (15 mg, 43%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol) and 3-iodo-1-methyl-5-(pyrimidin-2-yl)-1*H*-indole (30 mg, 0.089 mmol). LCMS: R_T = 2.086 min, MS (ES) 746.9 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.77 (d, *J* = 4.8 Hz, 1H), 8.76 (d, *J* = 4.9 Hz, 1H), 8.63 (dd, *J* = 5.1, 1.5 Hz, 1H), 8.38 (dt, *J* = 9.0, 1.5 Hz, 1H), 7.68 (dd, *J* = 8.5, 2.6 Hz, 1H), 7.44 (dd, *J* = 9.0, 2.9 Hz, 1H), 7.30 – 7.25 (m, 2H), 7.12 (dt, *J* = 8.5, 4.8 Hz, 1H), 6.61 (s, 2H), 4.53 – 4.46 (m, 1H), 4.35 – 4.20 (m, 1H), 4.02 – 3.97 (m, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.75 (ddd, *J* = 16.3, 12.7, 1.5 Hz, 1H), 3.47 – 3.31 (m, 2H), 2.29 (s, 6H), 2.24 – 2.19 (m, 5H), 2.06 (d, *J* = 2.1 Hz, 3H), 1.29 (d, *J* = 6.8 Hz, 1.4H), 1.22 (d, *J* = 6.4 Hz, 1.5H).

Example 395

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-2-(1-methyl-5-(3-methyl-1,2,4-oxadiazol-5-yl)-1*H*-indol-3-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of (*R*)-*N*-((3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carbonyl)oxy)acetimidamide

[00650] The title compound was prepared according to General Procedure E using (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (20 mg, 0.028 mmol) and *N*-hydroxyacetimidamide (10 mg, 0.135 mmol). The crude product was carried forward to Step 2 without purification. LCMS: R_T = 1.930 min, MS (ES) 766.0 (M+H).

Step B. Example 395

[00651] The title compound (8.1 mg, 31%) was prepared following the procedure described Example 393 Step B using (*R*)-*N*-((3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carbonyl)oxy)acetimidamide and sodium acetate (10 mg, 0.121 mmol). LCMS: R_T = 2.187 min, MS (ES) 747.8 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.23 (s, 1H), 8.31 – 8.18 (m, 1H), 8.03 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.88 – 7.80 (m, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.38 (m, 1H), 7.25 (s, 1H), 6.64 (s, 2H), 4.42 (dd, *J* = 24.4, 9.9 Hz, 1H), 4.02 (t, *J* = 6.1 Hz, 2H), 3.87 (s, 2H), 3.85 (d, *J* = 2.5 Hz, 1H), 3.72 - 3.69 (m, 1H), 3.61 (d, *J* = 12.6 Hz, 1H), 3.52 – 3.30 (m, 2H), 2.54 (s, 3H), 2.47 (s, 3H), 2.38 (s, 3H), 2.32 (s, 6H), 2.23 (t, *J* = 6.9 Hz, 2H), 1.27 (d, *J* = 6.5 Hz, 3H).

Example 396

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethyl-2-((4-methylpiperazin-1-yl)methyl)pyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00652] The title compound (9.5 mg, 48%) was prepared according to General Procedure J using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxylmethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (18 mg, 0.024 mmol) and *N*-methyl piperazine (100 mg, 1.0 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.799 min, MS (ES) 821.8 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.25 (s, 1H), 7.92 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 1H), 7.36 – 7.26 (m, 3H), 6.64 (s, 2H), 4.57 (s, 2H), 4.33 (dd, *J* = 13.3, 3.2 Hz, 1H), 4.06 – 3.87 (m, 6H), 3.81 (s, 3H), 3.81 –

3.68 (m, 6H), 3.51 – 3.30 (m, 2H), 2.95 (s, 3H), 2.40 (s, 3H), 2.33 (s, 6H), 2.25 - 2.17 (m, 5H), 1.24 (d, *J* = 6.4 Hz, 3H).

Example 397

3-((4*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-((3-hydroxypyrrolidin-1-yl)methyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00653] The title compound (5.5 mg, 29%) was prepared according to General Procedure J using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (18 mg, 0.024 mmol) and 3-hydroxypyrrolidine (100 mg, 1.4 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.787 min, MS (ES) 808.9 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.26 (s, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.79 (d, *J* = 8.6 Hz, 1H), 7.34 - 7.26 (m, 3H), 6.64 (s, 2H), 4.70 (s, 2H), 4.38 – 3.89 (m, 6H), 3.82 (s, 3H), 3.81 – 3.59 (m, 4H), 3.50-3.30 (m, 2H), 2.41 (s, 3H), 2.33 (s, 6H), 2.26 – 2.17 (m, 7H), 1.24 (d, J = 4.4 Hz, 3H).

Example 398

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethyl-2-(morpholinomethyl)pyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00654] The title compound (9 mg, 46%) was prepared according to General Procedure J using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (18 mg, 0.024 mmol) and morpholine (100 mg, 1.4 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.809, min, MS (ES) 808.9 (M+H).

Example 399

7-(8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethylpyrimidin-5-yl)-1-oxo-4,5-dihydro-1H-[1,4]diazepino[1,2-a]indol-2(3H)-yl)-1,5-dimethyl-1H-indole-2-carboxylic acid

[00655] The title compound was prepared following General Procedure B using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethylpyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one and methyl 7-bromo-1,5-dimethyl-1*H*-indole-2-carboxylate followed by saponification using General Procedure D. MS (ES) 724.2 (M+H).

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Example 400

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1H-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1,5-dimethyl-1H-indole-2-carboxylic acid

Step A. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,5-dimethyl-1*H*-indole-2-carboxylate

[00656] The title compound was prepared according to procedures described in Example 318 step A and B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one and methyl 7-bromo-1,5-dimethyl-1*H*-indole-2-carboxylate. MS (ES) 726.2 (M+H).

Step B. Example 400

[00657] The title compound was prepared following General Procedure D using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,5-dimethyl-1*H*-indole-2-carboxylate. LCMS: R_T = 0.873 min (LC method IV), MS (ES) 712.6 (M+H); ^{1}H NMR (DMSO, 400 MHz) δ (ppm) 7.72 (d, *J* = 8.8 Hz, 1H), 7.47 (s, 1H), 7.29 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.25 (s, 1H), 6.98 (s, 1H), 6.92 (s, 2H), 4.37-4.16 (m, 1H), 4.03 (s, 3H), 3.98 (t, *J* = 6.0 Hz, 2H), 3.68-3.62 (m, 1H), 3.46-3.40 (m, 1H), 2.43 (s, 3H), 2.28 (s, 6H), 2.22 (s, 3H), 2.17 (t, *J* = 6.4 Hz, 2H), 2.08-2.03 (m, 2H), 2.04 (s, 3H), 1.29 (d, *J* = 6.0 Hz, 3H).

Example 401

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-methyl-5-(pyrrolidin-1-ylmethyl)-1H-indole-2-carboxylic acid

Step A. Preparation of 1-(*tert*-butyl) 2-methyl 7-bromo-5-methyl-1*H*-indole-1,2-dicarboxylate

[00658] To a solution of 7-bromo-5-methyl-1*H*-indole-2-carboxylic acid (1.5 g, 5.9 mmol) in THF (50 mL) and MeOH (6 mL) was added trimethylsilyl diazomethane (4.4 mL, 8.9 mmol, 2.0 M in Et_2O), and the reaction mixture was stirred at RT for 1 h. The reaction was quenched with glacial acetic acid then concentrated. The residue was dissolved in DCM (30 mL), and Et_3N (2.94 mL, 2.15 g, 21.1 mmol), DMAP (0.144 g, 1.18 mmol) and di-*tert*-butyl dicarbonate (1.76 mL, 1.67 g, 7.67 mmol) were added. The reaction mixture was stirred at RT for 3 h then quenched with sat. NH_4Cl aq. solution and extracted with DCM (3 x 25 mL).

The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (1.7 g, 78%, 2 steps). LCMS: R_T = 1.900 min, MS (ES) 390.0 (M+Na); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 3.2 Hz, 2H), 7.21 (s, 1H), 3.92 (s, 3H), 2.41 (s, 3H), 1.69 (s, 9H).

Step B. Preparation of 1-(*tert*-butyl) 2-methyl 7-bromo-5-formyl-1*H*-indole-1,2-dicarboxylate

[00659] To a solution of 1-(*tert*-butyl) 2-methyl 7-bromo-5-methyl-1*H*-indole-1,2-dicarboxylate (1.7 g, 4.6 mmol) in CCl_4 (46 mL) was added AIBN (189 mg, 1.15 mmol) and NBS (822 mg, 4.6 mmol). The reaction mixture was reflux for 3 h then concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient). The crude mixture of products obtained was dissolved in MeCN (25 mL) then NMO (1.77 g, 15.2 mmol) and molecular sieves (4 Å, 6 g) were added. The reaction mixture was stirred at RT for 4 h then quenched with sat. NH_4Cl aq. solution and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (500 mg, 29%, 2 steps). LCMS: R_T = 1.699 min, MS (ES) 403.8 (M+Na); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 8.04 (d, *J* = 1.2 Hz, 1H), 7.99 (d, *J* = 1.2 Hz, 1H), 7.28 (s, 1H), 3.85 (s, 3H), 1.63 (s, 9H).

Step C. Preparation of methyl 7-bromo-1-methyl-5-(pyrrolidin-1-ylmethyl)-1*H*-indole-2-carboxylate

[00660] To a solution of 1-(*tert*-butyl) 2-methyl 7-bromo-5-formyl-1*H*-indole-1,2-dicarboxylate (220 mg, 0.58 mmol) in DCM (3.5 mL) was added TFA (0.6 mL, 0.894 g, 7.8 mmol) and stirred at RT for 16 h. The reaction mixture was quenched with sat. NH_4Cl aq. solution and extracted with DCM (3 x 10 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was re-dissolved in DMF (5.5 mL) then K_2CO_3 (0.56 g, 4.1 mmol) and MeI (72 µL, 163 mg, 1.15 mmol) were added and stirred for 4 h at 60 °C. The reaction was quenched with sat. NH_4Cl aq. solution and extracted with DCM (3 x 10 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was re-dissolved in DCM (5.6 mL) and Et_3N (1 mL). Pyrrolidine (52 µL, 44 mg, 0.624 mmol) and $Na(OAc)_3BH$ (220 mg, 1.04 mmol) were added and stirred at RT for 4 h. The reaction mixture was quenched with aqueous saturated $NaHCO_3$ solution and extracted with DCM (3 x 10 mL). The combined organic layer was dried over $MgSO_4$, filtered and

concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (118 mg, 58%, 3 steps). LCMS: R_T = 1.246 min, MS (ES) 351.0 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.44 (s, 1H), 7.13 (s, 1H), 4.37 (s, 3H), 3.83 (s, 3H), 3.57 (s, 2H), 2.47-2.43 (m, 4H), 1.73-1.70 (m, 4H).

Step D. Example 401

[00661] The title compound (1.1 mg, 3%, 2 steps) was prepared following General Procedure B using methyl 7-bromo-1-methyl-5-(pyrrolidin-1-ylmethyl)-1*H*-indole-2-carboxylate (20 mg, 0.057 mmol) and (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.057 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.851 min, MS (ES) 794.8 (M+H).

Example 402

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-morpholinoethyl)-1*H*-indole-6-carboxamide

[00662] The title compound (1.5 mg, 74%) was prepared following General Procedure E using (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-morpholinoethyl)-1*H*-indole-6-carboxylic acid (2.0 mg, 2.5 μmol). LCMS: R_T = 1.782 min, MS (ES) 810.0 (M+H).

Example 403

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 1-methyl-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[00663] The title compound (48 mg, 43%) was prepared following the procedure described Example 388, Step A using 2-bromo-1-methyl-1*H*-1,2,4-triazole (85 mg, 0.525 mmol) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (165 mg, 0.65 mmol) LCMS: R_T = 1.077 min, MS (ES) 213.1 (M+H).

Step B. Preparation of 3-iodo-1-methyl-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[00664] The title compound (46 mg, 61%) was prepared following the procedure described Example 388, Step B using 1-methyl-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (48 mg, 0.23 mmol). LCMS: R_T = 1.306 min, MS (ES) 338.7 (M+H).

Step C. Example 403

[00665] The title compound (15 mg, 43%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol) and 3-iodo-1-methyl-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (30 mg, 0.089 mmol). LCMS: R_T = 1.953 min, MS (ES) 749.9 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.23 (s, 1H), 8.86 (d, *J* = 1.8 Hz, 1H), 8.01 (d, *J* = 8.3 Hz, 1H), 7.67 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.40 (d, *J* = 8.6 Hz, 1H), 7.29 – 7.22 (m, 2H), 6.61 (s, 2H), 4.47 (dt, *J* = 12.6, 3.0 Hz, 1H), 4.34 – 4.19 (m, 1H), 4.01 – 3.97 (m, 2H), 3.95 (d, *J* = 3.2 Hz, 3H), 3.87 (s, 3H), 3.82 (s, 3H), 3.72 – 3.65 (m, 1H), 3.45 – 3.30 (m, 2H), 2.29 (s, 6H), 2.23 – 2.16 (m, 5H), 2.04 (s, 3H), 1.25 (d, *J* = 6.7 Hz, 1.5H), 1.20 (d, *J* = 6.5 Hz, 1.5H).

Example 404

(*R*)-3-(7-chloro-10-(3-(cyclopropylmethoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

Step A. Preparation of (*R*)-3-(10-(3-bromopropyl)-7-chloro-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00666] To a solution of methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (225 mg, 0.31 mmol) in DCM (20 mL) at 0 °C was added BBr_3 (1.0 M, 1.0 mL, 1.0 mmol), and the mixture was stirred for 1 h. The reaction was diluted with DCM (20 mL) and quenched with H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layer was washed with sat. aq. $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered, and concentrated to afford the crude title compound (122 mg, 62% yield), which was used in subsequent reactions without further purification. LCMS: R_T = 1.687 min, MS (ES) 637.9 (M+H).

Step B. Example 404

[00667] To a solution of cyclopropyl methanol (50 mg, 0.69 mmol) in DMF (2 mL) was added NaH (60 wt.%, 25 mg, 0.625 mmol) at RT, and the mixture was stirred for 30 min.

(*R*)-3-(10-(3-Bromopropyl)-7-chloro-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (15 mg, 0.024 mmol) was added to the mixture, and the reaction was stirred at 50 °C for 15 h. The reaction was diluted DCM/H_2O (10 mL, 1:1). The organic layer was separated and the aqueous layer was extracted with DCM (2 x 5 mL). The combined organic layers were dried and concentrated. The crude reaction mixture was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient 35-95 % MeCN 0.1% TFA) to afford the title compound (7.8 mg, 53%). LCMS: R_T = 1.666 min, MS (ES) 628.0 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.30 (s, 1H), 7.97 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.76 (dd, *J* = 8.6, 2.8 Hz, 1H), 7.38 – 7.27 (m, 3H), 4.41 (d, *J* = 11.5 Hz, 1H), 4.28-4.10 (m, 1H), 3.97 (s, 3H), 3.83 (s, 3H), 3.68 (d, *J* = 12.0 Hz, 1H), 3.50 (t, *J* = 6.5 Hz, 2H), 3.37-3.20 (m, 4H), 2.25 (d, *J* = 10.1 Hz, 3H), 2.13-1.97 (m, 5H), 1.28 – 1.18 (m, 3H), 1.11-1.01 (m, 1H), 0.56 – 0.46 (m, 2H), 0.22 - 0.16 (m, 2H).

Example 405

(*R*)-3-(7-Chloro-4-methyl-1-oxo-10-(3-(*m*-tolyloxy)propyl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00668] To a solution of (*R*)-3-(10-(3-bromopropyl)-7-chloro-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (15 mg, 0.024 mmol) in DMF (2 mL) was added 3-hydroxytoluene (20 mg, 0.19 mmol) and Cs_2CO_3 (30 mg, 0.092 mmol). The reaction was stirred at 50 °C for 15 h then diluted with DCM/H_2O (10 mL, 1:1). The organic layer was separated, and the aqueous layer was extracted with DCM (2 x 5 mL). The combined organic layer was dried and concentrated. The residue was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient 35-95 % MeCN 0.1% TFA) to afford the title compound (5.8 mg, 37%). LCMS: R_T = 1.822 min, MS (ES) 664.0 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.30 (s, 1H), 7.98 (d, *J* = 8.8, 1.6 Hz, 1H), 7.73 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.36 (d, *J* = 8.7 Hz, 1H), 7.32-7.27 (m, 2H), 7.12 (t, *J* = 7.8 Hz, 1H), 6.76-6.66 (m, 3H), 4.45-4.37 (m, 1H), 4.26-4.13 (m, 1H), 4.07-3.93 (m, 5H), 3.84 (s, 3H), 3.68 (d, *J* = 12.8 Hz, 1H), 3.49-3.31 (m, 2H), 2.31-2.18 (m, 8H), 2.12 (s, 1.5H), 2.08 (s, 1.5H), 1.28-1.20 (m, 3H).

Example 406

(*R*)-3-(7-Chloro-10-(3-methoxypropyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00669] The title compound (5.0 mg, 36%) was prepared following the procedure described Example 404 Step B using methanol (50 mg, 1.56 mmol), NaH (60 wt.%, 25 mg, 0.625 mmol) and (*R*)-3-(10-(3-Bromopropyl)-7-chloro-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (15 mg, 0.024 mmol). LCMS: R_T = 1.525 min, MS (ES) 588.0 (M+H).

Example 407

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3-methylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00670] The title compound (4.5 mg, 27%) was prepared following the procedure described Example 405 using (*R*)-3-(10-(3-bromopropyl)-7-chloro-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (15 mg, 0.024 mmol) and 4-chloro-3-methylphenol (20 mg, 0.14 mmol). LCMS: R_T = 1.909 min, MS (ES) 697.9 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.30 (s, 1H), 7.98 (d, *J* = 8.6 Hz, 1H), 7.71 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.29-7.25 (m, 2H), 7.17 (d, *J* = 8.7 Hz, 1H), 6.75 (s, 1H), 6.64 (dd, *J* = 8.8, 3.0 Hz, 1H), 4.41 (d, *J* = 12.6 Hz, 1H), 4.22-4.12 (m, 1H), 4.05-3.95 (m, 5H), 3.83 (s, 3H), 3.68 (d, *J* = 13.9 Hz, 1H), 3.45-3.29 (m, 2H), 2.29 (s, 4.5H), 2.25 (s, 1.5H), 2.20 (t, *J* = 6.5 Hz, 2H), 2.13 (s, 1.5H), 1.98 (s, 1.5H), 1.18-1.07 (m, 3H).

Example 408

(*R*)-3-(7-Chloro-4-methyl-1-oxo-10-(3-phenoxypropyl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00671] The title compound (4.3 mg, 28%) was prepared following the procedure described Example 405 using (*R*)-3-(10-(3-bromopropyl)-7-chloro-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (15 mg, 0.024 mmol) and phenol (20 mg, 0.21 mmol). LCMS: R_T = 1.765 min, MS (ES) 649.9 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.33 (s, 1H), 8.00 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.75 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.39 (d, *J* = 8.7 Hz, 1H), 7.35 – 7.24 (m, 4H), 6.96 – 6.85 (m, 3H), 4.46 – 4.18 (m, 2H), 4.09-3.99 (m, 5H), 3.86 (s, 3H), 3.70 (d, *J* = 12.7 Hz, 1H), 3.56 – 3.31 (m, 2H), 2.31 (s, 1H), 2.26 (s, 2H), 2.25-2.22 (m, 2H), 2.14 (s, 2H), 2.11 (s, 1H), 1.27 (d, *J* = 5.8 Hz, 1H), 1.24 (d, *J* = 5.1 Hz, 2H).

Example 409

(*R*)-3-(7-Chloro-10-(3-(4-chlorophenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00672] The title compound (4.7 mg, 29%) was prepared following the procedure described Example 405 using (*R*)-3-(10-(3-bromopropyl)-7-chloro-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (15 mg, 0.024 mmol) and 4-chlorophenol (20 mg, 0.16 mmol). LCMS: R_T = 1.845 min, MS (ES) 684.0 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.30 (s, 1H), 7.98 (d, *J* = 8.8 Hz, 1H), 7.71 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.32-7.28 (m, 2H), 7.21 – 7.15 (m, 2H), 6.84 – 6.75 (m, 2H), 4.41 (d, *J* = 12.6 Hz, 1H), 4.26-4.11 (m, 1H), 4.04-3.94 (m, 5H), 3.84 (s, 3H), 3.68 (d, *J* = 10.4 Hz, 1H), 3.50-3.31 (m, 2H), 2.31 – 2.16 (m, 5H), 2.11 (s, 1.5H), 2.09 (s, 1.5H), 1.25 (d, *J* = 5.2 Hz, 1.5H), 1.22 (d, *J* = 5.2 Hz, 1.5H).

Example 410

(*R*)-3-(7-Chloro-10-(3-(4-fluorophenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00673] The title compound (4.8 mg, 31%) was prepared following the procedure described Example 405 using (*R*)-3-(10-(3-bromopropyl)-7-chloro-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (15 mg, 0.024 mmol) and 4-fluorophenol (20 mg, 0.18 mmol). LCMS: R_T = 1.776 min, MS (ES) 667.9 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.32 (s, 1H), 8.00 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.73 (dd, *J* = 8.5, 2.6 Hz, 1H), 7.39 (d, *J* = 8.7 Hz, 1H), 7.36 – 7.28 (m, 2H), 7.00 – 6.90 (m, 2H), 6.88 – 6.75 (m, 2H), 4.44-4.19 (m, 2H), 4.05-3.96 (m, 5H), 3.86 (s, 3H), 3.70 (d, *J* = 12.6 Hz, 1H), 3.50-3.30 (m, 2H), 2.30 (s, 1.5H), 2.27 (s, 1.5H), 2.22 (p, *J* = 6.8 Hz, 2H), 2.13 (s, 1.5H), 2.11 (s, 1.5H). 1.27 (d, *J* = 5.1 Hz, 1.5H), 1.24 (d, *J* = 5.1 Hz, 1.5H).

Example 411

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1,3-dimethyl-1*H*-indole-2-carboxamide

[00674] The title compound (8 mg, 80%) was prepared following General Procedure E using (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1,3-

dimethyl-1*H*-indole-2-carboxylic acid (10 mg, 0.013 mmol). LCMS: R_T = 1.752 min, MS (ES) 754.9 (M+H).

Example 412

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-methyl-1*H*-indole-2-carboxamide

[00675] The title compound (6.3 mg, 62%) was prepared following General Procedure E using (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-methyl-1*H*-indole-2-carboxylic acid (10 mg, 0.013 mmol). LCMS: R_T = 2.002 min, MS (ES) 741.0 (M+H).

Example 413

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(5-(5-cyclohexyl-1,3,4-oxadiazol-2-yl)-1-methyl-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one

Example A. Preparation of 3-bromo-N'-(cyclohexanecarbonyl)-1-methyl-1*H*-indole-5-carbohydrazide

[00676] To a solution of 3-bromo-1-methyl-1H-indole-5-carboxylic acid (75 mg, 0.30 mmol) and DIPEA (100 mg, 0.78 mmol) in DMF (2 mL) was added HATU (120 mg, 0.32 mmol). The reaction mixture was stirred at RT for 10 min then cyclohexanecarbohydrazide (50 mg, 0.35 mmol) was added. The reaction was allowed to stir for 2 h at RT. The reaction was diluted into DCM/H_2O (20 mL, 1:1), and the layers were separated. The aqueous layer was extracted with DCM (2 x 10 mL), and the combined organic layer was dried and concentrated. The crude reaction mixture was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (66 mg, 59%). LCMS: R_T = 1.361 min, MS (ES) 379.9 (M+H).

Example B. Preparation of 2-(3-bromo-1-methyl-1H-indol-5-yl)-5-cyclohexyl-1,3,4-oxadiazole

[00677] A solution of 3-bromo-N'-(cyclohexanecarbonyl)-1-methyl-1*H*-indole-5-carbohydrazide (66 mg, 0.17 mmol) in $POCl_3$ (2 mL) was heated to 95 °C for 1 h. The cooled reaction mixture was quenched by pouring into ice/sat. aq. $NaHCO_3$ (50 mL), and the resulting mixture was stirred for 15 min then extracted with DCM (3 x 15 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was

purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (32 mg, 51%). LCMS: R_T = 1.814 min, MS (ES) 360.0 (M+H).

Step C. Example 413

[00678] The title compound (12.4 mg, 41%) was prepared according to General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one (20 mg, 0.038 mmol) and 2-(3-bromo-1-methyl-1H-indol-5-yl)-5-cyclohexyl-1,3,4-oxadiazole (21 mg, 0.61 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.674, 1.706 min, MS (ES) 817.9 (M+H) (Ultra aqueous method).

Example 414

(*R*)-2-(6-(2*H*-Tetrazol-5-yl)quinolin-4-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of (*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)quinoline-6-carbonitrile

[00679] The title compound (31 mg, 90%) was prepared according to General Procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol) and 4-bromo quinoline-6-carbonitrile (16 mg, 0.06 mmol). LCMS: R_T = 2.039 min, MS (ES) 691.0 (M+H).

Step B. Example 414

[00680] The title compound (26 mg, 80%) was prepared according to the procedure for Example 235 using (*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)quinoline-6-carbonitrile (30 mg, 0.04 mmol), sodium azide (14 mg, 0.22 mmol) and ammonium chloride (12 mg, 0.22 mmol). LCMS: R_T = 1.844 min, MS (ES) 733.9 (M+H).

Example 415

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxamide

[00681] The title compound (2.9 mg, 29%) was prepared following the procedure described Example 379 using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-

yl)-5-methyl-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylate (10 mg, 0.012 mmol) and NH_4OH (1 mL). LCMS: R_T = 1.900, 1.934 min, MS (ES) 801.9 (M+H).

Example 416

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethyl-2-(morpholinomethyl)pyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,5-dimethyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl (*R*)-7-(6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate

[00682] The title compound (279 mg, 72%) was prepared according to General Procedure B using (*R*)-6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (300 mg, 0.46 mmol) and methyl 7-iodo-5-methyl-1*H*-indole-2-carboxylate (300 mg, 0.952 mmol). LCMS: R_T = 2.387 min, MS (ES) 843.9 (M+H).

Step B. Preparation of methyl (*R*)-7-(6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,5-dimethyl-1*H*-indole-2-carboxylate

[00683] The title compound was prepared according to General Procedure I using methyl (*R*)-7-(6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (48 mg, 0.057 mmol) and MeI (14 mg, 0.10 mmol). LCMS: R_T = 2.464 min, MS (ES) 857.9 (M+H).

Step C. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,5-dimethyl-1*H*-indole-2-carboxylate

[00684] The title compound (33 mg, 73%, Steps B and C) was prepared following the procedure described Example 390 step D using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,5-dimethyl-1*H*-indole-2-carboxylate (0.057 mmol). LCMS: R_T = 2.175, 2.208 min, MS (ES) 767.9 (M+H).

Step D. Example 416

[00685] The title compound (7.6 mg, 44%) was prepared according to General Procedure J using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-

a]indol-2(1*H*)-yl)-1,5-dimethyl-1*H*-indole-2-carboxylate (16 mg, 0.021 mmol) and morpholine (50 mg, 0.57 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.959, 2.022 min, MS (ES) 822.9 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.79 (d, *J* = 8.6 Hz, 0.25H), 7.78 (d, *J* = 8.6 Hz, 0.75H), 7.38 – 7.25 (m, 3H), 6.95 – 6.83 (s, 1H), 6.63 (s, 1.5H), 6.61 (s, 0.5H), 4.64 (d, *J* = 14.7 Hz, 1H), 4.52 – 4.40 (m, 2H), 4.25 - 4.03 (m, 4H), 4.02 – 3.96 (m, 2H), 3.93 (s, 3H), 3.88 – 3.78 (s, 2H), 3.45 – 3.31 (m, 3H), 2.48 (s, 3H), 2.41 (s, 2.25H), 2.40 (s, 0.75H), 2.33 (s, 6H), 2.26 - 2.17 (m, 5H), 1.31 – 1.14 (m, 3H).

Example 417

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,2-dimethyl-1*H*-indole-3-carboxylic acid

[00686] The title compound was prepared according to General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one and methyl 7-bromo-1,2-dimethyl-1*H*-indole-3-carboxylate followed by saponification using General Procedure D. LCMS: R_T = 2.87 min, MS (ES) 726.2 (M+H) (LC method III). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.27 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.31 – 7.26 (m, 2H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.61 (s, 1.5H), 6.58 (s, 0.5H), 4.51 – 4.20 (m, 2H), 3.99 – 3.81 (m, 6H), 3.71 – 3.32 (m, 5H), 2.77 (s, 2H), 2.76 (s, 1H), 2.31 (s, 6H), 2.21 – 2.17 (m, 5H), 2.07 – 2.03 (m, 3H), 1.25 (d, *J* = 6.0 Hz, 2H), 1.13 (d, *J* = 6.0 Hz, 1H).

Example 418

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(4-methylpyrimidin-2-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 1-methyl-5-(4-methylpyrimidin-2-yl)-1*H*-indole

[00687] The title compound (110 mg, 95%) was prepared following the procedure described Example 388 Step A using 2-bromo-4-methylpyrimidine (90 mg, 0.52 mmol). LCMS: R_T = 0.901 min, MS (ES) 224.1 (M+H).

Step B. Preparation of 3-iodo-1-methyl-5-(4-methylpyrimidin-2-yl)-1*H*-indole

[00688] The title compound (110 mg, 64%) was prepared following the procedure described Example 388 Step B using 1-methyl-5-(4-methylpyrimidin-2-yl)-1*H*-indole (110 mg, 0.49 mmol). LCMS: R_T = 1.489 min, MS (ES) 349.9 (M+H).

Step C. Example 418

[00689] The title compound (22 mg, 62%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol) and 3-iodo-1-methyl-5-(4-methylpyrimidin-2-yl)-1*H*-indole (31 mg, 0.089 mmol). LCMS: R_T = 2.060 min, MS (ES) 760.9 (M+H).

Example 418

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(5-(6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazol-2-yl)-1-methyl-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 5-(6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazol-2-yl)-1-methyl-1*H*-indole

[00690] The title compound (60 mg, 39%) was prepared following the procedure described Example 388 Step A using 2-bromo-6,7-dihydro-5*H*-pyrrolo[1,2-a]imidazole (120 mg, 0.64 mmol) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (203 mg, 0.79 mmol). LCMS: R_T = 0.925 min, MS (ES) 238.2 (M+H).

Step B. Preparation of 5-(6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazol-2-yl)-3-iodo-1-methyl-1*H*-indole

[00691] The title compound (75 mg, 82%) was prepared following the procedure described Example 388 Step B using 5-(6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazol-2-yl)-1-methyl-1*H*-indole (60 mg, 0.25 mmol). LCMS: R_T = 1.240 min, MS (ES) 363.9 (M+H).

Step C. Example 419

[00692] The title compound (20 mg, 56%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol) and 5-(6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazol-2-yl)-3-iodo-1-methyl-1*H*-indole (32 mg, 0.089 mmol). LCMS: R_T = 1.932 min, MS (ES) 774.9 (M+H).

Example 420

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 1-methyl-5-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[00693] The title compound (80 mg, 39%) was prepared following the procedure described Example 388 Step A using 3-bromo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,4-triazol (170 mg,

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0.73 mmol) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (245 mg, 0.95 mmol). LCMS: R_T = 1.339 min, MS (ES) 283.0 (M+H).

Step B. Preparation of 3-iodo-1-methyl-5-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[00694] The title compound (100 mg, 72%) was prepared following the procedure described Example 388 Step B using 1-methyl-5-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (80 mg, 0.28 mmol). LCMS: R_T = 1.561 min, MS (ES) 408.9 (M+H)..

Step C. Preperation of (4*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00695] The title compound (20 mg, 38%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (35 mg, 0.065 mmol) and 3-iodo-1-methyl-5-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (51 mg, 0.13 mmol). LCMS: R_T = 2.104 min, MS (ES) 818.9 (M+H).

Step C. Example 420

[00696] TFA (1 mL) was added to a solution of (4*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (20 mg, 0.020 mmol) in DCM (2 mL) at 0 °C. The reaction mixture was stirred at RT for 18 h. The reaction mixture was diluted DCM and washed with water. Sat. aq. $NaHCO_3$ was added at 0 °C and extracted with DCM (3 x 5 mL). The combined organic layer was dried and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-2% gradient) to afford the title compound (17 mg, 95%). LCMS: R_T = 1.906 min, MS (ES) 735.9 (M+H).

Example 421

(*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(5-phenyl-1,3,4-oxadiazol-2-yl)-1H-indol-3-yl)-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one

Example A. Preparation of N'-benzoyl-3-bromo-1-methyl-1*H*-indole-5-carbohydrazide

[00697] The title compound (49 mg, 45%) was prepared following General coupling procedure E using 3-bromo-1-methyl-1H-indole-5-carboxylic acid (75 mg, 0.30 mmol),

DIPEA (100 mg, 0.78 mmol), HATU (120 mg, 0.32 mmol) and benzohydrazide (50 mg, 0.37 mmol). LCMS: R_T = 1.278 min, MS (ES) 373.9 (M+H).

Example B. Preparation of 2-(3-bromo-1-methyl-1H-indol-5-yl)-5-phenyl-1,3,4-oxadiazole

[00698] The title compound (22 mg, 47%) was prepared following the procedure described Example 413 Step B using N'-benzoyl-3-bromo-1-methyl-1H-indole-5-carbohydrazide (49 mg, 0.13 mmol). LCMS: R_T = 1.742 min, MS (ES) 353.9 (M+H).

Step C. Example 421

[00699] The title compound (17.8 mg, 59 % yield) was prepared according to General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one (20 mg, 0.038 mmol) and 2-(3-bromo-1-methyl-1*H*-indol-5-yl)-5-phenyl-1,3,4-oxadiazole (22 mg, 0.062 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.470, 2.503 min, MS (ES) 811.9 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.40 – 8.32 (m, 1H), 8.18 – 8.10 (m, 2H), 8.03 (ddd, *J* = 8.7, 4.9, 1.5 Hz, 2H), 7.78 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.62 – 7.49 (m, 3H), 7.39 – 7.27 (m, 2H), 6.63 (s, 2H), 4.61-4.45 (m, 1H), 4.28-4.15 (m, 1H), 4.07 – 3.95 (m, 5H), 3.90 (s, 3H), 3.73 (d, *J* = 12.5 Hz, 1H), 3.52 – 3.31 (m, 2H), 2.38 – 2.29 (m, 9H), 2.29 – 2.13 (m, 5H), 1.29 (d, *J* = 6.5 Hz, 3H).

Example 422

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-isopropyl-1-methyl-1*H*-indole-2-carboxamide

[00700] The title compound (5.2 mg, 52%) was prepared following General Procedure E using (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-isopropyl-1-methyl-1*H*-indole-2-carboxylic acid (10 mg, 0.013 mmol). LCMS: R_T = 2.111 min, MS (ES) 753.0 (M+H).

Example 423

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(5-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-1-methyl-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of *N*'-(cyclopropanecarbonyl)-1-methyl-1*H*-indole-5-carbohydrazide

[00701] The title compound (41 mg, 43%) was prepared following the procedure described Example 413 Step A using 1-methyl-1*H*-indole-5-carbohydrazide (70 mg, 0.37 mmol) and cyclopropanecarbonyl chloride (110 mg, 1.06 mmol). LCMS: R_T = 0.907 min, MS (ES) 258.1 (M+H).

Step B. Preparation of 2-cyclopropyl-5-(1-methyl-1*H*-indol-5-yl)-1,3,4-oxadiazole

[00702] The title compound (11 mg, 28% yield) was prepared following the procedure described Example 413 Step B using *N*'-(cyclopropanecarbonyl)-1-methyl-1*H*-indole-5-carbohydrazide (41 mg, 0.16 mmol). LCMS: R_T = 1.341 min, MS (ES) 240.1 (M+H).

Step C. Preparation of 2-(3-bromo-1-methyl-1*H*-indol-5-yl)-5-cyclopropyl-1,3,4-oxadiazole

[00703] The title compound (12 mg, 82% yield) was prepared according to General Procedure F using 2-cyclopropyl-5-(1-methyl-1*H*-indol-5-yl)-1,3,4-oxadiazole (11 mg, 0.046 mmol). LCMS: R_T = 1.538 min, MS (ES) 318.0 (M+H).

Step D. Example 423

[00704] The title compound (11.2 mg, 39%) was prepared according to General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (20 mg, 0.037 mmol) and 2-(3-bromo-1-methyl-1*H*-indol-5-yl)-5-cyclopropyl-1,3,4-oxadiazole (12 mg, 0.038 mmol) followed by saponification using General Procedure B. LCMS: R_T = 2.314, 2.342 min, MS (ES) 775.9 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.26 – 8.16 (m, 1H), 7.89 (t, *J* = 7.5 Hz, 1H), 7.77 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.47 (dd, *J* = 8.7, 1.0 Hz, 1H), 7.34 (d, *J* = 2.6 Hz, 1H), 7.35 – 7.28 (m, 1H), 6.63 (s, 2H), 4.55 - 4.45 (m, 1H), 4.27-4.13 (m, 1H), 4.08 – 3.96 (m, 5H), 3.87 (s, 3H), 3.70 (d, *J* = 12.5 Hz, 1H), 3.50 – 3.29 (m, 2H), 2.38 – 2.27 (m, 9H), 2.27 – 2.12 (m, 5H), 1.25 (m, 8H).

Example 424

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(pyridazin-3-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 1-methyl-5-(pyridazin-3-yl)-1*H*-indole

[00705] The title compound (143 mg, 91%) was prepared following the procedure described Example 388 Step A using 3-bromopyridazine (120 mg, 0.76 mmol) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (239 mg, 0.93 mmol). LCMS: R_T = 1.005 min, MS (ES) 210.1 (M+H).

Step B. Preparation of 3-iodo-1-methyl-5-(pyridazin-3-yl)-1*H*-indole

[00706] The title compound (160 mg, 80%) was prepared following the procedure described Example 388 Step B using 1-methyl-5-(pyridazin-3-yl)-1*H*-indole (143 mg, 0.60 mmol). LCMS: R_T = 1.251 min, MS (ES) 335.8 (M+H).

Step C. Example 424

[00707] The title compound (20 mg, 59%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol) and 3-iodo-1-methyl-5-(pyridazin-3-yl)-1*H*-indole (30 mg, 0.089 mmol). LCMS: R_T = 1.938 min, MS (ES) 746.8 (M+H).

Example 425

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(6-(2-methyl-2*H*-tetrazol-5-yl)quinolin-4-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00708] The title compound (14 mg, 69%) was prepared following General Procedure NGeneral Procedure G using (*R*)-2-(6-(2*H*-tetrazol-5-yl)quinolin-4-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino [1,2-*a*]indol-1(2*H*)-one (20 mg, 0.03 mmol) and methyl iodide (4 μL, 0.05 mmol). LCMS: R_T = 1.909 min, MS (ES) 747.9 (M+H).

Example 426

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethyl-2-((4-methylpiperazin-1-yl)methyl)pyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,5-dimethyl-1*H*-indole-2-carboxylic acid

[00709] The title compound (12.7 mg, 73%) was prepared according to General Procedure J using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,5-dimethyl-1*H*-indole-2-carboxylate (16 mg, 0.021 mmol) and N-methyl piperazine (50 mg, 0.20 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.841, 1.871 min, MS (ES) 835.9 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.78 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.37 – 7.20 (m, 3H), 6.92 – 6.76 (m, 1H), 6.62 (s, 1.5H), 6.60 (s, 0.5H), 4.62 (d, *J* = 15.5 Hz, 1H), 4.47 – 4.38 (m, 2H), 4.09 (s, 1H), 4.03 – 3.61 (m, 13H),3.34 (t, *J* = 7.5 Hz, 2H), 3.16 – 3.06 (m, 1H), 2.92 (s, 2.25H), 2.89 (s, 0.75H), 2.44 (s, 2.25H), 2.42 (s, 0.75H), 2.41 (s, 2.25H), 2.39 (s, 0.75H), 2.28 - 2.16 (m, 5H), 1.23 (d, *J* = 6.4 Hz, 2.25H), 1.13 (d, *J* = 6.4 Hz, 0.75H).

Example 427

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-*N*'-phenyl-1*H*-indole-5-carbohydrazide

[00710] The title compound (7.6 mg, 73%) was prepared following General Procedure E using (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (10 mg, 0.013 mmol) and phenylhydrazine hydrochloride (4 mg, 0.026 mmol). LCMS: R_T = 2.079 min, MS (ES) 802.0 (M+H).

Example 428

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(5-(4,5-dihydrooxazol-2-yl)-1-methyl-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 2-(1-methyl-1*H*-indol-5-yl)-4,5-dihydrooxazole

[00711] Aminoethanol (193 μL, 3.20 mmol) and $ZnCl_2$ (6 μL, 0.13 mmol) were added to a solution of 1-methyl-1*H*-indole-5-carbonitrile (100 mg, 0.64 mmol) in toluene (3 mL). The reaction mixture was stirred at 135 °C for 4 days. The reaction solution was cooled and concentrated. The residue was diluted with water and extracted with DCM (3 x 10 mL). The combined organic layer was dried, filtered and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-5% gradient) to afford the title compound (30 mg, 23%). LCMS: R_T = 0.775 min, MS (ES) 201.1 (M+H).

Step B. Preparation of 2-(3-iodo-1-methyl-1*H*-indol-5-yl)-4,5-dihydrooxazole

[00712] The title compound was prepared following the procedure described Example 388, Step B using 2-(1-methyl-1*H*-indol-5-yl)-4,5-dihydrooxazole (15 mg, 0.070 mmol). The crude compound (25 mg) was used for the next step without further purification. LCMS: R_T = 1.142 min, MS (ES) 326.9 (M+H).

Step C. Example 428

[00713] The title compound (25 mg, 73%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol) and 2-(3-iodo-1-methyl-1*H*-indol-5-yl)-4,5-dihydrooxazole (24 mg, 0.074 mmol). LCMS: R_T = 1.883 min, MS (ES) 737.8 (M+H).

Example 429

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 5-methyl-3-(1-methyl-1*H*-indol-5-yl)-1,2,4-oxadiazole

[00714] Hydroxylamine hydrochloride (116 mg, 1.66 mmol) and K_3PO_4 (408 mg, 1.92 mmol) were added to a solution of 1-methyl-1*H*-indole-5-carbonitrile (200 mg, 1.28 mmol) in DMF (4 mL). The reaction mixture was stirred at 95 °C for 16 h then acetyl chloride (137 μL, 1.92 mmol) was added at RT. The solution was stirred at 105 °C for additional 36 h. The reaction mixture was diluted EtOAc and washed with water, dried and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-3% gradient) to afford the title compound (21 mg, 64%). LCMS: R_T = 1.304 min, MS (ES) 214.1 (M+H).

Step B. Preparation of 3-(3-iodo-1-methyl-1*H*-indol-5-yl)-5-methyl-1,2,4-oxadiazole

[00715] The title compound was prepared following the procedure described Example 388, Step B using 5-methyl-3-(1-methyl-1*H*-indol-5-yl)-1,2,4-oxadiazole (21 mg, 0.10 mmol). The crude compound (55 mg) was used for the next step without further purification. LCMS: R_T = 1.594 min, MS (ES) 339.9 (M+H).

Step C. Example 429

[00716] The title compound (22 mg, 63%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol) and 3-(3-iodo-1-methyl-1*H*-indol-5-yl)-5-methyl-1,2,4-oxadiazole (25 mg, 0.074 mmol). LCMS: R_T = 2.121 min, MS (ES) 750.8 (M+H).

Example 430

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(pyrazin-2-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 1-methyl-5-(pyrazin-2-yl)-1*H*-indole

[00717] The title compound (90 mg, 98%) was prepared following the procedure described Example 388 Step A using 2-bromopyrazine (70 mg, 0.44 mmol) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (170 mg, 0.66 mmol). LCMS: R_T = 1.296 min, MS (ES) 210.1 (M+H).

Step B. Preparation of 3-iodo-1-methyl-5-(pyrazin-2-yl)-1*H*-indole

[00718] The title compound was prepared following the procedure described Example 388 Step B using 1-methyl-5-(pyrazin-2-yl)-1*H*-indole (90 mg, 0.43 mmol). The crude compound (120 mg) was used for the next step without further purification. LCMS: R_T = 1.530 min, MS (ES) 335.8 (M+H).

Step C. Example 430

[00719] The title compound (28 mg, 67%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.056 mmol) and 3-iodo-1-methyl-5-(pyrazin-2-yl)-1*H*-indole (30 mg, 0.089 mmol). LCMS: R_T = 2.096 min, MS (ES) 746.9 (M+H).

Example 431

6-(8-Chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1-methyl-1*H*-indole-4-carboxylic acid (Separated atropisomer 1, absolute stereochemistry unknown)

Step A. Separation of 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one

[00720] Racemic mixture of atropisomeric 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one was separated by preparative normal phase HPLC using chiral AD column. Optically pure atropisomers were isolated and absolute configurations were undetermined. 1st eluted isomer $[\alpha]_D^{25}$ = +9.9°, 2nd eluted isomer $[\alpha]_D^{25}$ = +6.1°

Step B. Example 431

[00721] The title compound was prepared according to General Procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (1st eluted isomer) and 6-bromo-1-methyl-1*H*-indole-4-carboxylic acid followed by saponification using General Procedure D. LCMS: R_T = 2.163 min, MS (ES) 711.9 (M+H).

Example 432

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethyl-2-((4-methyl-3-oxopiperazin-1-yl)methyl)pyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00722] The title compound (4.2 mg, 38%) was prepared according to General Procedure J using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-

a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (10 mg, 0.013 mmol) and 1-methylpiperazin-2-one (10 mg, 0.088 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.782 min, MS (ES) 835.9 (M+H).

Example 433

(*R*)-3-(6-(2-((4-Acetylpiperazin-1-yl)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00723] To a solution of methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethyl-2-(piperazin-1-ylmethyl)pyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino [1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (8 mg, 0.0098 mmol) in DCM (1 mL) was added DIPEA (5 mg, 0.038 mmol) followed by acetyl chloride (3 mg, 0.038 mmol) in DCM (0.5 mL) at 0 °C. The reaction mixture was stirred for 15 min at 0 °C then quenched with MeOH. The quenched mixture was diluted with DCM (5 mL) and washed with H_2O (5 mL). The organic layer was dried and concentrated. The residue was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient 35-95 % MeCN 0.1% TFA) to afford the title compound (2.1 mg, 25%). LCMS: R_T = 1.789 min, MS (ES) 849.9 (M+H).

Example 434

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,3',4,4'-tetrahydro-1*H*-[2,6'-bipyrazino[1,2-*a*]indole]-1,1'(2'*H*)-dione

Step A. Preparation of ethyl (*R*)-1-(2-((*tert*-butoxycarbonyl)amino)ethyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate

[00724] To a solution of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (15 mg, 0.021 mmol) and *tert*-butyl 1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (10 mg, 0.045 mmol) in MeCN (1 mL) was added Cs_2CO_3 (15 mg, 0.0416 mmol), and the reaction mixture was stirred at 80 °C for 18 h. The reaction was cooled to RT and diluted into DCM/H_2O (10 mL, 1:1). The layers were separated and extracted with DCM (2 x 5 mL). The combined organic layer was dried and concentrated to give the crude title compound which was used without further purification. LCMS: R_T = 2.289 min, MS (ES) 890.9 (M+Na).

Step B. Example 434

[00725] To a solution of crude ethyl (*R*)-1-(2-((*tert*-butoxycarbonyl)amino)ethyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate in DCM (3 mL) was added TFA (0.5 mL), and the reaction mixture was stirred for 6 h at RT then concentrated. The residue was dissolved in MeOH (3 mL), and K_2CO_3 (10 mg, 0.072 mmol) was added. The reaction mixture was stirred at 50 °C for 4 h then concentrated. The residue was dissolved in DCM/H_2O (10 mL, 1:1). The layers were separated and extracted with DCM (2 x 5 mL). The combined organic layer was dried and concentrated. The residue was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient 35-95 % MeCN 0.1% TFA) to afford the title compound (5.3 mg, 35%). LCMS: R_T = 2.116, 2.153 min, MS (ES) 723.0 (M+H).

Example 435

(*R*)-4-Chloro-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylic acid

[00726] The title compound was prepared according to General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one and methyl 7-bromo-4-chloro-1-methyl-1*H*-indole-3-carboxylate followed by saponification using General Procedure D. LCMS: R_T = 2.212, 2.254 min, MS (ES) 745.8 (M+H).

Example 436

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methoxy-1-methyl-1*H*-indole-3-carboxylic acid

[00727] The title compound was prepared according to General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one and methyl 7-bromo-5-methoxy-1-methyl-1*H*-indole-3-carboxylate followed by saponification using General Procedure D. LCMS: R_T = 2.182, 2.217 min, MS (ES) 741.9 (M+H).

Example 437

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethyl-2-(((1-methylpiperidin-4-yl)amino)methyl)pyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00728] The title compound (6.9 mg, 62%) was prepared according to General Procedure J using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (10 mg, 0.013 mmol) and 1-methylpiperidin-4-amine (20 mg, 0.18 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.762 min, MS (ES) 835.9 (M+H).

Example 438

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-fluoro-1*H*-indole-3-carboxylic acid

[00729] The title compound was prepared according to General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one and methyl 7-bromo-4-fluoro-1*H*-indole-3-carboxylate followed by saponification using General Procedure D. LCMS: R_T = 2.70, 2.73 min, MS (ES) 716.2 (M+H) (LC method III).

Example 439

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-((4-(2-methoxyethyl)piperazin-1-yl)methyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00730] The title compound (8.9 mg, 77%) was prepared according to General Procedure J using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (10 mg, 0.013 mmol) and 1-(2-methoxyethyl)piperazine (40 mg, 0.28 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.850 min, MS (ES) 865.9 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.26 (s, 1H), 7.92 (dd, *J* = 8.8, 1.4 Hz, 1H). 7.78 (d, *J* = 8.6 Hz, 1H), 7.35 – 7.28 (m, 3H), 6.64 (s, 2H), 4.51 – 4.38 (m, 2H), 4.30 (dd, *J* = 13.5, 3.8 Hz, 1H), 4.01 (dt, *J* = 6.2, 3.0 Hz, 2H), 3.91-3.71 (m, 14H), 3.44 – 3.29 (m, 8H), 2.39 (s, 3H), 2.33 (s, 6H), 2.29 – 2.19 (m, 5H), 1.25 (d, *J* = 6.4 Hz, 3H).

Example 440

6-(8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-oxo-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-[1,4]diazepino[1,2-*a*]indol-2(3*H*)-yl)-1-methyl-1*H*-indole-4-carboxylic acid (Separated atropisomer 2, absolute stereochemistry unknown)

[00731] The title compound was prepared according to General Procedure A using 8-chloro-11-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indol-1-one (2nd eluted isomer) and 6-bromo-1-methyl-1*H*-indole-4-carboxylic acid followed by saponification using General Procedure D. LCMS: R_T = 2.163 min, MS (ES) 711.9 (M+H).

Example 441

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethyl-2-(piperazin-1-ylmethyl)pyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00732] The title compound (17 mg, 79%) was prepared according to General Procedure J using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (20 mg, 0.039 mmol) and piperazine (50 mg, 0.58 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.727 min, MS (ES) 807.9 (M+H).

Example 442

(*R*)-3-(3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indol-5-yl)-1,2,4-oxadiazol-5(4*H*)-one

[00733] To a solution of methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (30 mg, 0.04 mmol) in DMF (1 mL) was added sodium acetate (14 mg, 0.16 mmol) and hydroxylamine hydrochloride (11 mg, 0.16 mmol), and the mixture was stirred at RT for 15 h. The reaction was quenched with water (10 mL) then extracted with DCM (3x5 mL). The organic layer was dried and concentrated. The residue was dissolved in THF (1 mL) and 1,1'-carbonyldiimidazole (17 mg, 0.08 mmol) and DBU (18 μL, 12 mmol) were added. The mixture was irradiated in a Biotage microwave at 120 °C for 20 min then concentrated. The residue was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA) to afford the title compound (7.8 mg, 26%). LCMS: R_T = 2.033 min, MS (ES) 751.8 (M+H).

Example 443

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethyl-2-((4-(tetrahydro-2*H*-pyran-4-yl)piperazin-1-yl)methyl)pyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00734] The title compound (10.6 mg, 89%) was prepared according to General Procedure J using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (10 mg, 0.013 mmol) and 4-(piperidin-4-yl)morpholine (50 mg, 0.29 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.848 min, MS (ES) 891.9 (M+H).

Example 444

(*R*)-5-(3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indol-5-yl)-1,3,4-oxadiazol-2(3*H*)-one

[00735] To a solution of (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carbohydrazide (15 mg, 0.02 mmol) in DMF (1 mL) was added 1,1'-carbonyldiimidazole (7 mg, 0.04 mmol) followed by Et_3N (6 μL, 0.04 mmol), and the mixture was stirred at RT for 6 h then concentrated. The residue was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA) to afford the title compound (6.1 mg, 40%). LCMS: R_T = 1.982 min, MS (ES) 751.8 (M+H).

Example 445

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-methyl-1*H*-indole-3-carboxylic acid

[00736] The title compound was prepared according to General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one and 7-bromo-4-methoxy-1-methyl-1*H*-indole-3-carboxylic acid followed by saponification using General Procedure D. LCMS: R_T = 2.76, 2.81 min, MS (ES) 742.2 (M+H) (LC method III). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.32 – 7.26 (m, 1H), 7.02 – 7.00 (m, 1H), 6.80 – 6.77 (m, 1H), 6.60 (s, 2H), 4.23 – 4.18 (m, 2H), 4.13 (s, 3H), 3.98 – 3.87 (m, 5H), 3.71 – 3.32 (m, 5H), 3.77 (s, 3H), 3.56 – 3.52 (m, 1H), 3.35 – 3.31 (m, 2H), 2.31 (s, 6H), 2.21 – 2.15 (m, 5H), 2.03 (s, 3H), 1.23 – 1.17 (m, 3H).

Example 446

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(4-fluoro-1*H*-indol-7-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00737] The title compound was prepared according to General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one and 7-bromo-4-fluoro-1*H*-indole followed by saponification using General Procedure D. LCMS: R_T = 3.04 min, MS (ES) 672.0 (M+H) (LC method III).

Example 447

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-fluoro-1-methyl-1*H*-indole-3-carboxylic acid

[00738] The title compound was prepared according to General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one and 7-bromo-4-fluoro-1-methyl-1*H*-indole-3-carboxylic acid followed by saponification using General Procedure D. LCMS: R_T = 2.77 min, MS (ES) 730.1 (M+H) (LC method III).

Example 448

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(((2-(dimethylamino)ethyl)(methyl)amino)methyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00739] The title compound (5.3 mg, 48%) was prepared according to General Procedure J using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (10 mg, 0.013 mmol) and N^1,N^1,N^2-trimethylethane-1,2-diamine (30 mg, 0.29 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.788 min, MS (ES) 823.9 (M+H).

Example 449

(*R*)-5-Chloro-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylic acid

[00740] The title compound was prepared according to General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one and methyl 7-bromo-5-chloro-1-

methyl-1*H*-indole-3-carboxylate followed by saponification using General Procedure D. LCMS: R_T = 2.284 min, MS (ES) 745.8 (M+H).

Example 450

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(5-methylpyrimidin-2-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 1-methyl-5-(5-methylpyrimidin-2-yl)-1*H*-indole

[00741] The title compound (70 mg, 78%) was prepared following the procedure described Example 388 Step A using 2-bromo-5-methylpyrimidine (70 mg, 0.44 mmol) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (156 mg, 0.61 mmol). LCMS: R_T = 1.156 min, MS (ES) 224.1 (M+H).

Step B. Preparation of 3-iodo-1-methyl-5-(5-methylpyrimidin-2-yl)-1*H*-indole

[00742] The title compound was prepared following the procedure described Example 388 Step B using 1-methyl-5-(5-methylpyrimidin-2-yl)-1*H*-indole (70 mg, 0.31 mmol). The crude compound (100 mg) was used for the next step without further purification. LCMS: R_T = 1.507 min, MS (ES) 350.8 (M+H).

Step C. Example 450

[00743] The title compound (29 mg, 69%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.056 mmol) and 3-iodo-1-methyl-5-(5-methylpyrimidin-2-yl)-1*H*-indole (31 mg, 0.089 mmol). LCMS: R_T = 2.132 min, MS (ES) 760.9 (M+H).

Example 451

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-((dimethylamino)methyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00744] The title compound (5.9 mg, 58%) was prepared according to General Procedure J using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (10 mg, 0.013 mmol) and dimethylamine hydrochloride salt (20 mg, 0.25 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.811 min, MS (ES) 766.9 (M+H).

Example 452

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1,5-dimethyl-1*H*-indole-2-carboxylic acid

[00745] The title compound was prepared following the procedure described Example 318 Step C using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,5-dimethyl-1*H*-indole-2-carboxylate and 4-(bromomethyl)tetrahydro-2*H*-pyran. LCMS: R_T = 1.63 min, MS (ES) 810.7 (M+H); ^{1}H NMR (DMSO, 400 MHz) δ (ppm) 7.76 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.48 (s, 1H), 7.29 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.21 (d, *J* = 1.6 Hz, 1H), 6.95 (s, 1H), 6.70 (s, 2H), 4.39-4.31 (m, 1H), 4.20-4.16 (m, 2H), 3.97-3.94 (m, 2H), 3.91 (s, 3H), 3.86-3.80 (m, 2H), 2.67-2.63 (m, 2H), 2.53 (s, 3H), 2.37 (s, 3H), 2.35-2.31 (m, 2H), 2.22 (s, 6H), 2.12 (s, 3H), 2.01 (s, 3H), 1.95-1.95 (m, 2H), 1.89-1.87 (m, 2H), 1.43-1.29 (m, 1H), 1.17-1.03 (m, 4H).

Example 453

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-5-(2-(4-methylpiperazin-1-yl)ethoxy)-1*H*-indole-2-carboxylic acid

[00746] To a solution of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-methyl-1*H*-indole-2-carboxylate (10 mg, 0.013 mmol), PPh_3 (10 mg, 0.038 mmol) and 2-(4-methylpiperazin-1-yl)ethan-1-ol (8 mg, 0.055 mmol) in THF (1 mL) was added di-*tert*-butyl (*E*)-diazene-1,2-dicarboxylate (10 mg, 0.044 mmol) at RT. The reaction mixture was stirred for 18 h at RT, then heated to 60 °C for additional 5 h. The reaction was cooled to RT and diluted with DCM/H_2O (10 mL, 1:1). The aqueous layer was extracted with DCM (2 x 5 mL). The combined organic layer was dried and concentrated. The crude product was saponified following General Procedure D. The crude reaction mixture was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient 35-95 % MeCN 0.1% TFA) to afford the title compound (2.2 mg, 19%). LCMS: R_T = 1.779 min, MS (ES) 853.9 (M+H).

Example 454

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(5-(1-isobutyl-1*H*-1,2,4-triazol-3-yl)-1-methyl-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 3-iodo-1-methyl-5-(1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[00747] 2N HCl (2 mL) was added to a solution of 3-iodo-1-methyl-5-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (150 mg, 0.37 mmol) in MeOH (1 mL) at 0 °C. The reaction was warmed to RT and stirred for 4 h. The reaction mixture was diluted with EtOAc, quenched with Sat. aq. $NaHCO_3$ at 0 °C and extracted with EtOAc (3 x 5 mL). The combined organic layer was dried and concentrated to give the title compound (80 mg), which was used for the next step without further purification. LCMS: R_T = 0.211 min, MS (ES) 324.9 (M+H).

Step B. Preparation of 3-iodo-5-(1-isobutyl-1*H*-1,2,4-triazol-3-yl)-1-methyl-1*H*-indole

[00748] NaH (4 mg, 0.15 mmol) was added to a solution of 3-iodo-1-methyl-5-(1*H*-1,2,4-triazol-3-yl)-1*H*-indole (40 mg, 0.12 mmol) in DMF (1 mL) at 0 °C. After 10 min, 1-bromo-2-methylpropane (16.1 μL, 0.15 mmol) was added slowly. The reaction was warmed to RT and stirred for 15 h. The reaction was quenched with water and extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with water, dried and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-20% gradient) to provide the title compound (35 mg, 74%). LCMS: R_T = 1.564 min, MS (ES) 380.8 (M+H).

Step C. Example 454

[00749] The title compound (40 mg, 91%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.056 mmol) and 3-iodo-5-(1-isobutyl-1*H*-1,2,4-triazol-3-yl)-1-methyl-1*H*-indole (34 mg, 0.089 mmol). LCMS: R_T = 2.132 min, MS (ES) 791.9 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.31 (d, *J* = 24.5 Hz, 1H), 8.20 (d, *J* = 11.2 Hz, 1H), 7.98 (dd, *J* = 9.0, 1.7 Hz, 1H), 7.68 (dd, *J* = 8.8, 3.0 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 1H), 7.29 – 7.23 (m, 2H), 6.61 (s, 2H), 4.50 – 4.41 (m, 1H), 4.31 – 4.20 (m, 1H), 4.00 – 3.95 (m, 4H), 3.90 (s, 3H), 3.83 (s, 3H), 3.74 – 3.67 (m, 1H), 3.46 – 3.30 (m, 2H), 2.34 – 2.27 (m, 7H), 2.22 – 2.18 (m, 5H), 2.06 (s, 3H), 1.26 (d, *J* = 6.4 Hz, 1.5H), 1.23 (d, *J* = 6.9 Hz, 1.5H), 0.97 (d, *J* = 6.9 Hz, 6H).

Example 455

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(2-(dimethylamino)ethoxy)-1-methyl-1*H*-indole-2-carboxylic acid

[00750] The title compound (2.6 mg, 24%) was prepared following the procedure described Example 453 using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-

methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-methyl-1*H*-indole-2-carboxylate (10 mg, 0.013 mmol) and 2-(dimethylamino)ethan-1-ol (5 mg, 0.056 mmol). LCMS: R_T = 1.810 min, MS (ES) 798.9 (M+H).

Example 456

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1-((4-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-3-carboxylate

[00751] The title compound (30 mg, 45%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (50 mg, 0.09 mmol) and methyl 7-bromo-5-methyl-1*H*-indole-2-carboxylate (58 mg, 0.19 mmol). LCMS: R_T = 2.16 min, MS (ES) 726 (M+H).

Step B. Example 456

[00752] The title compound (25 mg, 34%) was prepared following General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-3-carboxylate (60 mg, 0.08 mmol) and 2-(chloromethyl)-4-methylpyridine HCl (29 mg, 0.17 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.38 min, MS (ES) 817 (M+H).

Example 457

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1-((6-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

Step A. Preparation of pentyl 7-iodo-5-methyl-1*H*-indole-2-carboxylate

[00753] To a mixture of methyl 7-bromo-5-methyl-1*H*-indole-2-carboxylate (200 mg, 0.75 mmol) followed by CuI (7 mg, 0.04 mmol) and NaI (224 mg, 1.5 mmol) was added a solution of (*trans*)-1,2-*N*,*N*'-dimethylaminocyclohexane (11 mg, 0.07 mmol) in 1-pentanol (1 mL). The reaction mixture was sealed and stirred at 120°C for 24 h. The reaction was cooled to RT and diluted with 30% NH_4OH (5 mL) in water (20 mL) and extracted with DCM. The combined organics were dried and concentrated. The residue was purified by flash

chromatography (Combi-flash Rf, Hex/EtOAc = 0-5% gradient) to give the title compound (205 mg, 74%). LCMS: R_T = 2.04 min, MS (ES) 372 (M+H).

Step B. Preparation of pentyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate

[00754] The title compound (80 mg, 73%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl -1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (75 mg, 0.14 mmol) and pentyl 7-iodo-5-methyl-1*H*-indole-2-carboxylate (103 mg, 0.28 mmol). LCMS: R_T = 2.42 min, MS (ES) 782 (M+H).

Step C. Example 457

[00755] The title compound (45 mg, 68%) was prepared following General Procedure I using pentyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (80 mg, 0.10 mmol) and 2-(chloromethyl)-6-methylpyridine (36 mg, 0.26 mmol) followed by saponification using General Procedure D as TFA salt. LCMS: R_T = 1.40 min, MS (ES) 817 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, *J* = 8.6 Hz, 1H), 7.56 (s, 1H), 7.40 (s, 1H), 7.27 (d, *J* = 8.6 Hz, 1H), 7.01 (m, 1H), 6.87 (s, 0.5H), 6.86 (s, 0.5H), 6.74 (s, 1H), 6.70 (s, 1H), 6.11-6.24 (m, 2H), 5.74 (s, 2H), 4.01 (m, 2H), 3.88 (m, 1H), 3.73 (s, 1.5H), 3.70 (s, 1.5H), 3.24-3.28 (m, 1H), 3.08 (m, 1H), 2.32-2.38 (m, 5H), 2.23 (s, 3H), 2.21 (s, 3H), 2.08 (s, 1.5H), 2.06 (s, 1.5H), 1.95-1.99 (m, 2H), 1.91 (s, 1.5H), 1.89 (s, 1.5H), 1.85 (s, 1.5H), 1.75 (s, 1.5H), 1.03 (t, *J* = 6.8 Hz, 3H).

Example 458

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-5-(2-morpholinoethoxy)-1*H*-indole-2-carboxylic acid

[00756] The title compound (4.7 mg, 42%) was prepared following the procedure described Example 453 using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-methyl-1*H*-indole-2-carboxylate (10 mg, 0.013 mmol) and 2-morpholinoethan-1-ol (8 mg, 0.061 mmol). LCMS: R_T = 1.794 min, MS (ES) 840.9 (M+H).

Example 459

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-5-(oxetan-3-ylmethoxy)-1*H*-indole-2-carboxylic acid

[00757] The title compound (3.7 mg, 35%) was prepared according to General Procedure H using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-methyl-1*H*-indole-2-carboxylate (10 mg, 0.013 mmol) and 3-(bromomethyl)oxetane (5 mg, 0.033 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.990 min, MS (ES) 797.8 (M+H).

Example 460

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-5-(2-(pyrrolidin-1-yl)ethoxy)-1*H*-indole-2-carboxylic acid

[00758] The title compound (2.1 mg, 19%) was prepared following the procedure described Example 453 using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-methyl-1*H*-indole-2-carboxylate (10 mg, 0.013 mmol) and 2-(pyrrolidin-1-yl)ethan-1-ol (8 mg, 0.069 mmol). LCMS: R_T = 1.799 min, MS (ES) 824.9 (M+H).

Example 461

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(2-methoxyethoxy)-1-methyl-1*H*-indole-2-carboxylic acid

[00759] The title compound (5.2 mg, 50%) was prepared according to General Procedure H using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-methyl-1*H*-indole-2-carboxylate (10 mg, 0.013 mmol) and 1-bromo-2-methoxyethane (5 mg, 0.036 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.009 min, MS (ES) 785.8 (M+H).

Example 462

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(5-(1-(cyclopropylmethyl)-1*H*-1,2,4-triazol-3-yl)-1-methyl-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 5-(1-(cyclopropylmethyl)-1*H*-1,2,4-triazol-3-yl)-3-iodo-1-methyl-1*H*-indole

[00760] The title compound (35 mg, 75%) was prepared following the procedure described Example 454 Step B using 3-iodo-1-methyl-5-(1*H*-1,2,4-triazol-3-yl)-1*H*-indole (40 mg, 0.12 mmol) and (bromomethyl)cyclopropane (14.4 μL, 0.15 mmol). LCMS: R_T = 1.498 min, MS (ES) 378.9 (M+H).

Step B. Example 462

[00761] The title compound (38 mg, 87%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.056 mmol) and 5-(1-(cyclopropylmethyl)-1*H*-1,2,4-triazol-3-yl)-3-iodo-1-methyl-1*H*-indole (34 mg, 0.089 mmol). LCMS: R_T = 2.034 min, MS (ES) 789.0 (M+H).

Example 463

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1,5-dimethyl-1*H*-indole-2-carboxylic acid

[00762] The title compound was prepared following the procedure described Example 318 Step C using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,5-dimethyl-1*H*-indole-2-carboxylate and 1-(2-bromoethyl)pyrrolidine. LCMS: R_T = 1.37 min, MS (ES) 809.7 (M+H); ^{1}H NMR (DMSO, 400 MHz) δ (ppm) 7.90 (d, *J* = 8.8 Hz, 1H), 7.49 (s, 1H), 7.31 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.22 (d, *J* = 2.0 Hz, 1H), 6.96 (d, *J* = 10.0 Hz, 1H), 6.69 (s, 2H), 4.46-4.36 (m, 2H), 4.17-4.11 (m, 1H), 3.98-3.91 (m, 2H), 3.92 (s, 3H), 3.65-3.60 (m, 2H), 3.09-3.01 (m, 2H), 2.64-2.61 (m, 2H), 2.53 (s, 3H), 2.38 (s, 3H), 2.32-2.31 (m, 2H), 2.22 (s, 6H), 2.05 (d, *J* = 4.0 Hz, 3H), 2.06-1.95 (m, 2H), 1.93 (s, 3H), 1.90-1.84 (m, 2H), 1.22-1.05 (m, 4H).

Example 464

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(5-(4-methoxypyrimidin-2-yl)-1-methyl-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 5-(4-methoxypyrimidin-2-yl)-1-methyl-1*H*-indole

[00763] 2-Chloro-4-methoxypyrimidine (80 mg, 0.55 mmol), $Pd[P(t\text{-}Bu)_3]_2$ (28 mg, 0.060 mmol), Cs_2CO_3 (270 mg, 0.83 mmol) were added to a solution of 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (185 mg, 0.72 mmol) in dioxane (2.2 mL). The reaction mixture was degassed using Ar. The reaction was stirred at 90 °C for 5 h,

quenched with water and extracted with DCM (3 x 5 mL). The combined organic layer was dried and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-20% gradient) to provide the title compound (19 mg, 14%). LCMS: R_T = 0.163 min, MS (ES) 240.1 (M+H).

Step B. Preparation of 3-iodo-5-(4-methoxypyrimidin-2-yl)-1-methyl-1*H*-indole

[00764] The title compound was prepared following the procedure described Example 388 Step B using 5-(4-methoxypyrimidin-2-yl)-1-methyl-1*H*-indole (19 mg, 0.080 mmol). The crude compound (30 mg) was used for the next step without further purification. LCMS: R_T = 1.248 min, MS (ES) 365.8 (M+H).

Step C. Example 464

[00765] The title compound (35 mg, 80%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.056 mmol) and 3-iodo-5-(4-methoxypyrimidin-2-yl)-1-methyl-1*H*-indole (30 mg, 0.089 mmol). LCMS: R_T = 2.106 min, MS (ES) 776.8 (M+H).

Example 465

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(5-(5-methoxypyrimidin-2-yl)-1-methyl-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 5-(5-methoxypyrimidin-2-yl)-1-methyl-1*H*-indole

[00766] The title compound (63 mg, 48%) was prepared following the procedure described Example 464 Step A using 2-chloro-5-methoxypyrimidine (80 mg, 0.55 mmol) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (185 mg, 0.72 mmol). LCMS: R_T = 1.086 min, MS (ES) 240.1 (M+H).

Step B. Preparation of 3-iodo-5-(5-methoxypyrimidin-2-yl)-1-methyl-1*H*-indole

[00767] The title compound was prepared following the procedure described Example 388 Step B using 5-(5-methoxypyrimidin-2-yl)-1-methyl-1*H*-indole (63 mg, 0.26 mmol). The crude compound (85 mg) was used for the next step without further purification. LCMS: R_T = 1.601 min, MS (ES) 365.8 (M+H).

Step C. Example 465

[00768] The title compound (35 mg, 80%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.056 mmol) and 3-iodo-5-(5-methoxypyrimidin-2-yl)-1-methyl-1*H*-indole (32 mg, 0.089 mmol). LCMS:

R_T = 2.106 min, MS (ES) 776.8 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.51 (d, *J* = 8.1 Hz, 2H), 8.47 (dd, *J* = 6.6, 1.4 Hz, 1H), 8.26 (ddd, *J* = 8.7, 3.6, 1.7 Hz, 1H), 7.70 (dd, *J* = 8.6, 2.7 Hz, 1H), 7.43 (dd, *J* = 8.7, 2.8 Hz, 1H), 7.30 – 7.24 (m, 2H), 6.60 (s, 2H), 7.48 (td, *J* = 13.4, 3.7 Hz, 1H), 4.30 – 4.19 (m, 1H), 4.02 – 3.98 (m, 2H), 3.95 – 3.93 (m, 6H), 3.83 – 3.73 (m, 4H), 3.47 – 3.30 (m, 2H), 2.28 (s, 6H), 2.25 – 2.18 (m, 5H), 2.09 (d, *J* = 5.3 Hz, 3H), 1.30 (d, *J* = 6.5 Hz, 1.5H), 1.22 (d, *J* = 6.6 Hz, 1.5H).

Example 466

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxamide

[00769] The title compound (6 mg, 37%) was prepared according to General Procedure G using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1*H*-indole-2-carboxylate (15 mg, 0.02 mmol) and 2-(bromomethyl)pyridine hydrobromide (7.6 mg, 0.03 mmol) followed by primary carboxamide formation using General Procedure E. LCMS: R_T = 1.859 MS (ES) 817.9 (M+H).

Example 467

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(pyridin-3-ylmethyl)-1*H*-indole-3-carboxylic acid

Step A. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-3-carboxylate

[00770] The title compound (32 mg, 90%) was prepared according to General Procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol) and methyl 7-bromo-1*H*-indole-3-carboxylate (39 mg, 0.15 mmol). LCMS: R_T = 2.070 min, MS (ES) 711.9 (M+H).

Step B. Example 467

[00771] The title compound (10.1 mg, 63%) was prepared according to General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-3-carboxylate (15 mg, 0.02 mmol) and 3-(chloromethyl)pyridine hydrochloride (7 mg, 0.04 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.806 MS (ES)

788.8 (M+H); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.47 - 8.39 (m, 1H), 8.20 - 8.14 (m, 2H), 8.00 - 7.91 (m, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.33 - 7.28 (m, 2H), 7.20 - 7.11 (m, 1H), 7.04 - 6.94 (m, 1H), 6.72 (s, 2H), 5.65 - 5.58 (m, 1H), 4.02 - 3.97 (m, 2H), 3.93 - 3.88 (m, 2H), 3.74 (s, 1.5H), 3.72 (s, 1.5H), 3.42 - 3.34 (m, 1H), 3.16 - 3.11 (m, 2H), 2.96 - 2.87 (m, 2H), 2.23 (s, 6H), 2.07 (s, 1.5H), 2.06 - 2.02 (m, 2H), 1.98 (s, 1.5H), 1.90 (s, 1.5H), 1.80 (s, 1.5H), 1.06 - 1.00 (m, 3H)..

Example 468

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(pyridin-2-ylmethyl)-1*H*-indole-3-carboxylic acid

[00772] The title compound (8.7 mg, 55%) was prepared according to General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-3-carboxylate (15 mg, 0.02 mmol) and 2-(bromomethyl)pyridine hydrobromide (10 mg, 0.04 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.923 MS (ES) 788.8 (M+H); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.23 (s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 7.38 - 7.24 (m, 2H), 7.23 - 7.16 (m, 1H), 6.97 - 6.89 (m, 1H), 6.72 (s, 2H), 6.50 - 6.42 (m, 1H), 5.71 - 5.58 (m, 1H), 4.04 - 3.99 (m, 3H), 3.83 - 3.78 (m, 2H), 3.73 (s, 1.5H), 3.70 (s, 1.5H), 3.42 - 3.31 (m, 1H), 3.31 - 3.23 (m, 1H), 3.22 - 3.12 (m, 1H), 2.68 - 2.56 (m, 1H), 2.15 - 2.09 (m, 2H), 2.22 (s, 6H), 2.08 (s, 1.5H), 1.98 (s, 1.5H), 1.84 (s, 1.5H), 1.74 (s, 1.5H), 1.06 - 0.94 (m, 3H).

Example 469

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(trifluoromethoxy)-1*H*-indole-2-carboxylic acid

[00773] The title compound (20 mg, 57%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (75 mg, 0.14 mmol) and ethyl 7-bromo-5-(trifluoromethoxy)-1*H*-indole-2-carboxylate (98 mg, 0.28 mmol) followed by saponification following General Procedure D. LCMS: R_T = 2.07 min, MS (ES) 782 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (d, J = 8.6 Hz, 1H), 7.68 (bs, 1H), 7.28 (d, J = 8.6 Hz, 1H), 7.23 (d, J = 2.0 Hz, 1H), 7.16 (bs, 1H), 6.72 (s, 2H), 4.66-4.69 (m, 1H), 4.11-4.18 (m, 1H), 3.98 (m, 2H), 3.77 (s, 1.5H), 3.76 (s, 1.5H), 3.45-3.53 (m, 1H), 3.18-3.36 (m, 2H), 2.22 (s, 6H), 2.03-2.12 (m, 5H), 1.98 (s, 1.5H), 1.89 (s, 1.5H), 1.11 (d, J =6.4 Hz,

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3H).

Example 470

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-methoxyethyl)-5-methyl-1*H*-indole-2-carboxylic acid

[00774] The title compound (35 mg, 61%) was prepared following General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (70 mg, 0.10 mmol) and 2-bromoethyl methyl ether (20 mg, 0.14 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.06 min, MS (ES) 770 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (d, *J* = 8.4 Hz, 1H), 7.50 (s, 0.5H), 7.45 (s, 0.5H), 7.33 (m, 1H), 7.27 (m, 1H), 6.96 (s, 0.5H), 6.94 (s, 0.5H), 6.71 (s, 1H), 6.70 (s, 1H), 4.94 (m, 1H), 4.68 (m, 2H), 4.43 (m, 2H), 4.18 (m, 1H), 3.99 (t, *J* = 5.5 Hz, 2H), 3.79 (s, 1.5H), 3.77 (s, 1.5H), 3.71 (m, 1H), 3.35 (m, 2H), 3.22 (m, 2H), 3.00 (s, 1.5H), 2.95 (s, 1.5H), 2.39 (s, 1.5H), 2.36 (s, 1.5H), 2.24 (s, 6H), 2.14 (m, 1H), 1.88-2.07 (m, 5H), 1.17 (d, *J* = 6.4 Hz, 1.5H), 1.06 (d, *J* = 6.4 Hz, 1.5H).

Example 471

(*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(5-(1-methyl-1H-1,2,4-triazol-3-yl)-1H-indol-3-yl)-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one

Step A. Preparation of 5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1-((2-(trimethylsilyl)ethoxy) methyl)-1*H*-indole

[00775] The title compound (310 mg, 77%) was prepared following the procedure described Example 388 Step A using 3-bromo-1-methyl-1*H*-1,2,4-triazole (200 mg, 1.23 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole (567 mg, 1.52 mmol). LCMS: R_T = 1.488 min, MS (ES) 329.1 (M+H).

Step B. Preparation of 3-iodo-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1-((2-(trimethylsilyl) ethoxy)methyl)-1*H*-indole

[00776] The title compound (380 mg, 89%) was prepared following the procedure described Example 388 Step B using 5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1-((2-(trimethylsilyl)ethoxy) methyl)-1*H*-indole (310 mg, 0.94 mmol). LCMS: R_T = 1.740 min, MS (ES) 454.9 (M+H).

Step C. Preparation of (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00777] The title compound (150 mg, 63%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (150 mg, 0.28 mmol) and 3-iodo-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole (202 mg, 0.45 mmol). LCMS: R_T = 2.209 min, MS (ES) 865.9 (M+H).

Step D. Example 471

[00778] TBAF (2 mL, 1 M solution in THF) was added to a solution of (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (150 mg, 0.17 mmol) in THF (1.7 mL). The reaction was irradiated under microwave at 70 °C for 30 min (3 times). Aditional TBAF (1 mL) was added to the reaction then irradiated under microwave at 75 °C for 1 h (3 times). The reaction was quenched with water and extracted with DCM (3 x 10 mL). The combined organic layer was dried and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-3% gradient) to provide the title compound (95 mg, 75%). LCMS: R_T = 1.864 min, MS (ES) 735.9 (M+H).

Example 472

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(pyridin-4-ylmethyl)-1*H*-indole-3-carboxylic acid

[00779] The title compound (12.6 mg, 80%) was prepared according to General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-3-carboxylate (15 mg, 0.02 mmol) and 4-(bromomethyl)pyridine hydrobromide (10 mg, 0.04 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.751 MS (ES) 788.8 (M+H); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 - 8.47 (m, 1H), 8.40 - 8.32 (m, 1H), 8.28 - 8.21 (m, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.80 - 7.68 (m, 1H), 7.37 - 7.23 (m, 2H), 7.09 - 7.00 (m, 1H), 6.96 (t, *J* = 8.1 Hz, 1H), 6.72 (s, 1H), 6.68 (s, 1H), 5.75 - 5.61 (m, 1H), 4.06 - 3.95 (m, 3H), 3.89 - 3.85 (m, 2H), 3.73 (s, 1.5H), 3.70 (s, 1.5H), 3.39 - 3.27 (m, 2H), 3.18 -

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3.06 (m, 1H), 2.74 - 2.65 (m, 1H), 2.23 (s, 6H), 2.08 (s, 1.5H), 2.06 - 2.02 (m, 2H), 1.98 (s, 1.5H), 1.87 (s, 1.5H), 1.75 (s, 1.5H), 1.05 - 0.96 (m, 3H).

Example 473

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)imidazo[1,2-a]pyridine-6-carboxylic acid

[00780] The title compound (30 mg, 43 %) was prepared following General coupling procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (60 mg, 0.111 mmol) and methyl 3-bromoimidazo[1,2-a]pyridine-6-carboxylate (40 mg, 0.156 mmol) followed by saponification using General Procedure D. LCMS: RT = 0.858 min (LC method IV), MS (ES) 699.5 (M+H); ^{1}H NMR (DMSO, 400 MHz) δ (ppm) 8.81 (s, 1H), 7.92 (d, *J* = 10.0 Hz, 2H), 7.82 (d, *J* = 10.0 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 6.70 (s, 2H), 4.67-4.63 (m, 1H), 4.20-4.18 (m, 2H), 3.97-3.95 (m, 2H), 3.78 (s, 3H), 2.49 (s, 6H), 2.22-2.15 (m, 2H), 2.06 (s, 3H), 2.00-1.95 (m, 2H), 1.87 (s, 3H), 1.10 (d, *J* = 6.8 Hz, 3H).

Example 474

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((4-methylpyridin-2-yl)methyl)-5-(trifluoromethoxy)-1*H*-indole-2-carboxylic acid

[00781] To a solution of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(trifluoromethoxy)-1*H*-indole-2-carboxylate (34 mg, 0.04 mmol) and 2-(chloromethyl)-4-methylpyridine HCl (22 mg, 0.13 mmol) in DMF (0.7 mL) was added Cs_2CO_3 (68 mg, 0.21 mmol). The mixture was stirred under Ar at 80 °C overnight then an additional 2-(chloromethyl)-4-methylpyridine HCl (22 mg, 0.13 mmol) and Cs_2CO_3 (100 mg) were added. The reaction was stirred under Ar at 100 °C for 24 h. The title compound (21 mg, 50%) was isolated according to work up and purification protocols described in general coupling procedure **A** followed by saponification using General Procedure D as TFA salt. LCMS: R_T = 2.00 min, MS (ES) 887 (M+H).

Example 475

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1-(oxetan-3-ylmethyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 3-iodo-1-methyl-5-(1-(oxetan-3-ylmethyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[00782] The title compound (39 mg, 32%) was prepared following the procedure described Example 454 Step B using 3-iodo-1-methyl-5-(1*H*-1,2,4-triazol-3-yl)-1*H*-indole (100 mg, 0.31 mmol) and 3-(chloromethyl)oxetane (30 μL, 0.090 mmol). LCMS: R_T = 1.339 min, MS (ES) 395.8 (M+H). LCMS: R_T = 1.498 min, MS (ES) 378.9 (M+H).

Step B. Example 475

[00783] The title compound (22 mg, 59%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.046 mmol) and 3-iodo-1-methyl-5-(1-(oxetan-3-ylmethyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (37 mg, 0.093 mmol). LCMS: R_T = 1.963 min, MS (ES) 805.9 (M+H).

Example 476

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-((4-methoxypyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

[00784] The title compound (6.6 mg, 38%) was prepared according to General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1*H*-indole-2-carboxylate (15 mg, 0.020 mmol) and 2-(chloromethyl)-4-methoxypyridine HCl salt (10 mg, 0.052 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.883 min, MS (ES) 846.8 (M+H).

Example 477

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-((6-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

[00785] The title compound (7.5 mg, 45%) was prepared according to General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1*H*-indole-2-carboxylate (15 mg, 0.020 mmol) and 2-(chloromethyl)-6-methylpyridine (10 mg, 0.071 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.895 min, MS (ES) 830.8 (M+H).

Example 478

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-((5-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

[00786] The title compound (5.2 mg, 31%) was prepared according to General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1*H*-indole-2-carboxylate (15 mg, 0.020 mmol) and 2-(chloromethyl)-5-methylpyridine HCl salt (10 mg, 0.056 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.909 min, MS (ES) 830.8 (M+H).

Example 479

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-5-(trifluoromethoxy)-1*H*-indole-2-carboxylic acid

[00787] The title compound was prepared according to General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(trifluoromethoxy)-1*H*-indole-2-carboxylate (45 mg, 0.06 mmol) and MeI (16 mg, 0.11 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.12 min, MS (ES) 796 (M+H).

Example 480

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((4-methylpyridin-2-yl)methyl)-1*H*-indole-3-carboxylic acid (2nd eluted atropisomer, absolute configuration undeterminded)

[00788] The title compound (7.2 mg, 45%) was prepared according to General Procedure G using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-3-carboxylate (15 mg, 0.02 mmol) and 2-(chloromethyl)-4-methylpyridine HCl (7 mg, 0.04 mmol) followed by saponification using General Procedure D. The title compound was isolate as the 2nd eluting stereoisomer by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 40-90 % MeCN 0.1% TFA). LCMS: R_T = 1.888 min, MS (ES) 802.9 (M+H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 5.6 Hz, 0.5H), 8.38 (d, *J* = 5.6 Hz, 0.5H), 8.28 (t, *J* = 8.0 Hz, 1H), 7.90 (s, 0.5H), 7.84 (s, 0.5H), 7.68 - 7.61 (m, 1H), 7.40 - 7.29 (m, 2H), 7.10 - 7.02 (m, 2H), 6.61 (s, 1H), 6.60 (s, 1H), 5.80 - 5.75 (m, 1H), 4.51 - 4.34 (m, 1H), 4.23 - 4.07 (m, 1H), 3.98 (s, 1.5H), 3.97 (s, 1.5H), 3.94 - 3.75 (m, 3H), 3.58 - 3.49 (m,

0.5H), 3.47 - 3.39 (m, 0.5H), 3.20 - 2.86 (m, 2H), 2.80 - 2.60 (m, 1H), 2.44 (s, 3H), 2.34 (s, 3H), 2.33 (s, 3H), 2.28 (s, 1.5H), 2.24 (s, 1.5H), 2.10 (s, 1.5H), 2.07 (s, 1.5H), 2.04 - 1.96 (m, 1H), 1.94 - 1.86 (m, 1H), 1.26 (d, J = 6.8 Hz, 1.5H), 1.19 (d, J = 6.8 Hz, 1.5H).

Example 481

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-5-(pyridin-2-ylmethoxy)-1*H*-indole-2-carboxylic acid

[00789] The title compound (3.6 mg, 33%) was prepared according to General Procedure H using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-methyl-1*H*-indole-2-carboxylate (10 mg, 0.013 mmol) and 2-(bromomethyl)pyridine HBr salt (10 mg, 0.040 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.859 min, MS (ES) 818.8 (M+H).

Example 482

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-((dimethylamino)methyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl 7-iodo-4-methoxy-1*H*-indole-2-carboxylate

[00790] A solution of methyl 4-(benzyloxy)-7-bromo-1*H*-indole-2-carboxylate (200 mg, 0.71 mmol), CuI (10 mg, 0.052 mmol), (*trans*)-N^1,N^2-dimethylcyclohexane-1,2-diamine (15 mg, 0.11 mmol), and NaI (250 mg, 1.67 mmol) in 1,4-dioxane (2 mL) was sparged with Ar for 5 min, then sealed and heated to 110 °C for 48 h. The reaction was cooled to RT and diluted with DCM (20 mL). The organic soution was washed with 10% aq. NH_4OH (20 mL), and the aqueous layer was extracted with DCM. The combined organic layer was dried and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (196 mg, 84%). LCMS: R_T = 1.433 min, MS (ES) 331.8 (M+H).

Step B. Preparation of methyl (*R*)-7-(6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1*H*-indole-2-carboxylate

[00791] The title compound (156 mg, 61%) was prepared according to General Procedure B using (*R*)-6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (200 mg,

0.30 mmol) and methyl 7-iodo-4-methoxy-1*H*-indole-2-carboxylate (196 mg, 0.59 mmol). LCMS: R_T = 2.293 min, MS (ES) 859.8 (M+H).

Step C. Preparatio of methyl (*R*)-7-(6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylate

[00792] The title compound (26 mg, 47%) was prepared according to General Procedure I using methyl (*R*)-7-(6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylate (50 mg, 0.058 mmol) and 2-(bromomethyl)pyridine HBr salt (40 mg, 0.16 mmol). LCMS: R_T = 2.175 min, MS (ES) 950.8 (M+H).

Step D. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylate

[00793] The title compound was prepared following the procedure described Example 390 Step D using methyl (*R*)-7-(6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylate (26 mg, 0.027 mmol) and carried forward without further purification. LCMS: R_T = 0.864 min, MS (ES) 860.8 (M+H) (LC method II).

Step E. Example 482

[00794] The title compound (4.0 mg, 33% 2 steps) was prepared according to General Procedure J using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylate (12 mg, 0.014 mmol) and dimethylamine HCl salt (25 mg, 0.31 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.754 min, MS (ES) 873.9 (M+H).

Example 483

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-((dimethylamino)methyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-methyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl (*R*)-7-(6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-methyl-1*H*-indole-2-carboxylate

[00795] The title compound (11 mg, 19%) was prepared according to General Procedure I using methyl (*R*)-7-(6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1*H*-indole-2-carboxylate (50 mg, 0.058 mmol) and MeI (25 mg, 0.18 mmol). LCMS: R_T = 2.386 min, MS (ES) 873.9 (M+H).

Step B. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl) -6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino [1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-methyl-5-(pyridin-2-yl)-1*H*-indole-2-carboxylate

[00796] The crude title compound was prepared following the procedure described Example 390 Step D using methyl (*R*)-7-(6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-methyl-1*H*-indole-2-carboxylate (11 mg, 0.013 mmol). LCMS: R_T = 2.101 min, MS (ES) 783.9 (M+H).

Step C. Example 483

[00797] The title compound (3.0 mg, 29% 2 steps) was prepared according to General Procedure J using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylate (10 mg, 0.013 mmol) and dimethylamine HCl salt (25 mg, 0.31 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.860 min, MS (ES) 796.9 (M+H).

Example 484

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((4-methylpyridin-2-yl)methyl)-1*H*-indole-3-carboxylic acid (1st eluted atropisomer, absolute configuration undeterminded)

[00798] The title compound (5.6 mg, 35%) was isolated as the 1st eluting stereoisomer along with Example 480. LCMS: R_T = 1.870 min, MS (ES) 802.9 (M+H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 - 8.42 (m, 0.75H), 8.40 - 8.35 (m, 0.25H), 8.33 - 8.21 (m, 1H), 7.90 (s, 0.25H), 7.84 (s, 0.75H), 7.72 - 7.57 (m, 1H), 7.43 - 7.29 (m, 2H), 7.16 - 7.06 (m, 2H), 6.61 (s, 1H), 6.58 (s, 1H), 5.84 - 5.66 (m, 1H), 4.24 - 4.13 (m, 2H), 3.96 (s, 2H), 3.94 (s, 1H), 3.92 -

3.86 (m, 1H), 3.83 - 3.70 (m, 2H), 3.63 - 3.51 (m, 1H), 3.48 - 3.34 (m, 1H), 3.25 - 2.87 (m, 2H), 2.43 (s, 2H), 2.41 (s, 1H), 2.34 (s, 6H), 2.31 (s, 1H), 2.26 (s, 2H), 2.23 (s, 2H), 2.12 - 2.06 (m, 2H), 2.05 (s, 1H), 1.28 - 1.16 (m, 1H), 1.23 - 1.04 (m, 2H).

Example 485

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(cyclopropylmethoxy)-1-methyl-1*H*-indole-2-carboxylic acid

[00799] The title compound (7.3 mg, 71%) was prepared according to General Procedure H using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-methyl-1*H*-indole-2-carboxylate (10 mg, 0.013 mmol) and (bromomethyl)cyclopropane (8 mg, 0.059 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.337, 2.378 min, MS (ES) 781.9 (M+H).

Example 486

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-5-((2-(pyrrolidin-1-yl)ethyl)amino)-1*H*-indole-3-carboxylic acid.

Step A. Preparation of 1-(7-bromo-5-nitro-1*H*-indol-3-yl)-2,2,2-trifluoroethan-1-one

[00800] To a solution of 7-bromo-5-nitro-1*H*-indole (1 g, 4.1 mmol) in DMF (12 mL) was added trifluoroacetic anhydride (3.3 mL, 16.4 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for overnight then poured into brine and extracted with ethyl acetate. The organic layer was dried and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, hex/EtOAc = 0-100% gradient) to give the title compound. (1.30 g, 94%) ^{1}H-NMR (DMSO-d^6) δ 8.98 (d, 1H, J = 4 Hz), 8.7 (s, 1H), 8.43 (d, 1H, J = 4 Hz), ^{19}F NMR -75.2 (s)

Step B. Preparation of 7-bromo-5-nitro-1H-indole-3-carboxylic acid

[00801] 1-(7-Bromo-5-nitro-1*H*-indol-3-yl)-2,2,2-trifluoroethan-1-one (1.30 g, 3.9 mmol) was refluxed in NaOH aq. solution (30 mL, 20%) for 2h. The reaction mixture was cooled to RT and neutralized with conc. HCl. The mixture was extracted with EtOAc, and the organic layer was dried and concentrated to yield the title compound (0.9 g, 98%). ^{1}H NMR (DMSO-d^6) δ 8.90 (d, 1H, J = 4 Hz), 8.30 (s, 1H), 8.27 (d, 1H, J = 4 Hz).

Step C. Preparation of methyl 7-bromo-5-nitro-1H-indole-3-carboxylate

[00802] To a suspension of 7-bromo-5-nitro-1*H*-indole-3-carboxylic acid (0.9 g, 3.8 mmol) in MeOH (30 mL) was added H_2SO_4 (0.3 mL). The reaction mixture was refluxed for overnight then concentrated. The residue was dissolved in EtOAc, washed with sat. $NaHCO_3$ aq. Solution, dried and concentrated to yield the title compound. (0.8 g, 84%). ^{1}H NMR (DMSO-d^6) δ 8.82 (d, 1H, J = 4 Hz), 8.31 (s, 1H), 8.20 (d, 1H, J = 4 Hz), 3.85 (s, 3H).

Step D. Preparation of methyl 7-bromo-1-methyl-5-nitro-1*H*-indole-3-carboxylate

[00803] The title compound (0.75 g, 89%) was prepared following General Procedure G using methyl 7-bromo-5-nitro-1*H*-indole-3-carboxylate (0.8 g, 2.7 mol) in DMF (10 mL) and MeI (340 µL, 5.4 mmol). ^{1}H NMR (DMSO-d^6) δ 8.87 (d, 1H, J = 4 Hz), 8.48 (s, 1H), 8.27 (d, 1H, J = 4 Hz), 4.24 (s, 3H), 3.88 (s, 3H).

Step E. Preparation of methyl 5-amino-7-bromo-1-methyl-1*H*-indole-3-carboxylate

[00804] To a solution of methyl 7-bromo-1-methyl-5-nitro-1*H*-indole-3-carboxylate (0.75 g, 2.4 mmol) in 1,4-dioxane (60 mL) was added HCl aq. solution (30 mL, 1.2 N) followed by Tin chloride (2.7 g, 1.2 mmol). The reaction mixture was refluxed for 3h, cooled to RT, neutralized with NaOH and extracted with EtOAc. The organic layer was dried, concentrated and the residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-15% gradient) to give the title compound (0.55 g, 82%). ^{1}H NMR (DMSO-d^6) δ 7.96 (d, 1H, J = 4 Hz), 7.22 (s, 1H), 6.81 (d, 1H, J = 4 Hz), 5.0 (broad s, 2H), 4.00 (s, 3H), 3.76 (s, 3H).

Step F. Preparation of methyl 7-bromo-5-((tert-butoxycarbonyl)amino)-1-methyl-1H-indole-3-carboxylate

[00805] To a solution of methyl 5-amino-7-bromo-1-methyl-1H-indole-3-carboxylate (0.55 g, 2.0 mmol) in THF (5 mL) was added 1.2 N aq. NaOH aq. solution (5 mL, 6.0 mM) and $(Boc)_2O$ (920 mg, 4.0 mmol). The reaction mixture was stirred overnight at RT then quenched with MeOH and water (50 mL). The mixture was extracted with EtOAc and the combined organic layer was dried, concentrated and the residue was purified by flash chromatography (Combi-flash Rf, hex/EtO = 0-100% gradient) to give the title compound (0.60 g, 81%). ^{1}H NMR (DMSO-d^6) δ 9.42 (broad s, 1H), 8.23 (d, 1H, J = 4 Hz), 8.12 (s, 1H), 7.60 (d, 1H, J = 4 Hz), 4.11 (s, 3H), 3.79 (s, 3H), 1.49 (s, 9H).

Step G. Preparation of methyl (*R*)-5-((*tert*-butoxycarbonyl)amino)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylate

[00806] The title compound (400 mg, 78%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (330 mg, 0.6

mmol) and methyl 7-bromo-5-((tert-butoxycarbonyl)amino)-1-methyl-1H-indole-3-carboxylate (350 mg, 0.9 mmol). MS (ES) 841.2 (M+H).

Step H. Example 486

[00807] To a solution of methyl (*R*)-5-((tert-butoxycarbonyl)amino)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylate (40 mg, 0.047 mol) in DMF (2 mL) was added NaH (60%, 3.8 mg, 0.094 mol) under N_2 at 0 °C and stirred for 10 min. 1-(2-Bromoethyl)pyrrolidine (14.5 mg, 0.080 mmol) was added and the mixture was stirred for 10 min at 0 °C then at RT for 1h. The reaction mixture was diluted with EtOAc (20 mL), washed with brine (2 X 10 mL), dried, filtered and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-10% gradient). The purified intermediate was dissolved in 4N HCl in 1,4-dioxane and the reaction mixture was heated at 60 °C for 5 h then concentrated. The residue was dissolved in a mixture of 1,4-dioxane and MeOH (4 mL, 1:1) and aq. NaOH solution (2M, 1 mL) was added. The reaction was stirred for 3 h at RT then neutralized with aq. HCl (1.2M). The mixture was concentrated and purified by HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient from 50% to 95% CH_3CN for 4 min, 0.1% TFA) to give the title compound. MS (ES) 824.2 (M+H)

Example 487

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-5-(pyridin-3-ylmethoxy)-1*H*-indole-2-carboxylic acid

[00808] The title compound (7.1 mg, 66%) was prepared according to General Procedure H using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-methyl-1*H*-indole-2-carboxylate (10 mg, 0.013 mmol) and 3-(chlorrmethyl)pyridine HCl salt (8 mg, 0.049 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.913, 1.944 min, MS (ES) 818.8 (M+H).

Example 488

(*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4-hydroxy-2,6-dimethylphenyl)-4-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one

Step A. Preparation of ethyl-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4-(methoxymethoxy)-2,6-dimethylphenyl)-1H-indole-2-carboxylate

[00809] Ethyl-7-bromo-6-chloro-3-(3-((4-chloro-3,5-dimethylhexa-2,4-dien-1-yl)oxy)propyl)-1*H*-indole-2-carboxylate (1.6 g, 3.0 mmol), $Pd_2(dba)_3$ (550 g, 0.6 mmol), Sphos (0.62 g, 1.5 mmol), K_2CO_3 (1.24 g, 9 mmol) and (4-(methoxymethoxy)-2,6-dimethylphenyl)boronic acid (1.26 g, 6.0 mmol) were dissolved in 1,4-dioxane (10 mL) and water (2 mL). The mixture was sparged with Ar for 5 min then irradiated under microwave for 1 h at 110 °C in Biotage Initiator. The reaction mixture was cooled to RT, diluted with EtOAc/water (80 mL, 1:1). The aqueous layer was extracted with EtOAc, and the combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf, Hex/ EtOAc = 0-60% gradient) to give the title compound. (1.5 g, 85%). ^{1}H-NMR ($CDCl_3$) δ 8.24 (s, 1H), 7.62 (d, 1H, J= 8 Hz), 7.24 (d, 1H, J= 8 Hz), 6.91 (s, 2H), 6.64 (s, 1H), 6.55 (s, 1H), 5.27 (s, 2H) 5.27 (q, 2H, J_1= 12 Hz, J_2=8 Hz), 4.01 (tr, 1H, J = 8Hz), 3.58 (s, 3H), 3.29 (tr, 2H, J = 4Hz), 2.36 (s, 3H), 2.30 (s, 3H), 2.19 (tr, 2H, J = 4Hz), 1.98 (s, 6H), 1.41 (tr, 3H, J = 8Hz).

Step B. Preparation of ethyl (*R*)-1-(1-((tert-butoxycarbonyl)amino)propan-2-yl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4-(methoxymethoxy)-2,6-dimethylphenyl)-1*H*-indole-2-carboxylate

[00810] To a solution of ethyl-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4-(methoxymethoxy)-2,6-dimethylphenyl)-1H-indole-2-carboxylate (1.45 g, 0.0025 mol) in MeCN (30 mL) was added Cs_2CO_3 (1.2 g, 0.0037 mol) and *tert*-butyl (*S*)-5-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (0.88 gr, 0.0037 mol), and the mixture was stirred at 80 °C for overnight. Additional Cs_2CO_3 (0.5 eq) and *tert*-butyl (*S*)-5-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (0.5 eq) were added to the reaction and stirred for additional 6 h at 80 °C. The reaction mixture was concentrated to half of its original volume then diluted with EtOAc (150 mL). The solution was washed with brine, dried and concentrated to give the crude title compound. It was used for the next step without purification. ^{1}H-NMR ($CDCl_3$) δ 7.59 (d, 1H, J= 8 Hz), 7.24 (d, 1H, J= 8 Hz), 6.92 (s, 2H), 6.53 (s, 2H), 5.27 (s, 2H) 4.41 (q, 2H, J_1= 12 Hz, J_2=8 Hz), 4.12-4.10 (m, 1H), 4.01 (tr, 1H, J = 8Hz), 3.83-3.81 (m, 1H), 3.73-3.71 (m, 1H), 3.54 (s, 3H), 3.17 (m, 1H), 2.34 (s, 6H), 2.16 (tr, 2H, J = 4 Hz), 2.06 (s, 3H), 2.00 (s, 3H), 2.19 (tr, 2H, J = 4Hz), 1.46 (tr, 3H, J = 8Hz), 1.38 (s, 9 H), 1.20 (d, 3H, J = 8Hz).

Step C. Preparation of (*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4-(methoxymethoxy)-2,6-dimethylphenyl)-4-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one

[00811] Ethyl (*R*)-1-(1-((tert-butoxycarbonyl)amino)propan-2-yl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4-(methoxymethoxy)-2,6-dimethylphenyl)-1*H*-indole-2-carboxylate was dissolved in 1,4-dioxane (10 mL) and TFA (1.9 mL, 0.025 mol) and the reaction mixture was heated at 70 °C for overnight, then concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-50% gradient) to give the title compound (1.1 gr, 74% for 2 steps). ^{1}H-NMR ($CDCl_3$) δ 7.66 (d, 1H, J= 8 Hz), 7.24 (d, 1H, J= 8 Hz), 6.90 (d, 1H, J= 4 Hz), 6.86 (d, 1H, J= 4 Hz), 6.65 (s, 2H), 5.84 (broad s, 1H) 5.25 (s, 2H), 3.79 (tr, 2H, J= 4 Hz), 4.01-3.78 (m, 1H), 3.68 (dd, 1H, J_1 = 2 Hz, J_2= 12 Hz), 3.56 (s, 3H), 3.42-3.38 (m, 2H), 3.34-3.11 (m, 1H), 2.35 (s, 6H), 2.23 (tr, 2H, J= 4 Hz), 2.11 (s, 3H), 2.06 (s, 3H), 1.02 (d, 3H, J = 8Hz).

Step D. Example 488

[00812] (*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4-(methoxymethoxy)-2,6-dimethylphenyl)-4-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one was dissolved in 1,4-dioxane (2 mL) and 4N HCl in 1,4-dioxane (20 μL) and stirred at 50 °C for overnight. The reaction mixture was concentrated and the residue was purified by HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient from 50% to 95% CH_3CN for 4 min, 0.1% TFA) to give the title compound. ^{1}H-NMR ($CDCl_3$) δ 7.65 (d, 1H, J= 8 Hz), 7.24 (d, 1H, J= 8 Hz), 6.73 (d, 1H, J= 4 Hz), 6.69 (d, 1H, J= 4 Hz), 6.68 (d, 1H, J= 4 Hz) 6.65 (s, 2H), 5.79 (broad s, 1H), 4.04 (tr, 2H, J= 4 Hz), 4.01-3.78 (m, 1H), 3.68 (dd, 1H, J_1 = 2 Hz, J_2 = 12 Hz), 3.45-3.35 (m, 2H), 3.13-3.10 (m, 1H), 3.09 (s, 6H), 2.23 (tr, 2H, J= 4 Hz), 2.23 (s, 3H), 1.87 (s, 3H), 1.02 (d, 3H, J = 8 Hz) ; MS (ES) 551.3 (M+H).

Example 489

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylic acid

Step A. Preparation of methyl 3-bromo-1-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylate

[00813] The title compound (72 mg, 95%) was prepared following General Procedure F using 1*H*-pyrrolo[3,2-*b*]pyridine-6-carboxylic acid (46 mg, 0.28 mmol) and MeI (53 μL, 0.85 mmol). LCMS: R_T = 1.704 min, MS (ES) 268.3 (M+H).

Step B. Example 489

[00814] The title compound (18 mg, 50%) was prepared according to General Procedure I using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-

trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol) and methyl 3-bromo-1-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylate (16.1 mg, 0.06 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.894 MS (ES) 712.9 (M+H); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.14 (d, *J* = 8.1 Hz, 1H), 8.08 (d, *J* = 8.1 Hz, 1H), 7.93 (d, *J* = 8.7 Hz, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 6.73 (s, 2H), 4.51 (d, *J* = 13.1 Hz, 1H), 4.47 (d, *J* = 13.1 Hz, 1H), 4.39 - 4.28 (m, 1H), 4.00 - 3.92 (m, 2H), 3.88 (s, 3H), 3.78 (s, 1.5H), 3.77 (s, 1.5H), 3.40 - 3.30 (m, 1H), 3.28 - 3.18 (m, 1H), 2.24 (s, 6H), 2.11 (s, 1.5H), 2.09 - 2.04 (m, 2H), 2.02 (s, 1.5H), 1.96 (s, 1.5H), 1.87 (s, 1.5H), 1.15 (d, *J* = 6.3 Hz, 1.5H), 1.12 (d, *J* = 6.3 Hz, 1.5H).

Example 490

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-5-((4-methylpiperazin-1-yl)methyl)-1*H*-indole-3-carboxylic acid

Step A. Preparation of ethyl 7-bromo-1,5-dimethyl-1*H*-indole-3-carboxylate

[00815] To a solution of 7-bromo-5-methyl-1*H*-indole (100 mg, 0.45 mmol) in DMF (3 mL) was added K_2CO_3 (435 mg, 3.15 mmol) and MeI (60 μL, 135 mg, 0.90 mmol). The reaction mixture was stirred at 60 °C for 4 h then quenched with sat. NH_4Cl aq. solution and extracted with DCM. The combined organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in toluene (0.4 mL), and ethylchloroformate (46 μL, 52.3 mg, 0.48 mmol) and Me_2AlCl (0.4 mL, 0.4 mmol, 1.0 M solution in hexanes) were added. The reaction mixture was stirred at RT for 15 min then quenched with sat. NH_4Cl aq. solution and extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (110 mg, 93% 2 steps). LCMS: R_T = 1.770 min, MS (ES) 295.9 (M+H).

Step B. Preparation of ethyl 7-bromo-5-(bromomethyl)-1-methyl-1*H*-indole-3-carboxylate

[00816] To a solution of ethyl 7-bromo-1,5-dimethyl-1*H*-indole-3-carboxylate (110 mg, 0.37 mmol) in CCl_4 (4 mL) was added AIBN (15.2 mg, 0.093 mmol) and NBS (66 mg, 0.37 mmol) at 60 °C. The reaction mixture was refluxed for 3 h then concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (120 mg, 90%). LCMS: R_T = 1.772 min, MS (ES) 375.9 (M+H).

Step C. Preparation of ethyl 5-(acetoxymethyl)-7-bromo-1-methyl-1*H*-indole-3-carboxylate

[00817] To a solution of ethyl 7-bromo-5-(bromomethyl)-1-methyl-1*H*-indole-3-carboxylate (31 mg, 0.083 mmol) in DMF (0.8 mL) was added NaOAc (13.6 mg, 0.166 mmol), and the reaction mixture was stirred at RT for 24 h. The reaction was quenched with sat. NH_4Cl aq. solution and extracted with DCM. The combined organic layer was dried and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (25 mg, 85%). LCMS: R_T = 1.620 min, MS (ES) 375.9 (M+Na); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 1.2 Hz, 1H), 7.64 (s, 1H), 7.35 (d, *J* = 1.3 Hz, 1H), 5.09 (s, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 4.10 (s, 3H), 2.04 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).

Step D. Preparation of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(hydroxymethyl)-1-methyl-1*H*-indole-3-carboxylate

[00818] The title compound (8 mg, 32% yield) was prepared following General Procedure A using ethyl 5-(acetoxymethyl)-7-bromo-1-methyl-1*H*-indole-3-carboxylate (12 mg, 0.033 mmol) and (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (18.3 mg, 0.033 mmol). LCMS: R_T = 2.031, 2.055 min, MS (ES) 769.9 (M+H).

Step E. Example 490

[00819] To a solution of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(hydroxymethyl)-1-methyl-1*H*-indole-3-carboxylate (20 mg, 0.026 mmol) in DCM (0.2 mL) was added 4 Å molecular sieves (50 mg) and PCC (12 mg, 0.052 mmol), and the reaction mixture was stirred at rt for 30 min then quenched with sat. NH_4Cl aq. solution and extracted with DCM. The combined organic layer was dried and concentrated. The residue was re-dissolved in DCM (0.2 mL) and Et_3N (0.03 mL) then N-methyl piperazine (2 μL, 1.7 mg, 0.017 mmol) and $Na(OAc)_3BH$ (5.9 mg, 0.028 mmol) were added. The reaction mixture was stirred at rt for 4 h then quenched with sat. $NaHCO_3$ aq. solution and extracted with DCM. The combined organic layer was dried and concentrated. Subsequent saponification was carried out following General Procedure D. The crude was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient

35-95 % MeCN, 0.1% TFA) to afford the title compound (2.1 mg, 10%, 3 steps). LCMS: R_T = 1.809 min, MS (ES) 823.9 (M+H).

Example 491

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((6-methylpyridin-2-yl)methyl)-1*H*-indole-3-carboxylic acid (2nd eluted atropisomer, absolute configuration undeterminded)

[00820] The title compound (6.8 mg, 42%) was prepared according to General Procedure G using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-3-carboxylate (15 mg, 0.02 mmol) and 2-(chloromethyl)-6-methylpyridine (6 mg, 0.04 mmol) followed by saponification using General Procedure D. The title compound was isolate as the 2nd eluting stereoisomer by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 40-90 % MeCN 0.1% TFA). LCMS: R_T = 1.917 min, MS (ES) 802.9 (M+H).

Example 492

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethyl-2-((4-methylpiperazin-1-yl)methyl)pyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylic acid

[00821] The title compound (4.7 mg, 34% 2 steps) was prepared according to General Procedure J using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylate (13 mg, 0.015 mmol) and *N*-methylpiperazine (30 mg, 0.30 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.771 min, MS (ES) 928.8 (M+H).

Example 493

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-(2-methoxyethyl)-1*H*-indole-2-carboxylic acid

[00822] The title compound (8.3 mg, 52%) was prepared according to General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1*H*-indole-2-carboxylate (15 mg, 0.020 mmol) and 1-bromo-2-methoxyethane (5 mg, 0.036 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.048 min, MS (ES) 783.8 (M+H).

Example 494

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((6-methylpyridin-2-yl)methyl)-1*H*-indole-3-carboxylic acid (1st eluted atropisomer, absolute configuration undeterminded)

[00823] The title compound (4.2 mg, 26%) was isolated along with Example 491 as a separated atropisomer (1st fraction, absolute stereochemistry undeterminded). LCMS: R_T = 1.888 min, MS (ES) 802.9 (M+H).

Example 495

(*R*)-7-Bromo-5-((7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)methyl)-1-methyl-1*H*-indole-3-carboxylic acid

[00824] The title compound (4.6 mg, 10%, 2 steps) was isolated along with ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(hydroxymethyl)-1-methyl-1*H*-indole-3-carboxylate from Example Step D as a byproduct followed by saponification following General Procedure D. LCMS: R_T = 2.173, 2.227 min, MS (ES) 805.7 (M+H).

Example 496

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4-hydroxy-2,6-dimethylphenyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

Step A. Preparation of methyl-(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy) propyl)-6-(4-(methoxymethoxy)-2,6-dimethylphenyl)-4-methyl-1-oxo-3,4-dihydropyrazino [1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate

[00825] The title compound (160 mg, 86%) was prepared following General Procedure B using (R)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4-(methoxymethoxy)-2,6-dimethylphenyl)-4-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (120 mg, 2.0 mmol) and methyl 3-bromo-1-methyl-1H-indole-5-carboxylate (110 mg, 4.0 mol). MS (ES) 782.4 (M+H)..

Step B. Example 496

[00826] The title compound (16 mg, 86%) was prepared following the procedure described Example 488 Step D using methyl-(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy) propyl)-6-(4-(methoxymethoxy)-2,6-dimethylphenyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylate (20 mg, 0.026

mmol) followed by saponification following General Procedure D. ^{1}H-NMR (DMSO-d^6) δ 9.45 (broad s, 1H), 8.09 (s, 1H), 7.95 (s, 1H), 7.80 (d, 1H, J= 8 Hz), 7.75 (d, 1H, J= 8 Hz), 7.55 (d, 1H, J= 8 Hz), 7.50 (s, 1H), 7.30 (d, 1H, J= 8 Hz), 6.72 (s, 2H), 6.65 (d, 1H, J= 8 Hz), 4.38 (dd, 1H, J_1 = 2 Hz, J_2 = 12 Hz), 3.97 (tr, 2H, J= 4 Hz), 3.82 (s, 3H), 3.62 (m, 1H), 3.68 (dd, 1H, J_1 = 2 Hz, J_2 = 12 Hz), 3.45-3.35 (m, 1H), 2.27 (s, 6H), 2.06 (tr, 2H, J= 4 Hz), 1.96 (s, 3H), 1.82 (s, 3H), 1.01 (d, 3H, J = 8 Hz); MS (ES) 724.2 (M+H).

Example 497

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2,6-dimethyl-4-(pyridin-2-ylmethoxy)phenyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

Step A. Preparation of methyl 3-((R)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4-hydroxy-2,6-dimethylphenyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-methyl-3a,7a-dihydro-1H-indole-5-carboxylate

[00827] The title compound (140 mg, 93%) was prepared following the procedure described Example 488 Step D using methyl 3-((*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy) propyl)-6-(4-(methoxymethoxy)-2,6-dimethylphenyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-3a,7a-dihydro-1H-indole-5-carboxylate (160 mg, 0.2 mmol). ^{1}H-NMR ($CDCl_3$) δ 8.27 (s, 1H), 7.95 (d, 1H, J= 8 Hz), 7.67 (d, 1H, J= 8 Hz), 7.37 (d, 1H, J= 8 Hz), 6.73 (d, 1H, J= 4 Hz), 6.69 (d, 1H, J= 4 Hz) 6.63 (s, 2H), 4.34 (dd, 1H, J_1 = 2 Hz, J_2 = 12 Hz), 4.00 (tr, 2H, J= 4 Hz), 3.79 (s, 3H), 3.80 (m, 2H), 3.62 (dd, 1H, J_1 = 2 Hz, J_2 = 12 Hz), 3.45-3.35 (m, 1H), 2.35 (s, 6H), 2.23 (tr, 2H, J= 4 Hz), 2.09 (s, 3H), 1.95 (s, 3H), 1.22 (d, 3H, J = 8 Hz).

Step B. Example 497

[00828] To a solution of methyl 3-((*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4-hydroxy-2,6-dimethylphenyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-3a,7a-dihydro-1H-indole-5-carboxylate (20 mg, 0.027 mol) in anhydrous DMF (2 mL) was added NaH (60%, 3.8 mg, 0.094 mol) at 0 °C under N_2 atmosphere. The reaction mixture was stirred for 10 min then 2-(bromomethyl)pyridine (7.9 mg, 0.046 mmol) was added. The reaction mixture was stirred at 0 °C for 10 min then warmed to RT and stirred for additional 1 h. The reaction mixture was diluted with ethyl acetate (20 mL), washed with brine, dried and concentrated. The residue was dissolved in a mixture of 1,4-dioxane and MeOH (4 mL, 1:1) and aq. NaOH (2M, 1 mL) solution was added. The reaction was stirred for 5h at RT then neutralized with aq. HCl

(1.2M). The mixture was concentrated and purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 45-95 % MeCN 0.1% TFA) to give the title compound. ^{1}H-NMR (DMSO-d^6) δ 8.61 (s, 1H), 8.10 (d, 1H, J= 2 Hz), 7.93-7.91 (m, 1H), 7.80-7.78 (m, 1H), 7.77 (d, 1H, J= 8 Hz), 7.63 (m, 1H), 7.56 (d, 1H, J= 8 Hz), 7.51 (s, 1H), 7.39 (m, 1H), 7.32 (d, 1H, J = 8 Hz), 7.29 (s, 1H), 6.97 (s, 1H), 6.72 (s, 2H), 5.52 (s, 2H), 4.39 (dd, 1H, J_1 = 2 Hz, J_2 = 12 Hz), 4.03 (tr, 2H, J= 4 Hz), 3.82 (s, 3H), 3.75 (m, 2H), 3.48 (dd, 1H, J_1 = 2 Hz, J_2 = 12 Hz), 3.45-3.35 (m, 1H), 2.24 (s, 6H), 2.07 (tr, 2H, J = 4 Hz), 1.89 (s, 3H), 1.82 (s, 3H), 1.08 (d, 3H, J = 8 Hz); MS (ES) 815.3 (M+H).

Example 498

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-((2-(dimethylamino)ethyl)amino)-1-methyl-1*H*-indole-3-carboxylic acid

[00829] The title compound was prepared following the procedure described Example 486 Step H using methyl (*R*)-5-((tert-butoxycarbonyl)amino)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylate (40 mg, 0.047 mol) and 2-bromo-*N*,*N*-dimethylethan-1-amine (12.3 mg, 0.080 mmol). MS (ES) 798.2 (M+H).

Example 499

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1-((6-morpholinopyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

Step A. Preparation of ethyl (*R*)-1-((6-bromopyridin-2-yl)methyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate

[00830] The title compound (167 mg, 91%) was prepared following General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (150 mg, 0.20 mmol) and 2-bromo-6-(bromomethyl)pyridine (102 mg, 0.41 mmol). LCMS: R_T = 2.37 min, MS (ES) 909 (M+H).

Step B. Example 499

[00831] A solution of ethyl (*R*)-1-((6-bromopyridin-2-yl)methyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (25 mg, 0.03

mmol) in morpholine (0.5 mL) was stirred at 110 °C for overnight. The reaction mixture was diluted with water and EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layer was dried and concentrated. The residue was saponified following General Procedure D to give the title compound (15 mg, 56%) as TFA salt. LCMS: R_T = 2.05 min, MS (ES) 888 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (d, J = 8.6 Hz, 1H), 7.54 (s, 1H), 7.37 (s, 1H), 7.29-7.34 (m, 2H), 6.83 (m, 1H), 6.77 (s, 2H), 6.50 (m, 1H), 6.22 (m, 1H), 5.58 (m, 1H), 5.25 (m, 1H), 4.59 (m, 1H), 4.05 (m, 2H), 3.8 (m, 1H), 3.72 (s, 1.5H), 3.69 (s, 1.5H), 3.37-3.40 (m, 1H), 3.13-3.26 (m, 4H), 2.98-3.08 (m, 2H), 2.90-2.96 (m, 2H), 2.65-2.72 (m, 2H), 2.36 (s, 3H), 2.22 (s, 6H), 2.04 (s, 3H), 1.77-1.94 (m, 5H), 1.02 (m, 3H).

Example 500

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1-((4-morpholinopyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

Step A. Preparation of ethyl (*R*)-1-((4-bromopyridin-2-yl)methyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate

[00832] The title compound (104 mg, 85%) was prepared following General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (150 mg, 0.20 mmol) and 4-bromo-2-(chloromethyl)pyridine. LCMS: R_T = 2.33 min, MS (ES) 909 (M+H).

Step B. Example 500

[00833] The title compound (18 mg, 66%) was prepared following the procedure described in Example 499 Step B using ethyl (*R*)-1-((4-bromopyridin-2-yl)methyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (25 mg, 0.03 mmol). LCMS: R_T = 1.96 min, MS (ES) 888 (M+H).

Example 501

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((5-methylpyridin-2-yl)methyl)-1*H*-indole-3-carboxylic acid (1st eluted atropisomer, absolute configuration undeterminded)

[00834] The title compound (5.9 mg, 37%) was prepared according to General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-

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6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-3-carboxylate (15 mg, 0.02 mmol) and 2-(chloromethyl)-5-methylpyridine hydrochloride (3.5 mg, 0.04 mmol) followed by saponification using General Procedure D. The title compound was isolate as the 1st eluting stereoisomer by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 40-90 % MeCN 0.1% TFA). LCMS: R_T = 2.047 min, MS (ES) 802.9 (M+H).

Example 502

(*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethyl-2-((4-methylpiperazin-1-yl)methyl)pyrimidin-5-yl)-4-methyl-2-(1-methyl-5-(1-methyl-1H-1,2,4-triazol-3-yl)-1H-indol-3-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one

Step A. Preparation of (*R*)-6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00835] The title compound (60 mg, 76%) was prepared following General Procedure B using (*R*)-6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (60 mg, 0.090 mmol) and 3-iodo-1-methyl-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (62 mg, 0.18 mmol). LCMS: R_T = 2.166 min, MS (ES) 867.9 (M+H).

Step B. Preparation of (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-2-(1-methyl-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00836] To a solution of (*R*)-6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (60 mg, 0.070 mmol) in MeOH (4.6 mL) was added HCl solution (1 mL) followed by Pd/C (50 mg). The reaction mixture was stirred at RT for 20 h under H_2 atmosphere. The reaction mixture was filtered, and the filtrate was concentrated. The crude title compound (45 mg) was used for the next step without further purification. LCMS: R_T = 1.961 min, MS (ES) 777.9 (M+H).

Step C. Preparation of (*R*)-(5-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-1-oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-6-yl)-4,6-dimethylpyrimidin-2-yl)methyl methanesulfonate

[00837] DIPEA (13.1 μL, 0.080 mmol) and MsCl (5.4 μL, 0.070 mmol) were added to a solution of (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-2-(1-methyl-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (45 mg, 0.060 mmol) in DCM (0.5 mL) at 0 °C. The reaction was warm to RT and stirred for 1 h then concentrated. The crude compound (40 mg) was used for the next step without further purification. LCMS: R_T = 2.079 min, MS (ES) 855.8 (M+H).

Step D. Example 502

[00838] 1-Methylpiperazine (15.6 μL, 0.14 mmol) was added to a solution of (*R*)-(5-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-1-oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-6-yl)-4,6-dimethylpyrimidin-2-yl)methyl methanesulfonate (20 mg, 0.020 mmol) in DMF (1 mL). The reaction was stirred at 60 °C for 1 h, quenched with water then extracted with DCM. The combined organic layer was dried and concentrated. The residue was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/MeCN gradient to 42-95% MeCN 0.1% TFA). The isolated TFA salt was neutralized using sat. aq. $NaHCO_3$ to afford the title compound (7 mg, 35% yield). LCMS: R_T = 1.814 min, MS (ES) 859.9 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.19 (d, *J* = 1.0 Hz, 1H), 8.05 (s, 1H), 8.01 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.75 (d, *J* = 8.7 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 1H), 7.25 (d, *J* = 8.6 Hz, 1H), 6.61 (s, 2H), 4.40 (dd, *J* = 12.5, 3.3 Hz, 1H), 4.00 – 3.97 (m, 4H), 3.94 (s, 3H), 3.81 (s, 3H), 3.79 – 3.66 (m, 3H), 3.51 – 3.30 (m, 6H), 3.12 – 2.97 (m, 3H), 2.76 (s, 3H), 2.39 (s, 3H), 2.29 (s, 6H), 2.26 (s, 3H), 2.24 – 2.19 (m, 2H), 1.23 (d, *J* = 6.5 Hz, 3H).

Example 503

(*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethyl-2-(morpholinomethyl)pyrimidin-5-yl)-4-methyl-2-(1-methyl-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00839] The title compound (12 mg, 61%) was prepared following the procedure described Example 502 Step D using morpholine (12.1 μL, 0.14 mmol) and (*R*)-(5-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-1-oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-6-yl)-4,6-dimethylpyrimidin-2-yl)methyl methanesulfonate (20 mg, 0.020 mmol). LCMS: R_T = 1.878 min, MS (ES) 846.8 (M+H).

Example 504

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1-((4-(piperidin-1-yl)pyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

[00840] The title compound (15 mg, 55%) was prepared following the procedure described in Example 499 Step B using ethyl (*R*)-1-((4-bromopyridin-2-yl)methyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (25 mg, 0.03 mmol) and piperidine (0.5 mL). LCMS: R_T = 2.08 min, MS (ES) 886 (M+H).

Example 505

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1-((6-(piperidin-1-yl)pyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

[00841] The title compound (21 mg, 78%) was prepared following the procedure described in Example 517 Step B using ethyl (*R*)-1-((6-bromopyridin-2-yl)methyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (25 mg, 0.03 mmol) and piperidine (0.5 mL). LCMS: R_T = 2.09 min, MS (ES) 886 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (d, J = 8.4 Hz, 1H), 7.54 (s, 1H), 7.37 (s, 1H), 7.22-7.29 (m, 2H), 6.84 (s, 1H), 6.76 (s, 2H), 6.50 (bs, 1H), 6.19-6.22 (bs, 1H), 5.30-5.48 (m, 2H), 4.57 (m, 1H), 4.04 (bs, 2H), 3.83 (m, 1H), 3.73 (s, 1.5H), 3.69 (s, 1.5H), 3.39 (m, 1H), 3.14-3.26 (m, 3H), 2.97 (m, 2H), 2.76 (m, 2H), 2.36 (s, 3H), 2.22 (s, 6H), 2.04 (s, 3H), 1.94 (s, 1H), 1.85 (s, 1H), 1.75 (bs, 2H), 1.16-1.25 (m, 6H), 1.03 (m, 3H).

Example 506

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(hydroxymethyl)-1-methyl-1*H*-indole-3-carboxylic acid

[00842] The title compound (1.5 mg, 25%) was prepared following General Procedure D using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(hydroxymethyl)-1-methyl-1*H*-indole-3-carboxylate (6.2 mg, 0.008 mmol). LCMS: R_T = 2.041, 2.066 min, MS (ES) 741.9 (M+H).

Example 507

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((5-

methylpyridin-2-yl)methyl)-1*H*-indole-3-carboxylic acid (2nd eluted atropisomer, absolute configuration undeterminded)

[00843] The title compound (6.3 mg, 39% yield) was isolated along with Example 501 as a separated atropisomer (2nd fraction, absolute stereochemistry undeterminded). LCMS: R_T = 2.155 min, MS (ES) 802.9 (M+H).

Example 508

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2,6-dimethyl-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00844] The title compound was prepared following the procedure described Example 497 Step B using methyl 3-((*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4-hydroxy-2,6-dimethylphenyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-3a,7a-dihydro-1*H*-indole-5-carboxylate (20 mg, 0.027 mol) and 1-(2-bromoethyl)pyrrolidine (8.5 mg, 0.046 mmol). ^{1}H-NMR (MeOH-d^4) δ 8.23 (d, 1H, J = 1 Hz), 7.94 (dd, 1H, J = 1.5 Hz, J= 10 Hz), 7.75 (d, 1H, J = 8 Hz), 7.50 (d, 1H, J= 8 Hz), 7.34 (s, 1H), 7.30 (d, 1H, J= 8 Hz), 6.96 (s, 1H), 6.91 (s, 1H), 6.64 (s, 2H), 4.41 (tr, 2H, J= 4 Hz), 4.39 (dd, 1H, J_1 = 2 Hz, J_2 = 12 Hz), 3.99-3.67 (m, 2H), 3.87 (s, 3H), 3.75 (m, 2H), 3.69 (tr, 2H, J = 4Hz), 3.58 (dd, 1H, J_1 = 2 Hz, J_2 = 12 Hz), 3.49-3.45 (m, 1H), 2.31 (s, 6H), 2.21 (tr, 2H, J = 4 Hz), 2.20-2.18 (m, 4H), 2.12 (s, 3H), 2.09-2.06 (m, 4H), 1.98 (s, 3H), 1.23 (d, 3H, J = 8 Hz); MS (ES) 821.3 (M+H),

Example 509

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4-(2-(dimethylamino)ethoxy)-2,6-dimethylphenyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00845] The title compound was prepared following the procedure described Example 497, Step B using methyl 3-((*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4-hydroxy-2,6-dimethylphenyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-3a,7a-dihydro-1*H*-indole-5-carboxylate (20 mg, 0.027 mol) and 2-bromo-*N*,*N*-dimethylethan-1-amine (7.0 mg, 0.046 mmol). MS (ES) 795.5 (M+H),

Example 510

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-(dimethylamino)ethyl)-1*H*-indole-5-carboxylic acid

[00846] The title compound (3.6 mg, 33%) was prepared according to General Procedure G using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-5-carboxylate (10 mg, 0.01 mmol) and 2-bromo-*N*,*N*-dimethylethan-1-amine hydrobromide (7 mg, 0.03 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.844 min, MS (ES) 768.9 (M+H).

Example 511

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-indole-5-carboxylic acid

[00847] The title compound (7.2 mg, 65%) was prepared according to General Procedure G using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-5-carboxylate (10 mg, 0.01 mmol) and 1-(2-bromoethyl)pyrrolidine hydrobromide (7 mg, 0.03 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.899 min, MS (ES) 794.9 (M+H).

Example 512

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-methoxyethyl)-1*H*-indole-3-carboxylic acid

[00848] The title compound (11.9 mg, 79%) was prepared according to General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-3-carboxylate (15 mg, 0.02 mmol) and 1-bromo-2-methoxyethane (3 mg, 0.04 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.234 min, MS (ES) 755.8 (M+H).

Example 513

3-((2-Carboxy-7-((*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-methyl-1*H*-indol-5-yl)oxy)-1,1-dimethylpyrrolidin-1-ium 2,2,2-trifluoroacetate

[00849] To a solution of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-hydroxy-1-methyl-1H-indole-2-carboxylate (20 mg, 0.026 mmol) in DMF (1 mL) was added Cs_2CO_3 (25 mg, 0.77 mmol) and tert-butyl 3-

bromopyrrolidine-1-carboxylate (15 mg, 0.060 mmol). The reaction was heated to 80 °C for 16 h, then diluted with DCM/H_2O (10 mL, 1:1). The layers were separated, and the aqueous layer was extracted with DCM (2 x 5 mL). The combined organic extracts were dried by passage through a phase separator and concentrated. LCMS: R_T = 2.373 min, MS (ES) 946.8 (M+Na). The crude reaction product was dissolved in DCM (3 mL) and TFA (0.5 mL) was added. The reaction was stirred for 4 h at RT then concentrated. LCMS: R_T = 2.017, 2.088 min, MS (ES) 824.8 (M+H). The residue was dissolved in MeCN (2 mL) and K_2CO_3 (20 mg, 0.14 mmol) and MeI (8 mg, 0.057 mmol) were added in sequence. The reaction was stirred for 1 h at RT then diluted with DCM/H_2O (10 mL, 1:1). The layers were separated, and the aqueous layer was extracted with DCM. The combined organic extracts were dried and concentrated. LCMS: R_T = 2.062, 2.116 min, MS (ES) 952.9 (M). The residue was saponified according to General Procedure D to afford the title compound (3 mg, 14% yield). LCMS: R_T = 1.868 min, MS (ES) 824.8 (M).

Example 514

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1-((4-vinylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

[00850] A solution of ethyl (*R*)-1-((4-bromopyridin-2-yl)methyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (50 mg, 0.06 mmol), $Pd(OAc)_2$ (1 mg, 0.005 mmol), tricyclohexylphosphine tetrafluoroborate (4 mg, 0.011 mmol), K_3PO_4 (23 mg, 0.11 mmol), Vinylboronic acid pinacol ester (0.011 mL, 0.07 mmol) in 5:1 DME/water (1 mL) was purged with Ar and stirred at 80 °C overnight. The solution was cooled to RT, diluted with EtOAc, filtered through Celite, washing with EtOAc and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) followed by saponification following General Procedure D to give the title compound (28 mg, 78%) as TFA salt. LCMS: R_T = 2.09 min, MS (ES) 829 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (m, 1H), 7.73 (d, J = 8.6 Hz, 1H), 7.57 (s, 1H), 7.40 (s, 1H), 7.26-7.32 (m, 2H), 6.86 (m, 1H), 6.71 (s, 2H), 6.57 (bs, 1H), 6.40-6.50 (m, 1H), 6.08-6.27 (m, 1H), 5.73-5.81 (m, 1H), 5.45-5.60 (m, 1H), 5.31-5.35 (m, 1H), 3.96 (m, 2H), 3.84 (m, 1H), 3.73 (s, 3H), 3.26-3.34 (m, 1H), 3.06 (m, 1H), 2.53 (m, 2H), 2.37 (s, 3H), 2.21 (s, 6H), 2.07 (s, 3H), 1.70-1.97 (m, 5H), 1.02 (m, 3H).

Example 515

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-methyl-1-((4-(4-methylpiperazin-1-yl)pyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

[00851] The title compound (15 mg, 54% TFA salt) was prepared following the procedure described in Example 499 Step B using ethyl (*R*)-1-((4-bromopyridin-2-yl)methyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (32 mg, 0.04 mmol) and 1-methylpiperazine (0.5 mL, 4.6 mmol). LCMS: R_T = 1.75 min, MS (ES) 901 (M+H).

Example 516

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-methyl-1-((6-(4-methylpiperazin-1-yl)pyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

[00852] The title compound (18 mg, 55% TFA salt) was prepared following the procedure described in Example 499 Step B using ethyl (*R*)-1-((6-bromopyridin-2-yl)methyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (30 mg, 0.03 mmol) and 1-methylpiperazine (0.5 mL, 4.6 mmol). LCMS: R_T = 2.02 min, MS (ES) 901 (M+H).

Example 517

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-methyl-1-((6-vinylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

[00853] The title compound (21 mg, 49%) was prepared following the procedure described in Example 514 using ethyl (*R*)-1-((6-bromopyridin-2-yl)methyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (50 mg, 0.06 mmol). LCMS: R_T = 2.24 min, MS (ES) 829 (M+H).

Example 518

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-(pyrimidin-4-ylmethyl)-1*H*-indole-2-carboxylic acid

[00854] The title compound (5.8 mg, 29%) was prepared according to General Procedure G using (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-

(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-(pyrimidin-4-ylmethyl)-1H-indole-2-carboxylic acid (18 mg, 0.025 mmol) and pyrimidin-4-ylmethyl methanesulfonate (15 mg, 0.080 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.021 min, MS (ES) 789.8 (M+H).

Example 519

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-5-((1-methylpiperidin-4-yl)oxy)-1H-indole-2-carboxylic acid

[00855] To a solution of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-methyl-1*H*-indole-2-carboxylate (10 mg, 0.013 mmol), triphenylphosphine (10 mg, 0.038 mmol) and 1-methylpiperidin-4-ol (20 mg, 0.17 mmol) in THF (1 mL) was added di-*tert*-butyl (*E*)-diazene-1,2-dicarboxylate (10 mg, 0.044 mmol) at RT. The reaction was stirred for 18 h at RT, then heated to 60 °C for 16 h. The reaction was cooled to RT, diluted with DCM/H_2O (10 mL, 1:1) and extracted with DCM. The combined organic extracts were dried and concentrated. The crude product was saponified following General Procedure D and purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient 35-95 % MeCN 0.1% TFA) to afford the title compound (4.5 mg, 42%). LCMS: R_T = 1.839 min, MS (ES) 824.8 (M+H).

Example 520

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-4-methoxy-1-((4-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

[00856] The title compound (14 mg, 83%) was prepared according to General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1*H*-indole-2-carboxylate (15 mg, 0.020 mmol) and 2-(chloromethyl)-4-methylpyridine HCl salt (10 mg, 0.056 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.022 min, MS (ES) 830.8 (M+H).

Example 521

7-((*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-5-((1-methylpyrrolidin-3-yl)oxy)-1*H*-indole-2-carboxylic acid

[00857] The title compound (8.6 mg, 41%) was isolated along with Example 513 following the procedure described in Example 513. LCMS: R_T = 1.897, 1.929 min, MS (ES) 810.9 (M+H).

Example 522

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-5-(pyridin-2-yloxy)-1*H*-indole-2-carboxylic acid

[00858] The title compound (1.5 mg, 14%) was prepared according to General Procedure H using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-methyl-1*H*-indole-2-carboxylate (10 mg, 0.013 mmol) and 2-fluoropyridine (8 mg, 0.082 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.207, 2.246 min, MS (ES) 804.9 (M+H).

Example 523

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-5-((pyridin-2-ylmethyl)amino)-1*H*-indole-3-carboxylic acid

[00859] The title compound was prepared following the procedure described Example 486 Step H using methyl (*R*)-5-((tert-butoxycarbonyl)amino)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylate (40 mg, 0.047 mol) and 2-(bromomethyl)pyridine (13.8 mg, 0.080 mmol). MS (ES) 818.2 (M+H),

Example 524

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(1-(2-methoxyethyl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one

Step A. Prepareation of 1-(2-methoxyethyl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[00860] NaH (8.5 mg, 0.35 mmol) was added to a solution of 5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (35 mg , 0.18 mmol) in DMF (2 mL) at 0 °C. After 30 min, 2-bromoethyl methyl ether (22 μL, 0.23 mmol) was added slowly. The reaction was warmed to RT and stirred for 1 h. The reaction was quenched with water and extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with water, dried and concentrated to give the crude

title compound (34 mg), which was used for the next step without further purification. LCMS: R_T = 1.172 min, MS (ES) 257.1 (M+H).

Step B. Preparation of 3-iodo-1-(2-methoxyethyl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[00861] NIS (30 mg, 0.13 mmol) was added to a solution of 1-(2-methoxyethyl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (34 mg, 0.13 mmol) in DMF (1.3 mL) at 0 °C, and the reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched with water and extracted with EtOAc. The combined organic layer was washed with water, dried and concentrated to give the crude title compound (50 mg), which was used for the next step without further purification. LCMS: R_T = 1.241 min, MS (ES) 383.8 (M+H).

Step C. Example 524

[00862] The title compound (30 mg, 68%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.060 mmol) and 3-iodo-1-(2-methoxyethyl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (50 mg, 0.11 mmol). LCMS: R_T = 2.167 min, MS (ES) 793.9 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (s, 1H), 8.05 (s, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.50 (s, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 6.72 (s, 2H), 4.50 – 4.44 (m, 1H), 4.36 (t, *J* = 4.5 Hz, 2H), 4.19 – 4.16 (m, 2H), 3.98 (t, *J* = 7.0 Hz, 2H), 3.87 (s, 3H), 3.77 (d, *J* = 4.8 Hz, 3H), 3.70 (d, *J* = 5.2 Hz, 2H), 3.66 – 3.63 (m, 1H), 3.39 – 3.31 (m, 1H), 3.25 – 3.19 (m, 4H), 2.22 (s, 5H), 2.12 – 2.03 (m, 5H), 1.97 – 1.88 (m, 3H), 1.10 (d, *J* = 6.2 Hz, 3H).

Example 525

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1-(2-morpholino-2-oxoethyl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one

Step A. Preparation of 1-morpholino-2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-1-yl)ethan-1-one

[00863] Bis(pinacolato)diboron (434 mg, 1.71 mmol), KOAc (419 mg, 4.27 mmol) and $PdCl_2$(dppf)•DCM (58 mg, 0.07 mmol) were added to a solution of 2-(5-bromo-1*H*-indol-1-yl)-1-morpholinoethan-1-one (460 mg, 1.42 mmol) in toluene (2.9 mL) under Ar atmosphere. The reaction was stirred at 90 °C for 18 h then filtered through Celite and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-1%

gradient) to provide the title compound (520 mg, quant.). LCMS: R_T = 1.527 min, MS (ES) 371.1 (M+H).

Step B. Preparation of 2-(5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)-1-morpholinoethan-1-one

[00864] 3-Bromo-1-methyl-1*H*-1,2,4-triazole (50 mg, 0.31 mmol), $PdCl_2$(dppf)•DCM (13 mg, 0.020 mmol), K_2CO_3 (370 μL, 0.93 mmol, 2.5 M aq. solution) were added to a solution of 1-morpholino-2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-1-yl)ethan-1-one (149 mg, 0.40 mmol) in MeCN (1.5 mL). The reaction mixture was degassed using Ar and stirred at 85 °C for 16 h. The reaction mixture was filtered through Celite, and the filtrate concentrated. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-3% gradient) to provide the title compound (100 mg, quant.). LCMS: R_T = 1.155 min, MS (ES) 323.1 (M+H).

Step C. Preparation of 2-(3-iodo-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)-1-morpholinoethan-1-one

[00865] The crude title compound (65 mg) was prepared following the procedure described Example 524 Step B using 2-(5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)-1-morpholinoethan-1-one (55 mg, 0.17 mmol). LCMS: R_T = 1.245 min, MS (ES) 451.8 (M+H).

Step D. Example 543

[00866] The title compound (15 mg, 31%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.060 mmol) and 2-(3-iodo-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)-1-morpholinoethan-1-one (50 mg, 0.11 mmol). LCMS: R_T = 2.008 min, MS (ES) 862.9 (M+H).

Example 526

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1-(2-(4-methylpiperazin-1-yl)ethyl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[00867] The title compound (270 mg, 82%) was prepared following the procedure described Example 525 Step B using 3-Bromo-1-methyl-1*H*-1,2,4-triazole (150 mg, 0.93 mmol) and 1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-(4,4,5,5-tetramethyl-1,3,2-

dioxaborolan-2-yl)-1*H*-indole (483 mg, 1.20 mmol). LCMS: R_T = 1.858 min, MS (ES) 357.1 (M+H).

Step B. Preparation of 1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-iodo-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[00868] The title compound (100 mg, 27%) was prepared following the procedure described Example 524 Step B using 1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (270 mg, 0.76 mmol). LCMS: R_T = 2.077 min, MS (ES) 483.0 (M+H).

Step C. Preparation (*R*)-2-(1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00869] The title compound (67 mg, 67%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (60 mg, 0.11 mmol) and 1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-iodo-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (99 mg, 0.21 mmol). LCMS: R_T = 1.683 min, MS (ES) 893.0 (M+H).

Step D. Preparation of (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(1-(2-hydroxyethyl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00870] TBAF (75 μL, 0.070 mmol) was added to a solution of (*R*)-2-(1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (67 mg, 0.070 mmol) in THF (1 mL) at 0 °C. The reaction was stirred at 0 °C for 30 min then concentrated. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-2% gradient) to afford the title compound (34 mg, 59%). LCMS: R_T = 2.005 min, MS (ES) 779.9 (M+H).

Step E. Preparation of (*R*)-2-(3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethyl methanesulfonate

[00871] The crude title compound (37 mg) was prepared following the procedure described Example 502 Step C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(1-(2-hydroxyethyl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-

trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (34 mg, 0.060 mmol), DIPEA (9.9 μL, 0.060 mmol) and MsCl (4.1 μL, 0.050 mmol). LCMS: R_T = 2.056 min, MS (ES) 857.9 (M+H).

Step F. Example 526

[00872] 1-Methylpiperazine (29 μL, 0.26 mmol) was added to a solution of (*R*)-2-(3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethyl methanesulfonate (37 mg, 0.040 mmol) in DMF (1 mL). The reaction was stirred at 90 °C for 5 days. The reaction mixture was quenched with water and extracted with DCM. The combined organic layer was dried and concentrated. The residue was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/MeCN gradient to 45-95% MeCN 0.1% TFA) followed by neutralization using sat. aq. $NaHCO_3$ to provide the title compound (9 mg, 24%) LCMS: R_T = 1.827 min, MS (ES) 861.9 (M+H).

Example 527

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1-(2-oxo-2-(pyrrolidin-1-yl)ethyl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-1-yl)acetic acid

[00873] LiOH (2.22 mL, 4.44 mmol, 2M Solution) was added to a solution of methyl 2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-1-yl)acetate (700 mg, 2.22 mmol) in THF/MeOH/H_2O (8.9 mL, 4:1:1) at 0 °C. The reaction was stirred at 0 °C for 1 h then concentrated. The residue was diluted with water and acidified with 2 N HCl. The mixture was extracted with EtOAc. The combined organic layer was dried and concentrated to give the crude title compound (630 mg), which was used for the next step without further purification. LCMS: R_T = 1.473 min, MS (ES) 302.1 (M+H).

Step B. Preparation of 1-(pyrrolidin-1-yl)-2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-1-yl)ethan-1-one

[00874] BOP (441 mg, 1.00 mmol), pyrrolidine (273 μL, 3.32 mmol) and *N*-methylmorpholine (456 μL, 4.15 mmol) were added to a solution of 2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-1-yl)acetic acid (250 mg, 0.83 mmol) in DMF (5.5 mL). The reaction mixture was stirred at RT for 1 h. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic layer was washed with water,

dried and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-2% gradient) to afford the title compound (150 mg, 51%). LCMS: R_T = 1.606 min, MS (ES) 355.0 (M+H).

Step C. Preparation of 2-(5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)-1-(pyrrolidin-1-yl)ethan-1-one

[00875] The title compound (38 mg, 44% yield) was prepared following the procedure described Example 525 Step B using 3-Bromo-1-methyl-1*H*-1,2,4-triazole (45 mg, 0.28 mmol) and 1-(pyrrolidin-1-yl)-2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-1-yl)ethan-1-one (157 mg, 0.44 mmol). LCMS: R_T = 1.087 min, MS (ES) 310.0 (M+H).

Step D. Preparation of 2-(3-iodo-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)-1-(pyrrolidin-1-yl)ethan-1-one

[00876] The crude title compound (45 mg) was prepared following the procedure described Example 524 Step B using 2-(5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)-1-(pyrrolidin-1-yl)ethan-1-one (38 mg, 0.12 mmol). LCMS: R_T = 0.177 min, MS (ES) 435.9 (M+H).

Step E. Example 527

[00877] The title compound (15 mg, 32% yield) was prepared following General Procedure I using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.060 mmol) and 2-(3-iodo-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)-1-(pyrrolidin-1-yl)ethan-1-one (48 mg, 0.11 mmol). LCMS: R_T = 2.081 min, MS (ES) 846.9 (M+H).

Example 528

(*R*)-1-((6-(4-acetylpiperazin-1-yl)pyridin-2-yl)methyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1-((6-(piperazin-1-yl)pyridin-2-yl)methyl)-1*H*-indole-2-carboxylate

[00878] A solution of ethyl (*R*)-1-((6-bromopyridin-2-yl)methyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (50 mg, 0.05 mmol) and piperazine (24 mg, 0.27 mmol) in dioxane (0.5 mL) was stirred in a sealed vial at 110 °C overnight. The solution was diluted with EtOAc and water. The aqueous layer was

extracted with EtOAc. The combined organic solution were washed with brine, dried and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-8% gradient, with 1% conc. NH_4OH) to give the title compound (30 mg, 60%). LCMS: R_T = 2.20 min, MS (ES) 915 (M+H).

Step B. Example 528

[00879] To a solution of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1-((6-(piperazin-1-yl)pyridin-2-yl)methyl)-1*H*-indole-2-carboxylate (30 mg, 0.03 mmol) and Et_3N (0.01 mL, 0.08 mmol) in DCM (0.50 mL) at 0 °C under Ar was added dropwise a solution of acetyl chloride (5 mg, 0.07 mmol) in DCM (0.2 mL). After 15 minutes, the ice-bath was removed and the solution was stirred at RT for 2 h. The reaction mixture was diluted with DCM and methanol, and concentrated. The residue was saponified following General Procedure D to give the title compound (15 mg, 44%) as TFA salt. LCMS: R_T = 2.11 min, MS (ES) 929 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (d, *J* = 8.6 Hz, 1H), 7.54 (s, 1H), 7.38 (s, 1H), 7.25-7.34 (m, 2H), 6.86 (m, 1H), 6.78 (s, 2H), 6.51 (d, *J* = 8.5 Hz, 1H), 6.23 (m, 1H), 5.57 (m, 1H), 5.29 (m, 1H), 4.12-4.45 (bm, 4H), 4.07 (m, 2H), 3.80 (m, 1H), 3.72 (s, 3H), 3.43 (m, 1H), 2.95-3.35 (m, 5H), 2.89 (m, 3H), 2.72 (m, 1H), 2.36 (s, 3H), 2.22 (s, 6H), 2.04-2.19 (m, 3H), 1.72-1.94 (m, 6H), 1.04 (m, 3H).

Example 529

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(1-(2-chloroethyl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one

[00880] The title compound (5 mg, 15% yield) was isolated as a byproduct from the reaction of Example 526 Step E. LCMS: R_T = 2.209 min, MS (ES) 797.8 (M+H).

Example 530

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(5-(1-(2-methoxyethyl)-1*H*-1,2,4-triazol-3-yl)-1-methyl-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 3-iodo-5-(1-(2-methoxyethyl)-1*H*-1,2,4-triazol-3-yl)-1-methyl-1*H*-indole

[00881] The title compound (75 mg, 53%) was prepared following the procedure described Example 524 Step A using 3-iodo-1-methyl-5-(1*H*-1,2,4-triazol-3-yl)-1*H*-indole (120 mg,

0.37 mmol), NaH (18 mg, 0.74 mmol) and 2-bromoethyl methyl ether (45 μL, 0.48 mmol). LCMS: R_T = 1.527min, MS (ES) 382.9 (M+H).

Step B. Example 530

[00882] The title compound (20 mg, 45%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.060 mmol) and 3-iodo-5-(1-(2-methoxyethyl)-1*H*-1,2,4-triazol-3-yl)-1-methyl-1*H*-indole (43 mg, 0.11 mmol). LCMS: R_T = 2.211 min, MS (ES) 793.9 (M+H).

Example 531

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-(2-morpholino-2-oxoethyl)-5-(pyrimidin-2-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 1-morpholino-2-(5-(pyrimidin-2-yl)-1*H*-indol-1-yl)ethan-1-one

[00883] The title compound (100 mg, quant.) was prepared following the procedure described Example 525 Step B using 2-bromopyrimidine (50 mg, 0.31 mmol) and 1-morpholino-2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-1-yl)ethan-1-one (151 mg, 0.41 mmol). LCMS: R_T = 1.155 min, MS (ES) 323.1 (M+H).

Step B. Preparation of 2-(3-iodo-5-(pyrimidin-2-yl)-1*H*-indol-1-yl)-1-morpholinoethan-1-one

[00884] The crude title compound (100 mg) was prepared following the procedure described Example 524 Step B using 1-morpholino-2-(5-(pyrimidin-2-yl)-1*H*-indol-1-yl)ethan-1-one (100 mg, 0.31 mmol). LCMS: R_T = 1.439 min, MS (ES) 448.8 (M+H).

Step B. Example 531

[00885] The title compound (10 mg, 22%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.060 mmol) and 2-(3-iodo-5-(pyrimidin-2-yl)-1*H*-indol-1-yl)-1-morpholinoethan-1-one (50 mg, 0.11 mmol). LCMS: R_T = 2.184 min, MS (ES) 860.8 (M+H).

Example 532

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(thiazol-4-ylmethyl)-1*H*-indole-5-carboxylic acid

[00886] The title compound (5.2 mg, 47%) was prepared according to General Procedure G using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-5-carboxylate (10 mg, 0.01 mmol) and 4-(chloromethyl)thiazole HCl (5 mg, 0.03 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.085 min, MS (ES) 794.8 (M+H).

Example 533

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-5-(2-(piperidin-1-yl)acetamido)-1*H*-indole-3-carboxylic acid

[00887] To a solution of 2-(piperidin-1-yl)acetic acid (8.6 mg, 0.06 mmol) in DMF (0.5 mL) were added HATU (23 mg, 0.06 mmol) and DIPEA (11 μL, 0.06 mmol) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C then methyl (*R*)-5-amino-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylate (30 mg, 0.04 mmol) was added at 0 °C. The reaction mixture was warmed to RT and stirred for 10 h. The reaction mixture was diluted with ethyl acetate (10 mL), washed with brine, dried and concentrated. The residue was saponified in a mixture of 1,4-dioxane and MeOH (4 mL, 1:1) using NaOH (2M, 1mL). The crude was purified by reverse phase HPLC(Phenomenex Gemini C18, H_2O/CH_3CN gradient from 45% to 95% CH_3CN, 0.1% TFA) to give the title compound. ^{1}H-NMR (MeOH-d_4) δ 8.35 and 8.29 (two d, total 1H, J= 8 Hz), 7.91 (s, 1H), 7.79 (d, 1H, J= 8 Hz), 7.63 and 7.61 (two d, total 1H, J = 8 Hz), 7.73 (d, 1H, J= 8 Hz), 6.64 and 6.62 (two s, total 2H), 4.70-7.60 (m, 1H), 4.50-4.34 (m, 2H), 4.14 (s, 2H), 3.98-3.72 (multiples s, total 6H), 3.80-3.78 (m, 2H), 3.66-3.63 (m, 2H), 3.15-3.10 (m, 4H), 2.28 (s, 6H), 2.16-1.96 (multiple s and tr, total 8H), 1.90-1.87 (multiple m, total 4H), 1.60 (m, 2H), 1.30 and 1.19 (multiple d, total 3H); MS (ES) 852.2 (M+H).

Example 534

3-((*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((1-methylpyrrolidin-3-yl)methyl)-1*H*-indole-5-carboxylic acid

[00888] The title compound (4.8 mg, 43%) was prepared according to General Procedure G using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-5-

carboxylate (10 mg, 0.01 mmol) and 3-(bromomethyl)-1-methylpyrrolidine hydrobromide (7 mg, 0.03 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.817 min, MS (ES) 794.9 (M+H).

Example 535

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-methoxy-1-methyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate

[00889] The title compound (391 mg, 53%) was prepared according to General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (500 mg, 0.93 mmol) and methyl 5-(benzyloxy)-7-iodo-1*H*-indole-2-carboxylate (600 mg, 1.43 mmol). LCMS: R_T = 1.764 min, MS (ES) 815.8 (M+H).

Step B. Preparation of methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylate

[00890] The title compound (164 mg, 90%) was prepared according to General Procedure I using methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (180 mg, 0.22 mmol) and methyl iodide (75 mg, 0.53 mmol). LCMS: R_T = 1.959 min (LC method II), MS (ES) 829.8 (M+H) (Ultra Aqueous method).

Step C. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-methyl-1*H*-indole-2-carboxylate

[00891] To a solution of methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylate (164 mg, 0.20 mmol) in MeOH (10 mL) was added HCl in dioxane (4.0 M, 0.5 mL) followed by Pd/C (10 wt.%, 20 mg, 0.019 mmol). The reaction mixture was stirred for 24 h under H_2 atmosphere, filtered through celite, rinsed with DCM, and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (141 mg, 96%). LCMS: R_T = 1.335 min (LC method II), MS (ES) 739.9 (M+H).

Step D. Example 535

[00892] The title compound (6.1 mg, 31%) was prepared according to General Procedure H using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-hydroxy-1-methyl-1*H*-indole-2-carboxylate (20 mg, 0.027 mmol) and MeI (10 mg, 0.070 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.212 min, MS (ES) 739.9 (M+H).

Example 536

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-methoxy-1-((6-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate

[00893] The title compound (320 mg, 53%) was prepared according to General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (400 mg, 0.74 mmol) and methyl 5-(benzyloxy)-7-iodo-1*H*-indole-2-carboxylate (400 mg, 0.98 mmol). LCMS: R_T = 1.722 min, MS (ES) 817.9 (M+H).

Step B. Preparation of methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((6-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylate

[00894] The title compound (72 mg, 65%) was prepared according to General Procedure I using methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (100 mg, 0.12 mmol) and 2-(chloromethyl)-6-methylpyridine hydrochloride salt (75 mg, 0.53 mmol). LCMS: R_T = 1.375 min (LC method II), MS (ES) 922.9 (M+H).

Step C. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-((6-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylate

[00895] The title compound (59 mg, 91%) was prepared following the procedure described Example 535, Step C using methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((6-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylate (72 mg, 0.078 mmol). LCMS: R_T = 0.930 min (LC method II), MS (ES) 832.8 (M+H).

Step D. Example 536

[00896] The title compound (6.4 mg, 43%) was prepared according to General Procedure H using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-hydroxy-1-((6-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylate (15 mg, 0.018 mmol) and MeI (5 mg, 0.035 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.959, 1.990 min, MS (ES) 832.8 (M+H).

Example 537

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-(2-methoxyethoxy)-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylate

[00897] The title compound (88 mg, 41%) was prepared according to General Procedure I using methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (200 mg, 0.24 mmol) and 2-(bromomethyl)pyridine hydrobromide salt (200 mg, 0.80 mmol). LCMS: R_T = 1.384 min (LC method II), MS (ES) 908.8 (M+H).

Step B. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylate

[00898] The title compound (74 mg, 94%) was prepared following the procedure described Example 535 Step C using methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-

dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylate (88 mg, 0.090 mmol). LCMS: R_T = 0.926 min (LC method II), MS (ES) 818.8 (M+H).

Step C. Example 537

[00899] The title compound (7.5 mg, 48 %) was prepared according to General Procedure H using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-hydroxy-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylate (15 mg, 0.018 mmol) and 1-bromo-2-methoxyethane (5 mg, 0.036 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.953 min, MS (ES) 862.9 (M+H).

Example 538

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-methoxy-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylic acid

[00900] The title compound (6.6 mg, 44%) was prepared according to General Procedure H using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-hydroxy-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylate (15 mg, 0.018 mmol) and MeI (5 mg, 0.035 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.972 min, MS (ES) 818.8 (M+H).

Example 539

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-(2-methoxyethoxy)-1-methyl-1*H*-indole-2-carboxylic acid

[00901] The title compound (6.1 mg, 29%) was prepared according to General Procedure H using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-hydroxy-1-methyl-1*H*-indole-2-carboxylate (20 mg, 0.027 mmol) and 1-bromo-2-methoxyethane (10 mg, 0.072 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.181 min, MS (ES) 783.9 (M+H). ^{1}H NMR (400 MHz, DMSO-d^6) δ 9.08 (s, 1H), 7.92-7.87 (m, 1H), 7.42-7.38 (m, 1H), 7.18 (d, J = 2.2 Hz, 0.7H), 7.13-7.08 (m, 1H), 6.98 (d, J = 2.2 Hz, 0.3H), 6.71 (s, 1.5H), 6.67 (s, 1.5H), 4.69-4.63 (m, 0.5H), 4.36-4.30 (m, 0.5H), 4.08 (quart, *J* = 5.6 Hz, 2H), 4.01 (s, 1H), 4.00-3.94 (m, 2H), 3.90 (s, 2H), 3.72-3.59 (m, 4H), 3.29 (s, 3H), 3.27-3.16 (m, 2H), 2.30 (s, 1H), 2.25 (s, 2H), 2.23 (s, 4H), 2.22 (s, 2H), 2.18 (s, 2H), 2.16 (s, 1H), 2.07-2.03 (m, 2H), 1.17 (d, *J* = 6.5 Hz, 2H), 1.08 (d, *J* = 6.5 Hz, 1H)

Example 540

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-(2-methoxyethoxy)-1-((6-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

[00902] The title compound (4.4 mg, 28%) was prepared according to General Procedure H using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-hydroxy-1-((6-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylate (15 mg, 0.018 mmol) and 1-bromo-2-methoxyethane (5 mg, 0.036 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.944 min, MS (ES) 876.9 (M+H).

Example 541

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-(3-(dimethylamino)propanamido)-1-methyl-1*H*-indole-3-carboxylic acid

[00903] The title compound was prepared following the procedure described Example 533 using methyl (*R*)-5-amino-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylate (30 mg, 0.04 mmol) and 3-(dimethylamino)propanoic acid (7.0 mg, 0.06 mmol). MS (ES) 826.2 (M+H).

Example 542

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-(2-(dimethylamino)acetamido)-1-methyl-1*H*-indole-3-carboxylic acid

[00904] The title compound was prepared following the procedure described Example 533 using methyl (*R*)-5-amino-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylate (30 mg, 0.04 mmol) and dimethylglycine (6.2 mg, 0.06 mmol). MS (ES) 812.2 (M+H).

Example 543

(*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-(piperidin-1-yl)ethyl)-1*H*-indole-5-carboxylic acid

[00905] The title compound (3.6 mg, 32%) was prepared according to General Procedure G using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-

6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-5-carboxylate (10 mg, 0.01 mmol) and 1-(2-bromoethyl)piperidine hydrobromide (8 mg, 0.03 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.909 min, MS (ES) 808.9 (M+H).

Example 544

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-5-((4-methylpiperazin-1-yl)methyl)-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl 7-bromo-5-((methoxymethoxy)methyl)-1*H*-indole-2-carboxylate

[00906] To a solution of 1-(*tert*-butyl) 2-methyl 7-bromo-5-formyl-1*H*-indole-1,2-dicarboxylate (295 mg, 0.77 mmol) in DCM (7.3 mL) was added TFA (0.71 mL, 1.06 g, 9.3 mmol), and the reaction mixture was stirred at RT for 16 h. The reaction was quenched with sat. NH_4Cl aq. solution and extracted with DCM. The combined organic layer was dried, filtered and concentrated. The residue was re-dissolved in MeOH (6 mL) / THF (0.9 mL) and $NaBH_4$ (42 mg, 1.2 mmol) were added at RT. The reaction mixture was stirred for 30 min then quenched with sat. NH_4Cl aq. solution and extracted with DCM. The combined organic layer was dried, filtered and concentrated. The crude product was re-dissolved in DCM (4 mL), and MOMCl (92 μL, 98 mg, 1.22 mmol) and $^{i}Pr_2EtN$ (0.56 mL, 414 mg, 3.2 mmol) were added in sequence. The reaction mixture was stirred at RT for 24 h then quenched with sat. NH_4Cl aq. solution and extracted with DCM. The combined organic layer was dried, filtered and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (80 mg, 32% 3 steps). LCMS: R_T = 1.512 min, MS (ES) 327.8 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (br s, 1H), 7.63 (s, 1H), 7.54 (d, *J* = 1.2 Hz, 1H), 7.28 (d, *J* = 2.2 Hz, 1H), 4.74 (s, 2H), 4.67 (s, 2H), 3.98 (s, 3H), 3.45 (s, 3H).

Step B. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl) -4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*) -yl)-5-((methoxymethoxy)methyl)-1*H*-indole-2-carboxylate

[00907] The title compound was prepared according to General Procedure A using methyl 7-bromo-5-((methoxymethoxy)methyl)-1*H*-indole-2-carboxylate. (20 mg, 0.061 mmol) and (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-

pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (32 mg, 0.061 mmol). MS (ES) 786.2 (M+H).

Step C. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl) -4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*) -yl)-5-((methoxymethoxy)methyl)-1-methyl-1*H*-indole-2-carboxylate

[00908] The title compound was prepared according to General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-((methoxymethoxy)methyl)-1*H*-indole-2-carboxylate. MS (ES) 800.2 (M+H).

Step D. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl) -4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*) -yl)-5-(hydroxymethyl)-1-methyl-1*H*-indole-2-carboxylate

[00909] To a solution of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-((methoxymethoxy)methyl)-1-methyl-1*H*-indole-2-carboxylate in THF (1 mL) and MeOH (0.5 mL) was added conc. HCl (0.3 mL) at RT. The reaction mixture was stirred for 16 h at RT. The reaction was quenched with sat. $NaHCO_3$ aq. solution and extracted with DCM (3 x 10 mL). The combined organic layer was dried, filtered and concentrated to give the crude title compound, which was used to the next step directly.

Step E. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*) -yl)-5-formyl-1-methyl-1*H*-indole-2-carboxylate

[00910] The crude methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(hydroxymethyl)-1-methyl-1*H*-indole-2-carboxylate was dissolved in DCM (0.15 mL), and Dess-Martin periodinane (5 mg, 0.011 mmol) was added. The reaction mixture was stirred at RT for 1 h. The reaction was quenched with sat. sodium thiosulfate aq. solution and extracted with DCM. The combined organic layer was dried over $MgSO_4$, filtered and concentrated. The crude reaction mixture was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (9 mg, 20% 4 steps). LCMS: R_T = 2.445 min, MS (ES) 753.9 (M+H).

Step F. Example 544

[00911] To a solution of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-formyl-1-methyl-1*H*-indole-2-carboxylate (9 mg, 0.012 mmol) in DCM (0.15 mL) and Et_3N (0.03 mL) were added N-methyl piperazine (2 μL, 1.7 mg, 0.017 mmol) and $Na(OAc)_3BH$ (5.9 mg, 0.028 mmol) at RT. The reaction mixture was stirred at RT for 4 h. The reaction was quenched with sat. $NaHCO_3$ aq. solution and extracted with DCM. The combined organic layer was dried over $MgSO_4$, filtered and concentrated. Subsequent saponification was carried out following General Procedure D then purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient 35-95 % MeCN, 0.1% TFA) to afford the title compound (2.3 mg, 21%, 2 steps). LCMS: R_T = 1.762 min, MS (ES) 823.9 (M+H).

Example 545

(*R*)-3-(7-Chloro-4-methyl-10-(3-(naphthalen-1-yloxy)propyl)-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

[00912] To a solution of (*R*)-3-(10-(3-bromopropyl)-7-chloro-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid (15 mg, 0.024 mmol) in DMF (2 mL) were added 1-naphthol (20 mg, 0.14 mmol) and Cs_2CO_3 (30 mg, 0.092 mmol). The reaction was heated to 50 °C until complete by LCMS. The reaction was diluted with DCM/H_2O (10 mL, 1:1). The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layer was dried and concentrated. The residue was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient 35-95 % MeCN 0.1% TFA) to afford the title compound (11.6 mg, 69%). LCMS: R_T = 2.066 min, MS (ES) 699.9 (M+H). ^{1}H NMR (400 MHz, Chloroform-d^6) δ 8.31 (s, 1H), 8.29-8.25 (m, 1H), 7.98 (dt, *J* = 8.7, 1.5 Hz, 1H), 7.79-7.72 (m, 2H), 7.49-7.29 (m, 6H), 7.26-7.24 (m, 1H), 6.76 (d, *J* = 7.5 Hz, 1H), 4.43-4.33 (m, 1H), 4.24-4.10 (m, 3H), 4.03-3.94 (m, 3H), 3.83 (s, 3H), 3.71-3.44 (m, 3H), 2.40 (quint, *J* = 6.6 Hz, 2H), 2.27 (s, 1.5H), 2.20 (s, 1.5H), 2.11 (s, 1.5H), 2.05 (s, 1.5H), 1.20 (d, *J* = 5.0 Hz, 1.5H), 1.16 (d, *J* = 5.0 Hz, 1.5H).

Example 546

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1-(2-(4-methylpiperazin-1-yl)-2-oxoethyl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 1-(4-methylpiperazin-1-yl)-2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-1-yl)ethan-1-one

[00913] BOP reagent (529 mg, 1.20 mmol), 1-methylpiperazine (442 μL, 3.98 mmol) and *N*-methylmorpholine (548 μL, 4.98 mmol) were added to a solution of 2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-1-yl)acetic acid (300 mg, 1.00 mmol) in DMF (6.6 mL). The reaction mixture was stirred at RT for 1 h. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with water, dried and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-2% gradient) to afford the title compound (240 mg, 63%). LCMS: R_T = 1.128 min, MS (ES) 384.1 (M+H).

Step B. Preparation of 2-(5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)-1-(4-methylpiperazin-1-yl)ethan-1-one

[00914] The title compound (68 mg, 65%) was prepared following the procedure descried Example 388 Step A using 1-(4-methylpiperazin-1-yl)-2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-1-yl)ethan-1-one (154 mg, 0.40 mmol) and 3-bromo-1-methyl-1*H*-1,2,4-triazole (50 mg, 0.31 mmol). LCMS: R_T = 0.885 min, MS (ES) 339.1 (M+H).

Step C. Preparation of 2-(3-iodo-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)-1-(4-methylpiperazin-1-yl)ethan-1-one

[00915] The title crude compound (44 mg) was prepared following the procedure descried Example 388 Step B using 2-(5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)-1-(4-methylpiperazin-1-yl)ethan-1-one (68 mg, 0.20 mmol). LCMS: R_T = 0.224 min, MS (ES) 464.8 (M+H).

Step D. Example 546

[00916] The title compound (5 mg, 10%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 2-(3-iodo-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)-1-(4-methylpiperazin-1-yl)ethan-1-one (44 mg, 0.10 mmol). LCMS: R_T = 1.794 min, MS (ES) 874.9 (M+H).

Example 547

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-((4-(4-chlorophenoxy)piperidin-1-yl)methyl)-1-methyl-1*H*-indole-3-carboxylic acid

Step A. Preparation of ethyl 7-bromo-5-((methoxymethoxy)methyl)-1-methyl-1*H*-indole-3-carboxylate

[00917] To a solution of ethyl 7-bromo-5-(bromomethyl)-1-methyl-1*H*-indole-3-carboxylate (292 mg, 0.78 mmol) in MeCN (14 mL) were added NMO (44 mg, 0.38 mmol) and 4 Å molecular sieves (250 mg) and stirred at RT for 4 h. The reaction was quenched with aq. sat. NH_4Cl solution and extracted with EtOAc. The combined organic layer was washed with brine solution, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-60% gradient) to afford ethyl 7-bromo-5-formyl-1-methyl-1*H*-indole-3-carboxylate. The title compound (120 mg, 43% 3 steps) was prepared following the procedure described Example 544 Step A using ethyl 7-bromo-5-formyl-1-methyl-1*H*-indole-3-carboxylate. LCMS: R_T = 1.850 min, MS (ES) 377.9 (M+Na). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.70 (s, 1H), 7.46 (s, 1H), 4.74 (s, 2H), 4.67 (s, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.17 (s, 3H), 3.45 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H).

Step B. Preparation of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-((methoxymethoxy)methyl)-1-methyl-1*H*-indole-3-carboxylate

[00918] The title compound was prepared following General coupling procedure A using ethyl 7-bromo-5-((methoxymethoxy)methyl)-1-methyl-1*H*-indole-3-carboxylate (57 mg, 0.161 mmol) and (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (86 mg, 0.161 mmol).

Step C. Preparation of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-formyl-1-methyl-1*H*-indole-3-carboxylate

[00919] To a solution of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-((methoxymethoxy)methyl)-1-methyl-1*H*-indole-3-carboxylate (from Step B) in THF (3 mL) and MeOH (1.5 mL) was added Conc. HCl (0.9 mL) and stirred for16 h ar RT. The reaction mixture was quenched with aq. sat. $NaHCO_3$ solution and extracted with DCM. The combined organic layer was dried over $MgSO_4$,

filtered and concentrated. The crude product obtained was re-dissolved in DCM (1.6 mL). Dess-Martin periodinane (68 mg, 0.16 mmol) was added and stirred at RT for 1 h. Then, the reaction mixture was quenched with aq. sat. $Na_2S_2O_3$ solution and extracted with DCM. The combined organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-10% gradient) to afford the title compound (57 mg, 47%, 3 steps). LCMS: R_T = 2.386, 2.406, 2.449 min, MS (ES) 767.8 (M+H).

Step D. Example 547

[00920] To a solution of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-formyl-1-methyl-1*H*-indole-3-carboxylate (19 mg, 0.025 mmol) in DCM (0.25 mL) and Et_3N (0.05 mL) was added 4-(4-chlorophenoxy)piperidine (2.6 mg, 0.030 mmol) followed by $Na(OAc)_3BH$ (10.6 mg, 0.050 mmol). After stirring at RT for 4 h, the reaction mixture was quenched with aq. sat. NH_4Cl solution (2 mL) and extracted with DCM (3 x 5 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated. Subsequent saponification was carried out following general procedure D using 2M NaOH. The crude was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient 35-95 % MeCN, 0.1% TFA) and concentrated to afford the title compound (4.3 mg, 21%, 2 steps). LCMS: R_T = 2.078, 2.104 min, MS (ES) 934.8 (M+H). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.02 – 7.95 (m, 2H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.32 – 7.29 (m, 1H), 7.28 (d, *J* = 8.9 Hz, 2H), 7.18 (d, *J* = 9.6 Hz, 0.5 H), 6.98 – 6.95 (m, 2.5 H), 6.70 (d, *J* = 14.5 Hz, 2H), 4.24 – 4.13 (m, 1H), 4.00 – 3.93 (m, 2H), 3.82 (s, 1H), 3.79 – 3.77 (m, 2.2 H), 3.75 – 3.73 (m, 2.6 H), 3.68 (d, *J* = 13.0 Hz, 0.6 H), 3.64 (d, *J* = 13.0 Hz, 0.4 H), 3.62 – 3.56 (m, 1.7 H), 3.54 – 3.48 (m, 0.4 H), 3.30 – 3.27 (m, 0.7 H), 3.27 – 3.15 (m, 1.4 H), 2.69 (br s, 2H), 2.29 – 2.22 (m, 7.6 H), 2.12 – 2.11 (m, 2H), 2.06 – 1.99 (m, 4H), 1.96 (s, 1H), 1.94 – 1.89 (m, 2.5H), 1.88 (s, 1.5 H), 1.62 – 1.54 (m, 2H), 1.19 – 1.15 (m, 2H), 1.06 (dd, *J* = 6.6, 2.2 Hz, 1H).

Example 548

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(1-(2-methoxyethyl)-5-(pyrimidin-2-yl)-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 1-(2-methoxyethyl)-5-(pyrimidin-2-yl)-1*H*-indole

[00921] The title compound (100 mg, 90%) was prepared following the procedure descried Example 388 Step A using 1-(2-methoxyethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

yl)-1*H*-indole (172 mg, 0.57 mmol) and 2-bromopyrimidine (70 mg, 0.44 mmol). LCMS: R_T = 1.329 min, MS (ES) 254.1 (M+H).

Step B. Preparation of 3-iodo-1-(2-methoxyethyl)-5-(pyrimidin-2-yl)-1*H*-indole

[00922] The title compound (133 mg, 89%) was prepared following the procedure descried Example 388 Step B using 1-(2-methoxyethyl)-5-(pyrimidin-2-yl)-1*H*-indole (100 mg, 0.39 mmol). LCMS: R_T = 1.658 min, MS (ES) 379.9 (M+H).

Step C. Example 548

[00923] The title compound (40 mg, 82%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 3-iodo-1-(2-methoxyethyl)-5-(pyrimidin-2-yl)-1*H*-indole (42 mg, 0.10 mmol). LCMS: R_T = 2.243 min, MS (ES) 790.9 (M+H).

Example 549

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-5-(morpholinomethyl)-1*H*-indole-3-carboxylic acid

[00924] The title compound was prepared (4.3 mg, 21%, 2 steps) following the procedure described in Example 547 step D using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-formyl-1-methyl-1*H*-indole-3-carboxylate (19 mg, 0.025 mmol) and morpholine (2.6 mg, 2.6 μL, 0.030 mmol). LCMS: R_T = 1.886, 1.922 min, MS (ES) 810.9 (M+H).

Example 550

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-5-(pyrrolidin-1-ylmethyl)-1*H*-indole-3-carboxylic acid

[00925] The title compound was prepared (4.0 mg, 20%, 2 steps) following the procedure described in Example 547 step Dusing ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-formyl-1-methyl-1*H*-indole-3-carboxylate (19 mg, 0.025 mmol) and pyrrolidine (2.1 mg, 0.030 mmol). LCMS: R_T = 1.907, 1.943 min, MS (ES) 794.8 (M+H).

Example 551

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-5-(3-(4-methylpiperazin-1-yl)propanamido)-1*H*-indole-3-carboxylic acid

[00926] The title compound (60%) was prepared following the procedure described Example 533 using methyl (*R*)-5-amino-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylate and 3-(4-methylpiperazin-1-yl)propanoic acid. MS (ES) 881.2 (M+H).

Example 552

(*R*)-1-((4-(4-acetylpiperazin-1-yl)pyridin-2-yl)methyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of ethyl (*R*)-1-((4-bromopyridin-2-yl)methyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate.

[00927] The title compound (222 mg, 72%) was prepared following General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (250 mg, 0.34 mmol) and 4-bromo-2-(chloromethyl)-pyridine (174 mg, 0.84 mmol). LCMS: R_T = 2.43 min., MS (ES) 909 (M+H).

Step B. Preparation of pentyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)-propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1-((4-(piperazin-1-yl)pyridin-2-yl)methyl)-1*H*-indole-2-carboxylate.

[00928] To a solution of ethyl (*R*)-1-((4-bromopyridin-2-yl)methyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (85 mg, 0.09 mol) in pentanol (0.5 mL) was added piperazine (40 mg, 0.47 mmol). The reaction was sealed and stirred at 125 °C overnight. The reaction mixture was cooled to RT and diluted with EtOAc and water. The aqueous layer was separated and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf, DCM/methanol = 0-6% gradient) to give the title compound (66 mg, 74%). LCMS: R_T = 1.92 min., MS (ES) 957 (M+H).

Step C. Preparation of pentyl (*R*)-1-((4-(4-acetylpiperazin-1-yl)pyridin-2-yl)methyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate

[00929] To a solution of pentyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1-((4-(piperazin-1-yl)pyridin-2-yl)methyl)-1*H*-indole-2-carboxylate (66 mg, 0.07 mol) in DCM (1.0 mL) at 0 °C under Ar was added Et_3N (17 mg, 0.17 mmol) followed by acetyl chloride (11 mg, 0.14 mmol) then diluted with DCM (0.4 mL). The reaction was warmed to RT and stirred 3 h. The reaction was diluted with DCM and water. The aqueous layer was separated and extracted with DCM. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude title compound (69 mg, 100%). LCMS: R_T = 2.06 min., MS (ES) 999 (M+H).

Step D. Example 552

[00930] The title compound (40 mg, 62%, 2steps) was prepared following General Procedure D using pentyl (*R*)-1-((4-(4-acetylpiperazin-1-yl)pyridin-2-yl)methyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (69 mg, 0.07 mmol). LCMS: R_T = 1.87 min., MS (ES) 929 (M+H).

Example 553

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1-((4-(piperazin-1-yl)pyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

[00931] The title compound was obtained as a byproduct of Example 552 step D. LCMS: R_T = 1.71 min., MS (ES) 887 (M+H).

Example 554

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-5-(2-(4-methylpiperazin-1-yl)acetamido)-1*H*-indole-3-carboxylic acid

[00932] The title compound (62%) was prepared following the procedure described Example 533 using methyl (*R*)-5-amino-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-

dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylate and 2-(4-methylpiperazin-1-yl)acetic acid. MS (ES) 867.2 (M+H).

Example 555

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-(pyridin-4-ylmethyl)-1H-indole-5-carboxylic acid

[00933] The title compound (9.6 mg, 61%) was prepared according to General Procedure I using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5- trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-5-carboxylate (15 mg, 0.02 mmol) and 4-(bromomethyl)pyridine HBr (10 mg, 0.04 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.811 min, MS (ES) 788.80 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, *J* = 5.7 Hz, 2H), 8.16 (s, 1H), 7.82 - 7.74 (m, 3H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.50 (t, *J* = 6.7 Hz, 2H), 7.30 (d, *J* = 8.7 Hz, 1H), 6.73 (s, 2H), 5.76 (s, 2H), 4.53 (t, *J* = 3.4 Hz, 0.5 H), 4.50 (t, *J* = 3.6 Hz, 0.5 H), 4.28 - 4.11 (m, 1H), 3.99 (dt, *J* = 6.2 & 2.2 Hz, 2H), 3.78 (s, 1.5H), 3.77 (s, 1.5H), 3.75 - 3.69 (m, 1H), 3.41 - 3.29 (m, 1H), 3.28 - 3.18 (m, 1H), 2.24 (s, 6H), 2.13 (s, 1.5H), 2.10 - 2.04 (m, 2H), 2.03 (s, 1.5H), 1.98 (s, 1.5H), 1.89 (s, 1.5H), 1.10 (d, *J* = 6.4 Hz, 3H).

Example 556

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((4-cyanopyridin-2-yl)methyl)-5-methyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((4-cyanopyridin-2-yl)methyl)-5-methyl-1*H*-indole-2-carboxylate

[00934] To a solution of ethyl (*R*)-1-((4-bromopyridin-2-yl)methyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (102 mg, 0.11 mol) in DMF (1.0 mL) was added $Zn(CN)_2$ (18 mg, 0.16 mmol) and $Pd(PPh_3)_4$ (13 mg, 0.01 mmol). The reaction mixture was degassed, sealed and stirred at 110 °C for 3 h. The reaction mixture was cooled to RT and diluted with EtOAc and water. The aqueous layer was separated and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash

chromatography (Combi-flash Rf, DCM/methanol = 0-2.5% gradient) to give the title compound (74 mg, 77%). LCMS: R_T = 1.65 min., MS (ES) 856 (M+H).

Step B. Example 556

[00935] The title compound (40 mg, 62%) was prepared following General Procedure D using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((4-cyanopyridin-2-yl)methyl)-5-methyl-1*H*-indole-2-carboxylate (74 mg, 0.09 mmol). LCMS: R_T = 2.25 min., MS (ES) 828 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (d, *J* = 5.0 Hz, 0.5H), 8.42 (d, *J* = 5.0 Hz, 0.5H), 7.68 (m, 1H), 7.54 (m, 2H), 7.38 (m, 1H), 7.25 (m, 1H), 6.81 (m, 2H), 6.71 (s, 2H), 6.02 (m, 1H), 5.62-5.88 (bm, 1H), 4.54 (m, 1H), 3.87-3.95 (bm, 3H) 3.74 (s, 1.5H), 3.72 (s, 1.5H), 3.39 (m, 1H), 3.03-3.21 (bm, 3H), 2.38 (s, 3H), 2.24 (s, 3H), 2.22 (s, 3H), 1.99-2.08 (bm, 4H), 1.86 (s, 1.5H), 1.74 (s, 1.5H) 1.01 (m, 3H).

Example 557

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((6-cyanopyridin-2-yl)methyl)-5-methyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of ethyl (*R*)-1-((6-bromopyridin-2-yl)methyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate.

[00936] The title compound (293 mg, 95%) was prepared following General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (250 mg, 0.34 mmol, 1.0 eq) and 2-bromo-6-(bromomethyl)-pyridine (119 mg, 0.47 mmol). LCMS: R_T = 2.44 min., MS (ES) 909 (M+H).

Step B. Preparation of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((6-cyanopyridin-2-yl)methyl)-5-methyl-1*H*-indole-2-carboxylate

[00937] The title compound (53 mg, 84%) was prepared following the procedure described Example 556, Step A using ethyl (*R*)-1-((6-bromopyridin-2-yl)methyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (67 mg, 0.07 mol). LCMS: R_T = 1.62 min., MS (ES) 856 (M+H).

Step C. Example 557

[00938] The title compound (17 mg, 29%) was prepared following General Procedure D using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((6-cyanopyridin-2-yl)methyl)-5-methyl-1*H*-indole-2-carboxylate (53 mg, 0.06 mmol). LCMS: R_T = 2.23 min., MS (ES) 828 (M+H).

Example 558

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-methyl-5-(2-morpholinoethoxy)-1H-indole-2-carboxylic acid

[00939] The title compound (6.1 mg, 27%) was prepared following General Procedure H using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-hydroxy-1-methyl-1H-indole-2-carboxylate (20 mg, 0.027 mmol) and 4-(2-chloroethyl)morpholine HCl (10 mg, 0.054 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.853 min, MS (ES) 838.9 (M+H).

Example 559

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethyl-2-((4-methylpiperazin-1-yl)methyl)pyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-(2-methoxyethyl)-1H-indole-5-carboxylic acid

Step A. (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one

[00940] The title compound (94 mg, 95%) was prepared following the procedure described Example 390 Step D using (*R*)-6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (115 mg, 0.175 mmol) and Pd/C (10 wt%, 20 mg, 0.019 mmol) by hydrogenating in MeOH (5 mL) with HCl (4.0 M in dioxanes, 0.5 mL) for 6 h at 40 °C. LCMS: R_T = 0.946 min (Method B), MS (ES) 566.9 (M+H).

Step B. (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethyl-2-((4-methylpiperazin-1-yl)methyl)pyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one

[00941] The title compound (55 mg, 96%) was prepared following General Procedure J using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (50 mg, 0.088

mmol), MsCl (30 mg, 0.26 mmol), and *N*-methyl piperazine (50 mg, 0.50 mmol). The crude reaction product was carried forward without further purification. LCMS: R_T = 1.658 min, MS (ES) 648.9 (M+H).

Step C. Example 559

[00942] The title compound was prepared (2.4 mg, 9%) following General Procedure B using: (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethyl-2-((4-methylpiperazin-1-yl)methyl)pyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (20 mg, 0.031 mmol) and methyl 3-bromo-1-(2-methoxyethyl)-1H-indole-5-carboxylate (25 mg, 0.081 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.769 min, MS (ES) 865.9 (M+H).

Example 560

(*R*)-2-(3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)-*N*,*N*-dimethylacetamide

Step A. Preparation of *N*,*N*-dimethyl-2-(5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)acetamide

[00943] The title crude compound (120 mg) was prepared following the procedure descried Example 388 Step A using *N*,*N*-dimethyl-2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-1-yl)acetamide (152 mg, 0.46 mmol) and 3-bromo-1-methyl-1*H*-1,2,4-triazole (50 mg, 0.31 mmol). LCMS: R_T = 0.169 min, MS (ES) 284.1 (M+H).

Step B. Preparation of 2-(3-iodo-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)-*N*,*N*-dimethylacetamide

[00944] The title compound (70 mg, 40%) was prepared following the procedure descried Example 388 Step B using *N*,*N*-dimethyl-2-(5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)acetamide (120 mg, 0.42 mmol). LCMS: R_T = 1.118 min, MS (ES) 409.9 (M+H)

Step C. Example 560

[00945] The title compound (9.5 mg, 21%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 2-(3-iodo-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)-*N*,*N*-dimethylacetamide (46 mg, 0.11 mmol). LCMS: R_T = 1.971 min, MS (ES) 819.9 (M+H).

Example 561

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-(pyridin-2-ylmethyl)-1H-indole-5-carboxylic acid

[00946] The title compound (16 mg, 99%) was prepared according to General Procedure I using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5- trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-5-carboxylate (15 mg, 0.02 mmol) and 2-(bromomethyl)pyridine HBr (10 mg, 0.04 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.913 min (Method B), MS (ES) 788.80 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (d, J = 4.8 Hz, 1H), 8.12 (s, 1H), 7.84 - 7.76 (m, 2H), 7.75 - 7.71 (m, 2H), 7.59 (d, J = 8.6 Hz, 1H), 7.34 (t, J = 5.7 Hz, 1H), 7.29 (d, J = 8.6 Hz, 1H), 7.20 - 7.14 (m, 1H), 6.73 (s, 2H), 5.57 (s, 2H), 4.59 - 4.43 (m, 1H), 4.23 - 4.08 (m, 1H), 3.98 (dt, J = 6.0 & 2.7 Hz, 2H), 3.78 (s, 1.5H), 3.77 (s, 1.5H), 3.74 - 3.64 (m, 1H), 3.40 - 3.28 (m, 1H), 3.28 - 3.17 (m, 1H), 2.23 (s, 6H), 2.12 (s, 1.5H), 2.10 - 2.04 (m, 2H), 2.03 (s, 1.5H), 1.97 (s, 1.5H), 1.88 (s, 1.5H), 1.09 (d, J = 6.4 Hz, 3H).

Example 562

(*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2',4-dimethyl-1,1'-dioxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1',2',3,3',4,4'-hexahydro-1*H*-[2,6'-bipyrazino[1,2-*a*]indole]-10'-carboxylic acid

Step A. Preparation of 1,2-bis(2-bromophenyl)hydrazine.

[00947] To a solution of 1-bromo-2-nitrobenzene (0.97 g, 4.8 mmol) in 50% aq. NaOH (0.3 mL) was added Zn dust (0.9 g, 13.9 mmol) in small portions while maintaining the reaction temperature below 80 °C. The mixture was diluted with water (6 mL) and 20% aq. NaOH (12 mL) then zinc dust (1.2 g, 18.7 mmol) was added in one portion. The resulting mixture was heated at 80 °C for 1 h, cooled to RT and poured slowly to 10% sulfuric acid (20 mL) at 0 °C. The mixture was stirred for 30 min then extracted with diethyl ether. The combined organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-80% gradient) to afford the title compound (165 mg, 20%). LCMS: R_T = 1.818 min, MS (ES) 340.8 (M+H).

Step B. Preparation of dimethyl 7-bromo-1*H*-indole-2,3-dicarboxylate.

[00948] To a solution of 1,2-bis(2-bromophenyl)hydrazine (165 mg, 0.5 mmol) in MeOH (5 mL), dimethyl but-2-ynedioate (41 µL, 92 mg, 0.65 mmol) was added and refluxed for 16 h. The reaction was quenched with aq. sat. NH_4Cl solution and extracted with DCM. The combined organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was

purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-80% gradient) to afford the title compound (30 mg, 19%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (br s, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.54 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.17 (t, *J* = 8.1 Hz, 1H), 4.03 (s, 3H), 4.00 (s, 3H).

Step C. Preparation of methyl 6-bromo-2-methyl-1-oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole-10-carboxylate.

[00949] To a solution of dimethyl 7-bromo-1*H*-indole-2,3-dicarboxylate (30 mg, 0.10 mmol) in MeCN (1 mL) was added Cs_2CO_3 (78.2 mg, 0.24 mmol) followed by tert-butyl 1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (26.8 mg, 0.12 mmol). The reaction was heated at 75 °C for 16 h then quenched with aq. sat. NH_4Cl solution and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was re-dissolved in DCM (0.6 mL), TFA (138 mg, 1.2 mmol) was added and stirred at RT for 16 h. The reaction was quenched with aq. sat. $NaHCO_3$ and extracted with DCM. The combined organic layer was dried over $MgSO_4$, filtered and concentrated. The crude product was redissolved in CH_3CN (1.6 mL). Cs_2CO_3 (78 mg, 0.24 mmol) was added and heated at 70 °C for 12 h. Then, the reaction mixture was quenched with aq. sat. NH_4Cl solution and extracted with DCM. The combined organic layer was dried over $MgSO_4$, filtered and concentrated. The crude product was re-dissolved in DMF (1 mL). NaH (12 mg, 0.3 mmol) followed by MeI (63 μL, 142 mg, 1.0 mmol) were added and stirred at RT for 1 h. Then, the reaction mixture was quenched with aq. sat. NH_4Cl solution and extracted with DCM. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford the title compound (7 mg, 20% yield, 4 steps). LCMS: R_T = 1.337 min, MS (ES) 337.0 (M+H).

Step D. Example 562.

[00950] The title compound (1.5 mg, 10%, 2 steps)was prepared following General coupling procedure A using methyl 6-bromo-2-methyl-1-oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole-10-carboxylate (7 mg, 0.02 mmol) and (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (11 mg, 0.02 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.154, 2.186 min, MS (ES) 780.9 (M+H).

Example 563

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-(pyridin-3-ylmethyl)-1*H*-indole-5-carboxylic acid

[00951] The title compound (12 mg, 76%) was prepared according to General Procedure I using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5- trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-5-carboxylate (15 mg, 0.02 mmol) and 3-(bromomethyl)pyridine HBr (10 mg, 0.04 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.804 min (Method B), MS (ES) 788.80 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 - 8.65 (m, 1H), 8.64 - 8.57 (m, 1H), 8.12 (s, 1H), 7.86 (t, *J* = 7.6 Hz, 1H), 7.83 - 7.80 (m, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.69 (d, *J* = 8.6 Hz, 1H), 7.59 - 7.52 (m, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 6.73 (s, 2H), 5.59 (s, 2H), 4.50 (t, *J* = 3.5 Hz, 0.5 H), 4.47 (t, *J* = 3.6 Hz, 0.5 H), 4.25 - 4.09 (m, 1H), 3.98 (dt, *J* = 6.3 & 2.2 Hz, 2H), 3.78 (s, 1.5H), 3.77 (s, 1.5H), 3.75 - 3.65 (m, 1H), 3.39 - 3.28 (m, 1H), 3.27 - 3.17 (m, 1H), 2.23 (s, 6H), 2.12 (s, 1.5H), 2.10 - 2.04 (m, 2H), 2.03 (s, 1.5H), 1.97 (s, 1.5H), 1.88 (s, 1.5H), 1.09 (d, *J* = 6.5 Hz, 3H).

Example 564

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-5-(methyl(pyridin-2-ylmethyl)amino)-1*H*-indole-3-carboxylic acid

Step A. Preparation of methyl 7-bromo-5-((*tert*-butoxycarbonyl)(methyl)amino)-1-methyl-1*H*-indole-3-carboxylate

[00952] To a solution of methyl 7-bromo-5-((*tert*-butoxycarbonyl)amino)-1-methyl-1H-indole-3-carboxylate (450 mg, 1.17 moml) in DMF (5 mL) was added NaH (95 mg, 2.4 mmol) at 0 °C under N_2 stirred for 10 min. MeI (2.0 mmol) was added to the reaction mixture and stirred at 0 °C for 10 min then at RT for 1h. The reaction mixture was diluted with EtOAc, washed with brine, dried and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-10% gradient) to afford the title compound (440 mg, 94 %). ^{1}H-NMR (DMSO-d_6) δ 8.0 (s, 1H), 7.73 (s, 1H), 7.34 (s, 1H), 4.20 (s, 3H), 3.91 (s, 3H), 3.31 (s, 1H), 1.49 (s, 9H).

Step B. Preparation of methyl (*R*)-5-((tert-butoxycarbonyl)(methyl)amino)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-3-carboxylate

[00953] The title compound (78%) was prepared following General coupling procedure A using methyl 7-bromo-5-((*tert*-butoxycarbonyl)(methyl)amino)-1-methyl-1*H*-indole-3-carboxylate and (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one. MS (ES) 855.3 (M+H)

Step C. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy) propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-methyl-5-(methylamino)-1H-indole-3-carboxylate

[00954] (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy) propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-methyl-5-(methylamino)-1H-indole-3-carboxylate was dissolved in DCM/TFA (5/1) and stirred for 2h at RT. The reaction mixture was concentrated in vacuo to afford the title compound (95%) which was carried to the next step without further purification.

Step D. Example 564

[00955] The title compound (65%) was prepared following General procedure G using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy) propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-methyl-5-(methylamino)-1H-indole-3-carboxylate and 2-(bromomethyl)pyridine followed by saponification using General Procedure D. MS (ES) 832.1 (M+H)

Example 565

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-methoxy-1-((4-methylpyridin-2-yl)methyl)-1H-indole-2-carboxylic acid

Step A. Preparation of methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-((4-methylpyridin-2-yl)methyl)-1H-indole-2-carboxylate

[00956] The title compound (84 mg, 93%) was prepared following General Procedure I using methyl (R)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1H-indole-2-carboxylate (80 mg, 0.098 mmol) and 2-(chloromethyl)-4-methylpyridine HCl (30 mg, 0.17 mmol). LCMS: R_T = 1.299 min (Method B), MS (ES) 920.8 (M+H).

Step B. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-

dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-hydroxy-1-((4-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylate

[00957] The title compound (73 mg, 96%) was prepared following the procedure described Example 390 Step D using methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino [1,2-a]indol-2(1H)-yl)-1-((4-methylpyridin-2-yl)methyl)-1H-indole-2-carboxylate (84 mg, 0.092 mmol) and Pd/C (10 wt.%, 10 mg, 0.0092 mmol) by hydrogenating in MeOH (5 mL) with HCl for 5 h at RT. LCMS: R_T = 0.839, 0.864 min (Method B), MS (ES) 830.8 (M+H).

Step C. Example 565

[00958] The title compound (5.9 mg, 39%) was prepared following General Procedure H using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-hydroxy-1-((4-methylpyridin -2-yl)methyl)-1H-indole-2-carboxylate (15 mg, 0.018 mmol) and MeI (10 mg, 0.070 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.979 min, MS (ES) 830.8 (M+H).

Example 566

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-(2-(dimethylamino)ethoxy) -1-((6-methylpyridin-2-yl)methyl)-1H-indole-2-carboxylic acid

Step A. Preparation of methyl (R)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl) -6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-((6-methylpyridin-2-yl)methyl)-1H-indole-2-carboxylate

[00959] The title compound (86 mg, 96%) was prepared following General Procedure I using methyl (R)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1H-indole-2-carboxylate (80 mg, 0.098 mmol) and 2-(chloromethyl)-6-methylpyridine (30 mg, 0.21 mmol). LCMS: R_T = 1.319, 1.354 min (Method B), MS (ES) 920.8 (M+H).

Step 2: Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-hydroxy-1-((6-methylpyridin-2-yl)methyl)-1H-indole-2-carboxylate

[00960] The title compound (51 mg, 66%) was prepared following the procedure described

Example 390 Step D using methyl (R)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino [1,2-a]indol-2(1H)-yl)-1-((6-methylpyridin-2-yl)methyl)-1H-indole-2-carboxylate (86 mg, 0.093 mmol) and Pd/C (10 wt.%, 10 mg, 0.0092 mmol) by hydrogenating in MeOH (5 mL) with HCl for 5 h at RT. LCMS: R_T = 0.888 min (Method B), MS (ES) 830.8 (M+H).

Step 3: Example 566

[00961] The title compound (7.1 mg, 39%) was prepared following General Procedure H using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-hydroxy-1-((6-methylpyridin -2-yl)methyl)-1H-indole-2-carboxylate (17 mg, 0.020 mmol) and 2-bromo-*N*,*N*-dimethylethan-1-amine (10 mg, 0.043 mmol) followed by saponification using General Procedure D. LCMS: R_T = 0.476 min (Method B), MS (ES) 887.8 (M+H). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 9.18 (s, 0.34H), 9.14 (s, 0.66H), 7.85-7.81 (m, 1H), 7.66-7.63 (m, 1H), 7.31 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 7.00-6.92 (m, 1H), 6.87-6.65 (m, 3H), 6.58 (s, 1.34H), 6.54 (s, 0.66H), 6.24-6.11 (m, 1.34H), 5.88-5.65 (m, 0.66H), 4.59-4.55 (m, 1H), 4.43 (dd, *J* = 13.0, 4.0 Hz, 0.66H), 4.28-4.22 (m, 1.34H), 3.92-3.56 (m, 4H), 3.41-3.30 (m, 2H), 3.01 (s, 1H), 2.98 (s, 2H), 2.92 (s, 3H), 2.89-2.81 (m, 1H), 2.66 (s, 1H), 2.64 (s, 1H), 2.50 (s, 2H), 2.47 (s, 1H), 2.40 (s, 2H), 2.35 (s, 2H), 2.33 (s, 6H), 2.25 (s, 1H), 1.86-1.72 (m, 2H), 1.45 (d, *J* = 5.8 Hz, 1H), 1.21 (d, *J* = 6.8 Hz, 2H).

Example 567

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(5-(pyrimidin-2-yl)-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-(pyrimidin-2-yl)-1*H*-indole

[00962] The title compound (220 mg, 66%) was prepared following the procedure descried Example 388 Step A using 1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (492 mg, 1.23 mmol) and 2-bromopyrimidine (150 mg, 0.94 mmol). LCMS: R_T = 2.077 min, MS (ES) 354.1 (M+H).

Step B. Preparation of 2-(5-(pyrimidin-2-yl)-1*H*-indol-1-yl)ethan-1-ol

[00963] The title compound (140 mg, 94%) was prepared following the procedure descried Example 420 Step C using 1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-(pyrimidin-2-yl)-1*H*-indole (220 mg, 0.62 mmol). LCMS: R_T = 1.122 min, MS (ES) 240.1 (M+H).

Step C. Preparation of 5-(pyrimidin-2-yl)-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-indole

[00964] The title compound (78 mg, 85%) was prepared following General Procedure J using 2-(5-(pyrimidin-2-yl)-1*H*-indol-1-yl)ethan-1-ol (140 mg, 0.59 mmol) and pyrrolidine (233 μL, 2.84 mmol). LCMS: R_T = 0.167 min, MS (ES) 293.1 (M+H).

Step D. Preparation of 3-iodo-5-(pyrimidin-2-yl)-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-indole

[00965] The title compound (37 mg, 33%) was prepared following the procedure descried Example 388 Step B using 5-(pyrimidin-2-yl)-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-indole (78 mg, 0.27 mmol). LCMS: R_T = 1.282 min, MS (ES) 418.9 (M+H).

Step E. Example 567

[00966] The title compound (16.5 mg, 31%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (35 mg, 0.06 mmol) and 3-iodo-5-(pyrimidin-2-yl)-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-indole (37 mg, 0.09 mmol). LCMS: R_T = 1.959 min, MS (ES) 828.9 (M+H).

Example 568

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-(2-(4-methylpiperazin-1-yl)ethyl)-5-(pyrimidin-2-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00967] The title compound (13 mg, 23%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (35 mg, 0.06 mmol) and 3-iodo-1-(2-(4-methylpiperazin-1-yl)ethyl)-5-(pyrimidin-2-yl)-1*H*-indole (44 mg, 0.10 mmol). LCMS: R_T = 1.870 min, MS (ES) 858.0 (M+H).

Example 569

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-(2-(4-methylpiperazin-1-yl)ethyl)-1H-indole-5-carboxylic acid

[00968] The title compound (10.4 mg, 63%) was prepared according to General Procedure I using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-5-

carboxylate (15 mg, 0.02 mmol) and 1-(2-Bromoethyl)-4-methylpiperazine dihydrobromide (15 mg, 0.04 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.745 min, MS (ES) 823.90 (M+H).

Example 570

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-((2-methyl-2H-1,2,3-triazol-4-yl)methyl)-1H-indole-2-carboxylic acid

[00969] The title compound (7.2 mg, 43%) was prepared following General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1H-indole-2-carboxylate (15 mg, 0.021 mmol) and 4-(bromomethyl)-2-methyl-2H-1,2,3-triazole (10 mg, 0.039 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.165, 2.138 min, MS (ES) 792.8 (M+H). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.72-7.66 (m, 2H), 7.50 (s, 0.34H), 7.49 (s, 0.66H), 7.30 (d, *J* = 8.6 Hz, 0.34), 7.29 (d, *J* = 8.6 Hz, 0.66H), 7.23-7.02 (m, 3H), 6.61 (s, 1.34H), 6.58 (s, 0.66H), 6.21 (d, *J* = 16.6 Hz, 1H), 6.17 (d, *J* = 16.6 Hz, 1H), 5.85-5.55 (m, 1H), 4.48-4.19 (m, 2H), 4.15-3.93 (m, 4H), 3.89 (s, 4H), 3.88-3.83 (m, 1.5H), 3.72-3.64 (m, 0.5H), 3.46-3.24 (m, 3H), 2.30 (s, 2H), 2.29 (s, 4H), 2.23-2.10 (m, 5H), 2.07-2.00 (m, 3H), 1.25 (d, *J* = 6.5 Hz, 1H), 1.19 (d, *J* = 6.5 Hz, 2H).

Example 571

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-(2-methoxyethoxy)-1-((6-methylpyridin-2-yl)methyl)-1H-indole-2-carboxylic acid

[00970] The title compound (9.8 mg, 55%) was prepared following General Procedure H using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-hydroxy-1-((6-methylpyridin -2-yl)methyl)-1H-indole-2-carboxylate (17 mg, 0.020 mmol) and 1-bromo-2-methoxyethane (10 mg, 0.072 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.959 min, MS (ES) 874.8 (M+H). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 9.11 (s, 0.66H), 9.10 (s, 0.34H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.69-7.65 (m, 1H), 7.41 (s, 0.34H), 7.36 (s, 0.66H), 7.33-7.28 (m, 1H), 7.21-7.08 (m, 2H), 6.91 (d, *J* = 2.2 Hz, 0.34H), 6.86 (d, *J* = 2.2 Hz, 0.66H), 6.78-6.69 (m, 0.66H), 6.65-6.60 (m, 0.33H), 6.57 (s, 1.3H), 6.56 (s, 0.66H), 6.26-5.82 (m, 2H), 4.39-4.08 (m, 3H), 3.83-3.64 (m, 5H), 3.45 (s, 3H), 3.37-3.21 (m, 1H), 3.12-2.94 (m, 1H), 2.60 (s, 1H), 2.48 (s, 2H), 2.43 (s, 1H), 2.38 (s, 2H),

2.35-2.28 (m, 9H), 2.22 (s, 1H), 1.90-1.67 (m, 2H), 1.21 (d, *J* = 6.4 Hz, 2H), 1.09-0.98 (m, 1H).

Example 572

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-methoxy-1-((6-methylpyridin-2-yl)methyl)-1H-indole-2-carboxylic acid

[00971] The title compound (8.3 mg, 49%) was prepared following General Procedure H using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-hydroxy-1-((6-methylpyridin -2-yl)methyl)-1H-indole-2-carboxylate (17 mg, 0.020 mmol) and MeI (10 mg, 0.070 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.984 min, MS (ES) 830.8 (M+H). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 9.14 (s, 0.66H), 9.13 (s, 0.34H), 7.90-7.84 (m, 1H), 7.71-7.66 (m, 1H), 7.44-7.39 (m, 1H), 7.31(t, *J* = 8.5 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 0.34H), 7.17 (d, *J* = 7.8 Hz, 0.66H), 7.10 (d, *J* = 2.3 Hz, 1H), 6.83 (d, *J* = 2.4 Hz, 0.34H), 6.80 (d, *J* = 2.4 Hz, 0.66H), 6.78-6.64 (m, 1H), 6.57 (s, 1.34H), 6.55 (s, 0.66H), 6.26-6.21 (m, 1.34H), 5.93 (d, *J* = 17.8 Hz, 0.66H), 4.49 (d, *J* = 12.4 Hz, 0.66H), 4.34 (dd, *J* = 13.0, 3.9 Hz, 0.34H), 3.86 (s, 3H), 3.82-3.68 (m, 3H), 3.41 (d, *J* = 13.3 Hz, 1H), 3.12-2.96 (m, 1H), 2.62 (s, 1H), 2.58-2.54 (m, 3H), 2.45 (s, 1H), 2.41 (s, 2H), 2.35 (s, 2H), 2.33 (s, 6H), 2.25 (s, 1H), 1.8-1.72 (m, 2H), 1.22 (d, *J* = 6.5 Hz, 2H), 1.18-1.11 (m, 1H).

Example 573

(R)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-(2-methoxyethoxy)-1-((4-methylpyridin-2-yl)methyl)-1H-indole-2-carboxylic acid

[00972] The title compound (6.7 mg, 42%) was prepared following General Procedure H using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-hydroxy-1-((4-methylpyridin -2-yl)methyl)-1H-indole-2-carboxylate (15 mg, 0.018 mmol) and 1-bromo-2-methoxyethane (10 mg, 0.072 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.954 min, MS (ES) 874.9 (M+H). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 9.11 (s, 1H), 8.39 (d, *J* = 5.8 Hz, 0.34H), 8.31 (d, *J* = 5.8 Hz, 0.66H), 7.68-7.64 (m, 1H), 7.45 (s, 1H), 7.30 (d, *J* = 8.6 Hz, 0.34H), 7.29 (d, *J* = 8.6 Hz, 0.66H), 7.28-7.20 (m, 1H), 7.15 (d, *J* = 2.2 Hz, 0.66H), 7.13 (d, *J* = 2.2 Hz, 0.34H), 6.91 (d, *J* = 2.2 Hz, 0.34H), 6.88 (d, *J* = 2.2 Hz, 0.66H), 6.87-6.76 (m, 1H), 6.57 (s, 2H), 6.23-6.13 (m, 1H),

5.84 (d, *J* = 16.9 Hz, 1H), 4.32-4.10 (m, 3H), 3.86-3.66 (m, 5H), 3.45 (s, 3H), 3.40-3.33 (m, 1H), 3.02-2.97 (m, 1H), 2.73-2.62 (m, 1H), 2.41 (s, 1H), 2.38 (s, 2H), 2.36 (s, 1H), 2.35-2.31 (m, 8H), 2.29 (s, 2H), 2.21 (s, 1H), 1.89-1.77 (m, 2H), 1.20 (d, *J* = 6.5 Hz, 2H), 1.09-1.04 (m, 1H).

Example 574

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-2-(1-methyl-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[00973] The title compound (32 mg, 77%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 3-iodo-1-methyl-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (38 mg, 0.11 mmol). LCMS: R_T = 2.098 min, MS (ES) 746.8 (M+H).

Example 575

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid

Step A. Preparation of methyl 3-bromo-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-6-carboxylate

[00974] The title compound (88.6 mg, 88%) was prepared following General Procedure F using 1*H*-pyrrolo[2,3-*b*]pyridine-6-carboxylic acid (46 mg, 0.28 mmol), NBS (51 mg, 0.28 mmol), and MeI (53 μL, 0.85 mmol). LCMS: R_T = 1.712 min, MS (ES) 269.0 (M+H).

Step B. Example 575

[00975] The title compound (22 mg, 62%) was prepared according to General Procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*- pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol) and 3-bromo-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-6-carboxylate (22 mg, 0.06 mmol) followed by saponification using General Procedure D. LCMS R_T = 2.063 min (Method B), MS (ES) 712.8 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (t, *J* = 1.6 Hz, 1H), 8.44 (t, *J* = 1.6 Hz, 1H), 7.80 - 7.73 (m, 2H), 7.30 (d, *J* = 8.6 Hz, 1H), 6.72 (s, 2H), 4.56 - 4.49 (m, 2H), 4.25 - 4.10 (m, 1H), 4.04 - 3.93 (m, 2H), 3.88 (s, 3H), 3.78 (s, 1.5H), 3.77 (s, 1.5H), 3.43 - 3.29 (m, 1H), 3.28 - 3.17 (m, 1H), 2.23 (s, 6H), 2.12 (s, 1.5H), 2.09 (s, 1.5H), 2.07 - 2.02 (m, 2H), 1.98 (s, 1.5H), 1.89 (s, 1.5H), 1.06 (d, *J* = 6.5 Hz, 3H).

Example 576

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indole-2-carboxylic acid

Step A. methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-methyl-1H-indole-2-carboxylate

[00976] The title compound (145 mg, 54%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (200 mg, 0.37 mmol) and methyl 7-bromo-5-methyl-1H-indole-2-carboxylate (200 mg, 0.746 mmol). LCMS: R_T = 1.581 min, MS (ES) 723.9 (M+H).

Step B. Example 576

[00977] The title compound (13.3 mg, 48%) was prepared following General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-methyl-1H-indole-2-carboxylate (25 mg, 0.034 mmol) and 2-(chloromethyl)-6-methylpyridine (10 mg, 0.071 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.023 min, MS (ES) 814.8 (M+H).

Example 577

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-methyl-1-((4-methylpyridin-2-yl)methyl)-1H-indole-2-carboxylic acid

[00978] The title compound (13.2 mg, 47%) was prepared following General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-methyl-1H-indole-2-carboxylate (25 mg, 0.034 mmol) and 2-(chloromethyl)-4-methylpyridine HCl (10 mg, 0.056 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.012 min, MS (ES) 814.8 (M+H).

Example 578

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-isopropoxyethyl)-5-methyl-1*H*-indole-2-carboxylic acid

[00979] The title compound (37 mg, 74%) was prepared following General Procedure I

using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (50 mg, 0.07 mmol) and 2-(2-bromoethoxy)propane (28 mg, 0.17 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.32 min, MS (ES) 798 (M+H).

Example 579

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-ethoxyethyl)-5-methyl-1*H*-indole-2-carboxylic acid

[00980] The title compound (40 mg, 75%) was prepared following General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (50 mg, 0.07 mmol) and 2-bromoethyl ethyl ether (18 mg, 0.12 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.28 min, MS (ES) 784 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (s, 0.5H), 7.75 (s, 0.5H), 7.48 (s, 0.5H), 7.43 (s, 0.5H), 7.29 (m, 1H), 7.20 (m, 1H), 6.93 (m, 1H), 6.70 (s, 1H), 6.67 (s, 1H), 4.94 (m, 1H), 4.88 (m, 1H), 4.63 (m, 1H), 4.41 (m, 2H), 4.15 (m, 1H), 3.94 (t, *J* = 6.2 Hz, 2H), 3.77 (s, 1.5H), 3.75 (s, 1.5H), 3.71 (m, 1H), 3.45 (m, 1H), 3.36 (m, 1H), 3.07-3.26 (bm, 4H), 2.37 (s, 1.5H), 2.35 (s, 1.5H), 2.22 (s, 3H), 2.21 (s, 3H), 2.11 (m, 2H), 2.00 (m, 3H), 1.91-1.95 (m, 1H), 1.86 (s, 1H), 1.15 (d, *J* = 6.5 Hz, 1.5H), 1.04 (d, *J* = 6.5 Hz, 1.5H), 0.74 (m, 3H).

Example 580

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethyl-2-((4-methylpiperazin-1-yl)methyl)pyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-(2-(dimethylamino)ethyl)-1*H*-indole-5-carboxylic acid

Step A. methyl 3-bromo-1-(2-(dimethylamino)ethyl)-1H-indole-5-carboxylate

[00981] The title compound (74 mg, 58%) was prepared following General Procedure G using methyl 3-bromo-1H-indole-5-carboxylate (100 mg, 0.39 mmol) and 2-bromo-*N,N*-dimethylethan-1-amine HBr (180 mg, 0.77 mmol). LCMS: R_T = 1.154 min, MS (ES) 324.9 (M+H).

Step B. Example 580

[00982] The title compound (6.3 mg, 23% yield) was prepared following General Procedure B using (R)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethyl-2-((4-methylpiperazin-1-yl)methyl)pyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (20 mg, 0.031 mmol) and methyl 3-bromo-1-(2-

(dimethylamino)ethyl)-1H-indole-5-carboxylate (20 mg, 0.062 mmol) followed by saponification using General Procedure D. LCMS: R_T = 0.476 min, MS (ES) 887.8 (M+H).

Example 581

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(1-(2-methoxyethyl)-5-(1-(oxetan-3-ylmethyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 1-(2-methoxyethyl)-5-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[00983] The title compound (480 mg, 57%) was prepared following the procedure descried Example 388 Step A using 1-(2-methoxyethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (934 mg, 3.10 mmol) and 3-bromo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,4-triazole (600 mg, 2.59mmol). LCMS: R_T = 1.408 min, MS (ES) 327.1 (M+H).

Step B. Preparation of 3-iodo-1-(2-methoxyethyl)-5-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[00984] The title compound (650 mg, 98%) was prepared following the procedure descried Example 388 Step B using 1-(2-methoxyethyl)-5-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (480 mg, 1.47 mmol). LCMS: R_T = 1.674 min, MS (ES) 452.8 (M+H).

Step C. Preparation of 3-iodo-1-(2-methoxyethyl)-5-(1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[00985] 2N HCl (3 mL) was added to a solution of 3-iodo-1-(2-methoxyethyl)-5-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (650 mg, 1.44 mmol) in DMF (15 mL) at 0 °C. After 5 h, the reaction mixture was diluted with EtOAc, *i*PrOH and Sat. aq. $NaHCO_3$ at 0 °C. The solution was extracted with EtOAc. The combined organic layers were dried and concentrated to afford the crude title compound (500 mg), which was used for the next step without further purification. LCMS: R_T = 0.188 min, MS (ES) 368.8 (M+H).

Step D. Preparation of iodo-1-(2-methoxyethyl)-5-(1-(oxetan-3-ylmethyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[00986] The title crude compound (73 mg) was prepared following General Procedure G using 3-iodo-1-(2-methoxyethyl)-5-(1*H*-1,2,4-triazol-3-yl)-1*H*-indole (60 mg, 0.160 mmol) and 3-(chloromethyl)oxetane (17.4 μL, 0.18 mmol). LCMS: R_T = 1.336 min, MS (ES) 438.9 (M+H).

Step E. Example 581

[00987] The title compound (29 mg, 61%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and iodo-1-(2-methoxyethyl)-5-(1-(oxetan-3-ylmethyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (49 mg, 0.11 mmol). LCMS: R_T = 2.077 min, MS (ES) 848.8 (M+H).

Example 582

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-4-methoxy-1-((4-methylpyridin-2-yl)methyl)-1H-indole-2-carboxylic acid

Step A. methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-4-methoxy-1H-indole-2-carboxylate

[00988] The title compound (69 mg, 28%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (180 mg, 0.33 mmol) and methyl 7-iodo-4-methoxy-1H-indole-2-carboxylate (200 mg, 0.60 mmol). LCMS: R_T = 1.386, 1.422 min, (Method B) MS (ES) 741.9 (M+H).

Step B. Example 582

[00989] The title compound (12.5 mg, 44%) was prepared following General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-4-methoxy-1H-indole-2-carboxylate (23 mg, 0.031 mmol) and 2-(chloromethyl)-4-methylpyridine hydrochloride (10 mg, 0.056 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.952, 1.982 min, MS (ES) 832.8 (M+H).

Example 583

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1-(2-morpholinoethyl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 4-(2-(5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethyl) morpholine

[00990] The title compound (42 mg, 41%) was prepared following General Procedure J using 2-(5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethan-1-ol (105 mg, 0.33 mmol) and morpholine (283 μL, 3.28 mmol). LCMS: R_T = 0.163 min, MS (ES) 312.1 (M+H).

Step B. Preparation of 4-(2-(3-iodo-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethyl) morpholine

[00991] The title compound (55 mg, 93%) was prepared following the procedure descried Example 388 Step B using 4-(2-(5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethyl)morpholine (42 mg, 0.13 mmol). LCMS: R_T = 0.168 min, MS (ES) 437.8 (M+H).

Step C. Example 583

[00992] The title compound (30 mg, 64%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 4-(2-(3-iodo-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethyl)morpholine (49 mg, 0.11 mmol). LCMS: R_T = 1.825 min, MS (ES) 847.9 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.11 (s, 1H), 7.92 (d, *J* = 8.6 Hz, 1H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.62 (s, 1H), 7.30 (d, *J* = 8.6 Hz, 1H), 6.72 (s, 2H), 4.62 (t, *J* = 7.2 Hz, 2H), 4.51 – 4.46 (m, 1H), 4.20 – 4.18 (m, 1H), 4.00 – 3.95 (m, 3H), 3.88 (s, 3H), 3.77 (d, *J* = 4.8 Hz, 3H), 3.70 (dd, *J* = 11.6, 7.4 Hz, 3H), 3.62 – 3.57 (m, 2H), 3.36 – 3.19 (m, 4H), 2.54 (s, 3H), 2.22 (s, 6H), 2.12 – 2.04 (m, 5H), 1.98 – 1.89 (m, 3H), 1.12 – 1.10 (m, 3H).

Example 584

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-(2-(dimethylamino)ethoxy)-1-((4-methylpyridin-2-yl)methyl)-1H-indole-2-carboxylic acid

[00993] The title compound (6.1 mg, 38%) was prepared following General Procedure H using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-hydroxy-1-((4-methylpyridin -2-yl)methyl)-1H-indole-2-carboxylate (15 mg, 0.018 mmol) and 2-bromo-*N*,*N*-dimethylethan-1-amine hydrobromide (10 mg, 0.043 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.660 min, MS (ES) 887.8 (M+H).

Example 585

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-methyl-5H-pyrrolo[2,3-b]pyrazine-2-carboxylic acid

Step A. Preparation of methyl 7-bromo-5-methyl-5*H*-pyrrolo[2,3-*b*]pyrazine-2-carboxylate

[00994] The title compound (65.1 mg, 85%) was prepared following General Procedure F

using methyl 5*H*-pyrrolo[2,3-*b*]pyrazine-2-carboxylate (49 mg, 0.28 mmol), NBS (51 mg, 0.28 mmol), and MeI (53 μL, 0.85 mmol). LCMS: R_T = 1.165 min, MS (ES) 269.9 (M+H).

Step B. Example 585

[00995] The title compound (19.5 mg, 55%) was prepared according to General Procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*- pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol) and methyl 7-bromo-5-methyl-5*H*-pyrrolo[2,3-*b*]pyrazine-2-carboxylate (22 mg, 0.06 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.154 min (Method B), MS (ES) 713.8 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.48 (s, 0.5H), 8.45 (s, 0.5H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 1H), 6.74 (s, 2H), 4.61 - 4.52 (m, 0.5H), 4.50 - 4.44 (m, 0.5H), 4.41 - 4.30 (m, 1H), 4.27 - 4.15 (m, 1H), 3.99 (d, *J* = 5.8 Hz, 2H), 3.92 (s, 3H), 3.80 (s, 1.5H), 3.78 (s, 1.5H), 3.30 - 3.20 (m, 2H), 2.24 (s, 6H), 2.12 (s, 1.5H), 2.08 (t, *J* = 6.9 Hz, 1H), 2.03 (s, 1.5H), 1.98 (s, 1.5H), 1.89 (s, 1.5H), 1.12 (d, *J* = 6.6 Hz, 3H).

Example 586

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-indole

[00996] The title compound (54 mg, 56%) was prepared following General Procedure J using 2-(5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethan-1-ol (105 mg, 0.33 mmol) and pyrrolidine (161 μL, 1.97 mmol). LCMS: R_T = 0.158 min, MS (ES) 296.1 (M+H).

Step B. Preparation of 3-iodo-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-indole

[00997] The title compound (40 mg, 52%) was prepared following the procedure descried Example 388 Step B using 5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-indole (54 mg, 0.18 mmol). LCMS: R_T = 1.122 min, MS (ES) 421.9(M+H).

Step C. Example 586

[00998] The title compound (40 mg, 87%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol)

and 3-iodo-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-indole (40 mg, 0.10 mmol). LCMS: R_T = 1.855 min, MS (ES) 831.9 (M+H).

Example 587

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-4-methoxy-1-(2-methoxyethyl)-1H-indole-2-carboxylic acid

[00999] The title compound (13.8 mg, 57%) was prepared following General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-4-methoxy-1H-indole-2-carboxylate (23 mg, 0.031 mmol) and 1-bromo-2-methoxyethane (10 mg, 0.072 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.165, 2.196 min, MS (ES) 785.8 (M+H).

Example 588

(*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-(pyridin-2-ylmethyl)-1H-indole-2-carboxylic acid

Step A. Preparation of ethyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-3-carboxylate

[001000] The title compound (39 mg, 94%) was prepared according to General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*- pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol) and ethyl 5-(benzyloxy)-7-bromo-1*H*-indole-3-carboxylate (22 mg, 0.06 mmol). LCMS: R_T = 1.619 min, MS (ES) 831.9 (M+H).

Step B. Example 588

[001001] The title compound (33 mg, 79%) was prepared according to General Procedure I using methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-3-carboxylate (39 mg, 0.02 mmol) and 2-(bromomethyl)pyridine HBr (19 mg, 0.074 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.502 min, MS (ES) 895.9 (M+H).

Example 589

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(5-(1-(cyclopropylmethyl)-1*H*-1,2,4-triazol-3-yl)-1-(2-methoxyethyl)-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 5-(1-(cyclopropylmethyl)-1*H*-1,2,4-triazol-3-yl)-3-iodo-1-(2-methoxyethyl)-1*H*-indole

[001002] The crude title compound (65 mg) was prepared following General Procedure G using 3-iodo-1-(2-methoxyethyl)-5-(1*H*-1,2,4-triazol-3-yl)-1*H*-indole (60 mg, 0.16 mmol) and (bromomethyl)cyclopropane (19 μL, 0.20 mmol). LCMS: R_T = 1.605min, MS (ES) 422.9 (M+H).

Step B. Example 589

[001003] The title compound (28 mg, 60%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 5-(1-(cyclopropylmethyl)-1*H*-1,2,4-triazol-3-yl)-3-iodo-1-(2-methoxyethyl)-1*H*-indole (47 mg, 0.11 mmol). LCMS: R_T = 2.182 min, MS (ES) 832.9 (M+H).

Example 590

(R)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-(2-(dimethylamino)ethoxy)-1-(pyridin-2-ylmethyl)-1H-indole-2-carboxylic acid

[001004] The title compound (2 mg, 12%) was prepared following General Procedure H using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylate (15 mg, 0.019 mmol) and 2-bromo-*N*,*N*-dimethylethan-1-amine HBr (15 mg, 0.064 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.717 min, MS (ES) 875.8 (M+H).

Example 591

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-5-(morpholine-4-carbonyl)-1*H*-indole-2-carboxylic acid

Step A. Preparation of ethyl 7-bromo-5-formyl-1-methyl-1*H*-indole-2-carboxylate.

[001005] To a solution of 1-(*tert*-butyl) 2-ethyl 7-bromo-5-formyl-1*H*-indole-1,2-dicarboxylate (585 mg, 1.47 mmol) in DCM (14 mL) was added TFA (1.13 mL, 14.7 mmol) and stirred at RT for 16 h. The reaction was quenched with aq. sat. NH_4Cl solution and

extracted with DCM. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was redissolved in DMF (8 mL). K_2CO_3 (1.22 g, 8.82 mmol) and MeI (275 μL, 626 mg, 4.41 mmol) were added and heated to 60 °C for 4 h. The reaction mixture was quenched with aq. sat. NH_4Cl solution and extracted with DCM. The combined organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-60% gradient) to afford the title compound (360 mg, 79%, 2 steps). LCMS: R_T = 1.886 min, MS (ES) 309.9 (M+H).

Step B. Preparation of ethyl 7-bromo-5-((methoxymethoxy)methyl)-1-methyl-1*H*-indole-2-carboxylate.

[001006] To a solution of the ethyl 7-bromo-5-formyl-1-methyl-1*H*-indole-2-carboxylate (356 mg, 1.15 mmol) in THF (1 mL) and MeOH (10 mL) was added $NaBH_4$ (65 mg, 1.72 mmol) and stirred at rt for 5 min. The reaction was quenched with aq. sat. NH_4Cl and extracted with DCM. The combined organic layer was dried over $MgSO_4$, filtered and concentrated. The crude product was redissolved in DCM. MOMCl (262 μL, 278 mg, 3.45 mmol) followed by $^{i}Pr_2EtN$ (1 mL, 742 mg, 5.75 mmol) were added and stirred at RT for 16 h. The reaction was quenched with aq. sat. NH_4Cl and extracted with DCM. The combined organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-50% gradient) to afford the title compound (336 mg, 82%, 2 steps). LCMS: R_T = 1.971 min, MS (ES) 355.9 (M+H).

Step C. Ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(hydroxymethyl)-1-methyl-1*H*-indole-2-carboxylate.

[001007] Coupling reaction was carried out following general procedure A using ethyl 7-bromo-5-((methoxymethoxy)methyl)-1-methyl-1*H*-indole-2-carboxylate (336 mg, 0.94 mmol) and (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (509 mg, 0.94 mmol). To a solution of the resulting ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-((methoxymethoxy)methyl)-1-methyl-1*H*-indole-2-carboxylate in THF (10 mL) and MeOH (5 mL) was added Conc. HCl (2.4 mL), and the reaction mixture was stirred at RT for 16 h. The reaction was quenched with aq. sat. $NaHCO_3$ and extracted with DCM. The combined organic layer was dried over $MgSO_4$, filtered and

concentrated. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-10% gradient) to afford the title compound compound (289 mg, 40%, 2 steps). LCMS: R_T = 2.274, 2.302, 2.324 min, MS (ES) 769.9 (M+H).

Step D. Example 591.

[001008] To a solution of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(hydroxymethyl)-1-methyl-1*H*-indole-2-carboxylate (7.6 mg, 0.01 mmol) in acetone (0.12 mL) at 0 °C was added water (15 μL) and Conc. H_2SO_4 (5 μL). CrO_3 (3 mg, 0.03 mmol) was added to the reaction, slowly warmed to rt and stirred for 90 min. The reaction was quenched with ^{i}PrOH (1 mL), filtered through Celite pad and washed with EtOAc. The filtrate was dried over $MgSO_4$, filtered and concentrated. The title compound (1.6 mg, 20%, 3 steps) was prepared following General Procedure E using crude (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-2-(ethoxycarbonyl)-1-methyl-1*H*-indole-5-carboxylic acid and morpholine (50 μL, 50 mg, 0.58 mmol) followed by saponification using General procedure D. LCMS: R_T = 2.006, 2.035, 2.088 min, MS (ES) 824.8 (M+H).

Example 592

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-(2-(dimethylamino)ethoxy)-1-((6-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

[001009] The title compound (1.8 mg, 10%) was prepared following General Procedure H using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-((6-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylate (15 mg, 0.019 mmol) and 2-bromo-*N*,*N*-dimethylethan-1-amine (15 mg, 0.064 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.685 min, MS (ES) 889.8 (M+H).

Example 593

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-4-methoxy-1-((6-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

[001010] The title compound (13.3 mg, 51%) was prepared following General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-

6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-4-methoxy-1H-indole-2-carboxylate (23 mg, 0.031 mmol) and 2-(chloromethyl)-6-methylpyridine (10 mg, 0.070 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.985, 1.953 min, MS (ES) 832.8 (M+H).

Example 594

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-(2-methoxyethyl)-5-methyl-1*H*-indole-2-carboxylic acid

[001011] The title compound (13.2 mg, 47%) was prepared following General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-methyl-1H-indole-2-carboxylate (25 mg, 0.034 mmol) and 1-bromo-2-methoxyethane (10 mg, 0.072 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.288, 2.302 min, MS (ES) 767.8 (M+H). ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 9.10 (s, 1H), 7.92 (d, *J* = 8.6 Hz, 0.34H), 7.91 (d, *J* = 8.6 Hz, 0.66H), 7.43 (d, *J* = 8.6 Hz, 0.34H), 7.41 (d, *J* = 8.6 Hz, 0.66H), 7.23-7.19 (m, 1H), 7.16-6.98 (m, 2H), 6.73 (s, 1.34H), 6.69 (s, 0.66H), 4.71-4.64 (m, 0.34H), 4.35 (dd, *J* = 13.4, 3.4 Hz, 0.66H), 4.13-4.07 (m, 2H), 4.03 (s, 1H), 3.99 (t, *J* = 6.0 Hz, 2H), 3.92 (s, 2H), 3.75-3.59 (m, 4H), 3.39-3.17 (m, 5H), 2.32 (s, 1H), 2.27 (s, 2H), 2.25 (s, 4H), 2.24 (s, 2H), 2.20 (s, 2H), 2.18 (s, 1H), 2.07 (quint, *J* = 6.7 Hz, 2H), 1.19 (d, *J* = 6 .4 Hz, 2H), 1.10 (d, *J* = 6.6 Hz, 1H).

Example 595

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-((2-methoxyethoxy)methyl)-1-methyl-1*H*-indole-2-carboxylic acid

[001012] To a solution of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(hydroxymethyl)-1-methyl-1*H*-indole-2-carboxylate (11 mg, 0.014 mmol) in DMF (0.1 mL) at 0 °C was added NaH (0.8 mg, 0.021 mmol) and stirring 10 min. 1-Bromo-2-methoxyethane (2 μL, 2.9 mg, 0.021 mmol) was added, warmed to rt and stirred for 4 h. The reaction was quenched with aq. sat. NH_4Cl and extracted with DCM. The combined organic layer was dried over $MgSO_4$, filtered and concentrated. Subsequent saponification was followed using General procedure D. The title compound (8.0 mg, 71%, 2 steps) was obtained by reverse phase HPLC (Phenomenex

Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA). LCMS: R_T = 2.147, 2.180, 2.234 min, MS (ES) 799.9 (M+H).

Example 596

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-(dimethylamino)-2-oxoethyl)-5-methyl-1*H*-indole-2-carboxylic acid

[001013] The title compound (29 mg, 55%) was prepared following General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (50 mg, 0.07 mmol), and 2-chloro-N,N-dimethylacetamide (10 mg, 0.08 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.21 min, MS (ES) 797 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (m, 1H), 7.50 (s, 0.5H), 7.45 (s, 0.5H), 7.32 (m, 0.5H), 7.30 (m, 10.5H), 7.26 (s, 0.5H), 7.23 (s, 0.5H), 6.86 (m, 1H), 6.70 (s, 1H), 6.69 (s, 1H), 5.84 (m, 1H), 4.92 (m, 1H), 4.55 (m, 1H), 4.10 (m, 1H), 3.97 (m, 2H), 3.75 (m, 3H), 3.58 (m, 1H), 3.22 (m, 2H), 2.60 (m, 3H), 3.51 (m, 3H), 2.37 (s, 1.5H), 2.35 (s, 1.5H), 2.22 (s, 6H), 2.11 (m, 2H), 1.97 (m, 3H), 1.89 (m, 1.5H), 1.84 (s, 1.5H), 1.11 (d, *J* = 6.4 Hz, 3H).

Example 597

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylic acid

[001014] The title compound (40 mg, 70%) was prepared following General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (50 mg, 0.07 mmol) and 4-(2-chloroethyl)-morpholine HCl (25 mg, 0.14 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.03 min, MS (ES) 825 (M+H).

Example 598

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1-(2-morpholino-2-oxoethyl)-1*H*-indole-2-carboxylic acid

[001015] The title compound (20 mg, 36%) was prepared following General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-

indole-2-carboxylate (50 mg, 0.07 mmol) abd 4-(chloroacetyl)morpholine (13 mg, 0.08 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.17 min, MS (ES) 839 (M+H).

Example 599

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((4,6-dimethylpyridin-2-yl)methyl)-5-methyl-1*H*-indole-2-carboxylic acid

[001016] The title compound (30 mg, 47%) was prepared following General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (50 mg, 0.07 mmol) and 2-(chloromethyl)-4,6-dimethylpyridine (26 mg, 0.17 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.05 min, MS (ES) 831 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (m, 1H), 7.57 (bs, *1*H), 7.41 (m, 1H), 7.27 (m, 2H), 6.96 (m, 1H), 6.87 (m, 1H), 6.69 (m, 2H), 6.09 (m, 2H), 4.61 (m, 1H), 3.96 (m, 2H) 3.87 (m, 1H), 3.72 (m, 3H), 3.50 (m, 1H), 3.24-3.33 (bm, 2H), 3.02-3.10 (bm, 2H), 2.39 (s, 1.5H), 2.37 (s, 1.5H), 2.23 (s, 3H), 2.21 (s, 3H), 2.04-2.10 (bm, 5H), 1.94-2.00 (bm, 3H), 1.87 (m, 1H), 1.78 (s, 2H), 1.03 (m, 3H).

Example 600

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((4-(4,5-dihydrooxazol-2-yl)pyridin-2-yl)methyl)-5-methyl-1*H*-indole-2-carboxylic acid

[001017] The title compound (25 mg, 42%) was prepared following General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (40 mg, 0.05 mmol) and 2-(2-(chloromethyl)pyridin-4-yl)-4,5-dihydrooxazole (27 mg, 0.14 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.14 min, MS (ES) 872 (M+H).

Example 601

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(2,4,6-trimethylpyrimidin-5-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-5-carboxylic acid

Step A. Preparation of (4,6-dimethylpyrimidin-2-yl)methanol

[001018] To a solution of 4,6-Dimethylpyrimidine (7.17 g, 66.3 mmol) in MeOH (18 mL), H_2O (66 mL) and H_2SO_4 (5.0 mL, conc.) was added ammonium persulfate (32.2 g, 141.2

mmol) at RT, and the reaction was heated to 60 °C and stirred overnight. The reaction mixture was concentrated to remove MeOH basified with aq. K_2CO_3, extracted with DCM followed by 10% *i*-PrOH in $CHCl_3$. Combined organic fractions were dried over MgSO4, filtered, and concentrated. The crude title compound (8.69 g, 95%) was obtained as a yellow solid and carried forward without further purification. ^{1}H NMR: (400 MHz in $CDCl_3$) δ 6.96 (s, 1H), 4.77 (s, 2H), 2.51 (s, 6H); LCMS: RT = 0.096 min, MS (ES) 139.17 (M+H).

Step B. Preparation of (4, 6-dimethylpyrimidin-2-yl)methyl methanesulfonate.

[001019] To a solution of (4,6-dimethyl pyrimidin-2-yl)methanol (3.0 g, 21.7 mmol) in DCM (72 mL) was added Et_3N (6.06 mL, 43.4 mmol), followed by MsCl (2.86 mL, 36.9 mL) at 0 °C. The reaction mixture was stirred for 3h at RT, quenched with sat. NH_4Cl (50 mL), and extracted with DCM. The combined organic layer was dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-90% gradient) to afford the title compound (4.32 g, 92%).^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.3, 162.4, 119.4, 71.2, 38.8, 23.8; LCMS: RT = 0.344 min, MS (ES) 217.3 (M+H).

Step C. Preparation of 5-bromo-2-(bromomethyl)-4, 6-dimethylpyrimidine

[001020] To a solution of (4,6-dimethylpyrimidin-2-yl)methyl methanesulfonate (4.68 g, 21.7 mmol) in EtOH (108 mL) was added bromine (3.34 mL, 65.13 mmol) at 0 °C. The reaction was warmed to RT and stirred overnight. Solvent was removed *in vacuo*. The reaction mixture was diluted with DCM, washed with aqueous $Na_2S_2O_3$, and the combined organic layer was concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-50% gradient) to afford the title compound (4.5 g, 70%). ^{1}H NMR: (400 MHz in CDCl3) δ 4.47 (s, 2H), 2.63 (6H); LCMS: RT = 0.754 min, MS (ES) 278.9 (M+H).

Step D. Preparation of 5-bromo-2, 4, 6-trimethylpyrimidine

[001021] To a solution of 5-bromo-2-(bromomethyl)-4,6-dimethyl pyrimidine (4.5 g, 16.4 mmol) in THF (160 mL) was added Raney-Nickel (30 g). The reaction mixture was vigorously stirred at RT overnight, diluted with DCM then filtered through Celite pad. The filtrate was dried over $MgSO_4$, filtered, concentrated to afford the crude title compound as a green solid obtained and carried forward without further purification. ^{1}H NMR: (400 MHz in MeOD) δ 2.55 (s, 6H), 2.51 (s, 3H); LCMS: RT = 0.746 min, MS (ES) 201.07 (M+H).

Step E. Preparation of (2,4,6-trimethylpyrimidin-5-yl)boronic acid

[001022] A mixture of 5-bromo-2,4,6-trimethylpyrimidine (1.0 g, 4.97 mmol) and triisopropoxy borate (2.52 mL, 10.94 mmol) in THF (4.97 mL)/toluene (15.0 mL) was added

n-BuLi (6.83 mL, 10.94 mmol) at -40 °C. The reaction mixture was warmed to -20 °C, quenched with HCl solution (1N, 10 mL), diluted with water and extracted with DCM. The combined organic layer was dried over $MgSO_4$ and concentrated to afford the crude title compound that was carried forward without further purification. ^{1}H NMR: (400 MHz in MeOD) δ 3.58 (s, OH), 2.46 (s, 6H), 2.42 (s, 3H); LCMS: RT = 0.085 min, MS (ES) 166.09 (M+H).

Step F. Preparation of ethyl 6-chloro-3-(3-(4-chloro-3, 5-dimethylphenoxy)propyl)-7-(2,4,6-trimethylpyrimidin-5-yl)-1H-indole-2-carboxylate

[001023] A solution of ethyl 3-(3-(l1-oxidanyl)propyl)-7-bromo-6-chloro-1H-indole-2-carboxylate (124 mg, 0.25 mmol), (2,4,6-trimethylpyrimidin-5-yl)boronic acid (83 mg, 0.5 mmol), Sphos (51 mg, 0.125 mmol), $Pd_2(dba)_3$ (37 mg, 0.04 mmol) and K_3PO_4 (186 mg, 0.875 mmol) in THF (1.5 ml)/toluene (1.5 mL) was heated at 110 °C overnight. The Reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-80% gradient) to afford the title compound (40 mg, 30%). LCMS: RT = 1.004 min, MS (ES) 540.21 (M+H).

Step G. Preparation of (*R*)-1-(1-((tert-butoxycarbonyl)amino)propan-2-yl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(2,4,6-trimethylpyrimidin-5-yl)-1H-indole-2-carboxylate

[001024] A solution of ethyl 6-chloro-3-(3-(4-chloro-3, 5-dimethylphenoxy)propyl)-7-(2,4,6-trimethylpyrimidin-5-yl)-1H-indole-2-carboxylate (156 g, 0.29 mmol), *tert*-butyl (*S*)-5-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (96 mg, 0.41 mmol), and Cs_2CO_3 (151 mg, 0.46 mmol) in MeCN (3 ml) was stirred at 60 °C for 12h. The reaction mixture was concentrated and the residue was diluted with EtOAc (10 mL)/water (10 mL), extracted with EtOAc, dried and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-30% gradient) to afford the title compound (192 mg, 95 %). LCMS: RT = 1.231min, MS (ES) 697.31 (M+H).

Step H. Preparation of (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(2,4,6-trimethyl pyrimidin-5-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one

[001025] The title compound (81 mg, 50%) was prepared following the procedure described Example 1 Step G using (*R*)-1-(1-((tert-butoxycarbonyl)amino)propan-2-yl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(2,4,6-trimethylpyrimidin-5-yl)-1H-indole-2-carboxylate (192 mg, 0.27 mmol). 1H NMR: (400 MHz in MeOD) δ 7.76 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 6.63 (s, 2H), 4.48-4.69 (m, 1H), 3.97 (dt, J = 6.0, 1.6 Hz, 2H), 3.71-3.65 (m, 2H), 3.42-3.35 (m, 2H), 2.76 (s, 3H), 2.32 (s, 3H), 2.31 (s, 6H), 2.21-2.16 (m, 2H),

2.15 (s, 3H), 1.01 (d, J = 6.0 Hz, 3H); LCMS: RT = 0.857 min, > 98% purity at 215 nm and 254 nm; MS (ES) 551.20 (M+H).

Step I. Example 601

[001026] The title compound was prepared following General Procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(2,4,6-trimethyl pyrimidin-5-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one and methyl 3-bromo-1-methyl-1*H*-indole-5-carboxylate followed by saponification (29 mg, 0.07 mmol) using General Procedure D. ^{1}H NMR: (400 MHz in MeOD) δ 8.25 (d, *J* = 1.2 Hz, 1H), 7.94 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.38 (s, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 6.65 (s, 2H), 4.43 (dd, *J* = 12.8, 3.6 Hz, 1H), 3.99 (dt, *J* = 6.0, 2.4 Hz, 2H), 3.88 (s, 3H), 3.90-3.75 (m, 1H), 3.67 (dd, *J* = 12.8, 1.2 Hz, 1H), 3.55-3.46 (m, 1H), 3.41-3.34 (m, 1H), 2.77 (s, 3H), 2.39 (s, 3H), 2.29 (s, 6H), 2.24 (s, 3H), 2.28-2.15 (m, 2H), 1.26 (d, *J* = 6.4 Hz, 3H); LCMS: R_T = 0.766 min, > 98% purity at 215 nm and 254 nm; MS (ES) 724.24 (M+H).

Example 602

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(1-(2-methoxyethyl)-5-(1-(2-(4-methylpiperazin-1-yl)ethyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 5-(1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1*H*-1,2,4-triazol-3-yl)-3-iodo-1-(2-methoxyethyl)-1*H*-indol

[001027] The crude title compound (200 mg) was prepared following General Procedure G using 3-iodo-1-(2-methoxyethyl)-5-(1*H*-1,2,4-triazol-3-yl)-1*H*-indole (150 mg, 0.41 mmol) and (2-bromoethoxy)-*tert*-butyldimethylsilane (105 μL, 0.49 mmol). LCMS: R_T = 0.196 min, MS (ES) 412.9 (M+H).

Step B. Preparation of 2-(3-(3-iodo-1-(2-methoxyethyl)-1*H*-indol-5-yl)-1*H*-1,2,4-triazol-1-yl)ethan-1-ol

[001028] The title compound (110 mg, 70%) was prepared following the procedure descried Example 420 Step C using 5-(1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1*H*-1,2,4-triazol-3-yl)-3-iodo-1-(2-methoxyethyl)-1*H*-indol (200 mg, 0.38 mmol). LCMS: R_T = 1.317 min, MS (ES) 412.9 (M+H).

Step C. Preparation of 3-iodo-1-(2-methoxyethyl)-5-(1-(2-(4-methylpiperazin-1-yl)ethyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[001029] The crude title compound (46 mg) was prepared following General Procedure J using 2-(3-(3-iodo-1-(2-methoxyethyl)-1*H*-indol-5-yl)-1*H*-1,2,4-triazol-1-yl)ethan-1-ol (110

mg, 0.27 mmol) and 1-methylpiperazine (82 μL, 0.73 mmol). LCMS: R_T = 0.166 min, MS (ES) 494.8 (M+H).

Step D. Example 602

[001030] The title compound (27 mg, 54%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 3-iodo-1-(2-methoxyethyl)-5-(1-(2-(4-methylpiperazin-1-yl)ethyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (45 mg, 0.09 mmol). LCMS: R_T = 1.879 min, MS (ES) 904.9 (M+H).

Example 603

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1-(2-(4-methyl-3-oxopiperazin-1-yl)ethyl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 2-(3-iodo-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethan-1-ol

[001031] The crude title compound (210 mg) was prepared following the procedure descried Example 388 Step B using 2-(5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethan-1-ol (160 mg, 0.66 mmol). LCMS: R_T = 1.217 min, MS (ES) 368.8 (M+H).

Step B. Preparation of 4-(2-(3-iodo-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethyl)piperazin-2-one

[001032] The title compound (23 mg, 29%) was prepared following General Procedure J using 2-(3-iodo-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethan-1-ol (210 mg, 0.57 mmol) and piperazin-2-one (54 mg, 0.54 mmol). LCMS: R_T = 1.099 min, MS (ES) 450.9 (M+H).

Step C. Preparation of 4-(2-(3-iodo-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethyl)-1-methylpiperazin-2-one

[001033] The crude title compound (200 mg) was prepared following General Procedure G using 4-(2-(3-iodo-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethyl)piperazin-2-one (23 mg, 0.05 mmol) and MeI (4 μL, 0.06 mmol). LCMS: R_T = 1.123 min, MS (ES) 464.8 (M+H).

Step D. Example 603

[001034] The title compound (2.1 mg, 5%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.05 mmol)

and 4-(2-(3-iodo-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethyl)-1-methylpiperazin-2-one (24 mg, 0.05 mmol). LCMS: R_T = 1.855 min, MS (ES) 874.9 (M+H).

Example 604

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-5-(*N*-methyl-2-(4-methylpiperazin-1-yl)acetamido)-1*H*-indole-3-carboxylic acid

[001035] The title compound (68%) was prepared following General procedure E using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy) propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-methyl-5-(methylamino)-1H-indole-3-carboxylate and 2-(4-methylpiperazin-1-yl)acetic acid followed by saponification using General Procedure D. ^{1}H-NMR (MeOH-d_4), δ 8.16 and 8.12 (s, total 1H), 8.00 (s, 1H), 7.79 (d, 1H, J= 12 Hz), 7.34 (d, 1H, J= 12 Hz), 7.25 and 7.09 (two s, total 1H), 6.64 and 6.63 (two s, total 2H), 4.46-4.37 (m, 1H), 4.00-3.96 (m, 2H), 3.87-3.76 (multiples s, total 5H), 3.79-3.76 (m, 2H), 3.51-3.48 (m, 2H), 3.24-3.22 (m, 4H), 3.34 (s, 2H), 2.85 (s, 6H), 2.29 (s, 6H), 2.24-2.23 (multiple s, total 3H), 2.18 and 2.15 (multiple d, total 4H, J = 4 Hz), 2.02 (m, 2H), 2.01 and 2.99 (multiple d, total 4H, J= 4 Hz), 1.29-1.21 (multiple d, total 3H, J= 8Hz); MS (ES) 881.2 (M+H).

Example 605

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-methoxy-1-(pyridin-2-ylmethyl)-1H-indole-3-carboxylic acid

Step A. Preparation of ethyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(pyridin-2-ylmethyl)-1*H*-indole-3-carboxylate

[001036] The title compound (37 mg, 99%) was prepared according to General Procedure I using methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-3-carboxylate (39 mg, 0.02 mmol) and 2-(bromomethyl)pyridine HBr (19 mg, 0.074 mmol). LCMS: R_T = 2.443 MS (ES) 922.90 (M+H).

Step B. Preparation of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-(pyridin-2-ylmethyl)-1*H*-indole-3-carboxylate

[001037] To a solution of ethyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(pyridin-2-ylmethyl)-1*H*-indole-3-carboxylate (37 mg, 0.04 mmol) in ethanol (2 mL) was added Pd/C (18.5 mg, 10%) and the mixture was stirred under H_2 for 10 h. The reaction mixture was filtered through a pad of silica gel and eluted with DCM. The filtrate was concentrated and purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-20% gradient) to afford the title compound (28 mg, 90%). LCMS R_T = 1.988 min, MS (ES) 833.8 (M+H).

Step C. Example 605

[001038] The title compound (11 mg, 67%) was prepared according to General Procedure H using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-(pyridin-2-ylmethyl)-1*H*-indole-3-carboxylate (17 mg, 0.02 mmol) and MeI (5 μL, 0.08 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.122 min (Method B), MS (ES) 818.0 (M+H).

Example 606

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-(2-isopropoxyethoxy)-1-(pyridin-2-ylmethyl)-1H-indole-3-carboxylic acid

[001039] The title compound (13 mg, 73%) was prepared according to General Procedure H using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-(pyridin-2-ylmethyl)-1*H*-indole-3-carboxylate (17 mg, 0.02 mmol) and 1-bromo-4-methylpentane (12 μL, 0.08 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.153 min, MS (ES) 890.80 (M+H).

Example 607

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(methoxymethyl)-1-methyl-1*H*-indole-2-carboxylic acid

[001040] The title compound was prepared (140 mg, 77%, 2 steps) following the procedure described Example 595 using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy) propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(hydroxymethyl)-1-methyl-1*H*-indole-2-carboxylate (185 mg, 0.24

mmol) and MeI (22 μL, 51 mg, 0.36 mmol). LCMS: R_T = 2.159, 2.193, 2.245 min, MS (ES) 755.8 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (d, J = 8.6 Hz, 1H), 7.66 (s, 0.6 H), 7.61 (s, 0.3 H), 7.35 – 7.27 (m, 2.4 H), 7.08 – 7.05 (m, 0.6 H), 6.74 – 6.67 (m, 2H), 4.73 – 4.65 (m, 0.4 H), 4.49 – 4.44 (m, 2H), 4.37 (dd, J = 13.2, 3.6 Hz, 0.6 H), 4.29 – 4.14 (m, 1H), 4.06 (s, 1H), 4.02 – 3.92 (m, 4H), 3.82 – 3.75 (m, 3.2 H), 3.74 – 3.63 (m, 1H), 3.29 (s, 3H), 3.27 – 3.14 (m, 1.4 H), 2.23 (br s, 6H), 2.15 – 2.10 (m, 2H), 2.10 – 1.96 (m, 4.6 H), 1.94 – 1.87 (m, 2H), 1.18 (d, J = 6.4 Hz, 2H), 1.07 (d, J = 6.1 Hz, 1.2 H).

Example 608

7-((*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-((*S*)-2-(dimethylamino)-*N*-methylpropanamido)-1-methyl-1*H*-indole-3-carboxylic acid

[001041] The title compound (70%) was prepared following General procedure E using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy) propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-methyl-5-(methylamino)-1H-indole-3-carboxylate and dimethyl-*L*-alanine followed by saponification using General Procedure D. MS (ES) 840.3 (M+H).

Example 609

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-(2-methoxyethoxy)-1-(pyridin-2-ylmethyl)-1H-indole-3-carboxylic acid

[001042] The title compound (16 mg, 93%) was prepared according to General Procedure H using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-(pyridin-2-ylmethyl)-1*H*-indole-3-carboxylate (17 mg, 0.02 mmol) and 1-bromo-2-methoxyethane (8 μL, 0.08 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.052 min, MS (ES) 862.8 (M+H).

Example 610

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-(2-ethoxyethoxy)-1-(pyridin-2-ylmethyl)-1H-indole-3-carboxylic acid

[001043] The title compound (11 mg, 63% yield) was prepared according to General Procedure H using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-

yl)-5-hydroxy-1-(pyridin-2-ylmethyl)-1*H*-indole-3-carboxylate (17 mg, 0.02 mmol) and 1-bromo-2-ethoxyethane (9 μL, 0.08 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.126 min, MS (ES) 876.9 (M+H).

Example 611

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-(2-(dimethylamino)-*N*-methylacetamido)-1-methyl-1*H*-indole-3-carboxylic acid

[001044] The title compound (47%) was prepared following General procedure E using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy) propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-methyl-5-(methylamino)-1H-indole-3-carboxylate and dimethylglycine followed by saponification using General Procedure D. MS (ES) 826.2 (M+H).

Example 612

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-5-(*N*-methyl-2-(piperidin-1-yl)acetamido)-1*H*-indole-3-carboxylic acid

[001045] The title compound (75%) was prepared following General procedure E using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy) propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-methyl-5-(methylamino)-1H-indole-3-carboxylate and 2-(piperidin-1-yl)acetic acid followed by saponification using General Procedure D. ^{1}H-NMR (MeOH-d_4), δ 8.18 and 8.13 (s, total 1H), 8.03 (s, 1H), 7.80 (d, 1H, J= 12 Hz), 7.32 (d, 1H, J= 12 Hz), 7.14 and 7.13 (two s, total 1H), 6.64 and 6.63 (two s, total 2H), 4.46-4.42 (m, 1H), 4.04-4.02 (m, 2H), 3.99-3.82 (multiples s, total 6H), 3.50 -3.39 (m, 4H), 3.39 (multiples s, total 3H), 3.35-3.30 (m, 4H), 2.89-2.86 (m, 2H), 2.29 (s, 6H), 2.24-2.08 (multiple s, total 3H), 2.02 (m, 2H), 2.08 and 2.00 (two s, total 3H), 1.84- 1.78 (m, 6H), 1.29-1.21 (multiple d, total 3H, J= 8Hz); MS (ES) 865.3 (M+H).

Example 613

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-5-(*N*-methyl-2-(pyrrolidin-1-yl)acetamido)-1*H*-indole-3-carboxylic acid

[001046] The title compound (82%) was prepared following General procedure E using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy) propyl)-4-methyl-1-oxo-6-

(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-methyl-5-(methylamino)-1H-indole-3-carboxylate and 2-(pyrrolidin-1-yl)acetic acid followed by saponification using General Procedure D. MS (ES) 852.3 (M+H).

Example 614

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-((2-(dimethylamino)ethoxy)methyl)-1-methyl-1*H*-indole-2-carboxylic acid

[001047] The title compound was prepared (1.2 mg, 11%, 2 steps) following the procedure described Example 595 using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy) propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(hydroxymethyl)-1-methyl-1*H*-indole-2-carboxylate (11 mg, 0.014 mmol) and 2-bromo-*N*,*N*-dimethylethan-1-amine HCl (4.9 mg, 0.021 mmol). LCMS: R_T = 1.900, 1.931 min, MS (ES) 812.8 (M+H).

Example 615

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(1-(2-methoxyethyl)-5-(1-(2-morpholinoethyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 4-(2-(3-(3-iodo-1-(2-methoxyethyl)-1*H*-indol-5-yl)-1*H*-1,2,4-triazol-1-yl)ethyl)morpholine

[001048] The crude title compound (50 mg) was prepared following General Procedure J using 2-(3-(1-(2-methoxyethyl)-1*H*-indol-5-yl)-1*H*-1,2,4-triazol-1-yl)ethan-1-ol (110 mg, 0.27 mmol) and morpholine (35 μL, 0.41 mmol). LCMS: R_T = 0.184 min, MS (ES) 481.9 (M+H).

Step B. Example 615

[001049] The title compound (11 mg, 22%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 4-(2-(3-(3-iodo-1-(2-methoxyethyl)-1*H*-indol-5-yl)-1*H*-1,2,4-triazol-1-yl)ethyl)morpholine (50 mg, 0.10 mmol). LCMS: R_T = 1.920 min, MS (ES) 891.9 (M+H).

Example 616

((*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-((3-methyloxetan-3-yl)methyl)-1H-indole-5-carboxylic acid

[001050] The title compound (4.6 mg, 42%) was prepared according to General Procedure I using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5- trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-5-carboxylate (15 mg, 0.02 mmol) and 3-(bromomethyl)-3-methyloxetane (5 mg, 0.03 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.111 min, MS (ES) 781.80 (M+H).

Example 617

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-4-methoxy-1-(pyridin-2-ylmethyl)-1H-indole-3-carboxylic acid

[001051] The title compound (15 mg, 91%) was prepared according to General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1*H*-indole-3-carboxylate (15 mg, 0.02 mmol) and 2-(bromomethyl)pyridine HBr (10 mg, 0.04 mmol). LCMS: R_T = 2.132 min, MS (ES) 818.8(M+H).

Example 618

(*R*)-2-(5-(1-((1-Acetylazetidin-3-yl)methyl)-1*H*-1,2,4-triazol-3-yl)-1-(2-methoxyethyl)-1*H*-indol-3-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of *tert*-butyl 3-((3-(3-iodo-1-(2-methoxyethyl)-1*H*-indol-5-yl)-1*H*-1,2,4-triazol-1-yl)methyl)azetidine-1-carboxylate

[001052] The title compound (100 mg, 69%) was prepared following General Procedure G using 3-iodo-1-(2-methoxyethyl)-5-(1*H*-1,2,4-triazol-3-yl)-1*H*-indole (100 mg, 0.27 mmol) and 1-Boc-3-(bromomethyl)azetidine (136 mg, 0.54 mmol). LCMS: R_T = 1.772 min, MS (ES) 481.8 (M+H).

Step B. Preparation of 5-(1-(azetidin-3-ylmethyl)-1*H*-1,2,4-triazol-3-yl)-3-iodo-1-(2-methoxyethyl)-1*H*-indole

[001053] TFA (0.3 mL) was added to a solution of *tert*-butyl 3-((3-(3-iodo-1-(2-methoxyethyl)-1*H*-indol-5-yl)-1*H*-1,2,4-triazol-1-yl)methyl)azetidine-1-carboxylate (100 mg, 0.19 mmol) in DCM (0.5 mL) at 0 °C. The reaction was stirred at RT for 1 h, concentrated and diluted with DCM. The solution was washed with sat. aq. $NaHCO_3$, dried and concentrated to afford the crude title compound (75 mg) that was used for the next step without further purification. LCMS: R_T = 1.258 min, MS (ES) 437.8 (M+H).

Step C. Preparation of 1-(3-((3-(3-iodo-1-(2-methoxyethyl)-1*H*-indol-5-yl)-1*H*-1,2,4-triazol-1-yl)methyl)azetidin-1-yl)ethan-1-one

[001054] Acetyl chloride (19 μL, 0.26 mmol) and DIPEA (48 μL, 0.27 mmol) was added to a solution of 5-(1-(azetidin-3-ylmethyl)-1*H*-1,2,4-triazol-3-yl)-3-iodo-1-(2-methoxyethyl)-1*H*-indole (75 mg, 0.17 mmol) in DCM (1 mL) at 0 °C. The reaction was warm to RT and stirred for 3 h. The reaction mixture was diluted with water and extracted with DCM. The combined organic layers were dried and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-3% gradient) to afford the title compound (50 mg, 60%). LCMS: R_T = 1.407 min, MS (ES) 479.8 (M+H).

Step D. Example 618

[001055] The title compound (22 mg, 44%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 1-(3-((3-(3-iodo-1-(2-methoxyethyl)-1*H*-indol-5-yl)-1*H*-1,2,4-triazol-1-yl)methyl)azetidin-1-yl)ethan-1-one (49 mg, 0.10 mmol). LCMS: R_T = 2.033 min, MS (ES) 889.9 (M+H).

Example 619

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-4-methoxy-1-((4-methylpyridin-2-yl)methyl)-1H-indole-3-carboxylic acid

[001056] The title compound (8.8 mg, 53%) was prepared according to General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1*H*-indole-3-carboxylate (15 mg, 0.02 mmol) and 2-(chloromethyl)-4-methylpyridine (10 mg, 0.04 mmol). LCMS: R_T = 2.036 min, MS (ES) 832.8(M+H).

Example 620

(*R*)-1-(2-amino-2-oxoethyl)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1H-indole-5-carboxylic acid

[001057] The title compound (8.2 mg, 54%) was prepared according to General Procedure I using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-5-carboxylate (15 mg, 0.02 mmol) and 2-bromoacetonitrile (5 mg, 0.04 mmol) followed by

saponification using General Procedure D. LCMS: R_T = 1.951 min, MS (ES) 755.80 (M+H).

Example 621

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-4-methoxy-1-((6-methylpyridin-2-yl)methyl)-1H-indole-3-carboxylic acid (2nd eluted atropisomer, absolute configuration undeterminded)

[001058] The title compound (6.7 mg, 40%) was prepared according to General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1*H*-indole-3-carboxylate (15 mg, 0.02 mmol) and 2-(chloromethyl)-6-methylpyridine (10 mg, 0.04 mmol) as the 2nd eluted isomer from reverse phase HPLC. LCMS: R_T = 2.034 min, MS (ES) 832.8(M+H).

Example 622

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-4-methoxy-1-((6-methylpyridin-2-yl)methyl)-1H-indole-3-carboxylic acid (1st eluted atropisomer, absolute configuration undeterminded)

[001059] The title compound (5.2 mg, 11%) was isolated along with Example 621 as the 1st eluted isomer from reverse phase HPLC. LCMS: R_T = 1.998 min, MS (ES) 832.8(M+H).

Example 623

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-5-(morpholinomethyl)-1*H*-indole-2-carboxylic acid

[001060] To a solution of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(hydroxymethyl)-1-methyl-1*H*-indole-2-carboxylate (135 mg, 0.175 mmol) in DCM (2 mL) was added $^{i}Pr_2EtN$ (47 μL, 34 mg, 0.263 mmol) followed by MsCl (13.3 μL, 20 mg, 0.175 mmol). After stirring for 10 min, morpholine (46 μL, 46 mg, 0.53 mmol) was added and stirred for additional 30 min. The reaction was quenched with aq. sat. NH_4Cl and extracted with DCM. The combined organic layer was dried over $MgSO_4$, filtered and concentrated. Subsequent saponification following General procedure D to afford the title compound (100 mg, 70%, 2 steps). LCMS: R_T = 1.913, 1.963 min, MS (ES) 810.9 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 – 7.73 (m,

1H), 7.51 – 7.46 (m, 0.9H), 7.34 – 7.28 (m, 1.1H), 7.16 – 7.12 (m, 0.3H), 7.02 (br s, 0.7 H), 6.97 – 6.90 (m, 0.7 H), 6.74 – 6.67 (m, 2H), 4.71 – 4.64 (m, 0.3 H), 4.36 – 4.29 (m, 0.7 H), 4.26 – 4.14 (m, 1.1 H), 4.11 (s, 0.9 H), 4.01 (s, 1.7 H), 4.00 – 3.94 (m, 2.2 H), 3.81 – 3.77 (m, 2.4 H), 3.76 (br s, 0.9 H), 3.73 – 3.60 (m, 1.2 H), 3.59 – 3.54 (m, 4H), 3.53 – 3.45 (m, 2.2 H), 3.39 – 3.26 (m, 2H), 3.25 – 3.15 (m, 1.2 H), 2.27 – 2.19 (m, 6H), 2.15 – 2.10 (m, 2H), 2.08 – 2.02 (m, 2.8 H), 2.01 (s, 0.8 H), 1.97 (s, 0.8 H), 1.92 (s, 0.7 H), 1.89 (s, 1.3 H), 1.75 – 1.66 (m, 0.3 H), 1.63 – 1.44 (m, 0.7 H), 1.20 – 1.15 (m, 2.1 H), 1.09 – 1.03 (m, 1.3 H).

Example 624

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(1-(2-methoxyethyl)-5-(1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 3-iodo-1-(2-methoxyethyl)-5-(1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[001061] The crude title compound (150 mg) was prepared following General Procedure G using 3-iodo-1-(2-methoxyethyl)-5-(1*H*-1,2,4-triazol-3-yl)-1*H*-indole (120 mg, 0.33 mmol) and 4-bromomethyltetrahydropyran (117 μL, 0.65 mmol). LCMS: R_T = 1.517 min, MS (ES) 466.9 (M+H).

Step B. Example 624

[001062] The title compound (26 mg, 53%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 3-iodo-1-(2-methoxyethyl)-5-(1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (52 mg, 0.11 mmol). LCMS: R_T = 2.167 min, MS (ES) 876.9 (M+H).

Example 625

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-4-methoxy-1-(2-methoxyethyl)-1H-indole-3-carboxylic acid

[001063] The title compound (14 mg, 89%) was prepared according to General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1*H*-indole-3-carboxylate (15 mg, 0.02 mmol) and 1-bromo-2-methoxyethane (10 mg, 0.04 mmol). LCMS: R_T = 2.029 min, MS (ES) 785.8(M+H).

Example 626

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-5-(4-methylpiperazine-1-carbonyl)-1*H*-indole-2-carboxylic acid

[001064] The title compound has was (6.0 mg, 40%, 3 steps) following the procedure described Example 591 step D using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(hydroxymethyl)-1-methyl-1*H*-indole-2-carboxylate (13 mg, 0.018 mmol) and N-methyl piperazine (50 μL, 45 mg, 0.45 mmol). LCMS: R_T = 1.852, 1.879 min, MS (ES) 837.9 (M+H).

Example 627

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((4-ethylpyridin-2-yl)methyl)-5-methyl-1*H*-indole-2-carboxylic acid

[001065] The title compound (39 mg, 61%) was prepared following General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (50 mg, 0.07 mmol) and 2-(chloromethyl)-4-ethylpyridine (21 mg, 0.14 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.07 min, MS (ES) 831 (M+H).

Example 628

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-5-((4-methyl-3-oxopiperazin-1-yl)methyl)-1*H*-indole-2-carboxylic acid

[001066] To a solution of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(hydroxymethyl)-1-methyl-1*H*-indole-2-carboxylate (8 mg, 0.011 mmol) in DCM (0.1 mL) was added Dess-Martin periodinane reagent (5 mg, 0.011 mmol) and stirred at RT for 30 min. The reaction was quenched with aq. sat. $Na_2S_2O_3$ solution and extracted with DCM. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The resulting crude product was redissolved in DCM (0.2 mL) and Et_3N (0.04 mL). 1-methylpiperazin-2-one (2.6 μL, 2.6 mg, 0.026 mmol) and $Na(OAc)_3BH$ (4.7 mg, 0.022 mmol) were added to the reaction mixture and stirred at RT for 4 h. The reaction was quenched with aq. sat. NH_4Cl and extracted with

DCM. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. Subsequent saponification was followed using General procedure D to afford the title compound (1.5 mg, 17%, 3 steps). LCMS: R_T = 1.856, 1.895 min, MS (ES) 837.9 (M+H).

Example 629

(*R*)-5-(4-acetylpiperazine-1-carbonyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylic acid

[001067] The title compound was prepared (1.8 mg, 12%, 3 steps) following the procedures described Example 591 in step D using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(hydroxymethyl)-1-methyl-1*H*-indole-2-carboxylate (13 mg, 0.018 mmol) and 1-(piperazin-1-yl)ethan-1-one (50 μL, 0.39 mmol). LCMS: R_T = 1.941, 1.966 min, MS (ES) 865.8 (M+H).

Example 630

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-5-(4-methyl-3-oxopiperazine-1-carbonyl)-1*H*-indole-2-carboxylic acid

[001068] The title compound was prepared (2.1 mg, 14%, 3 steps) following the procedures described in Example 591 step D using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(hydroxymethyl)-1-methyl-1*H*-indole-2-carboxylate (13 mg, 0.018 mmol) and 1-methylpiperazin-2-one (50 μL, 0.44 mmol). LCMS: R_T = 1.966 min, MS (ES) 851.8 (M+H).

Example 631

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-(2-(2-methoxyethoxy)ethoxy)-1-methyl-1*H*-indole-2-carboxylic acid

[001069] The title compound (2.2 mg, 13%) was prepared following General Procedure H using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-methyl-1*H*-indole-2-carboxylate (15 mg, 0.020 mmol) and 1-bromo-2-(2-methoxyethoxy)ethane (10 mg, 0.054 mmol) followed by saponification using General

Procedure D. LCMS: R_T = 2.181 min, MS (ES) 827.8 (M+H).

Example 632

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-4-(2-methoxyethoxy)-1-((4-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

Step A. Methyl (*R*)-4-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl) -4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate

[001070] The title compound (105 mg, 35%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (200 mg, 0.37 mmol) and methyl 4-(benzyloxy)-7-iodo-1*H*-indole-2-carboxylate (300 mg, 0.74 mmol). LCMS: R_T = 1.596, 1.627 min, MS (ES) 817.8 (M+H).

Step B. methyl (*R*)-4-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((4-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylate

[001071] The title compound (31 mg, 78%) was prepared following General Procedure I using methyl (*R*)-4-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (35 mg, 0.043 mmol) and 2-(chloromethyl)-4-methylpyridine HBr (15 mg, 0.085 mmol). LCMS: R_T = 1.314, 1.343, 1.403 min, MS (ES) 922.8 (M+H).

Step C. methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-hydroxy-1-((4-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylate

[001072] The title compound (16.2 mg, 58%) was prepared following the procedure described Example 390 Step D using methyl (*R*)-4-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-((4-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylate (31 mg, 0.034 mmol) and Pd/C (10 wt.%, 10 mg, 0.0093 mmol) by hydrogenating in MeOH (5 mL) for 16 h at RT. LCMS: R_T = 0.902, 0.860 min (Method B), MS (ES) 832.9 (M+H).

Step D. Example 632

[001073] The title compound (10.8 mg, 63%) was prepared following General Procedure H

using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-hydroxy-1-((4-methylpyridin-2-yl)methyl)-1*H*-indole-2-carboxylate (11 mg, 0.013 mmol) and 1-bromo-2-methoxyethane (5 mg, 0.036 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.977, 2.005 min, MS (ES) 876.9 (M+H).

Example 633

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-(2-(2-methoxyethoxy)ethoxy)-1-methyl-1H-indole-2-carboxylic acid

[001074] The title compound (9.6 mg, 58%) was prepared following General Procedure H using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-methyl-1*H*-indole-2-carboxylate (15 mg, 0.020 mmol) and 1-bromo-2-(2-methoxyethoxy)ethane (10 mg, 0.054 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.132, 2.161 min, MS (ES) 876.9 (M+H). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) (7.77 (d, *J* = 8.6 Hz, 1H), 7.34-7.31 (m, 1H), 7.28-7.21 (m, 1H), 7.08-6.96 (m, 1H), 6.88-6.83 (m, 0.66H), 6.74-6.70 (m, 0.34H), 6.60 (s, 1.34H), 6.58 (s, 0.66H), 4.45-4.07 (m, 8H), 4.01-3.92 (m, 4H), 3.91-3.81 (m, 3H), 3.77-3.71 (m, 2H), 3.63-3.56 (m, 2H), 3.40 (s, 2H), 3.39 (s, 1H), 3.37-3.30 (m, 2H), 2.45 (s, 1H), 2.35-2.31 (m, 2H), 2.30 (s, 6H), 2.29-2.25 (m, 2H), 2.20-2.09 (m, 3H), 1.31-1.22 (m, 2H), 1.21-1.11 (m, 1H).

Example 634

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-(2-(2-methoxyethoxy)ethyl)-1*H*-indole-2-carboxylic acid

[001075] The title compound (10.2 mg, 46%) was prepared following General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (20 mg, 0.028 mmol) and 1-bromo-2-(2-methoxyethoxy)ethane (10 mg, 0.054 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.182, 2.210 min, MS (ES) 799.9 (M+H).

Example 635

(R)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-(2-(2-methoxyethoxy)ethyl)-5-methyl-1H-indole-2-carboxylic acid

[001076] The title compound (6.4 mg, 38%) was prepared following General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (15 mg, 0.021 mmol) and 1-bromo-2-(2-methoxyethoxy)ethane (10 mg, 0.054 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.292, 2.316 min, MS (ES) 811.8 (M+H).

Example 636

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid

[001077] The title compound (6.4 mg, 18%) was prepared according to General Procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol) and methyl 3-bromo-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (16 mg, 0.06 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.267 min, MS (ES) 710.8 (M+H).

Example 637

(*R*)-2-(3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(pyrimidin-2-yl)-1*H*-indol-1-yl)-*N*,*N*-dimethylacetamide

Step A. Preparation of *N*,*N*-dimethyl-2-(5-(pyrimidin-2-yl)-1*H*-indol-1-yl)acetamide

[001078] The title compound (135 mg, 96%) was prepared following the procedure descried Example 388 Step A using *N*,*N*-dimethyl-2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-1-yl)acetamide (248 mg, 0.75 mmol) and 2-bromopyrimidine (80 mg, 0.50 mmol). LCMS: R_T = 1.181 min, MS (ES) 281.1 (M+H).

Step B. Preparation of 2-(3-iodo-5-(pyrimidin-2-yl)-1*H*-indol-1-yl)-*N*,*N*-dimethylacetamide

[001079] The crude title compound (150 mg) was prepared following the procedure descried Example 388 Step B using *N*,*N*-dimethyl-2-(5-(pyrimidin-2-yl)-1*H*-indol-1-yl)acetamide (135 mg, 0.48 mmol). LCMS: R_T = 1.384 min, MS (ES) 406.8 (M+H).

Step C. Example 637

[001080] The title compound (16 mg, 36%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol)

and 2-(3-iodo-5-(pyrimidin-2-yl)-1*H*-indol-1-yl)-*N*,*N*-dimethylacetamide (45 mg, 0.11 mmol). LCMS: R_T = 2.123 min, MS (ES) 816.9 (M+H).

Example 638

(*R*)-2-(3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(1-(pyridin-2-ylmethyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)-*N*,*N*-dimethylacetamide

Step A. Preparation of *N*,*N*-dimethyl-2-(5-(1-(pyridin-2-ylmethyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)acetamide

[001081] The title compound (66 mg, 49%) was prepared following the procedure descried Example 388 Step A using *N*,*N*-dimethyl-2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-1-yl)acetamide (185 mg, 0.56 mmol) and 2-((3-bromo-1*H*-1,2,4-triazol-1-yl)methyl)pyridine (90 mg, 0.38 mmol). LCMS: R_T = 0.167 min, MS (ES) 361.0 (M+H).

Step B. Preparation of 2-(3-iodo-5-(1-(pyridin-2-ylmethyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)-*N*,*N*-dimethylacetamide

[001082] The crude title compound (100 mg) was prepared following the procedure descried Example 388 Step B using *N*,*N*-dimethyl-2-(5-(1-(pyridin-2-ylmethyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)acetamide (66 mg, 0.18 mmol). LCMS: R_T = 0.199 min, MS (ES) 486.9 (M+H).

Step C. Example 638

[001083] The title compound (14 mg, 27%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 2-(3-iodo-5-(1-(pyridin-2-ylmethyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)-*N*,*N*-dimethylacetamide (54 mg, 0.11 mmol). LCMS: R_T = 1.943 min, MS (ES) 896.8 (M+H).

Example 639

(*R*)-2-(3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(1-((6-methylpyridin-2-yl)methyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)-*N*,*N*-dimethylacetamide

Step A. Preparation of *N*,*N*-dimethyl-2-(5-(1-((6-methylpyridin-2-yl)methyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)acetamide

[001084] The title compound (130 mg, 98%) was prepared following the procedure descried Example 388 Step A using *N*,*N*-dimethyl-2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-

1*H*-indol-1-yl)acetamide (175 mg, 0.53 mmol) and 2-((3-bromo-1*H*-1,2,4-triazol-1-yl)methyl)-6-methylpyridine (90 mg, 0.36 mmol). LCMS: R_T = 1.069 min, MS (ES) 375.0 (M+H).

Step B. Preparation of 2-(3-iodo-5-(1-((6-methylpyridin-2-yl)methyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)-*N*,*N*-dimethylacetamide

[001085] The title compound (100 mg, 58%) was prepared following the procedure descried Example 388 Step B using *N*,*N*-dimethyl-2-(5-(1-((6-methylpyridin-2-yl)methyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)acetamide (130 mg, 0.35 mmol). LCMS: R_T = 1.231 min, MS (ES) 500.8 (M+H).

Step C. Example 639

[001086] The title compound (35 mg, 69%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 2-(3-iodo-5-(1-((6-methylpyridin-2-yl)methyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)-*N*,*N*-dimethylacetamide (56 mg, 0.11 mmol). LCMS: R_T = 1.895 min, MS (ES) 910.9 (M+H).

Example 640

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-methyl-1H-pyrrolo[2,3-c]pyridine-5-carboxylic acid

Step A. Preparation of methyl 3-bromo-1-methyl-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate

[001087] The title compound (26 mg, 34%) was prepared following General Procedure F using methyl 1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (49 mg, 0.28 mmol), NBS (51 mg, 0.28 mmol), and MeI (21 μL, 0.34 mmol). LCMS: R_T = 1.083 min, MS (ES) 268.9 (M+H).

Step B. Example 640

[001088] The title compound (12 mg, 34%) was prepared according to General Procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol) and methyl 3-bromo-1-methyl-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (16 mg, 0.06 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.131 MS (ES) 710.8 (M+H).

Example 641

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1-((4-(prop-1-en-2-yl)pyridin-2-yl)methyl)-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1-((4-(prop-1-en-2-yl)pyridin-2-yl)methyl)-1*H*-indole-2-carboxylate

[001089] To a solution of methyl (*R*)-1-((4-bromopyridin-2-yl)methyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (110 mg, 0.12 mol) in (4:1) dioxane/water (1.5 mL) was added 2-isopropenylboronic acid pinacol ester (41 mg, 0.25 mmol) and $Pd(PPh_3)_4$ (14 mg, 0.01 mmol) and K_2CO_3 (34 mg, 0.25 mmol). The reaction was stirred under Ar at 90°C for 5 h then cooled to RT. The reaction mixture was diluted with EtOAc and water. The aqueous layer was separated and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf, CH_2Cl_2/methanol = 0-3% gradient) to give the title compound (75 mg, 71%). LCMS: R_T = 1.41 min., MS (ES) 857 (M+H).

Step B. Example 641

[001090] The title compound (63 mg, 75%) was prepared following General Procedure D using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1-((4-(prop-1-en-2-yl)pyridin-2-yl)methyl)-1*H*-indole-2-carboxylate (75 mg, 0.09 mmol). LCMS: R_T = 2.11 min., MS (ES) 843 (M+H).

Example 642

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-2-(1-methyl-5-(pyrimidin-2-yl)-1*H*-indol-3-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[001091] The title compound (40 mg, 96%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 3-iodo-1-methyl-5-(pyrimidin-2-yl)-1*H*-indole (37 mg, 0.11 mmol). LCMS: R_T = 2.301 min, MS (ES) 743.8 (M+H).

Example 643

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(5-(1,5-dimethyl-1*H*-1,2,4-triazol-3-yl)-1-methyl-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 5-(1,5-dimethyl-1*H*-1,2,4-triazol-3-yl)-1-methyl-1*H*-indole

[001092] The crude title compound (150 mg) was prepared following the procedure descried Example 388 Step A using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (176 mg, 0.68 mmol) and 3-bromo-1,5-dimethyl-1*H*-1,2,4-triazole (100 mg, 0.57 mmol). LCMS: R_T = 1.153 min, MS (ES) 227.1 (M+H).

Step B. Preparation of 5-(1,5-dimethyl-1*H*-1,2,4-triazol-3-yl)-3-iodo-1-methyl-1*H*-indole

[001093] The crude title compound (190 mg) was prepared following the procedure descried Example 388 Step B using 5-(1,5-dimethyl-1*H*-1,2,4-triazol-3-yl)-1-methyl-1*H*-indole (150 mg, 0.66 mmol). LCMS: R_T = 1.189 min, MS (ES) 352.9 (M+H).

Step C. Example 643

[001094] The title compound (28 mg, 66%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 5-(1,5-dimethyl-1*H*-1,2,4-triazol-3-yl)-3-iodo-1-methyl-1*H*-indole (39 mg, 0.11 mmol). LCMS: R_T = 2.016 min, MS (ES) 762.9 (M+H).

Example 644

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-methyl-5H-pyrrolo[2,3-b]pyrazine-2-carboxylic acid

[001095] The title compound (22 mg, 62%) was prepared according to General Procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol) and methyl 7-bromo-5-methyl-5*H*-pyrrolo[2,3-*b*]pyrazine-2-carboxylate (16 mg, 0.06 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.200 MS (ES) 711.9 (M+H).

Example 645

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-(3,4-difluorobenzyl)-1H-indole-5-carboxylic acid

[001096] The title compound (7 mg, 51%) was prepared according to General Procedure I

using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5- trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-5-carboxylate (15 mg, 0.02 mmol) and 4-(bromomethyl)-1,2-difluorobenzene (5 mg, 0.03 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.109 min (Method B), MS (ES) 823.8 (M+H).

Example 646

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1-(pyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 2-(3-bromo-1*H*-1,2,4-triazol-1-yl)pyrimidine

[001097] Cs_2CO_3 (4.40 g, 13.5 mmol), CuI (257 mg, 1.35 mmol) and 2-bromopyrimidine (1.40 g, 8.79 mmol) were added to a solution of 5-bromo-1*H*-1,2,4-triazole (1.00 g, 6.76 mmol) in DMF (13.5 mL). The reaction mixture was stirred at 120 °C for 18 h under Ar. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic layer was washed with water, dried and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-70% gradient) to afford the title compound (340 mg, 22%). LCMS: R_T = 0.194 min, MS (ES) 226.0 (M+H).

Step B. Preparation of 1-methyl-5-(1-(pyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[001098] The title compound (53 mg, 43%) was prepared following the procedure descried Example 388 Step A using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (137 mg, 0.53 mmol) and 2-(3-bromo-1*H*-1,2,4-triazol-1-yl)pyrimidine (100 mg, 0.44 mmol). LCMS: R_T = 1.373 min, MS (ES) 227.0 (M+H).

Step C. Preparation of 3-iodo-1-methyl-5-(1-(pyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[001099] The crude title compound (35 mg) was prepared following the procedure descried Example 388 Step B using 1-methyl-5-(1-(pyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (53 mg, 0.19 mmol). LCMS: R_T = 1.614 min, MS (ES) 402.9 (M+H).

Step D. Example 646

[001100] The title compound (20 mg, 43%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 3-iodo-1-methyl-5-(1-(pyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (34 mg, 0.08 mmol). LCMS: R_T = 2.205 min, MS (ES) 812.8 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ

9.25 (d, *J* = 5.0 Hz, 1H), 8.82 (dd, *J* = 4.8, 2.5 Hz, 2H), 8.43 (s, 1H), 8.28–8.24 (m, 1H), 7.67 (dd, *J* = 8.6, 2.7 Hz 1H), 7.43 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.33–7.28 (m, 2H), 7.27–7.22 (m, 1H), 6.61 (s, 2H), 4.47–4.51 (m, 1H), 4.35–4.23 (m, 1H), 3.99 (t, *J* = 6.2 Hz, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.66 (t, *J* = 11.8 Hz, 1H), 3.47–3.30 (m, 2H), 2.29 (s, 6H), 2.24–2.17 (m, 5H), 2.00 (s, 3H), 1.26–1.20 (m, 3H).

Example 647

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1-(pyridin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 1-methyl-5-(1-(pyridin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[001101] The title compound (58 mg, 14%) was prepared following the procedure descried Example 646 Step A using 1-methyl-5-(1*H*-1,2,4-triazol-3-yl)-1*H*-indole (300 mg, 1.51 mmol) and 2-bromopyridine (144 μL, 1.51 mmol). LCMS: R_T = 2.205 min, MS (ES) 812.8 (M+H).

Step B. Preparation of 3-iodo-1-methyl-5-(1-(pyridin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[001102] The title compound (58 mg, 69%) was prepared following the procedure descried Example 388 Step B using 1-methyl-5-(1-(pyridin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (58 mg, 0.21 mmol). LCMS: R_T = 1.854 min, MS (ES) 401.8 (M+H).

Step C. Example 647

[001103] The title compound (30 mg, 67% yield) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 3-iodo-1-methyl-5-(1-(pyridin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (67 mg, 0.17 mmol). LCMS: R_T = 2.357 min, MS (ES) 811.8 (M+H).

Example 648

(*R*)-2-(5-([1,2,4]Triazolo[1,5-*a*]pyridin-2-yl)-1-methyl-1*H*-indol-3-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 2-(1-methyl-1*H*-indol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine

[001104] The title compound (60 mg, 96%) was prepared following the procedure descried Example 388 Step A using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-

indole (78 mg, 0.30 mmol) and 2-Bromo-[1,2,4]triazolo[1,5-a]pyridine (50 mg, 0.25 mmol). LCMS: R_T = 1.262 min, MS (ES) 249.1 (M+H).

Step B. Preparation of 2-(3-iodo-1-methyl-1*H*-indol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine

[001105] The crude title compound (56 mg) was prepared following the procedure descried Example 388 Step B using 2-(1-methyl-1*H*-indol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (60 mg, 0.24 mmol). LCMS: R_T = 1.605 min, MS (ES) 374.8 (M+H).

Step C. Example 648

[001106] The title compound (40 mg, 92%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 2-(3-iodo-1-methyl-1*H*-indol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (52 mg, 0.14 mmol). LCMS: R_T = 2.182 min, MS (ES) 784.9 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.89 (d, *J* = 7.0 Hz, 1H), 8.30 (s, 1H), 8.08 (d, *J* = 9.6 Hz, 1H), 7.78 – 7.75 (m, 2H), 7.64 – 7.60 (m, 2H), 7.51 (s, 1H), 7.31 (d, *J* = 8.7 Hz, 1H), 7.14 (t, *J* = 6.8 Hz, 1H), 6.70 (s, 2H), 4.53 – 4.48 (m, 1H), 4.21 – 4.18 (m, 1H), 4.05 – 3.98 (m, 2H), 3.85 (s, 3H), 3.77 (d, *J* = 4.5 Hz, 3H), 3.72 – 3.67 (m, 1H), 3.83 – 3.22 (m, 2H), 2.19 (s, 6H), 2.13 – 2.04 (m, 5H), 1.99 – 1.90 (m, 3H), 1.13 – 1.11 (m, 3H).

Example 649

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-((4-methoxypiperidin-1-yl)methyl)-1-methyl-1*H*-indole-2-carboxylic acid

[001107] The title compound (5.1 mg, 46%, 3 steps) was prepared following the procedures described Example 628 using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy) propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(hydroxymethyl)-1-methyl-1*H*-indole-2-carboxylate (10 mg, 0.013 mmol) and 4-methoxypiperidine (20 μL, 18.6 mg, 0.16 mmol). LCMS: R_T = 1.961, 1.988 min MS (ES) 838.9 (M+H).

Example 650

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-((4-(2-methoxyethoxy)piperidin-1-yl)methyl)-1-methyl-1*H*-indole-2-carboxylic acid

[001108] The title compound (6.5 mg, 57%, 3 steps) was prepared following the procedures described Example 628 using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)

propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(hydroxymethyl)-1-methyl-1*H*-indole-2-carboxylate (10 mg, 0.013 mmol) and 4-(2-methoxyethoxy)piperidine (20 μL, ~20 mg, 0.13). LCMS: R_T = 1.953, 2.012 min, MS (ES) 882.9 (M+H).

Example 651

(*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-methyl-1H-pyrrolo[3,2-b]pyridine-5-carboxylic acid

Step A. Preparation of methyl 3-bromo-1-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylate

[001109] The title compound (61 mg, 80%) was prepared following General Procedure F using methyl 1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylate (49 mg, 0.28 mmol), NBS (51 mg, 0.28 mmol), and MeI (53 μL, 0.85 mmol). LCMS: R_T = 1.077 min, MS (ES) 268.9 (M+H).

Step B. Example 651

[001110] The title compound (17 mg, 48%) was prepared according to General Procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol) and 3-bromo-1-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylate (16 mg, 0.06 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.051 MS (ES) 710.8 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1H), 8.16 (s, 1H), 8.08 (d, *J* = 8.7 Hz, 1H), 7.94 (d, *J* = 8.6 Hz, 1H), 7.89 (d, *J* = 8.6 Hz, 1H), 7.39 (d, *J* = 8.7 Hz, 1H), 6.75 (s, 2H), 4.52 - 4.45 (m, 1H), 4.35 - 4.29 (m, 1H), 4.06 - 3.95 (m, 2H), 3.89 (s, 3H), 3.78 - 3.69 (m, 1H), 3.44 - 3.33 (m, 1H), 3.32 - 3.22 (m, 1H), 2.27 (s, 3H), 2.24 (s, 6H), 2.18 (s, 3H), 2.15 - 2.03 (m, 2H), 1.17 (d, *J* = 6.4 Hz, 3H).

Example 652

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-((4,6-dimethylpyridin-2-yl)methyl)-5-(2-methoxyethoxy)-1H-indole-3-carboxylic acid

[001111] The title compound (8.8 mg, 49%) was prepared following General Procedure I from ethyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-3-carboxylate (17 mg, 0.02 mmol), 2-(chloromethyl)-4,6-dimethylpyridine hydrochloride (19 mg, 0.10 mmol) followed by hydrogenation procedure decribed in step B

example 605. The crude material was subjected to General Procedure H using 1-bromo-2-methoxyethane (8 μL, 0.08 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.965 min, MS (ES) 890.8 (M+H).

Example 653

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(pyrimidin-5-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 1-methyl-5-(pyrimidin-5-yl)-1*H*-indole

[001112] The title compound (100 mg, 95%) was prepared following the procedure descried Example 388 Step A using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (129 mg, 0.50 mmol) and 5-bromopyrimidine (80 mg, 0.50 mmol). LCMS: R_T = 1.391 min, MS (ES) 210.1 (M+H).

Step B. Preparation of 3-iodo-1-methyl-5-(pyrimidin-5-yl)-1*H*-indole

[001113] The title compound (140 mg, 88%) was prepared following the procedure descried Example 388 Step B using 1-methyl-5-(pyrimidin-5-yl)-1*H*-indole (100 mg, 0.48 mmol). LCMS: R_T = 1.618 min, MS (ES) 335.8 (M+H).

Step C. Example 653

[001114] The title compound (30 mg, 72%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 3-iodo-1-methyl-5-(pyrimidin-5-yl)-1*H*-indole (22 mg, 0.07 mmol). LCMS: R_T = 2.231 min, MS (ES) 745.9 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (s, 2H), 9.11 (s, 1H), 7.88 (d, *J* = 6.0 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.65 (s, 2H), 7.53 (s, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 6.71 (s, 2H), 4.57 – 4.52 (m, 1H), 4.21 – 4.12 (m, 1H), 4.00 – 3.96 (m, 2H), 3.85 (s, 3H), 3.77 (d, *J* = 6.2 Hz, 4H), 3.37 – 3.18 (m, 2H), 2.21 (s, 6H), 2.11 – 2.03 (m, 5H), 1.98 – 1.89 (m, 3H), 1.12 (d, *J* = 5.7 Hz, 3H).

Example 654

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-(2-methoxyethoxy)-1-methyl-1*H*-indole-3-carboxylic acid

[001115] The title compound (6.3 mg, 40%) was prepared following General Procedure I from ethyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-

yl)-1*H*-indole-3-carboxylate (17 mg, 0.02 mmol), MeI (6 μL, 0.10 mmol) followed by hydrogenation procedure decribed in step B example 605. The crude material was subjected to General Procedure H using 1-bromo-2-methoxyethane (8 μL, 0.08 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.172 min, MS (ES) 785.8 (M+H).

Example 655

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-2-(1-methyl-5-(1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of (4*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-2-(1-methyl-5-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[001116] The crude title compound (70 mg) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 3-iodo-1-methyl-5-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (28 mg, 0.14 mmol). LCMS: R_T = 2.320 min, MS (ES) 816.8 (M+H).

Step B. Example 655

[001117] The title compound (31 mg, 49%) was prepared following the procedure descried Example 581 Step C using (4*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-2-(1-methyl-5-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (70 mg, 0.09 mmol). LCMS: R_T = 2.046 min, MS (ES) 732.9 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (s, 1H), 8.31 (br s, 1H), 7.88 (t, *J* = 8.5 Hz, 1H), 7.60 (d, *J* = 8.6 Hz, 1H), 7.49 (s, 1H), 7.40 (d, *J* = 8.6 Hz, 1H), 6.73 (s, 2H), 4.46 (dd, *J* = 13.1, 3.5 Hz, 1H), 3.99 (t, *J* = 5.7 Hz, 5H), 3.83 (s, 6H), 3.71 – 3.60 (m, 2H), 3.39 – 3.22 (m, 2H), 2.28 (s, 3H), 2.23 (s, 6H), 2.18 (s, 3H), 2.12 – 2.05 (m, 2H), 1.13 (d, *J* = 6.5 Hz, 3H).

Example 656

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-(2-methoxyethoxy)-1-(2-methoxyethyl)-1H-indole-3-carboxylic acid

Step A. Preparation of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-(2-methoxyethyl)-1*H*-indole-3-

carboxylate

[001118] The title compound (15 mg, 94%) was prepared following General Procedure I from ethyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-3-carboxylate (17 mg, 0.02 mmol), 1-bromo-2-methoxyethane (8 μL, 0.08 mmol) followed by hydrogenation procedure decribed in step B example 605. LCMS: R_T = 2.131 min, MS (ES) 799.7 (M+H).

Step B. Example 656

[001119] The title compound (12 mg, 72%) was prepared following General Procedure H from ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-(2-methoxyethyl)-1*H*-indole-3-carboxylate (15 mg, 0.018 mmol), 1-bromo-2-methoxyethane (8 μL, 0.08 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.178 min, MS (ES) 829.8 (M+H).

Example 657

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-(2-hydroxyethyl)-5-methyl-1*H*-indole-2-carboxylic acid

Step A. Methyl (*R*)-1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate

[001120] The title compound (28 mg, 95%) was prepared following General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (24 mg, 0.033 mmol) and (2-bromoethoxy)(*tert*-butyl)dimethylsilane (20 mg, 0.084 mmol). LCMS: R_T = 2.199, 2.232 min (Method B), MS (ES) 883.9 (M+H).

Step B. Example 657

[001121] To a solution of methyl (*R*)-1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (28 mg, 0.032 mmol) in THF (3 mL) was added TBAF (1.0 M, 200 uL, 0.20 mmol) at RT, and the reaction mixture was stirred for 4 h. LiOH (10 mg, 0.42 mmol) was added to the

reaction, followed by MeOH (1 mL) and H_2O (1 mL). The reaction was heated to 35 °C and stirred for 18 h. The crude reaction was diluted with DCM/H_2O (20 mL, 1:1). The layers were separated and extracted with DCM. The combined organic extract was dried and concentrated *in vacuo*. The crude reaction product was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient from 30-95% CH_3CN, 0.1% TFA to yield the title compound (12.9 mg, 47%). LCMS: R_T = 2.196, 2.228 min, MS (ES) 755.8 (M+H).

Example 658

(*R*)-8-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2- a]indol-2(1H)-yl)-6-methylquinoline-3-carboxylic acid

[001122] The title compound (23 mg, 63%) was prepared according to General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*- pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol) and methyl 8-bromo-6-methylquinoline-3-carboxylate (16.8 mg, 0.06 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.232 MS (ES) 723.9 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.19 (dd, *J* = 4.6 & 1.9 Hz, 1H), 8.98 (t, *J* = 1.6 Hz, 1H), 7.99 (s, 1H), 7.80 - 7.71 (m, 2H), 7.31 (d, *J* = 8.5 Hz, 1H), 6.70 (s, 2H), 4.69 - 4.49 (m, 1H), 4.28 - 4.12 (m, 1H), 3.96 (t, *J* = 6.3 Hz, 2H), 3.78 (s, 1.5H), 3.76 (s, 1.5H), 3.66 - 3.53 (m, 1H), 3.32 - 3.24 (m, 1H), 3.23 - 3.13 (m, 1H), 2.55 (s, 3H), 2.23 (s, 6H), 2.13 (s, 1.5H), 2.04 (s, 1.5H), 2.03 - 2.01 (m, 2H), 1.98 (s, 1.5H), 1.89 (s, 1.5H), 1.19 (d, *J* = 5.9 Hz, 3H).

Example 659

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1*H*-1,2,3-triazol-1-yl)-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 1-methyl-5-(1*H*-1,2,3-triazol-1-yl)-1*H*-pyrrolo[3,2-*b*]pyridine

[001123] The title compound (100 mg, 53%) was prepared following the procedure descried Example 646 Step A using 1*H*-1,2,3-triazole (71.4 µL, 1.23 mmol) and 5-bromo-1-methyl-1*H*-pyrrolo[3,2-*b*]pyridine (200 mg, 0.95 mmol). LCMS: R_T = 1.183 min, MS (ES) 200.1 (M+H).

Step B. Preparation of 3-iodo-1-methyl-5-(1*H*-1,2,3-triazol-1-yl)-1*H*-pyrrolo[3,2-*b*]pyridine

[001124] The title compound (106 mg, 65%) was prepared following the procedure descried Example 388 Step B using 1-methyl-5-(1*H*-1,2,3-triazol-1-yl)-1*H*-pyrrolo[3,2-*b*]pyridine (100 mg, 0.50 mmol). LCMS: R_T = 1.512 min, MS (ES) 325.9 (M+H).

Step C. Example 659

[001125] The title compound (38 mg, 93%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 3-iodo-1-methyl-5-(1*H*-1,2,3-triazol-1-yl)-1*H*-pyrrolo[3,2-*b*]pyridine (27 mg, 0.08 mmol). LCMS: R_T = 2.297 min, MS (ES) 735.9 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, *J* = 8.3 Hz, 1H), 8.27 (dd, *J* = 8.9, 2.4 Hz, 1H), 8.07 (d, *J* = 7.4 Hz, 1H), 7.96 – 7.94 (m, 2H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 6.73 (s, 2H), 4.42 – 4.34 (m, 1H), 4.27 – 4.22 (m, 2H), 4.03 – 3.97 (m, 2H), 3.93 (s, 3H), 3.78 (d, *J* = 8.6 Hz, 3H), 3.37 – 3.21 (m, 2H), 2.23 (s, 6H), 2.12 – 2.03 (m, 5H), 1.97 – 1.88 (m, 3H), 1.16 (d, *J* = 5.7 Hz, 3H).

Example 660

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-methoxy-1-(2-methoxyethyl)-1*H*-indole-2-carboxylic acid

Step A. methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl) -6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate

[001126] The title compound (72 mg, 47%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (100 mg, 0.19 mmol) and methyl 5-(benzyloxy)-7-iodo-1*H*-indole-2-carboxylate (150 mg, 0.37 mmol). LCMS: R_T = 1.834 min, MS (ES) 815.8 (M+H).

Step B. methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl) -6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-methoxyethyl)-1*H*-indole-2-carboxylate

[001127] The title compound (70 mg, 88%) was prepared following General Procedure I using methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (75 mg, 0.092 mmol) and 1-bromo-2-methoxyethane (30 mg, 0.22 mmol). LCMS: R_T = 1.932, 1.959 min (Method B), MS (ES) 873.8 (M+H).

Step C. methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-(2-methoxyethyl)-1*H*-indole-2-carboxylate

[001128] The title compound (58 mg, 92%) was prepared following the procedure described Example 390 Step D using methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-methoxyethyl)-1*H*-indole-2-carboxylate (70 mg, 0.12 mmol) and Pd/C (10 wt.%, 20 mg, 0.019 mmol) by hydrogenating in MeOH (5 mL) for 16 h at RT. LCMS: R_T = 1.515, 1.550 min, MS (ES) 783.9 (M+H).

Step D. Example 660

[001129] The title compound (9.4 mg, 47%) was prepared following General Procedure H using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethylpyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-(2-methoxyethyl)-1*H*-indole-2-carboxylate (20 mg, 0.026 mmol) and MeI (10 mg, 0.070 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.491 min, MS (ES) 783.9 (M+H).

Example 661

(*R*)-8-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)quinoline-4-carboxylic acid

[001130] The title compound (10 mg, 28%) was prepared according to General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*- pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol) and methyl 8-bromoquinoline-4-carboxylate (16 mg, 0.06 mmol) followed by saponification using General Procedure D. LCMS : R_T = 2.184 MS (ES) 709.8 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.00 (t, *J* = 4.8 Hz, 1H), 8.69 (d, *J* = 8.2 Hz, 1H), 8.02 - 7.90 (m, 1H), 7.85 - 7.81 (m, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 6.70 (s, 2H), 4.69 - 4.45 (m, 1H), 4.31 - 4.10 (m, 1H), 3.95 (t, *J* = 6.6 Hz, 2H), 3.77 (s, 1.5H), 3.75 (s, 1.5H), 3.68 - 3.50 (m, 1H), 3.37 - 3.22 (m, 1H), 3.21 - 3.08 (m, 1H), 2.23 (s, 6H), 2.13 (s, 1.5H), 2.04 (s, 1.5H), 2.03 - 2.00 (m, 2H), 1.98 (s, 1.5H), 1.89 (s, 1.5H), 1.19 (d, *J* = 5.7 Hz, 3H).

Example 662

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(2*H*-1,2,3-triazol-2-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 1-methyl-5-(2*H*-1,2,3-triazol-2-yl)-1*H*-indole

[001131] The title compound (50 mg, 18%) was prepared following the procedure descried Example 646 Step A using 1*H*-1,2,3-triazole (108 μL, 1.86 mmol) and of 5-bromo-1-methyl-1*H*-indole (300 mg, 1.43 mmol). LCMS: R_T = 1.516 min, MS (ES) 199.1 (M+H).

Step B. Preparation of 3-iodo-1-methyl-5-(2*H*-1,2,3-triazol-2-yl)-1*H*-indole

[001132] The title compound (80 mg, 98%) was prepared following the procedure descried Example 388 Step B using 1-methyl-5-(2*H*-1,2,3-triazol-2-yl)-1*H*-indole (50 mg, 0.25 mmol). LCMS: R_T = 1.830 min, MS (ES) 324.9 (M+H).

Step C. Example 662

[001133] The title compound (31 mg, 75%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 3-iodo-1-methyl-5-(2*H*-1,2,3-triazol-2-yl)-1*H*-indole (27 mg, 0.08 mmol). LCMS: R_T = 2.345 min, MS (ES) 734.8 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 – 8.02 (m, 3H), 7.90 (d, *J* = 8.6 Hz, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.56 (d, *J* = 3.1 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 6.71 (s, 2H), 4.52 – 4.46 (m, 1H), 4.20 – 4.12 (m, 1H), 4.02 – 3.95 (m, 2H), 3.86 (s, 3H), 3.77 (d, *J* = 5.2 Hz, 3H), 3.70 – 3.65 (m, 1H), 3.36 – 3.19 (m, 2H), 2.21 (s, 6H), 2.12 – 2.03 (m, 5H), 1.97 – 1.88 (m, 3H), 1.10 (d, *J* = 6.4 Hz, 3H).

Example 663

(*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethyl-2-((4-methyl-3-oxopiperazin-1-yl)methyl)pyrimidin-5-yl)-4-methyl-2-(1-methyl-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one

Step A. (*R*)-6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[001134] The title compound (96 mg, 74%) was prepared following General Procedure C using (*R*)-6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (100 mg, 0.15 mmol) and 3-iodo-1-methyl-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (70 mg, 0.21 mmol). LCMS: R_T = 1.616 min , MS (ES) 866.8 (M+H).

Step B. (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-2-(1-methyl-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[001135] The title compound (80 mg, 93%) was prepared following the procedure described Example 390 Step D using (*R*)-6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (96 mg, 0.11 mmol) and Pd/C (10 wt.%, 15 mg, 0.014 mmol) by hydrogenating in MeOH (5 mL) with HCl (4.0 M in dioxanes, 0.5 mL)for 16 h at RT. LCMS: R_T = 1.155 min, MS (ES) 776.8 (M+H).

Step C. Example 663

[001136] The title compound (8.4 mg, 37%) was prepared following General Procedure J using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-4-methyl-2-(1-methyl-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (20 mg, 0.026 mmol) and 1-methylpiperazin-2-one (15 mg, 0.13 mmol). LCMS: R_T = 0.962 min, MS (ES) 872.8 (M+H).

Example 664

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(2*H*-1,2,3-triazol-2-yl)-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 1-methyl-5-(2*H*-1,2,3-triazol-2-yl)-1*H*-pyrrolo[3,2-*b*]pyridine

[001137] The title compound (100 mg) was isolated from Example 659 Step A. LCMS: R_T = 0.195 min, MS (ES) 200.1 (M+H).

Step B. Preparation of 3-iodo-1-methyl-5-(2*H*-1,2,3-triazol-2-yl)-1*H*-pyrrolo[3,2-*b*]pyridine

[001138] The crude title compound (175 mg) was prepared following the procedure descried Example 388 Step B using 1-methyl-5-(2*H*-1,2,3-triazol-2-yl)-1*H*-pyrrolo[3,2-*b*]pyridine (100 mg, 0.50 mmol). LCMS: R_T = 1.272 min, MS (ES) 325.9 (M+H).

Step C. Example 664

[001139] The title compound (23 mg, 56%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 3-iodo-1-methyl-5-(2*H*-1,2,3-triazol-2-yl)-1*H*-pyrrolo[3,2-*b*]pyridine (27 mg, 0.08 mmol). LCMS: R_T = 2.295 min, MS (ES) 735.9 (M+H).

Example 665

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-methoxy-1-(2-methoxyethyl)-1*H*-indole-2-carboxylic acid

Step A. methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl) -4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-methoxyethyl)-1*H*-indole-2-carboxylate

[001140] The title compound (49 mg, 86%) was prepared following General Procedure I using methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (53 mg, 0.065 mmol) and 1-bromo-2-methoxyethane (25 mg, 0.18 mmol). LCMS: R_T = 1.829, 1.858 min (Method B), MS (ES) 875.8 (M+H).

Step B. methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1*H*-indole-2-carboxylate

[001141] The title compound (43 mg, 98%) was prepared following the procedure described Example 390 Step D using methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-methoxyethyl)-1*H*-indole-2-carboxylate (49 mg, 0.056 mmol) and Pd/C (10 wt.%, 10 mg, 0.0093 mmol) by hydrogenating in MeOH (5 mL) with HCl (4.0 M in dioxanes, 0.5 mL) for 16 h at RT. LCMS: R_T = 1.461, 1.485 min, MS (ES) 785.8 (M+H).

Step C. Example 665

[001142] The title compound (7.8 mg, 39%) was prepared following General Procedure H using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1*H*-indole-2-carboxylate (20 mg, 0.025 mmol) and MeI (10 mg, 0.070 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.262 min, MS (ES) 785.8 (M+H).

Example 666

(R)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)quinoline-2-carboxylic acid

[001143] The title compound (17 mg, 48%) was prepared according to General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-

trimethyl-1*H*- pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol) and methyl 7-bromoquinoline-2-carboxylate (16 mg, 0.06 mmol) followed by saponification using General Procedure D. LCMS : R_T = 2.223 MS (ES) 709.9 (M+H).

Example 667

(*R*)-2-((5-carboxy-3-((*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1*H*-indol-1-yl)methyl)-1,1-dimethylpyrrolidin-1-ium

[001144] The title compound (3.6 mg, 29%) was prepared according to General Procedure I using methyl 3-((*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(((*R*)-pyrrolidin-2-yl)methyl)-1*H*-indole-5-carboxylate (10 mg, 0.013 mmol) and MeI (4 μL, 0.056 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.913 min, MS (ES) 808.9 (M+H).

Example 668

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1*H*-1,2,3-triazol-1-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 1-methyl-5-(1*H*-1,2,3-triazol-1-yl)-1*H*-indole

[001145] The title compound (75 mg, 27%) was isolated from Example 662 Step A. LCMS: R_T = 1.335 min, MS (ES) 199.2 (M+H).

Step B. Preparation of 3-iodo-1-methyl-5-(1*H*-1,2,3-triazol-1-yl)-1*H*-indole

[001146] The title compound (60 mg, 54%) was prepared following the procedure descried Example 388 Step B using 1-methyl-5-(1*H*-1,2,3-triazol-1-yl)-1*H*-indole (75 mg, 0.38 mmol). LCMS: R_T = 1.509 min, MS (ES) 324.9 (M+H).

Step C. Example 668

[001147] The title compound (35 mg, 86%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 3-iodo-1-methyl-5-(1*H*-1,2,3-triazol-1-yl)-1*H*-indole (27 mg, 0.08 mmol). LCMS: R_T = 2.212 min, MS (ES) 734.8 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 1H), 7.92 – 7.90 (m, 2H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.70 (s, 2H), 7.60 (s, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 6.72 (s, 2H), 4.55 – 4.50 (m, 1H), 4.20 – 4.12 (m, 1H), 4.00 – 3.95 (m, 2H), 3.87 (s, 3H), 3.77

(d, *J* = 5.3 Hz, 3H), 3.71 – 3.63 (m, 1H), 3.35 – 3.18 (m, 2H), 2.22 (s, 6H), 2.11 – 2.02 (m, 5H), 1.97 – 1.88 (m, 3H), 1.10 (d, *J* = 6.5 Hz, 3H).

Example 669

(*R*)-4-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)quinoline-2-carboxylic acid

[001148] The title compound (28 mg, 79%) was prepared according to General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*- pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (27 mg, 0.05 mmol) and methyl 4-bromoquinoline-2-carboxylate (16 mg, 0.06 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.489 min (Method B), MS (ES) 709.9 (M+H).

Example 670

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1-(4-methylpyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 2-(3-bromo-1*H*-1,2,4-triazol-1-yl)-4-methylpyrimidine

[001149] The title compound (234 mg, 28%) was prepared following the procedure descried Example 646 Step A using 2-bromomethylpyrimidine (775 mg, 4.48 mmol) and 5-bromo-1*H*-1,2,4-triazole (510 mg, 3.45 mmol). LCMS: R_T = 1.125 min, MS (ES) 240.0 (M+H).

Step B. Preparation of 1-methyl-5-(1-(4-methylpyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[001150] The title compound (100 mg, 69%) was prepared following the procedure descried Example 388 Step A using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (192 mg, 0.75 mmol) and 2-(3-bromo-1*H*-1,2,4-triazol-1-yl)-4-methylpyrimidine (120 mg, 0.50 mmol). LCMS: R_T = 1.409 min, MS (ES) 291.1 (M+H).

Step C. Preparation of 3-iodo-1-methyl-5-(1-(4-methylpyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[001151] The title compound (135 mg, 94%) was prepared following the procedure descried Example 388 Step B using 1-methyl-5-(1-(4-methylpyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (100 mg, 0.34 mmol). LCMS: R_T = 1.709 min, MS (ES) 416.8 (M+H).

Step D. Example 670

[001152] The title compound (36 mg, 78%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-

trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 3-iodo-1-methyl-5-(1-(4-methylpyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (35 mg, 0.08 mmol). LCMS: R_T = 2.294 min, MS (ES) 826.8 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (d, *J* = 3.4 Hz, 1H), 8.76 (d, *J* = 5.1 Hz, 1H), 8.23 (d, *J* = 4.3 Hz, 1H), 8.02 (d, *J* = 8.7 Hz, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.51 (d, *J* = 3.0 Hz, 1H), 7.45 (d, *J* = 4.9 Hz, 1H), 7.30 (d, *J* = 8.7 Hz, 1H), 6.70 (s, 2H), 4.53 – 4.47 (m, 1H), 4.21 – 4.15 (m, 1H), 4.00 – 3.97 (m, 2H), 3.85 (s, 3H), 3.77 (d, *J* = 4.7 Hz, 3H), 3.73 – 3.67 (m, 1H), 3.39 – 3.20 (m, 2H), 2.58 (s, 3H), 2.12 – 2.04 (m, 5H), 1.98 – 1.89 (m, 3H), 1.13 – 1.11 (m, 3H).

Example 671

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-(2-(dimethylamino)ethoxy)-1-(2-methoxyethyl)-1H-indole-3-carboxylic acid

[001153] The title compound (3.7 mg, 22%) was prepared following General Procedure H using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-(2-methoxyethyl)-1*H*-indole-3-carboxylate (17 mg, 0.02 mmol) and 2-bromo-*N*,*N*-dimethylethan-1-amine hydrobromide (9.3 mg, 0.04 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.969 min, MS (ES) 842.9 (M+H).

Example 672

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-methoxy-1-(2-methoxyethyl)-1*H*-indole-3-carboxylic acid

[001154] The title compound (6 mg, 38%) was prepared following produdure described in Example 673 from ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-(2-methoxyethyl)-1*H*-indole-3-carboxylate (17 mg, 0.02 mmol), MeI (6 μL, 0.08 mmol) followed by saponification using General Procedure D. The title compound was isolated as the second eluted isomer from the reverse phase HPLC purification. LCMS: R_T = 2.239 min, MS (ES) 785.8 (M+H).

Example 673

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-methoxy-1-(2-methoxyethyl)-1H-indole-3-carboxylic acid

[001155] The title compound (5 mg, 32%) was prepared following General Procedure H from ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-(2-methoxyethyl)-1*H*-indole-3-carboxylate (17 mg, 0.02 mmol), methyl iodide (6 μL, 0.08 mmol) followed by saponification using General Procedure D. The title compound was isolated as the first eluted isomer from the reverse phase HPLC purification. LCMS: R_T = 2.206 min, MS (ES) 785.8 (M+H).

Example 674

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(5-(5-(methoxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl)-1-methyl-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 5-(5-(methoxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl)-1-methyl-1*H*-indole

[001156] The title compound (15 mg, 17%) was prepared following the procedure descried Example 388 Step A using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (105 mg, 0.41 mmol) and 3-bromo-5-(methoxymethyl)-1-methyl-1*H*-1,2,4-triazole (70 mg, 0.34 mmol). LCMS: R_T = 1.363 min, MS (ES) 257.1 (M+H).

Step B. Preparation of 3-iodo-5-(5-(methoxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl)-1-methyl-1*H*-indole

[001157] The title compound (22 mg, quant.) was prepared following the procedure descried Example 388 Step B using 5-(5-(methoxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl)-1-methyl-1*H*-indole (15 mg, 0.06 mmol). LCMS: R_T = 1.517 min, MS (ES) 382.9 (M+H).

Step C. Example 674

[001158] The title compound (27 mg, 61%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 3-iodo-5-(5-(methoxymethyl)-1-methyl-1*H*-1,2,4-triazol-3-yl)-1-methyl-1*H*-indole (22 mg, 0.06 mmol). LCMS: R_T = 2.212 min, MS (ES) 792.9 (M+H).

Example 675

(*R*)-2-(5-([1,2,4]Triazolo[4,3-*a*]pyridin-3-yl)-1-methyl-1*H*-indol-3-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 3-(1-methyl-1*H*-indol-5-yl)-[1,2,4]triazolo[4,3-*a*]pyridine

[001159] The title compound (83 mg, 95%) was prepared following the procedure descried Example 388 Step A using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (109 mg, 0.42 mmol) and 3-bromo-[1,2,4]triazolo[4,3-*a*]pyridine (70 mg, 0.35 mmol). LCMS: R_T = 0.210 min, MS (ES) 249.1 (M+H).

Step B. Preparation of 3-(3-iodo-1-methyl-1*H*-indol-5-yl)-[1,2,4]triazolo[4,3-*a*]pyridine

[001160] The title compound (75 mg, 60%) was prepared following the procedure descried Example 388 Step B using 3-(1-methyl-1*H*-indol-5-yl)-[1,2,4]triazolo[4,3-*a*]pyridine (83 mg, 0.33 mmol). LCMS: R_T = 1.133 min, MS (ES) 374.8 (M+H).

Step C. Example 675

[001161] The title compound (50 mg, 86%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (40 mg, 0.07 mmol) and 3-(3-iodo-1-methyl-1*H*-indol-5-yl)-[1,2,4]triazolo[4,3-*a*]pyridine (36 mg, 0.10 mmol). LCMS: R_T = 2.081 min, MS (ES) 784.9 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 – 8.57 (m, 1H), 7.96 (s, 1H), 7.92 – 7.87 (m, 1H), 7.75 (t, *J* = 8.6 Hz, 2H), 7.68 (d, *J* = 8.6 Hz, 1H), 7.61(d, *J* = 1.9 Hz, 1H), 7.57 – 7.51 (m, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 7.11 – 7.06 (m, 1H), 6.69 (s, 2H), 4.53 – 4.49 (m, 1H), 4.19 – 4.10 (m, 1H), 4.00 – 3.95 (m, 2H), 3.90 (s, 3H), 3.77 – 3.70 (m, 4H), 3.33 – 3.20 (m, 2H), 2.20 (s, 6H), 2.10 – 2.01 (m, 5H), 1.96 – 1.87 (m, 3H), 1.08 (d, *J* = 6.3 Hz, 3H).

Example 676

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-(2-methoxyethyl)-5-(2-(4-methylpiperazin-1-yl)ethoxy)-1*H*-indole-3-carboxylic acid

[001162] The title compound (11 mg, 61%) was prepared following General Procedure H using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-(2-methoxyethyl)-1*H*-indole-3-carboxylate (17 mg, 0.02 mmol) and 1-(2-bromoethyl)-4-methylpiperazine dihydrobromide (15 mg, 0.04 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.887 min, MS (ES) 897.9 (M+H).

Example 677

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-methoxyethyl)-5-(methoxymethyl)-1*H*-indole-2-carboxylic acid

Step A. Preparation of ethyl 7-bromo-5-formyl-1-(2-methoxyethyl)-1*H*-indole-2-carboxylate.

[001163] To a solution of 1-(*tert*-butyl) 2-ethyl 7-bromo-5-formyl-1*H*-indole-1,2-dicarboxylate (67 mg, 0.17 mmol) in DCM (1 mL) was added TFA (129 µL, 194 mg, 1.7 mmol) and stirred at RT for 16 h. The reaction was quenched with aq. sat. NH_4Cl and extracted with DCM. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. To a solution of the crude product in DMF (1 mL) was added Cs_2CO_3 (366 mg, 1.08 mmol) and 1-bromo-2-methoxyethane (78 µL, 114 mg, 0.82 mmol) and stirred at 40 °C for 16 h. The reaction was quenched with aq. sat. NH_4C and ßextracted with DCM. The combined organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-60% gradient) to afford the title compound (29 mg, 49%, 2 steps). LCMS: R_T = 1.893 min, MS (ES) 353.9 (M+H).

Step B. Preparation of ethyl 7-bromo-1-(2-methoxyethyl)-5-((methoxymethoxy)methyl)-1*H*-indole-2-carboxylate.

[001164] The title compound (30 mg, 68%, 2 steps) was prepared following the reduction by $NaBH_4$ and OH protection by MOMCl procedures described Example 544 Step A using ethyl 7-bromo-5-formyl-1-(2-methoxyethyl)-1*H*-indole-2-carboxylate (29 mg, 0.082 mmol). LCMS: R_T = 2.010 min, MS (ES) 399.9 (M+H).

Step C. Preparation of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(hydroxymethyl)-1-(2-methoxyethyl)-1*H*-indole-2-carboxylate.

[001165] The title compound (8 mg, 24%, 2 steps) was prepared following the procedure described Example 591 Step C using ethyl 7-bromo-1-(2-methoxyethyl)-5-((methoxymethoxy)methyl)-1*H*-indole-2-carboxylate (30 mg, 0.075 mmol) and (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy) propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (40 mg, 0.075 mmol). LCMS: R_T = 1.574, 1.595, 1.643 min, (Method B) MS (ES) 813.9 (M+H).

Step D. Example 677.

[001166] The title compound (2.2 mg, 27%, 2 steps) was prepared following the procedure described Example 595 using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy) propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-

a]indol-2(1*H*)-yl)-5-(hydroxymethyl)-1-(2-methoxyethyl)-1*H*-indole-2-carboxylate (8 mg, 0.01 mmol) and MeI (3.0 mg, 0.021 mmol). LCMS: R_T = 2.245, 2.272, 2.318 min, MS (ES) 799.9 (M+H).

Example 678

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-(2-(2-methoxyethoxy)ethyl)-5-methyl-1*H*-indole-2-carboxylic acid

[001167] The title compound (8 mg, 29%) was prepared following General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (27 mg, 0.037 mmol) and 1-bromo-2-(2-methoxyethoxy)ethane (30 mg, 0.16 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.517, 1.552 min, MS (ES) 813.9 (M+H).

Example 679

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(5-methyl-1*H*-tetrazol-1-yl)-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 1-methyl-5-(5-methyl-1*H*-tetrazol-1-yl)-1*H*-pyrrolo[3,2-*b*]pyridine

[001168] 5-Methyl-1*H*-tetrazole (60 mg, 0.71 mmol), CuI (68 mg, 0.36 mmol), K_2CO_3 (308 mg, 2.23 mmol), *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (79 μL, 0.36 mmol) were added to a solution of 5-bromo-1-methyl-1*H*-pyrrolo[3,2-*b*]pyridine (196 mg, 0.93 mmol) in DMF (1.4 mL). The reaction mixture was stirred at 100 °C for 3 days under Ar. The reaction mixture was filtered through Celite pad. Water was added to the filtrate and extracted with EtOAc. The combined organic layers were washed with water, dried and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-2% gradient) to afford the title compound (90 mg, 59%). LCMS: R_T = 0.205 min, MS (ES) 215.1 (M+H).

Step B. Preparation of 3-iodo-1-methyl-5-(5-methyl-1*H*-tetrazol-1-yl)-1*H*-pyrrolo[3,2-*b*]pyridine

[001169] The crude title compound (90 mg) was prepared following the procedure descried Example 388 Step B using 1-methyl-5-(5-methyl-2*H*-tetrazol-2-yl)-1*H*-pyrrolo[3,2-*b*]pyridine (90 mg, 0.42 mmol). LCMS: R_T = 1.411 min, MS (ES) 340.9 (M+H).

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Step C. Example 679

[001170] The title compound (38 mg, 64%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (40 mg, 0.07 mmol) and 3-iodo-1-methyl-5-(5-methyl-1*H*-tetrazol-1-yl)-1*H*-pyrrolo[3,2-*b*]pyridine (38 mg, 0.11 mmol). LCMS: R_T = 2.315 min, MS (ES) 750.9 (M+H).

Example 680

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-(ethyl(methyl)amino)-1-methyl-1H-indole-2-carboxylic acid

Step A. Preparation of methyl (*E*)-2-(2-(2-bromo-4-(*N*-methylacetamido)phenyl)-2-methylhydrazono)propanoate

[001171] To a solution of methyl (*E*)-2-(2-(4-acetamido-2-bromophenyl)hydrazono)propanoate (500 mg, 1.53 mmol) in dry DMF (2 mL) was added NaH (245 mg, 6.12 mmol) followed by MeI (285 µL, 4.6 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 5h. The reaction was quenched by pouring into brine and extracted with EtOAc. The organic layer was dried and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-5% gradient) to afford the title compound (430 mg, 80%). ^{1}H-NMR ($CDCl_3$) δ 7.50 (s, 1H), 7.22 (m, 1H), 7.14 (s, 1H), 3.87 (s, 2H), 3.39 (s, 3H), 3.26 (s, 1H), 1.92 (s, 3H), 1.70 (s, 1H).

Step B. Preparation of methyl 7-bromo-1-methyl-5-(N-methylacetamido)-1H-indole-2-carboxylate

[001172] A solution of methyl (*E*)-2-(2-(2-bromo-4-(*N*-methylacetamido)phenyl)-2-methylhydrazono)propanoate (150 mg, 0.42 mmol) in glacial acetic acid (8 mL) and PPA, 0.5 mL) was heated at 90 °C for 1h. The reaction mixture was concentrated, and the residue was diluted with water. The mixture was extracted with EtOAc, and the organic layer was concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-30% gradient) to afford the title compound (100 mg, 70%). ^{1}H-NMR (DMSO-d_6) δ 7.70 (s, 1H), 7.61 (s, 1H), 7.37 (s, 1H), 4.38 (s, 3H), 3.87 (s, 3H), 3.15 (s, 3H), 1.76 (s. 3H).

Step C. Preparation of methyl 7-bromo-1-methyl-5-(methylamino)-1H-indole-2-carboxylate

[001173] To a solution of methyl 7-bromo-1-methyl-5-(N-methylacetamido)-1H-indole-2-carboxylate (100 mg, 0.30mmol) in dioxane (2 mL) was added HCl (2 mL, 4M in dioxane). The reaction mixture was stirred at 55 °C for 3h then concentrated to afford the title compound (83 mg, 95%), which was used in next step without further purification. MS (ES) 297/299 (M+H).

Step D. Preparation of methyl 7-bromo-5-(ethyl(methyl)amino)-1-methyl-1H-indole-2-carboxylate

[001174] To a solution of methyl 7-bromo-1-methyl-5-(methylamino)-1H-indole-2-carboxylate (40 mg, 0.134 mmol) in DCE (2 mL) was added acetaldehyde (0.2 mmol) and stirred for 30 min at RT. $NaBH(OAc)_3$ (0.27 mmol) was added to the reaction mixture and stirred at RT for 3 h. The reaction mixture was removed concentrated and in vacuum and the residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-10% gradient) to afford the title compound. MS (ES) 325.3/327.3 (M+H).

Step E. Example 680

[001175] The title compound (28%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one and methyl 7-bromo-5-(ethyl(methyl)amino)-1-methyl-1H-indole-2-carboxylate followed by saponification using General Procedure D. MS (ES) 769.2 (M+H).

Example 681

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1*H*-1,2,4-triazol-1-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 3-iodo-1-methyl-5-(1*H*-1,2,4-triazol-1-yl)-1*H*-indole

[001176] The crude title compound (43 mg) was prepared following the procedure descried Example 388 Step B using 1-methyl-5-(1*H*-1,2,4-triazol-1-yl)-1*H*-indole (31 mg, 0.16 mmol). LCMS: R_T = 1.469 min, MS (ES) 324.9 (M+H).

Step B. Example 681

[001177] The title compound (30 mg, 73%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 3-iodo-1-methyl-5-(1*H*-1,2,4-triazol-1-yl)-1*H*-indole (23 mg, 0.07 mmol). LCMS: R_T = 2.263 min, MS (ES) 734.8 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.18 (s, 1H), 8.16 (s,

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1H), 7.86 (d, *J* = 4.8 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.67 (s, 2H), 7.57 (s, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 6.71 (s, 2H), 4.54 – 4.48 (m, 1H), 4.21 – 4.12 (m, 1H), 4.00 – 3.95 (m, 2H), 3.86 (s, 3H), 3.77 (d, *J* = 5.3 Hz, 3H), 3.70 – 3.63 (m, 1H), 3.36 – 3.18 (m, 2H), 2.22 (s, 6H), 2.12 – 2.03 (m, 5H), 1.97 – 1.88 (m, 3H), 1.10 (d, *J* = 6.4 Hz, 3H).

Example 682

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-((2-methoxyethyl)(methyl)amino)-1-methyl-1H-indole-2-carboxylic acid

Step A. Preparation of methyl 7-bromo-5-((2-methoxyethyl)(methyl)amino)-1-methyl-1H-indole-2-carboxylate

[001178] The title compound was prepared following the procedure described Example 680 Step D using methyl 7-bromo-1-methyl-5-(methylamino)-1H-indole-2-carboxylate and 2-methoxyacetaldehyde. MS (ES) 355.3/357.3 (M+H).

Step E. Example 682

[001179] The title compound (36%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one and methyl 7-bromo-5-((2-methoxyethyl)(methyl)amino)-1-methyl-1H-indole-2-carboxylate followed by saponification using General Procedure D. ^{1}H-NMR (MeOH-d$_4$) δ 8.02 (s, 0.6 H), 7.91 (s, 0.4H), 7.80 (d, 1H, J = 12Hz), 7.58 (s, 0.4), 749 (d, 1H, J =12Hz), 7.35-7.32 (two s, 2H), 6.63 and 6.61 (two s, total 2H), 4.46-4.23 (m, 1H), 4.23 and 4.22 (two s, total 1H), 4.09 (two s, total 2H), 4.00 (m, 2H), 3.81 (s, 1H), 3.76-3.61 (m, 6H), 3.40 (two s, total 3H), 2.67 (two s, 6H), 2.25 (s, 6H), 2.18-2.15 (two s, total 3H), 2.02 (m, 2H), 2.00 (two s, total 3H), 1.31 (d, 2H, J= 8Hz), 1.19(d, 1H, J = 8Hz); MS (ES) 799.2 (M+H)

Example 683

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-(dimethylamino)-1-methyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl 7-bromo-5-(dimethylamino)-1-methyl-1H-indole-2-carboxylate

[001180] The title compound was prepared following the procedure described Example 680 Step D using methyl 7-bromo-1-methyl-5-(methylamino)-1H-indole-2-carboxylate and formaldehyde. MS (ES) 311.3/313.3 (M+H).

Step E. Example 683

[001181] The title compound (23%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one and methyl 7-bromo-5-(dimethylamino)-1-methyl-1H-indole-2-carboxylate followed by saponification using General Procedure D. MS (ES) 755.3 (M+H).

Example 684

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(5-methyl-2*H*-tetrazol-2-yl)-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[001182] The title compound (11 mg, 19% yield) was obtained along with Example 679 from Step C. LCMS: R_T = 2.380 min, MS (ES) 772.8 (M+Na).

Example 685

(*R*)-6-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-8-methyl-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indol-1-one

[001183] The title compound (25 mg, 43%) was prepared following General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (75 mg, 0.10 mmol) and 1-bromo-2-(trifluoromethoxy)ethane (49 mg, 0.25 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.55 min, MS (ES) 738 (M+H).

Example 686

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(3-methoxypropyl)-5-methyl-1*H*-indole-2-carboxylic acid

[001184] The title compound (25 mg, 43%) was prepared following General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (75 mg, 0.10 mmol) and 1-bromo-3-methoxypropane (39 mg, 0.25 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.55 min, MS (ES) 784 (M+H).

Example 687

(*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(2H-tetrazol-5-yl)-1H-pyrrolo[3,2-b]pyridin-3-yl)-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one

Step A. Preparation of (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxamide

[001185] The title compound (13 mg, 93%) was prepared according to General Procedure E using (*R*)-3-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5- trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylic acid (14 mg, 0.02 mmol) and ammonia (100 μL, 2M in methanol). LCMS: R_T = 1.873 min, MS (ES) 711.8 (M+H).

Step B. Preparation of (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carbonitrile

[001186] To a solution of (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxamide (13 mg, 0.018 mmol) in DCM (1 mL) were added trifluoromethanesulfonic anhydride (7 μL , 0.04 mmol), triethylamine (6 μL , 0.04 mmol), and the mixture was stirred at room temperature for 2h. Water (10 mL) was added to the mixture and extracted in DCM. The organic layers was dried and concentrated to afford the title compound (10 mg, 78%). LCMS: R_T = 1.604 min (Method B), MS (ES) 693.90 (M+H).

Step C. Example 687

[001187] To a solution of (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carbonitrile (10 mg, 0.014 mmol) in DMF (1 mL) were added sodium azide (6.5 mg, 0.11 mmol), ammonium chloride (5.5 mg, 0.11 mmol) and the mixture was heated at 120 ^oC for 6h. The reaction mixture was extracted in DCM, dried and concentrated. The crude was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95 % MeCN 0.1% TFA) to afford the title compound (7 mg, 68%). LCMS: R_T = 1.342 min (Method B), MS (ES) 736.9 (M+H).

Example 688

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-5-((thiazol-4-ylmethoxy)methyl)-1*H*-indole-2-carboxylic acid

[001188] The title compound was prepared (5.0 mg, 43%, 2 steps) following the procedures described Example 607 using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy) propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(hydroxymethyl)-1-methyl-1*H*-indole-2-carboxylate (11 mg, 0.014 mmol) and 4-(chloromethyl)thiazole hydrochloride (5 mg, 0.021 mmol). LCMS: R_T = 2.145, 2.172, 2.224 min, MS (ES) 838.8 (M+H).

Example 689

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(2*H*-tetrazol-2-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 1-methyl-5-(2*H*-tetrazol-2-yl)-1*H*-indole

[001189] 1-Methyl-1*H*-indole-5-diazonium tetrafluoroborate (200 mg, 0.82 mmol) and $AgNO_3$ (208 mg, 1.22 mmol) were suspended in THF (4 mL) under Ar and cooled at -78 °C. Et_3N (171 μL, 1.22 mmol) was added dropwise and stirred for 10 min then $TMSCHN_2$ (408 μL, 0.98 mmol) was added slowly. The mixture was stirred 1 h at -78°C and warmed to RT. A solution of CsF (124 mg, 0.82 mmol) in MeOH (0.5 mL) was added and the mixture was stirred 1.5 h at RT. EtOAc and brine were added and the organic phase was separated, dried and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-30% gradient) to afford the title compound (50mg, 30%). LCMS: R_T = 1.493 min, MS (ES) 200.1 (M+H).

Step B. Preparation of 3-iodo-1-methyl-5-(2*H*-tetrazol-2-yl)-1*H*-indole

[001190] The crude title compound (45 mg) was prepared following the procedure descried Example 388 Step B using 1-methyl-5-(2*H*-tetrazol-2-yl)-1*H*-indole (50 mg, 0.25 mmol). LCMS: R_T = 1.752 min, MS (ES) 325.9 (M+H).

Step C. Example 689

[001191] The title compound (35 mg, 86%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 3-iodo-1-methyl-5-(2*H*-tetrazol-2-yl)-1*H*-indole (24 mg, 0.07 mmol). LCMS: R_T = 2.279 min, MS (ES) 735.9 (M+H).

Example 690

3-((*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-(((*S*)-1-methylpyrrolidin-2-yl)methyl)-1H-indole-5-carboxylic acid

Step A. Preparation of *tert*-butyl (*S*)-2-(((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate

[001192] To a solution of *tert*-butyl (*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (201 mg, 1.0 mmol) in DCM (6 mL) was added Et_3N (279 μL, 2.0 mmol) followed by MsCl (117 μL, 1.5 mmol). The mixture was stirred at RT for 2h. The reaction mixture was quenched with water and extracted with DCM. The organic layer was dried, concentrated and purified by flash chromatography (Combi-flash Rf, Hex 100%) to afford the title compound (166 mg, 59%). LCMS R_T = 1.589 min, MS (ES) 224.1 (M+H-56).

Step B. Preparation of methyl 1-(((*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)methyl)-3-((*S*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-5-carboxylate

[001193] The title compound (12 mg, 96%) was prepared according to General Procedure I using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5- trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-5-carboxylate (15 mg, 0.02 mmol) and methyl *tert*-butyl (*S*)-2-(((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate (8 mg, 0.03 mmol). LCMS: R_T = 1.864 min (Method B), MS (ES) 894.90 (M+H).

Step C. Preparation of methyl 3-((*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(((*S*)-pyrrolidin-2-yl)methyl)-1*H*-indole-5-carboxylate

[001194] To a solution of methyl 1-(((*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)methyl)-3-((*S*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-5-carboxylate (12 mg, 0.013 mmol) in DCM (1 mL) was added TFA (200 μL, 2.61 mmol), and the mixture was stirred at RT for 3h. The reaction mixture was washed with sat. $NaHCO_3$ aq. solution (3 mL) and extracted with DCM. The organic layer was dried, concentrated and purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-100% gradient) to afford

the title compound (10 mg, 90%). LCMS R_T = 1.892 min, MS (ES) 794.8 (M+H).

Step D. Example 690

[001195] To a solution of methyl 3-((*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(((*S*)-pyrrolidin-2-yl)methyl)-1*H*-indole-5-carboxylate (10 mg, 0.012 mmol) in DCM (0.5 mL) were added Et_3N (4 μL, 0.028 mmol) and formaldehyde (1 mg, 0.028 mmol). The mixture was stirred at RT for 10 min then washed with water (3 mL) and extracted with DCM. The organic layer was dried, concentrated and saponified using General Procedure D to yield the title compound (7.7 mg, 69%). LCMS: R_T = 1.918 MS (ES) 794.9 (M+H).

Example 691

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(methoxymethyl)-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylic acid

Step A. Preparation of ethyl 7-bromo-5-((methoxymethoxy)methyl)-1*H*-indole-2-carboxylate.

[001196] The title compound (52 mg, 47%, 2 steps) was prepared following the procedure described Example 544 Step A using 1-(*tert*-butyl) 2-ethyl 7-bromo-5-formyl-1*H*-indole-1,2-dicarboxylate (127 mg, 0.32 mmol). LCMS: R_T = 1.796 min, MS (ES) 341.9 (M+H).

Step B. Preparation of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-((methoxymethoxy)methyl)-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylate.

[001197] The title compound (10 mg, 13%, 2 steps) was prepared following General coupling procedure A using ethyl 7-bromo-5-((methoxymethoxy)methyl)-1*H*-indole-2-carboxylate (30 mg, 0.088 mmol) and (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (47 mg, 0.088 mmol) followed by NH alkylation using General procedure I with 2-(bromomethyl)pyridine HBr (19 mg, 0.075 mmol) by substituting Cs_2CO_3 with K_2CO_3 (31 mg, 0.225 mmol). LCMS: R_T = 2.277, 2.333 min, MS (ES) 890.9 (M+H).

Step C. Example 691.

[001198] To a solution of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-((methoxymethoxy)methyl)-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylate (9 mg, 0.041 mmol) in THF (0.25 mL) and MeOH (0.15 mL) was added conc. HCl (0.02 mL). After stirring at RT for 16 h, the reaction was quenched with aq. sat. $NaHCO_3$ solution and extracted with DCM. The combined organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in DMF (0.5 mL), and NaH (3.0 mg, 0.061 mmol) was added at 0 °C. After stirring at 0 °C for 5 min, MeI (3.8 μL, 8.7 mg, 0.061 mmol) was added then warmed to RT and stirred for 4 h. The reaction was quenched with aq. sat. NH_4Cl and extracted with DCM. The combined organic layer was dried over $MgSO_4$, filtered and concentrated. Subsequent saponification following general procedure D afforded the title compound (6.5 mg, 30%, 2 steps). LCMS: R_T = 2.035, 2.057 min, MS (ES) 832.8 (M+H).

Example 692

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-5-((oxetan-3-ylmethoxy)methyl)-1*H*-indole-2-carboxylic acid

[001199] The title compound was prepared (4.0 mg, 33%, 2 steps) following the procedures described Example 607 using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy) propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(hydroxymethyl)-1-methyl-1*H*-indole-2-carboxylate (11 mg, 0.014 mmol) and 3-(chloromethyl)oxetane (5 mg, 0.021 mmol). LCMS: R_T = 2.129, 2.157, 2.207 min, MS (ES) 811.9 (M+H). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.76 – 7.75 (m, 1H), 7.67 – 7.63 (m, 0.6 H), 7.63 – 7.59 (m, 0.4 H), 7.33 – 7.26 (m, 2.3 H), 7.09 – 7.05 (m, 0.7 H), 6.71 (s, 1.2 H), 6.68 (s, 0.8 H), 4.71 – 4.63 (m, 0.6 H), 4.62 – 4.56 (m, 1.2 H), 4.55 – 4.47 (m, 1.2 H), 4.45 – 4.40 (m, 0.6 H), 4.39 – 4.33 (m, 1H), 4.29 (dt, *J* = 6.0, 3.0 Hz, 1.2 H), 4.26 – 4.20 (m, 1H), 4.19 – 4.13 (m, 0.6 H), 4.07 – 4.03 (m, 1H), 3.98 – 3.95 (m, 1.6 H), 3.94 (s, 2H), 3.79 – 3.77 (m, 1.2 H), 3.75 (s, 0.6 H), 3.74 – 3.72 (m, 0.4 H), 3.72 – 3.66 (m, 0.6 H), 3.65 – 3.63 (m, 1H), 3.45 – 3.37 (m, 1.6 H), 3.36 – 3.28 (m, 1H), 3.27 – 3.22 (m, 0.6 H), 3.21 – 3.14 (m, 1H), 2.25 – 2.19 (m, 6.5 H), 2.14 – 2.10 (m, 1.8 H), 2.06 – 2.01 (m, 3.2 H), 2.00 – 1.99 (m, 0.7 H), 1.98 – 1.96 (m, 1H), 1.92 – 1.90 (m, 0.7 H), 1.89 (s, 1.3 H), 1.19 – 1.15 (m, 2.2 H), 1.06 (d, *J* = 6.6 Hz, 1.1 H).

Example 693

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-5-((2-morpholinoethoxy)methyl)-1*H*-indole-2-carboxylic acid

[001200] The title compound was prepared (4.0 mg, 35%ß, 2 steps) following the procedures described in the synthesis of example 607 using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(hydroxymethyl)-1-methyl-1*H*-indole-2-carboxylate (11 mg, 0.014 mmol) and 4-(2-chloroethyl)morpholine HCl (3.8 mg, 0.021 mmol). LCMS: R_T = 1.960, 1.989 min, MS (ES) 854.9 (M+H).

Example 694

3-((*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-(((R)-1-methylpyrrolidin-2-yl)methyl)-1H-indole-5-carboxylic acid

Step A. Preparation of *tert*-butyl (*R*)-2-(((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate

[001201] The title compound (174 mg, 62%) was prepared according to method described in Example 690 step A using *tert*-butyl (*R*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (201 mg, 1.0 mmol). LCMS R_T = 1.522 min, MS (ES) 224.1 (M+H-56).

Step B. Example 694

[001202] The title compound (6 mg, 54%) was prepared according to steps B-D in Example 690 using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-5-carboxylate (10 mg, 0.014 mmol) and *tert*-butyl (*R*)-2-(((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate (8 mg, 0.028 mmol). LCMS: R_T = 1.911 min, MS (ES) 794.9 (M+H).

Example 695

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(5-(8-(methoxymethyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)-1-methyl-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 2-bromo-8-(bromomethyl)-[1,2,4]triazolo[1,5-*a*]pyridine

[001203] AIBN (23 mg, 0.14 mmol) and NBS (92 mg, 0.52 mmol) were added to a solution of 2-bromo-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridine (100 mg, 0.47 mmol) in CCl_4 (5 mL). The reaction mixture was stirred at 85 °C under Ar for 4 h then concentrated. The residue was

purified by flash chromatography (Combi-flash Rf, DCM 100%) to afford the title compound (56 mg, 41%). LCMS: R_T = 1.121 min, MS (ES) 289.7 (M+H).

Step B. Preparation of 2-bromo-8-(methoxymethyl)-[1,2,4]triazolo[1,5-*a*]pyridine

[001204] A mixture of MeOH (15.6 μL, 0.38 mmol) and NaH (9.3 mg, 0.38 mmol) in THF (2 mL) was added to a solution of 2-bromo-8-(bromomethyl)-[1,2,4]triazolo[1,5-*a*]pyridine (56 mg, 0.19 mmol) in THF (3 mL) at 0 °C. The reaction mixture was stirred at RT for 30 min. The reaction was quenched with water and extracted with EtOAc. The combined organic layers were dried and concentrated. The crude compound (50 mg) was used for the next step without further purification. LCMS: R_T = 0.205 min, MS (ES) 241.9 (M+H).

Step C. Preparation of 8-(methoxymethyl)-2-(1-methyl-1*H*-indol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine

[001205] The title compound (60 mg, quant.) was prepared following the procedure descried Example 388 Step A using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (64 mg, 0.25 mmol) and 2-bromo-8-(methoxymethyl)-[1,2,4]triazolo[1,5-*a*]pyridine (50 mg, 0.21 mmol). LCMS: R_T = 1.531 min, MS (ES) 293.1 (M+H).

Step D. Preparation of 2-(3-iodo-1-methyl-1*H*-indol-5-yl)-8-(methoxymethyl)-[1,2,4]triazolo[1,5-*a*]pyridine

[001206] The title compound (61 mg, 71%) was prepared following the procedure descried Example 388 Step B using 8-(methoxymethyl)-2-(1-methyl-1*H*-indol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (60 mg, 0.21 mmol). LCMS: R_T = 1.778 min, MS (ES) 418.9 (M+H).

Step E. Example 695

[001207] The title compound (40 mg, 86%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 2-(3-iodo-1-methyl-1*H*-indol-5-yl)-8-(methoxymethyl)-[1,2,4]triazolo[1,5-*a*]pyridine (28 mg, 0.07 mmol). LCMS: R_T = 2.290 min, MS (ES) 828.9 (M+H).

Example 696

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(5-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 5-methyl-2-(1-methyl-1*H*-indol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine

[001208] The title compound (180 mg, 97%) was prepared following the procedure descried Example 388 Step A using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (218 mg, 0.85 mmol) and 2-bromo-5-methyl-[1,2,4]triazolo[1,5-*a*]pyridine (150 mg, 0.71 mmol). LCMS: R_T = 1.654 min, MS (ES) 263.1 (M+H).

Step B. Preparation of 2-(3-iodo-1-methyl-1*H*-indol-5-yl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyridine

[001209] The title compound (64 mg, 24%) was prepared following the procedure descried Example 388 Step B using 5-methyl-2-(1-methyl-1*H*-indol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (180 mg, 0.69 mmol). LCMS: R_T = 1.679 min, MS (ES) 388.9 (M+H).

Step C. Example 696

[001210] The title compound (40 mg, 90%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 2-(3-iodo-1-methyl-1*H*-indol-5-yl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyridine (26 mg, 0.07 mmol). LCMS: R_T = 2.208 min, MS (ES) 798.9 (M+H).

Example 697

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2,5-dicarboxylic acid

Step A. Preparation of 3-bromo-4-hydrazinylbenzoic acid

[001211] To a solution of methyl 4-amino-3-bromo benzoate (1.41 g, 6.52 mmol) was added a solution of $NaNO_2$ (0.675 g, 9.78 mmol) in water (6.52 mL) at RT and stirred for 45 min. The reaction mixture was cooled to 0 °C then $SnCl_2$ (3.83 g, 20 mmol) in con. HCl (12.0 mL) was added. The reaction mixture was stirred for 3h, diluted with water (30 mL). The precipitate was filtered and washed with ether to afford the title compound (0.994 g, 66%) as a white solid. ^{1}H NMR: (400 MHz in MeOD) δ 8.23 (d, J = 2.0 Hz, 1H), 8.05 (dd, J = 8.4, 2.0 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H); LCMS: RT = 0.135 min, MS (ES) 230.9 (M+H).

Step B. Preparation of (*E*)-3-bromo-4-(2-(1-methoxy-1-oxopropan-2-ylidene)hydrazinyl) benzoic acid

[001212] To a solution of 3-bromo-4-hydrazinylbenzoic acid (1.14 g, 4.91 mmol) in EtOH (25 mL) was added methyl pyruvate (0.54 mL, 5.89 mmol) at 0 °C then stirred for 20 min. Precipitate was filtered and washed with ether to afford the title compound (1.05 g, 68%) as a yellow solid. ^{1}H NMR: (400 MHz in MeOD) δ 8.15 (d, J = 1.6 Hz, 1H), 7.95 (dd, J = 8.4, 1.6

Hz, 1H), 7.85 (s, NH), 7.65 (d, J = 8.4 Hz, 1H), 3.90 (s, 3H), 2.23 (s, 3H); LCMS: RT = 0.884 min, MS (ES) 314.9 (M+H).

Step C. Preparation of allyl (*E*)-3-bromo-4-(2-(1-methoxy-1-oxopropan-2-ylidene) hydrazinyl)benzoate.

[001213] To a solution of (*E*)-3-bromo-4-(2-(1-methoxy-1-oxopropan-2-ylidene)hydrazinyl) benzoic acid (0.4 g, 1.27 mmol) in DMF (6.4 mL) was added K_2CO_3 (0.70 g, 5.1 mmol), followed by allyl bromide (0.55 mL, 6.37 mmol). The reaction mixture was stirred for 3 h, diluted with EtOAc, and washed with water. The combined organic layer was dried and concentrated *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-30% gradient) to afford the title compound (0.39 g, 87%).^{1}H NMR: (400 MHz in $CDCl_3$) δ 12.5 (s, NH), 8.19 (d, *J* = 2.0 Hz, 1H), 7.96 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 6.09-5.97 (m, 1H), 5.43-5.37 (m, 1H), 5.31-5.27 (m, 1H), 4.80 (dt, *J* = 5.6, 1.2 Hz, 2H), 3.88 (s, 3H), 2.22 (s, 3H); LCMS: R_T = 1.215 min, MS (ES) 355.12 (M+H).

Step D. Preparation of allyl (*E*)-3-bromo-4-(2-(1-methoxy-1-oxopropan-2-ylidene)-1-methylhydrazinyl)benzoate

[001214] To a solution of allyl (*E*)-3-bromo-4-(2-(1-methoxy-1-oxopropan-2-ylidene)hydrazinyl) benzoate (132 mg, 0.372 mmol) in MeCN (3.0 mL)/DMF (1.0 mL) was added Cs_2CO_3 (182 mg, 0.56 mmol), followed by MeI (69 mg, 0.484 mmol). The reaction mixture was stirred for 3 h, diluted with EtOAc and washed with water. The combined organic layer was dried and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-30% gradient) to afford the title compound (134 mg, 97%). LCMS: RT = 1.167 min, MS (ES) 369.04 (M+H).

Step E. Preparation of 5-allyl 2-methyl 7-bromo-1-methyl-1H-indole-2, 5-dicarboxylate

[001215] A solution of allyl (*E*)-3-bromo-4-(2-(1-methoxy-1-oxopropan-2-ylidene)-1-methylhydrazinyl)benzoate (134 mg, 0.364 mmol) in AcOH (3 mL) was heated to 90 °C and PPA (0.3 mL) was added. The reaction mixture was stirred for 2h at 90 °C then excess organic solvent was removed *in vacuo*. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-50% gradient) to afford the title compound (30 mg, 25%).^{1}H NMR: (400 MHz in $CDCl_3$) δ 8.33 (d, *J* = 1.6 Hz, 1H), 8.18 (d, *J* = 1.6 Hz, 1H), 7.33 (s, 1H), 6.10-6.01 (m, 1H), 5.42 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.31 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.83 (dt, *J* = 5.6, 1.2 Hz, 2H), 4.48 (s, 3H), 3.92 (s, 3H); LCMS: R_T = 1.311 min, MS (ES) 352.02 (M+H).

Step F. Example 697

[001216] The title compound was prepared following General Procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one and 5-allyl 2-methyl 7-bromo-1-methyl-1H-indole-2, 5-dicarboxylate. ^{1}H NMR: (400 MHz in MeOD) δ 8.44 (s, 1H), 7.81 (s, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.47 (s, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 6.61 (s, 2H), 4.39-4.35 (m, 1H), 4.10 (s, 3H), 3.98-3.92 (m, 2H), 3.87 (s, 3H), 3.86-3.84 (m, 2H), 3.46-3.38 (m, 2H), 2.28 (s, 6H), 2.23 (s, 3H), 2.21- 2.16 (m, 2H), 2.01 (s, 3H), 1.31 (d, *J* = 6.4 Hz, 3H); LCMS: R_T = 0.856 min, MS (ES) 756.23 (M+H).

Example 698

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(8-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 8-methyl-2-(1-methyl-1*H*-indol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine

[001217] The title compound (180 mg, 97%) was prepared following the procedure descried Example 388 Step A using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (218 mg, 0.85 mmol) and 2-bromo-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridine (150 mg, 0.71 mmol). LCMS: R_T = 1.404 min, MS (ES) 263.1 (M+H).

Step B. Preparation of 2-(3-iodo-1-methyl-1*H*-indol-5-yl)-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridine

[001218] The title compound (82 mg, 31%) was prepared following the procedure descried Example 388 Step B using 8-methyl-2-(1-methyl-1*H*-indol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (180 mg, 0.69 mmol). LCMS: R_T = 1.702 min, MS (ES) 388.9 (M+H).

Step C. Example 698

[001219] The title compound (34 mg, 76%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 2-(3-iodo-1-methyl-1*H*-indol-5-yl)-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridine (26 mg, 0.07 mmol). LCMS: R_T = 2.231 min, MS (ES) 798.9 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (d, *J* = 6.8 Hz, 1H), 8.30 (s, 1H), 7.10 (d, *J* = 8.7 Hz, 1H), 7.77 (d, *J* = 8.7 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.51 (s, 1H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 7.04 (t, *J* = 7.2 Hz, 1H), 6.69 (s, 2H), 4.54 – 4.48 (m, 1H), 4.22 – 4.15 (m, 1H), 3.99 (t, *J* = 6.6 Hz, 2H),

3.85 (s, 3H), 3.78 – 3.67 (m, 4H), 3.41 – 3.21 (m, 2H), 2.55 (s, 3H), 2.18 (s, 6H), 2.12 – 2.04 (m, 5H), 1.99 – 1.90 (m, 3H), 1.12 (d, J = 6.3 Hz, 3H).

Example 699

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(5-(8-((2-methoxyethoxy)methyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)-1-methyl-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 2-bromo-[1,2,4]triazolo[1,5-*a*]pyridine-8-carbaldehyde

[001220] 4-Methylmorpholine *N*-oxide (531 mg, 4.54 mmol) was added to a solution of 2-bromo-8-(bromomethyl)-[1,2,4]triazolo[1,5-*a*]pyridine (330 mg, 1.13 mmol) in THF (5 mL). The reaction was refluxed for 30 min. The reaction was quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried and concentrated. The crude title compound (250 mg) was used for the next step without further purification. LCMS: R_T = 0.977 min, MS (ES) 226.0 (M+H).

Step B. Preparation of (2-bromo-[1,2,4]triazolo[1,5-*a*]pyridin-8-yl)methanol

[001221] NaH (140.5 mg, 3.63 mmol) was added to a solution of 2-bromo-[1,2,4]triazolo[1,5-*a*]pyridine-8-carbaldehyde (410 mg, 1.81 mmol) in THF/MeOH (12 mL, 10:1) at 0 °C. The reaction was stirred for 10 min and then refluxed for 30 min. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried and concentrated. The crude title compound (420 mg) was used for the next step without further purification. LCMS: R_T = 0.974 min, MS (ES) 228.0 (M+H).

Step C. Preparation of 2-bromo-8-(((*tert*-butyldimethylsilyl)oxy)methyl)-[1,2,4]triazolo[1,5-*a*]pyridine

[001222] *tert*-Butyldimethylsilyl chloride (833 mg, 5.53 mmol), 4-DMAP (22.5 mg, 0.180 mmol) and Et_3N (770 µL, 5.53 mmol) were added to a solution of (2-bromo-[1,2,4]triazolo[1,5-*a*]pyridin-8-yl)methanol (420 mg, 1.84 mmol) in DCM (8 mL) at 0 °C. The reaction was stirred at RT for 20 h. The reaction was quenched with water and extracted with DCM. The combined organic layer was washed with brine, dried and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-20% gradient) to afford the title compound (270 mg, 43%). LCMS: R_T = 2.099 min, MS (ES) 341.9 (M+H).

Step D. Preparation of 8-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(1-methyl-1*H*-indol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine

[001223] The title compound (45 mg, 15%) was prepared following the procedure descried Example 388 Step A using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (243 mg, 0.95 mmol) and 2-bromo-8-(((*tert*-butyldimethylsilyl)oxy)methyl)-[1,2,4]triazolo[1,5-*a*]pyridine (270 mg, 0.79 mmol). LCMS: R_T = 2.176 min, MS (ES) 393.1 (M+H).

Step E. Preparation of 8-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(3-iodo-1-methyl-1*H*-indol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine

[001224] The title compound (58 mg, quant.) was prepared following the procedure descried Example 388 Step B using 8-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(1-methyl-1*H*-indol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (45 mg, 0.11 mmol). LCMS: R_T = 2.382 min, MS (ES) 518.8 (M+H).

Step F. Preparation of (2-(3-iodo-1-methyl-1*H*-indol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-8-yl)methanol

[001225] The title compound (50 mg, quant.) was prepared following the procedure descried Example 420 Step C using 8-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(3-iodo-1-methyl-1*H*-indol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (58 mg, 0.11 mmol). LCMS: R_T = 1.558 min, MS (ES) 404.8 (M+H).

Step G. Preparation of 2-(3-iodo-1-methyl-1*H*-indol-5-yl)-8-((2-methoxyethoxy)methyl)-[1,2,4]triazolo[1,5-*a*]pyridine

[001226] The title crude compound (31 mg) was prepared following General Procedure G using (2-(3-iodo-1-methyl-1*H*-indol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-8-yl)methanol (50 mg, 0.12 mmol) and 2-bromoethyl methyl ether (15.1 μL, 0.16 mmol). LCMS: R_T = 1.763 min, MS (ES) 462.9 (M+H).

Step H. Example 699

[001227] The title compound (19 mg, 46%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (25 mg, 0.06 mmol) and 2-(3-iodo-1-methyl-1*H*-indol-5-yl)-8-((2-methoxyethoxy)methyl)-[1,2,4]triazolo[1,5-*a*]pyridine (26 mg, 0.06 mmol). LCMS: R_T = 2.248 min, MS (ES) 872.8 (M+H).

Example 700

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(1-(5-methylpyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 2-(3-bromo-1*H*-1,2,4-triazol-1-yl)-5-methylpyrimidine

[001228] The title compound (220 mg, 45%) was prepared following the procedure descried Example 646 Step A using 2-bromo-5-methylpyrimidine (421 mg, 2.43 mmol). LCMS: R_T = 1.146 min, MS (ES) 240.0 (M+H).

Step B. Preparation of 1-methyl-5-(1-(5-methylpyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[001229] The title compound (250 mg, 94%) was prepared following the procedure descried Example 388 Step A using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (283 mg, 1.10 mmol) and 2-(3-bromo-1*H*-1,2,4-triazol-1-yl)-5-methylpyrimidine (220 mg, 0.92 mmol). LCMS: R_T = 1.528 min, MS (ES) 291.1 (M+H).

Step C. Preparation of 3-iodo-1-methyl-5-(1-(5-methylpyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[001230] The title compound (45 mg, 13% yield) was prepared following the procedure descried Example 388 Step B using 1-methyl-5-(1-(5-methylpyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (250 mg, 0.86 mmol). LCMS: R_T = 1.748 min, MS (ES) 416.8 (M+H).

Step D. Example 700

[001231] The title compound (25 mg, 38%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (40 mg, 0.07 mmol) and 3-iodo-1-methyl-5-(1-(5-methylpyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (45 mg, 0.11 mmol). LCMS: R_T = 2.269 min, MS (ES) 826.9 (M+H).

Example 701

3-((*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-(((*R*)-1-methylpyrrolidin-3-yl)methyl)-1H-indole-5-carboxylic acid

Step A. Preparation of *tert*-butyl (*R*)-3-(((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate

[001232] The title compound (121 mg, 43%) was prepared according to method described in Example 690 step A using *tert*-butyl (*R*)-3-(hydroxymethyl)pyrrolidine-1-carboxylate (201 mg, 1.0 mmol). LCMS: R_T = 1.441 min (Method B), MS (ES) 224.1 (M+H-56).

Step B. Example 701

[001233] The title compound (5.6 mg, 50%) was prepared according to steps B-D in

Example 690 using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-5-carboxylate (10 mg, 0.014 mmol) and *tert*-butyl (*R*)-3-(((methylsulfonyl)oxy)methyl) pyrrolidine-1-carboxylate (8 mg, 0.028 mmol). LCMS: R_T = 2.004 min, MS (ES) 794.9 (M+H).

Example 702

3-((*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-(((*S*)-1-methylpyrrolidin-3-yl)methyl)-1H-indole-5-carboxylic acid

Step A. Preparation of *tert*-butyl (*S*)-3-(((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate

[001234] The title compound (178 mg, 64%) was prepared according to method described in Example 690 step A using *tert*-butyl (*S*)-3-(hydroxymethyl)pyrrolidine-1-carboxylate (201 mg, 1.0 mmol). LCMS: R_T = 1.426 min, MS (ES) 224.1 (M+H-56).

Step B. Example 702

[001235] The title compound (10 mg, 90%) was prepared according to steps B-D in Example 690 using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-5-carboxylate (10 mg, 0.014 mmol) and *tert*-butyl (*S*)-3-(((methylsulfonyl)oxy)methyl) pyrrolidine-1-carboxylate (8 mg, 0.028 mmol). LCMS: R_T = 1.849 min, MS (ES) 792.9 (M+H).

Example 703

(*R*)-3-(3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-methyl-1H-indol-5-yl)-4-methyl-1,2,4-oxadiazol-5(4H)-one

[001236] The title compound (16.2 mg, 78%) was prepared according to General Procedure I using (*R*)-3-(3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indol-5-yl)-1,2,4-oxadiazol-5(4*H*)-one (20 mg, 0.027 mmol) and MeI (6 μL, 0.08 mmol). LCMS: R_T = 2.249 min, MS (ES) 765.8 (M+H).

Example 704

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(5-(1-(5-methoxypyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1-methyl-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 2-(3-bromo-1*H*-1,2,4-triazol-1-yl)-5-methoxypyrimidine

[001237] The title compound (310mg, 83%) was prepared following the procedure descried Example 646 Step A using 2-bromo-5-methoxypyrimidine (460 mg, 2.43 mmol). LCMS: R_T = 0.222 min, MS (ES) 255.9 (M+H).

Step B. Preparation of 5-(1-(5-methoxypyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1-methyl-1*H*-indole

[001238] The title crude compound (400 mg) was prepared following the procedure descried Example 388 Step A using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (398 mg, 1.55 mmol) and 2-(3-bromo-1*H*-1,2,4-triazol-1-yl)-5-methoxypyrimidine (310 mg, 1.29 mmol). LCMS: R_T = 1.529 min, MS (ES) 307.0 (M+H).

Step C. Preparation of 3-iodo-5-(1-(5-methoxypyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1-methyl-1*H*-indole

[001239] The title compound (260 mg, 46%) was prepared following the procedure descried Example 388 Step B using 5-(1-(5-methoxypyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1-methyl-1*H*-indole (400 mg, 1.31 mmol). LCMS: R_T = 1.741 min, MS (ES) 432.9 (M+H).

Step D. Example 704

[001240] The title compound (29 mg, 62%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 3-iodo-5-(1-(5-methoxypyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1-methyl-1*H*-indole (29 mg, 0.07 mmol). LCMS: R_T = 2.176 min, MS (ES) 842.8 (M+H).

Example 705

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(2,4,6-trimethylpyrimidin-5-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-4-methoxy-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylic acid

[001241] The title compound was This compound was prepared following General Procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(2,4,6-trimethylpyrimidin-5-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one and 7-iodo-4-methoxy-1*H*-indole-2-carboxylic acid followed by installation of the 2-methylpyridyl group using General Procedure G, and saponification using General Procedure D. ^{1}H NMR: (400

MHz in MeOD) δ 8.47 (d, *J* = 4.4 Hz, 1H), 8.06 (t, *J* = 7.2 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.64 (s, 1H), 7.56 (t, *J* = 6.8 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.65 (s, 2H), 6.10 (d, *J* = 18.4 Hz, 1H), 5.95 (d, *J* = 18.4 Hz, 1H), 4.03 (s, 3H), 3.89 (t, *J* = 6.4 Hz, 2H), 3.86-3.69 (m, 2H), 3.48 (d, *J* = 13.2 Hz, 1H), 3.15-3.06 (m, 1H), 2.89-2.79 (m, 1H), 2.75 (s, 3H), 2.35 (s, 3H), 2.31 (s, 6H), 2.18 (s, 3H), 2.01-1.94 (m, 2H), 1.21 (d, *J* = 6.8 Hz, 3H); LCMS: R_T = 0.850 min, MS (ES) 831.30 (M+H).ß

Example 706

3-((*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-(((*R*)-pyrrolidin-3-yl)methyl)-1H-indole-5-carboxylic acid

[001242] The title compound (3.4 mg, 31%) was prepared according to steps B-C in Example 690 using methyl (*R*)-3-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-5-carboxylate (10 mg, 0.014 mmol) and *tert*-butyl (*R*)-3-(((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate (8 mg, 0.028 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.963 min, MS (ES) 780.8 (M+H).

Example 707

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-methyl-5-(7-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 7-methyl-2-(1-methyl-1*H*-indol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine

[001243] The title compound (200 mg, 95%) was prepared following the procedure descried Example 388 Step A using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (247 mg, 0.96 mmol) and 2-bromo-7-methyl-[1,2,4]triazolo[1,5-*a*]pyridine (170mg, 0.80 mmol). LCMS: R_T = 1.309 min, MS (ES) 263.1 (M+H).

Step B. Preparation of 2-(3-iodo-1-methyl-1*H*-indol-5-yl)-7-methyl-[1,2,4]triazolo[1,5-*a*]pyridine

[001244] The title compound (190 mg, 64%) was prepared following the procedure descried Example 388 Step B using 7-methyl-2-(1-methyl-1*H*-indol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (200 mg, 0.76 mmol). LCMS: R_T = 1.557 min, MS (ES) 388.9 (M+H).

Step C. Example 707

[001245] The title compound (7.5 mg, 17%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 2-(3-iodo-1-methyl-1*H*-indol-5-yl)-7-methyl-[1,2,4]triazolo[1,5-*a*]pyridine (28 mg, 0.07 mmol). LCMS: R_T = 2.146 min, MS (ES) 798.9 (M+H).

Example 708

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(5-(1-(2-methoxyethyl)-1*H*-1,2,4-triazol-3-yl)-1-(2-morpholinoethyl)-1*H*-indol-3-yl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 4-(2-(3-iodo-5-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethyl)morpholine

[001246] The crude title compound (250 mg) was prepared following General Procedure J using 2-(3-iodo-5-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethan-1-ol (210 mg, 0.48 mmol) and morpholine (376 μL, 4.36 mmol). LCMS: R_T = 1.424 min, MS (ES) 407.9 (M+H).

Step B. Preparation of 4-(2-(3-iodo-5-(1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethyl)morpholine

[001247] The crude title compound (220 mg) was prepared following the procedure descried Example 581 Step C using 4-(2-(3-iodo-5-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethyl)morpholine (250 mg, 0.49 mmol). LCMS: R_T = 1.132 min, MS (ES) 423.9 (M+H).

Step C. Preparation of 4-(2-(3-iodo-5-(1-(2-methoxyethyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethyl)morpholine

[001248] The crude title compound (199 mg) was prepared following General Procedure G using 4-(2-(3-iodo-5-(1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethyl)morpholine (220 mg, 0.52 mmol) and 2-bromoethyl methyl ether (63.5 μL, 0.68 mmol). LCMS: R_T = 1.292 min, MS (ES) 481.9 (M+H).

Step D. Example 708

[001249] The title compound (25 mg, 49%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 4-(2-(3-iodo-5-(1-(2-methoxyethyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethyl)morpholine (32 mg, 0.07 mmol). LCMS: R_T = 1.982 min, MS (ES) 891.9 (M+H).

Example 709

(*M, R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-(2-methoxyethyl)-5-methyl-1*H*-indole-2-carboxylic acid

Step A. Separation of (*M*, *R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[001250] Diastereomeric mixture of (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl) -4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one was separated by HPLC (Chiralcel OZ-H column Hex/EtOAc 7/3).

Step B. Preparation of ethyl (*M*, *R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy) propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*] indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate

[001251] The title compound (206 mg, 75%) was prepared following General Procedure K using (*M*, *R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (200 mg, 0.37 mmol) and ethyl 7-iodo-5-methyl-1*H*-indole-2-carboxylate (200 mg, 0.61 mmol). LCMS: R_T = 1.708 min, MS (ES) 739.9 (M+H).

Step C. Example 709

[001252] The title compound (138 mg, 64%) was prepared following General Procedure I using ethyl (*M*, *R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (206 mg, 0.28 mmol) and 1-bromo-2-methoxyethane (100 mg, 0.72 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.503 min, MS (ES) 769.9 (M+H). ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 7.813 (d, J =8.7, Hz, 0.34H), 7.810 (d, J =8.7 Hz, 0.66H), 7.50-7.46 (m, 1H), 7.37 (d, J =8.7 Hz, 0.33H), 7.36 (d, J =8.4 Hz, 0.66H), 7.25-7.18 (m, 1.34H), 6.94 (s, 0.66H), 6.76 (s, 1.34H), 6.74 (s, 0.66H), 5.03-5.00 (m, 0.34H), 4.88-4.81 (m, 0.66H), 4.70 (dd, J =12.5, 4.4 Hz, 0.5H), 4.60-4.57 (m, 0.5H), 4.48-4.45 (m, 1H), 4.31-4.22 (m, 1H), 4.02 (t, J =6.2 Hz, 2H), 3.84 (s, 3H), 3.77 (d, J =13.1, 1H), 3.50-3.25 (m, 4H), 3.05 (s, 2H), 3.00 (s, 1H), 2.43 (s, 2H), 2.40 (s, 1H), 2.28 (s, 2.28, 4H), 2.27 (s, 2H), 2.19 (s, 1H), 2.18 (s, 2H), 2.14-2.04 (m, 2H), 1.97 (s, 1H), 1.92 (s, 2H), 1.21 (d, J =6.5 Hz, 2H), 1.10 (d, J =6.6 Hz, 1H).

Example 710

(*P, R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-(2-methoxyethyl)-5-methyl-1H-indole-2-carboxylic acid

[001253] The title compound (131 mg, 46% yield) was prepared following the same procedure as Example 709 starting from (*P*, *R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (200 mg, 0.037 mmol). LCMS: R_T = 1.466, 1.495 min (Method B), MS (ES) 769.9 (M+H). ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 7.772 (d, J =8.6 Hz, 0.66H), 7.768 (d, J =8.6 Hz, 0.34 H), 7.47-7.43 (m, 1H), 7.33 (d, J =8.7 Hz, 0.34H), 7.32 (d, J =08.7 Hz, 0.66H), 7.19 (s, 1.34H), 6.93 (s, 0.66H), 6.71 (s, 1.34H), 6.69 (s, 0.66H), 4.97-4.92 (m, 0.34H), 4.77-4.72 (m, 0.66H), 4.66 (dd, J =12.7, 4.4 Hz, 0.34H), 4.55-4.46 (m, 1H), 4.41 (dd, J =13.5, 3.7 Hz, 0.66H), 4.21-4.12 (m, 1H), 3.98 (t, J =6.3 Hz, 2H), 3.79 (s, 1H), 3.77 (s, 2H), 3.67 (d, J =12.8 Hz, 1H), 3.45-3.20 (m, 4H), 3.00 (s, 2H), 2.95 (s, 1H), 2.38 (s, 2H), 2.36 (s, 1H), 2.24 (s, 4H), 2.23 (s, 2H), 2.07-1.97 (m, 8H), 1.15 (d, J =6.5 Hz, 2H), 1.05 (d, J =6.6 Hz, 1H).

Example 711

(*M, R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-(2-methoxyethoxy)-1-methyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl (M, *R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate

[001254] The title compound (99 mg, 65%) was prepared following General Procedure K using (*M*, *R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (100 mg, 0.19 mmol) and methyl 5-(benzyloxy)-7-iodo-1*H*-indole-2-carboxylate (150 mg, 0.37 mmol). LCMS: R_T = 1.756 min, MS (ES) 817.8 (M+H).

Step B. Preparation of methyl (M, *R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylate

[001255] The title compound (70 mg, 70%) was prepared following General Procedure I using methyl (*M*, *R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-

dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (99 mg, 0.12 mmol) and MeI (40 mg, 0.28 mmol). LCMS: R_T = 1.847, 1.874 min, MS (ES) 831.9 (M+H).

Step C. Preparation of methyl (M, *R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy) propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-methyl-1*H*-indole-2-carboxylate

[001256] The title compound (62 mg, 99%) was prepared following the procedure described Example 390 Step D using methyl (*M, R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylate (70 mg, 0.084 mmol) and Pd/C (10 wt.%, 15 mg, 0.014 mmol) by hydrogenating in MeOH (5 mL) with HCl (4.0 M in dioxanes, 0.5 mL) for 16 h at RT. LCMS: R_T = 1.462, 1.517 min, MS (ES) 741.9 (M+H).

Step D. Example 711

[001257] The title compound (36 mg, 53%) was prepared following General Procedure H using methyl (*M, R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-methyl-1*H*-indole-2-carboxylate (64 mg, 0.086 mmol) and 1-bromo-2-methoxyethane (35 mg, 0.25 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.393 min, MS (ES) 785.8 (M+H).

Example 712

(*P, R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-(2-methoxyethoxy)-1-methyl-1H-indole-2-carboxylic acid

[001258] The title compound (23 mg, 15% overall yield) was prepared following the same procedure as Example 711 starting from (*P, R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino [1,2-*a*]indol-1(2*H*)-one (100 mg, 0.19 mmol). LCMS: R_T = 1.353, 1.388 min, MS (ES) 785.8 (M+H).

Example 713

(*M, R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-methyl-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylic acid

[001259] The title compound (30 mg, 29%) was prepared following General Procedure I using ethyl (*M, R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-

oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (94 mg, 0.13 mmol) and 2-(chloromethyl)pyridine hydrochloride (50 mg, 0.31 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.255 min, MS (ES) 802.9 (M+H).

Example 714

(*P, R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-methyl-1-(pyridin-2-ylmethyl)-1H-indole-2-carboxylic acid

[001260] The title compound (72 mg, 31%) was prepared following General Procedure I using ethyl (*P*, *R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (72 mg, 0.097 mmol) and 2-(chloromethyl)pyridine hydrochloride (40 mg, 0.24 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.227 min, MS (ES) 802.8 (M+H).

Example 715

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-5-(2-morpholinoethyl)-1*H*-indole-2-carboxylic acid

Step A. Preparation of 2-(4-amino-3-bromophenyl)ethan-1-ol

[001261] To a solution of 2-(4-Aminophenyl)ethan-1-ol (2.0 g, 145 mmol) in DMF (10 mL) was added NBS (2.5 g, 145 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred overnight then quenched with brine and extracted with EtOAc. The organic layers were dried and concentrated. and the residue was purified flash chromatography (Combi-flash Rf, hexane-ethyl acetate = 0-50% gradient for 15 min) to give the title compound (2.5 g, 80%). ^{1}H-NMR (DMSO-d_6) δ 7.18 (d, 1H, J = 1.8Hz), 6.91 (dd, 1H, J_1= 1.8 Hz, J_2= 12.0 Hz), 6.72 (d, 1H, J = 12Hz), 5.06 (s, 2H), 4.55 (s, 1H), 3.51 (m, 2H), 2.25 (tr, 2H, J = 12 Hz).

Step B. Preparation of 2-(3-bromo-4-hydrazinylphenyl)ethan-1-ol

[001262] To a solution of 2-(4-Amino-3-bromophenyl)ethan-1-ol (2.5 g, 12 mmol) in conc. HCl (25 mL) at -5 °C was added a solution of sodium nitrate (1.2 g, 17 mmol) in water (3 mL) dropwise. The reaction mixture was stirred at -5 °C for 1h then a solution of $SnCl_2$ (6.8 g, 36 mmol) conc. HCl (5 mL) was added slowly. The reaction mixture was warmed to RT and stirred for 5 h. The mixture was neutralized with NaOH and filtered. The filtrate was extracted with EtOAc and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-40% gradient) to afford the title compound (1.9 g, 66%).

^{1}H-NMR (DMSO-d_6) δ 7.21 (d, 1H, *J* = 1.8 Hz), 7.10-7.06 (m, 2H), 6.05 (s, 1H), 4.56 (tr, 2H, *J* = 6 Hz), 4.10 (s, 2H), 3.55 (m, 2H), 2.59 (tr, 2H, *J* = 12 Hz).

Step C. Preparation of methyl (*E*)-2-(2-(2-bromo-4-(2-hydroxyethyl)phenyl)hydrazono) propanoate

[001263] To a solution of 2-(3-bromo-4-hydrazinylphenyl)ethan-1-ol (1.9 g, 8 mmol) in THF (5 mL) was added methyl puravate (0.8 mL, 10 mmol). The reaction mixture was heated at 50 °C for 30 min then concentrated. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-10% gradient) to afford the title compound (2.3 g, 90%). ^{1}H-NMR ($CDCl_3$) δ 8.02 (d, 1H, *J* = 1.8 Hz), 7.53 (dd, 1H, J_1= 1.8 Hz, J_2= 12.0 Hz), 7.32 (s, 1H), 7.15 (d, 1H, *J* = 12 Hz), 3.78 (s, 3H), 2.84 (tr, 2H, *J* = 12 Hz), 2.15(s, 3H), 1.32 (tr, 2H, *J* = 12 Hz).

Step D. Preparation of methyl (*E*)-2-(2-(2-bromo-4-(2-hydroxyethyl)phenyl)-2-methylhydrazono)propanoate

[001264] To a solution of methyl (*E*)-2-(2-(2-bromo-4-(2-hydroxyethyl)phenyl)hydrazono) propanoate (2.3 g, 7 mmol) in MeCN (20 mL) was added Cs_2CO_3 (2.8 g, 84 mmol) followed by MeI (480 μL, 77 mmol) at RT. The reaction mixture was stirred at RT for 15 h. The reaction was quenched with brine, extracted with EtOAc and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-5% gradient) to afford the title compound (2.4 g, 94%).

Step E. Preparation of methyl 5-(2-acetoxyethyl)-7-bromo-1-methyl-1H-indole-2-carboxylate

[001265] The title compound (650 mg, 30%) was prepared following the procedure described Example 680 Step B using methyl (*E*)-2-(2-(2-bromo-4-(2-hydroxyethyl)phenyl)-2-methylhydrazono)propanoate (2 g, 62 mmol) by heating at 90°C for 6h. ^{1}H-NMR ($CDCl_3$) δ 7.44 (s, 1H), 7.41 (s, 1H), 7.18 (s, 1H), 4.47 (s, 3H), 4.31 (tr, 2H, *J* = 12 Hz), 3.90 (s, 3H), 3.29 (tr, 2H, *J* = 12 Hz), 2.06 (s. 3H).

Step F. Preparation of methyl (*R*)-5-(2-acetoxyethyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylate

[001266] The title compound (98 mg, 80%) was prepared following General coupling procedure A using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one and methyl 5-(2-acetoxyethyl)-7-bromo-1-methyl-1H-indole-2-carboxylate. MS (ES) 812.3 (M+H)

Step G. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl) -4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-(2-hydroxyethyl)-1-methyl-1*H*-indole-2-carboxylate

[001267] To a solution of methyl (R)-5-(2-acetoxyethyl)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1-methyl-1H-indole-2-carboxylate (130 mg, 0.16 mmol) in MeOH/THF (3/1, 4 mL) was added solid NaOMe (10mg, 0.176 mmol) at -40 ^{o}C. The reaction mixture was wormed to RT over 1 h and few drops of water, methanol and silica gel were added then concentrated. The residue was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-10% gradient) to afford the title compound (100 mg, 81%). MS (ES) 770.3 (M+H).

Step H. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl) -4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*) -yl)-1-methyl-5-(2-oxoethyl)-1*H*-indole-2-carboxylate

[001268] To a solution of methyl (R)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl) -4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-5-(2-hydroxyethyl)-1-methyl-1H-indole-2-carboxylate (110 mg, 0.143 mmol) in DCM was added Dess-Martin periodinane (91 mg, 0.22 mmol). The reaction mixture was stirred at RT for 1 h. The reaction mixture was diluted with DCM, washed with sat $NaHCO_3$, dried and concentrated to yield the title compound, which was used in next step without further purification. MS (ES) 768.3 (M+H).

Step I. Example 715

[001269] To a solution of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl) -4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-5-(2-oxoethyl)-1*H*-indole-2-carboxylate (30 mg, 0.039 mmol) in DCE (2 mL) was added morpholine (6 μL, 0.059 mmol) and stirred at RT for 30 min then $NaBH(OAc)_3$ was added. The reaction mixture was stirred at RT for 1 h then concentrated. The residue was subjected to saponification using General procedure D to give the title compound (20 mg, TFA salt, 54%). MS (ES) 825.3 (M+H).

Example 716

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-(2-methoxyethoxy)-1-methyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate

[001270] The title compound (206 mg, 36%) following General Procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (400 mg, 0.61 mmol) and methyl 5-(benzyloxy)-7-iodo-1*H*-indole-2-carboxylate (420 mg, 1.03 mmol) in toluene instead of DMF. LCMS: R_T = 2.153 min, MS (ES) 933.9 (M+H).

Step B. Preparation of methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylate

[001271] The title compound (33 mg, 64%) was prepared following General Procedure I using methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1*H*-indole-2-carboxylate (51 mg, 0.054 mmol) and MeI (20 mg, 0.14 mmol). LCMS: R_T = 2.286 min (Method B), MS (ES) 947.8 (M+H).

Step C. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-methyl-1*H*-indole-2-carboxylate

[001272] The title compound (26 mg, 87%) was prepared following the procedure described Example 390 Step D using methyl (*R*)-5-(benzyloxy)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylate (33 mg, 0.035 mmol) and Pd/C (10 wt.%, 10 mg, 0.0093 mmol) by hydrogenating in MeOH (5 mL) for 16 h at RT. LCMS: R_T = 1.869, 1.928 min (Method B), MS (ES) 857.8 (M+H).

Step D. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(2-methoxyethoxy)-1-methyl-1*H*-indole-2-carboxylate

[001273] The title compound was prepared following General Procedure H using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-hydroxy-1-methyl-1*H*-indole-2-carboxylate (26 mg, 0.030 mmol) and 1-bromo-2-methoxyethane (15 mg, 0.11 mmol). The crude reaction mixture was carried forward to the next step without further purification. LCMS: R_T = 2.059, 2.139 min (Method B), MS (ES) 915.8 (M+H).

Step E. Example 716

[001274] In a microwave vial equipped with a stir bar, methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-(2-methoxyethoxy)-1-methyl-1*H*-indole-2-carboxylate (from Step 4) was dissolved in THF (2 mL). Tetrabutylammonium fluoride (1.0 M, 0.75 mL, 0.75 mmol) was added and the reaction was capped and heated to 110 °C for 45 min. The reaction was diluted into DCM/H2O (1:1, 10 mL) and the layers were separated. The aqueous layer was extracted with DCM (2 x 5 mL), and the combined organic layers were dried with a phase separator and concentrated *in vacuo*. The crude reaction product was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient from 30-95% CH_3CN, 0.1% TFA to yield the title compound (9 mg, 38% yield over Steps 4 and 5). LCMS: R_T = 1.227 min (Method), MS (ES) 771.9 (M+H).

Example 717

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethyl-2-(morpholinomethyl)pyrimidin-5-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-(2-methoxyethyl)-5-methyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of ethyl (*R*)-7-(6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-3,4-dihydropyrazino [1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate

[001275] The title compound (742 mg, 76%) was prepared following General Procedure C using (*R*)-6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (750 mg,

1.14 mmol) and ethyl 7-iodo-5-methyl-1*H*-indole-2-carboxylate (600 mg, 1.82 mmol) in toluene instead of DMF. LCMS: R_T = 1.944 min, MS (ES) 857.8 (M+H).

Step B. Preparation of ethyl (*R*)-7-(6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-3,4-dihydropyrazino [1,2-*a*]indol-2(1*H*)-yl)-1-(2-methoxyethyl)-5-methyl-1*H*-indole-2-carboxylate

[001276] The title compound (152 mg, 68%) was prepared following General Procedure I using ethyl (*R*)-7-(6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (210 mg, 0.25 mmol) and 1-bromo-2-methoxyethane (80 mg, 0.58 mmol). LCMS: R_T = 2.023, 2.050 min, MS (ES) 915.9 (M+H).

Step C. Example 717

[001277] The title compound (15.6 mg, 51%) was prepared following General Procedure J using ethyl (*R*)-7-(6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-methoxyethyl)-5-methyl-1*H*-indole-2-carboxylate (29 mg, 0.035 mmol) and morpholine (25 mg, 0.29 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.021 min, MS (ES) 866.8 (M+H).

Example 718

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-(2-methoxyethyl)-5-methyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate

[001278] The title compound (146 mg, 28%) was prepared following General Procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (400 mg, 0.61 mmol) and ethyl 7-iodo-5-methyl-1*H*-indole-2-carboxylate (400 mg, 1.21 mmol) in toluene instead of DMF and stirred for 5 days. LCMS: R_T = 2.092 min, MS (ES) 855.9 (M+H).

Step B. Preparation of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-

pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-methoxyethyl)-5-methyl-1*H*-indole-2-carboxylate

[001279] The title compound was prepared following General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (55 mg, 0.064 mmol) and 1-bromo-2-methoxyethane (20 mg, 0.14 mmol). LCMS: R_T = 2.217, 2.260 min (Method B), MS (ES) 913.9 (M+H).

Step C. Example 718

[001280] To a solution of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-methoxyethyl)-5-methyl-1*H*-indole-2-carboxylate in THF (2 mL) was added TBAF (1.0 M, 0.75 mL, 0.75 mmol), and the reaction was stirred at 110 °C for 45 min. The reaction was diluted into DCM/H_2O (1:1, 10 mL) and the layers were separated. The aqueous layer was extracted with DCM, and the combined organic layer was dried and concentrated *in vacuo*. The crude reaction product was purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient from 40-95% CH_3CN, 0.1% TFA to yield the title compound (23.8 mg, 49% 2 steps). LCMS: R_T = 2.129 min, MS (ES) 755.8 (M+H).

Example 719

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-5-methyl-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylic acid

Step A. Preparation of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylate

[001281] The title compound (22 mg, 57%) was prepared following General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1*H*-indole-2-carboxylate (35 mg, 0.041 mmol) and 2-(chloromethyl)pyridine HCl (30 mg, 0.12 mmol). LCMS: R_T = 1.838, 1.891 min, MS (ES) 946.9 (M+H).

Step B. Example 719

[001282] The title compound (9 mg, 49%) was prepared following the procedure described Example 718 Step C using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-5-methyl-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylate (22 mg, 0.023 mmol). LCMS: R_T = 1.998 min, MS (ES) 788.8 (M+H).

Example 720

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-2-(1-(2-morpholinoethyl)-5-(1-(pyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-3-yl)-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of 1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-(1-(pyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[001283] The title compound (180 mg, 69%) was prepared following the procedure descried Example 388 Step A using 1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (273 mg, 0.68 mmol) and 2-(3-bromo-1*H*-1,2,4-triazol-1-yl)pyrimidine (140 mg, 0.62 mmol). LCMS: R_T = 2.019 min, MS (ES) 421.0 (M+H).

Step B. Preparation of 1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-iodo-5-(1-(pyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole

[001284] The crude title compound (170 mg) was prepared following the procedure descried Example 388 Step B using 1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-(1-(pyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (180 mg, 0.43 mmol). LCMS: R_T = 2.183 min, MS (ES) 546.9 (M+H).

Step C. Preparation of 2-(3-iodo-5-(1-(pyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethan-1-ol

[001285] The crude title compound (170 mg) was prepared from the procedure descried Example 420 Step C using 1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-iodo-5-(1-(pyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (170 mg, 0.31 mmol). LCMS: R_T = 1.275 min, MS (ES) 432.9 (M+H).

Step D. Preparation of 4-(2-(3-iodo-5-(1-(pyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethyl)morpholine

[001286] The crude title compound (250 mg) was prepared following General Procedure J using 2-(3-iodo-5-(1-(pyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethan-1-ol (170

mg, 0.39 mmol) and morpholine (338 μL, 3.92 mmol). LCMS: R_T = 1.317 min, MS (ES) 501.9 (M+H).

Step E. Example 720

[001287] The title compound (22 mg, 43%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (30 mg, 0.06 mmol) and 4-(2-(3-iodo-5-(1-(pyrimidin-2-yl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethyl)morpholine (36 mg, 0.07 mmol). LCMS: R_T = 1.994 min, MS (ES) 911.8 (M+H).

Example 721

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4,5-dimethoxy-1-methyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl (*Z*)-2-azido-3-(5-bromo-2,3-dimethoxyphenyl)acrylate

[001288] A solution of 5-bromo-2,3-dimethoxybenzaldehyde (1.0 g, 4.1 mmol) was stirred at 0 °C under Ar in 1:1 MeOH/THF (4 mL). A solution of methyl azidoacetate (1.6 mL, 16.3 mmol) in MeOH (2 mL) was added. The reaction mixture was cooled to -20 °C and a mixture of NaOMe (881 mg, 16.3 mmol) in MeOH (12 mL) was added dropwise. After stirring 15 min, the reaction was placed in an ice-bath and stirred for about 6 h then was left to sit overnight in a freezer. The reaction was quenched with aq. Sat. NH_4Cl and diluted with water and EtOAc. The aqueous layer was separated and extracted with EtOAc. The combined organics was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (Combi-flash Rf, hex/EtOAc = 0-12.5% gradient) to give the title compound (903 mg, 65%). LCMS: R_T = 2.04 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (d, *J* = 2.2 Hz, 1H), 7.27 (d, *J* = 2.2 Hz, 1H), 7.04 (s, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.72 (s, 3H).

Step B. Preparation of methyl 7-bromo-4,5-dimethoxy-1*H*-indole-2-carboxylate

[001289] A solution of methyl (*Z*)-2-azido-3-(5-bromo-2,3-dimethoxyphenyl)acrylate (523 mg, 1.53 mmol) in toluene (31 mL) was irradiated under microwave at 200 °C for 15 minutes . The reaction mixture was concentrated, and the residue was purified by flash chromatography (Combi-flash Rf, Hex/EtOAc = 0-10% gradient) to give the title compound (282 mg, 59%). LCMS: R_T = 1.71 min, MS (ES) 314 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35 (s, 1H), 7.22 (s, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H).

Step C. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-

dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4,5-dimethoxy-1*H*-indole-2-carboxylate

[001290] The title compound (8 mg, 11%) was prepared following General Procedure B using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (50 mg, 0.09 mmol), methyl 7-bromo-4,5-dimethoxy-1*H*-indole-2-carboxylate (58 mg, 0.19 mmol), CuI (9 mg, 0.05 mmol), (trans)-1,2-*N*,*N*'-dimethylaminocyclohexane (7 mg, 0.05 mmol), and K_3PO_4 (59 mg, 0.28 mmol). LCMS: R_T = 1.52 min, MS (ES) 772 (M+H).

Step D. Example 721

[001291] The title compound (4 mg, 50%) was prepared following General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4,5-dimethoxy-1*H*-indole-2-carboxylate (8 mg, 0.01 mmol) and MeI (6 mg, 0.04 mmol) followed by saponification using General Procedure D. LCMS: R_T = 2.18 min, MS (ES) 772 (M+H).

Example 722

(*R*)-7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethyl-2-((4-methyl-3-oxopiperazin-1-yl)methyl)pyrimidin-5-yl)-2-(5-(1-(2-methoxyethyl)-1*H*-1,2,4-triazol-3-yl)-1-(2-morpholinoethyl)-1*H*-indol-3-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

Step A. Preparation of (*R*)-6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(5-(1-(2-methoxyethyl)-1*H*-1,2,4-triazol-3-yl)-1-(2-morpholinoethyl)-1*H*-indol-3-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[001292] The title compound (66 mg, 72%) was prepared following General Procedure B using (*R*)-6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (60 mg, 0.09 mmol) and 4-(2-(3-iodo-5-(1-(2-methoxyethyl)-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl)ethyl) morpholine (57 mg, 0.12 mmol). LCMS: R_T = 2.181 min, MS (ES) 1009.8 (M+H).

Step B. Preparation of (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-2-(5-(1-(2-methoxyethyl)-1*H*-1,2,4-triazol-3-yl)-1-(2-morpholinoethyl)-1*H*-indol-3-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one

[001293] The title crude compound (19 mg, 33% yield) was prepared following the procedure descried Example 390 Step D using (*R*)-6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(5-(1-(2-methoxyethyl)-1*H*-1,2,4-triazol-3-yl)-1-(2-morpholinoethyl)-1*H*-indol-3-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (66 mg, 0.07 mmol). LCMS: R_T = 1.892 min, MS (ES) 919.9 (M+H).

Step C. Example 722

[001294] The title compound (6.5 mg, 32%) was prepared following General Procedure J using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(2-(hydroxymethyl)-4,6-dimethylpyrimidin-5-yl)-2-(5-(1-(2-methoxyethyl)-1*H*-1,2,4-triazol-3-yl)-1-(2-morpholinoethyl)-1*H*-indol-3-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (19 mg, 0.02 mmol). LCMS: R_T = 2.080 min, MS (ES) 1015.9 (M+H).

Example 723

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-5-(2-(piperidin-1-yl)ethyl)-1*H*-indole-2-carboxylic acid

[001295] The title compound (30 mg, TFA salt, 81%) was prepared following the procedure described Example 715 Step I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-5-(2-oxoethyl)-1*H*-indole-2-carboxylate (30 mg, 0.039 mmol) and piperidine (6 μL, 0.059 mmol). MS (ES) 823.3 (M+H).

Example 724

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-4-methoxy-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl) -6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1*H*-indole-2-carboxylate

[001296] The title compound (176 mg, 34%) was prepared following General Procedure C using (*R*)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-

1(2*H*)-one (400 mg, 0.61 mmol) and methyl 7-iodo-4-methoxy-1*H*-indole-2-carboxylate (400 mg, 1.21 mmol) in toluene instead of DMF. LCMS: R_T = 1.917 min, MS (ES) 857.8 (M+H).

Step B. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylate

[001297] The title compound was prepared following General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl) ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1*H*-indole-2-carboxylate (45 mg, 0.53 mmol) and 2-(chloromethyl)pyridine HCl (25 mg, 0.15 mmol). LCMS: R_T = 1.811, 1.860 min (Method B), MS (ES) 948.9 (M+H).

Step C. Example 724

[001298] The title compound (6 mg, 14% 2 steps) was prepared following the procedure described Example 718 Step C using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-(pyridin-2-ylmethyl)-1*H*-indole-2-carboxylate. LCMS: R_T = 1.066 min (Method B), MS (ES) 804.9 (M+H).

Example 725

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-5-(2-(4-methylpiperazin-1-yl)ethyl)-1*H*-indole-2-carboxylic acid

[001299] The title compound (30 mg, TFA salt, 71%) was prepared following the procedure described Example 715 Step I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-methyl-5-(2-oxoethyl)-1*H*-indole-2-carboxylate (30 mg, 0.039 mmol) and 1-methylpiperazine (7 μL, 0.059 mmol). ^{1}H-NMR (DMSO-d_6) δ 7.79 (d, 1H, J= 6 Hz), 7.60 and 7.55 (s, total 1H), 7.34 (d, 1H, J= 6 Hz), 7.31 and 7.30 (two s, total 1H), 7.02 and 7.00 (two s, total 1H), 6.71 and 6.69 (two s, total 2H), 4.62 (m, 1H), 4.39-4.36 (m, 2H), 4.05-3.98 (multiple s and m, total 7H), 3.76-3.66 (several s and m, total 8H), 3.37.-3.24 (m, 6H), 3.14-2.98 (m, 2H), 2.85-2.82 (m, 2H), 2.26 (s, 6H), 2.14 and 2.13 (two s, total 2H), 2.06-2.04 (m, total 3H), 2.00 and 1.99 (two s, total 1H), 1.92 and 1.90 (two s, total 2H), 1.21 (d, 2H, J= 8 Hz), 1.07 (d, 1H, J= 8 Hz); MS (ES) 838.2 (M+H).

Example 726

(*R*)-7-(7-Chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,6-dimethyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-6-methyl-1*H*-indole-2-carboxylate

[001300] The title compound (25 mg, 10%) was prepared following General Procedure B using (*R*)-6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (200 mg, 0.36 mmol) and ethyl 7-bromo-6-methyl-1*H*-indole-2-carboxylate (200 mg, 0.72 mmol). LCMS: R_T = 2.206 min, MS (ES) 740.0 (M+H).

Step B. Preparation of ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,6-dimethyl-1*H*-indole-2-carboxylate

[001301] The title compound (17 mg, 68%) was prepared following General Procedure I using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-6-methyl-1*H*-indole-2-carboxylate (25 mg, 0.03 mmol) and methyl iodide (2.3 μL, 0.04 mmol). LCMS: R_T = 1.738 min, MS (ES) 753.9 (M+H).

Step C. Example 726

[001302] The title compound (6 mg, 37%) was prepared following General Procedure D using ethyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-6-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1,6-dimethyl-1*H*-indole-2-carboxylate (17 mg, 0.02 mmol). LCMS: R_T = 1.447 min, MS (ES) 725.8 (M+H).

Example 727

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-4-methoxy-1-methyl-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy) propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1*H*-indole-2-carboxylate

[001303] The title compound was prepared following General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1*H*-indole-2-carboxylate (48 mg, 0.056 mmol) and MeI (20 mg, 0.14 mmol). LCMS: R_T = 2.040 min, MS (ES) 871.8 (M+H).

Step B. Example 727

[001304] The title compound (23.1 mg, 57% 2 steps) was prepared following the procedure described Example 718 Step C using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1*H*-indole-2-carboxylate. LCMS: R_T = 2.071 min, MS (ES) 727.9 (M+H).

Example 728

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-4-methoxy-1-(2-methoxyethyl)-1*H*-indole-2-carboxylic acid

Step A. Preparation of methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy) propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-(2-methoxyethyl)-1*H*-indole-2-carboxylate

[001305] The title compound was prepared following General Procedure I using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl) ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1*H*-indole-2-carboxylate (48 mg, 0.056 mmol) and 1-bromo-2-methoxyethane (20 mg, 0.14 mmol). LCMS: R_T = 2.086, 2.124 min (Method B), MS (ES) 915.8 (M+H).

Step B. Example 728

[001306] The title compound (12.1 mg, 28% 2 steps) was prepared following the procedure described Example 718 Step C using methyl (*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-4-methoxy-1-(2-methoxyethyl)-1*H*-indole-2-carboxylate. LCMS: R_T = 2.081 min, MS (ES) 771.9 (M+H).

Example 729

(*R*)-7-(7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-6-(4,6-dimethyl-2-((4-methyl-3-oxopiperazin-1-yl)methyl)pyrimidin-5-yl)-4-methyl-1-oxo-3,4-

dihydropyrazino[1,2-a]indol-2(1*H*)-yl)-1-(2-methoxyethyl)-5-methyl-1*H*-indole-2-carboxylic acid

[001307] The title compound (10.2 mg, 34%) was prepared following General Procedure J using ethyl (*R*)-7-(6-(2-((benzyloxy)methyl)-4,6-dimethylpyrimidin-5-yl)-7-chloro-10-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-4-methyl-1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-2(1*H*)-yl)-1-(2-methoxyethyl)-5-methyl-1*H*-indole-2-carboxylate (29 mg, 0.035 mmol) and 1-methylpiperazin-2-one (20 mg, 0.18 mmol) followed by saponification using General Procedure D. LCMS: R_T = 1.989, 2.021 min, MS (ES) 893.8 (M+H).

Example 730

3-[[6-chloro-3-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-(2-morpholinoethyl)-7-(1,3,5-trimethylpyrazol-4-yl)indole-2-carbonyl]-methyl-amino]benzoic acid

Step A. Preparation of 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-morpholinoethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid

[001308] To asolution of ethyl 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (180 mg, 0.34 mmol) in DMF (10 mL) was added NaH (18 mg, 0.75 mmol) and stirred at RT for 30 min. 4-(2-Bromoethyl)morpholine (100 mg, 0.515 mmol) was added and the reaction mixture was stirred for 5 h at RT. The reaction was quenched with H_2O, diluted into DCM/brine (40 mL, 1:1), the organic layer was separated, and extracted with DCM. The combined organic extract was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography (Combi-flash Rf, DCM/MeOH = 0-20% gradient) to afford the title compound (198 mg, 94% yield).

Step B. Example 730

[001309] To a solution of 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-morpholinoethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (20 mg, 0.033 mmol) in DCM (2 mL) and DMF (20 μL) was added oxalyl chloride (5 mg, 0.039 mmol) at RT and stirred for 30 min. Et_3N (25 mg, 0.24 mmol) was added to the reaction mixture followed by methyl 3-(methylamino)benzoate (30 mg, 0.18 mmol), and the reaction was stirred at RT until complete by LCMS. The reaction was diluted into DCM/H_2O (10 mL, 1:1) and extracted with DCM (2 x 5 mL). The combined organic extract was concentrated *in vacuo* and purified by reverse phase preparative HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient 35-95 % MeCN 0.1% TFA). The resulting ester intermediate was

saponified using General Procedure D to afford the title compound (4 mg, 16% yield). LCMS: R_T = 1.661 min, MS (ES) 745.8 (M+H).

Example 731

4-[[6-Chloro-3-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-(2-morpholinoethyl)-7-(1,3,5-trimethylpyrazol-4-yl)indole-2-carbonyl]-methyl-amino]benzoic acid

[001310] The title compound (7 mg, 28% yield) was prepared following the same procedure as described in Example 730 employing 3-[[6-chloro-3-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-(2-morpholinoethyl)-7-(1,3,5-trimethylpyrazol-4-yl)indole-2-carbonyl]-methyl-amino]benzoic acid (20 mg, 0.033 mmol) and 4-(methylamino)benzoate (30 mg, 0.18 mmol). LCMS: R_T = 1.626 min, MS (ES) 745.8 (M+H).

Example 732

3-(4-(6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carbonyl)piperazin-1-yl)benzoic acid

Step A. Preparation of methyl 3-(4-(6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carbonyl)piperazin-1-yl)benzoate

[001311] The title compound was prepared following General procedure E using 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (0.043 mmol) and methyl 3-(piperazin-1-yl)benzoate (0.086 mmol), HBTU (0.158 mmol). MS (ES) 702.3 (M+H).

Step B. Example 732

[001312] Methyl 3-(4-(6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carbonyl)piperazin-1-yl)benzoate was dissolved in THF and 2 N aq. LiOH solution (2:1), and the mixture was stirred for 24 h at ambient temperature. The reaction was acidified with 4M HCl to pH 7, extracted with EtOAc, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by the reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient from 30-75% CH_3CN, 0.1% TFA) to give the title compound. MS (ES) 688.2 (M+H).

Example 733

4-[[6-chloro-3-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-1-(2-morpholinoethyl)-7-(1,3,5-trimethylpyrazol-4-yl)indole-2-carbonyl]-methyl-amino]-1-methyl-indole-6-carboxylic acid

Step A. preparation of 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-methyl-1-(2-morpholinoethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxamide

[001313] The title compound was prepared following the same procedure described in Example 730 Step B using 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-morpholinoethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (20 mg, 0.033 mmol) and methylamine hydrochloride (25 mg, 0.38 mmol).

Step 2. Example 733

[001314] The title compound (1.4 mg, 5% yield) was prepared following General coupling procedure A using the product obtained in Step 1, methyl 4-bromo-1-methyl-1*H*-indole-6-carboxylate (15 mg, 0.056 mmol), $Pd_2(dba)_3$ (3 mg, 0.0032 mmol), Xantphos (6 mg, 0.010 mmol), and cesium carbonate (30 mg, 0.092 mmol), followed by subjection to General Procedure D using LiOH (5 mg, 0.21 mmol). LCMS: R_T = 1.695 min, MS (ES) 798.7 (M+H).

Example 734

5-(4-(6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(pyridin-3-ylmethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carbonyl)piperazin-1-yl)nicotinic acid

[001315] To a solution of 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (25 mg, 0.05 mmol) in DMF (1 mL) were added methyl 5-(piperazin-1-yl)nicotinate (11 mg, 0.05 mmol), HBTU (70 mg, 0.185 mmol), triethylamine (56 μL, 0.4 mmol), and the mixture was stirred at RT for 10 h. The reaction was quenched with H_2O (5 mL) and extracted with DCM (3 x 5 mL). The combined organic layer was dried and concentrated *in vacuo*. The residue was dissolved in DMF (1 mL), and NaH (6 mg, 0.15 mmol) was added at RT. The reaction mixture was stirred for 30 min at RT then a solution of 3-(bromomethyl)pyridine hydrobromide (15 mg, 0.06 mmol) in DMF (1 mL) was added dropwise. The resulting reaction mixture was stirred for additional 2 h at RT. The reaction was quenched with water (4 mL) and extracted with DCM (3 x 5 mL). The organic layer was dried and concentrated. The residue was dissolved in THF (2 mL) and 2M aq. LiOH solution (1 mL) and the mixture was stirred at RT for 10 h. The reaction mixture was concentrated, acidified to pH 7 with 4M HCl, and extracted in EtOAc. The organic layer was dried, concentrated and purified by reverse phase HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient from 30-70% CH_3CN, 0.1% TFA) to give the title compound (33 mg, 77%) as a white solid. MS (ES) 780.2 (M+H).

Example 735

3-(4-(6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(pyridin-3-ylmethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carbonyl)piperazin-1-yl)benzoic acid

[001316] To a solution of methyl 3-(4-(6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carbonyl)piperazin-1-yl)benzoate (0.05 mmol) in DMF (1 mL) was added NaH (6 mg, 0.15 mmol) and stirred for 30 min at ambient temperature. A solution of 3-(bromomethyl)pyridine hydrobromide (15 mg, 0.06 mmol) in DMF (1 mL) was added dropwise to the reaction mixture at room temperature and stirred for additional 2 h. The title compound was obtained by following the saponification procedure described Example 734 (80% yield) as a white solid; MS (ES) 779.2 (M+H).

Example 736

5-(4-(6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carbonyl)piperazin-1-yl)picolinic acid

[001317] The title compound was prepared following the procedure described Example 732 Step A and B using 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid methyl 5-(piperazin-1-yl)picolinate. MS (ES) 689.1 (M+H).

Example 737

5-(4-(6-Chloro-3-(4-(4-chloro-3,5-dimethylphenyl)butyl)-1-(pyridin-3-ylmethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carbonyl)piperazin-1-yl)picolinic acid

[001318] The title compound was prepared following the procedure described Example 734 by substituting methyl 5-(piperazin-1-yl)nicotinate with methyl 5-(piperazin-1-yl)picolinate. MS (ES) 778.3 (M+H).

Example 738

4-(4-(6-Chloro-3-(4-(4-chloro-3,5-dimethylphenyl)butyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carbonyl)piperazin-1-yl)picolinic acid

[001319] The title compound was prepared following the procedure described Example 732 Step A and B using 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid and methyl 4-(piperazin-1-yl)nicotinate. MS (ES) 689.1 (M+H).

Example 739

2-(4-(6-Chloro-3-(4-(4-chloro-3,5-dimethylphenyl)butyl)-1-(pyridin-3-ylmethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carbonyl)piperazin-1-yl)benzoic acid

[001320] The title compound was prepared following the procedure described Example 734 by substituting methyl 5-(piperazin-1-yl)nicotinate with methyl 2-(piperazin-1-yl)benzoate. MS (ES) 777.3 (M+H).

Example 740

5-(4-(6-Chloro-3-(4-(4-chloro-3,5-dimethylphenyl)butyl)-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-indole-2-carbonyl)piperazin-1-yl)nicotinic acid

[001321] The title compound was prepared following the procedure described Example 732 Step A and B using 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid and methyl 5-(piperazin-1-yl)nicotinate. MS (ES) 689.1 (M+H).

Example 741

2-(4-(6-Chloro-3-(4-(4-chloro-3,5-dimethylphenyl)butyl)-1-(pyridin-3-ylmethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carbonyl)piperazin-1-yl)isonicotinic acid

[001322] The title compound was prepared following the procedure described Example 734 by substituting methyl 5-(piperazin-1-yl)nicotinate with methyl 2-(piperazin-1-yl)isonicotinate. MS (ES) 778.3 (M+H).

Example 742

4-(4-(6-Chloro-3-(4-(4-chloro-3,5-dimethylphenyl)butyl)-1-(pyridin-3-ylmethyl)-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-indole-2-carbonyl)piperazin-1-yl)picolinic acid

[001323] The title compound was prepared following the procedure described Example 734 by substituting methyl 5-(piperazin-1-yl)nicotinate with methyl 4-(piperazin-1-yl)picolinate. MS (ES) 778.3 (M+H).

Example 743

2-(4-(6-Chloro-3-(4-(4-chloro-3,5-dimethylphenyl)butyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carbonyl)piperazin-1-yl)isonicotinic acid

[001324] The title compound was prepared following the procedure described Example 732 Step A and B using 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid and methyl 2-(piperazin-1-yl)isonicotinate. MS (ES) 689.1 (M+H).

Example 744

2-(4-(6-Chloro-3-(4-(4-chloro-3,5-dimethylphenyl)butyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carbonyl)piperazin-1-yl)benzoic acid

[001325] The title compound was prepared following the procedure described Example 732 Step A and B using 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid and methyl 2-(piperazin-1-yl)benzoate. MS (ES) 686.1 (M+H).

Example 745

1-[6-Chloro-3-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-7-(4,6-dimethylpyrimidin-5-yl)-1*H*-indole-2-carbonyl]pyrrolidine-3-carboxylic acid

[001326] To a solution of ethyl 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethylpyrimidin-5-yl)-1*H*-indole-2-carboxylate (13 mg, 0.025 mmol in THF, MeOH, and H_2O (3 mL, 0.5 mL, 0.5 mL), and LiOH (5 mg, 0.21 mmol) was added. The reaction was heated to 50 °C for 3 h. The reaction was acidified with 2M HCl, diluted with brine (5 mL) and extracted with DCM (3 x 10 mL). The combined organic extracts were dried by passage through a phase separator and concentrated *in vacuo*. The crude residue was subjected to amide coupling following General Procedure E using methyl pyrrolidine-3-carboxylate (10 mg, 0.078 mmol), HATU (15 mg, 0.39 mmol), and DIPEA (20 mg, 0.15 mmol) followed by saponification using General Procedure D to afford the title compound (2 mg, 14% yield). LCMS: R_T = 1.792 min, MS (ES) 595.2 (M+H).

Example 746

4-(6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethylpyrimidin-5-yl)-1*H*-indole-2-carboxamido)cyclohexane-1-carboxylic acid (separated stereoisomer A)

[001327] The title compound (1.3 mg, 9% yield) was prepared following the reaction sequence and procedures described in Example 745 substituting methyl pyrrolidine-3-carboxylate with methyl 4-aminocyclohexane-1-carboxylate (10 mg, 0.070 mmol). LCMS: R_T = 1.910 min, MS (ES) 623.2 (M+H). Described reaction sequence resulted in mixture of cis/trans isomers. They were separated but stereochemistry was not determined.

Example 747

4-(6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(4,6-dimethylpyrimidin-5-yl)-1*H*-indole-2-carboxamido)cyclohexane-1-carboxylic acid (separated stereoisomer B)

[001328] The title compound (1.2 mg, 8% yield) was obtained along with Example 746. LCMS: R_T = 1.927 min, MS (ES) 623.2 (M+H). Stereochemistry was not determined.

Example 748

3-[[[6-Chloro-3-[3-(4-chloro-3,5-dimethyl-phenoxy)propyl]-7-(4,6-dimethylpyrimidin-5-yl)-1H-indole-2-carbonyl]amino]methyl]benzoic acid

[001329] The title compound (2.8 mg, 18% yield) was prepared following the reaction sequence and procedures described in Example 745 substituting methyl pyrrolidine-3-carboxylate with methyl 3-(aminomethyl)benzoate (10 mg, 0.061 mmol). LCMS: R_T = 1.925 min, MS (ES) 631.2 (M+H).

Example 749

ASSAYS FOR BCL-2 FAMILY PROTEINS ACTIVITY

[001330] The *in vitro* modulation of Bcl-2 family proteins was determined as follows.

Bak Peptide Binding Assay

General

[001331] Provided compounds of the present invention can be demonstrated to compete for binding with fluorescently labeled peptides derived from relevant BH3 domains. In some embodiments, a provided compound exhibit selectivity for Mcl-1 over Bcl-xL and Bcl-2.

Fluorescence polarization anisotropy competition assay

[001332] Anisotropy measurements were carried out in 384-well, black, flat-bottom plates (Greiner Bio-one, Monroe, NC, USA). The assay was run using either a fluorescein isothiocyanate-labeled BH3 peptide derived from Bak (FITC-AHx-GQVGRQLAIIGDDINR-NH_2) or a fluorescein isothiocyanate-labeled BH3 peptide derived from Bim (FITC-AHx-EARIAQELRRIGDEFNETYTR-NH_2) that were purchased from GenScript (Piscataway, NJ) at >95% purity and used without further purification. 10 nM FITC-Bak peptide and 15 nM recombinant Mcl-1 (residues 172-327) were added to assay buffer (3 mM dithiothreitol, 50 mM NaCl, 20 mM Tris, pH 7.5). The Bim based assay was run with 1 nM FITC-Bim peptide and 1.5 nM recombinant Mcl-1 (residues 172-327) added to assay buffer (20 mM TRIS pH 7.5, 50 mM NaCl, 3 mM DTT, 0.01% CHAPS). For selectivity assays, 40 nM Bcl-2 (residues 1-$207^{A96T,G110R}$, Δ35-91, replaced with Bcl-xL_{35-50}) or 4 nM Bcl-xL (residues 1-209, loop 45-86 deleted) were incubated with 10 nM FITC-Bak in assay buffer.

[001333] Compounds are diluted in DMSO in a 10-point, 3-fold serial dilution scheme. For the FITC –BAK assay 2.5 uL compound is added to 47.5 µL of assay buffer containing FITC-Bak and protein, for a final DMSO concentration of 5% and a top concentration of 20 µM. A FITC-Bak peptide alone (100% inhibition) and peptide plus protein (0 % inhibition) control is included on each assay plate. For the FITC –Bim assay, compound is added to 40 uL of assay buffer containing protein, 15 minutes prior to addition of 10 µL of the FITC-Bim peptide, for a final DMSO concentration of 0.165% and a top concentration of 200 nM. A FITC-Bim peptide alone (100 % inhibition) and peptide plus protein (0 % inhibition) control is included on each assay plate. The plate was mixed and incubated for 90 minutes at room temperature. Anisotropy is measured at excitation wavelength 480 nm and emission wavelength 535 nm using an EnVision Multi-label plate reader (PerkinElmer, Wellesley, MA, USA) or a BioTek Cytation 3 (BioTek, Winooski, VT, USA). Fluorescence anisotropy is plotted against compound concentration to generate an IC_{50} (inhibitor concentration at which 50% of bound peptide is displaced) by fitting the data to a 4-parameter logistic model

using XLFit software (Guildford, Surrey, UK). IC_{50} is converted to a binding dissociation constant (K_i value) according to the formula of Wang Z. FEBS Lett (1996) 3, 245.

$$K_i = [I]_{50}/([L]_{50}/K_d + [P]_0/K_d + 1)$$

where $[I]_{50}$ is the concentration of the free inhibitor at 50% inhibition, $[L]_{50}$ is the concentration of the free labeled ligand at 50% inhibition, $[P]_0$ is the concentration of the free protein at 0% inhibition, K_d represents the dissociation constant of the FITC peptide probe.

TR-FRET binding assay

[001334] Measurements were carried out in OptiPlate-384 White Opaque 384-well plates (Perkin Elmer, Shelton, CT). The assay was run using a fluorescein isothiocyanate-labeled BH3 peptide derived from Bak (FITC-AHx-GQVGRQLAIIGDDINR-NH2) that was purchased from GenScript (Piscataway, NJ) at >95% purity and used without further purification. 300 nM FITC-Bak peptide, 1 nM recombinant Maltose Binding Protein (MBP) tagged Mcl-1 (residues 172-327) and 1 nM terbium conjugated -MBP antibody were added to assay buffer (4.5 mM Monobasic potassium phosphate, 15.5 mM Dibasic potassium phosphate, 1 mM Sodium EDTA, 50 mM NaCl, 1 mM DTT, 0.05% Pluronic F-68, pH 7.5). Compounds are diluted in DMSO in a 16-point, semilog serial dilution scheme. For the BAK FITC TR-FRET assay 50 nL compound is added to 20 µL of assay buffer containing Bak-FITC, MBP tagged Mcl-1 protein and antibody, for a final DMSO concentration of 0.25% and a top concentration of 10 µM. A FITC-Bak peptide alone (100 % inhibition) and peptide plus protein (0 % inhibition) control is included on each assay plate. The plate was mixed and incubated for 3 hours at room temperature. TR-FRET signal (Delta F) is measured on a Biotek Cytation 3 multimode plate reader equipped with a filter cube containing an Ex 340/30 Em 620/10 nm filter and an Ex 340/30 Em 520 filter. TR-FRET signal is plotted and IC_{50} and K_i values are calculated in the same manner as the fluorescence polaraization anisotropy based competition assays. The results for representative compounds are shown in Table 2 and 3.

[001335] Table 2. K_i for Examplified Compounds for Inhibition of Mcl-1 by FPA assay

Example	K_i (nM)	Example	K_i (nM)	Example	K_i (nM)
2	<1	**160**	1.1	**319**	3.2
3	1.1	**161**	2.8	**320**	2.7
4	3.3	**162**	<1	**321**	<1
5	2.7	**163**	<1	**322**	1.7
6	54	**164**	1.7	**323**	<1
7	2.2	**165**	1	**324**	<1

8	27	**166**	<1	**325**	<1
9	20	**167**	<1	**326**	<1
10	57	**168**	1.1	**327**	1.6
11	4	**169**	<1	**328**	<1
12	1.2	**170**	2.7	**329**	<1
13	<1	**171**	<1	**330**	1.3
14	<1	**172**	<1	**331**	1.1
15	2.2	**173**	2.7	**332**	2.8
16	<1	**174**	4.2	**333**	1.3
17	10	**175**	<1	**334**	<1
18	5.8	**176**	<1	**335**	4.5
19	1.9	**177**	<1	**336**	<1
20	2.5	**178**	<1	**337**	2.6
21	2.3	**179**	<1	**338**	<1
22	151	**180**	2.1	**339**	<1
23	<1	**181**	1.4	**340**	4.4
24	25	**182**	<1	**341**	4.2
25	1.1	**183**	<1	**342**	<1
26	1.3	**184**	<1	**343**	3.7
27	39	**185**	4.6	**344**	<1
28	1.8	**186**	<1	**345**	3.5
29	6.2	**187**	<1	**346**	5.1
30	1.2	**188**	6.4	**347**	3.6
31	<1	**189**	1.2	**348**	1.8
32	<1	**190**	<1	**349**	2.8
33	<1	**191**	<1	**350**	<1
34	12.0	**192**	<1	**351**	<1
35	1.5	**193**	3.9	**352**	2.8
36	<1	**194**	<1	**353**	2.1
37	3	**195**	3.6	**354**	4.3
38	62	**196**	<1	**355**	1.0
39	1.1	**197**	<1	**356**	1.9
40	3.9	**198**	<1	**357**	7.9
41	1.8	**199**	12	**358**	4.2
42	8	**200**	6.6	**359**	1.4
43	1.1	**201**	<1	**360**	2.5
44	<1	**202**	12	**361**	2.0
45	1.7	**203**	6	**362**	1.7
46	26	**204**	1.1	**363**	1.6
47	19	**205**	2.4	**364**	1.0
48	<1	**206**	<1	**365**	1.7
49	<1	**207**	<1	**366**	2.9
50	<1	**208**	<1	**367**	1.2
51	<1	**209**	1.2	**368**	1.4
52	<1	**210**	1.3	**369**	3.2

53	<1	**211**	3.1	**370**	2.8
54	<1	**212**	5.9	**371**	<1
55	2.4	**213**	<1	**372**	1.2
56	<1	**214**	<1	**373**	1.6
57	<1	**215**	<1	**374**	3.7
58	<1	**218**	<1	**375**	10
59	<1	**219**	2.2	**376**	6.5
60	<1	**220**	<1	**377**	4.9
61	5.7	**221**	2.5	**378**	1.9
62	<1	**222**	6.9	**379**	3.6
63	<1	**223**	1.1	**380**	7.9
64	4.8	**224**	<1	**381**	2.6
65	3.1	**225**	<1	**382**	1.2
66	4.3	**226**	4.9	**383**	2.6
67	<1	**227**	<1	**384**	6.8
68	<1	**228**	1.6	**385**	4.1
69	<1	**229**	3.7	**386**	3.2
70	<1	**230**	<1	**387**	2.1
71	<1	**231**	1.2	**388**	1.5
72	<1	**232**	<1	**389**	<1
73	<1	**233**	<1	**390**	2.3
74	<1	**234**	<1	**391**	2.1
75	<1	**235**	<1	**392**	23
76	<1	**236**	<1	**393**	2.3
77	<1	**237**	14	**394**	2.8
78	<1	**238**	<1	**395**	2.2
79	<1	**239**	<1	**396**	1.8
80	<1	**240**	<1	**397**	1.2
81	2.4	**241**	<1	**398**	<1
82	<1	**242**	<1	**399**	2.4
83	<1	**243**	45	**400**	1.4
84	<1	**244**	<1	**401**	<1
85	1.5	**245**	<1	**402**	4.9
86	47	**246**	8.6	**403**	1.5
87	<1	**247**	<1	**404**	44
88	<1	**248**	<1	**405**	<1
89	<1	**249**	<1	**406**	>250
90	8.7	**250**	<1	**407**	1.1
91	7.3	**251**	<1	**408**	2.2
92	<1	**252**	1.3	**409**	1.3
93	<1	**253**	1.2	**410**	1.4
94	<1	**254**	<1	**411**	5.6
95	<1	**255**	1.3	**412**	1.3
96	2.9	**256**	<1	**413**	3.5
97	<1	**257**	2.3	**414**	<1

98	<1	**258**	<1	**415**	3.4
99	<1	**259**	<1	**416**	<1
100	<1	**260**	<1	**417**	1.3
101	<1	**261**	<1	**418**	1.4
102	1.5	**262**	<1	**419**	2.3
103	<1	**263**	1.8	**420**	2
104	<1	**264**	<1	**421**	3.4
105	<1	**265**	8.2	**422**	<1
106	<1	**266**	9.2	**423**	2.3
107	<1	**267**	4.7	**424**	2.6
108	<1	**268**	<1	**425**	1.8
109	<1	**269**	7.4	**426**	<1
110	<1	**270**	1.1	**427**	1.2
111	<1	**271**	<1	**428**	2
112	3.3	**272**	<1	**429**	1.8
113	<1	**273**	<1	**430**	1.9
114	<1	**274**	4.8	**431**	1.6
115	3.1	**275**	<1	**432**	<1
116	<1	**276**	<1	**433**	1.7
117	<1	**277**	6.6	**434**	5.5
118	<1	**278**	5.4	**435**	<1
119	<1	**279**	1	**436**	2.1
120	39	**280**	1.5	**437**	4.7
121	1.9	**281**	2.2	**438**	1.1
122	2.2	**282**	8.4	**439**	1.9
123	<1	**283**	1.2	**440**	2.5
124	<1	**284**	3.6	**441**	7
125	<1	**285**	<1	**442**	2.3
126	<1	**286**	3.3	**443**	4.3
127	<1	**287**	3	**444**	1.3
128	<1	**288**	3	**445**	2.2
129	<1	**289**	15	**446**	8.2
130	<1	**290**	12	**447**	<1
131	<1	**291**	1.1	**448**	2.2
132	<1	**292**	<1	**449**	2.6
133	<1	**293**	<1	**450**	2.2
134	<1	**294**	<1	**451**	<1
135	<1	**295**	<1	**452**	2.2
136	<1	**296**	<1	**453**	1.7
137	1.2	**297**	2.4	**454**	3.5
138	2.2	**298**	<1	**455**	<1
139	1.1	**299**	2	**456**	<1
140	79	**300**	2	**457**	<1
141	4.5	**301**	2.8	**458**	1.2
142	3.8	**302**	<1	**459**	1.0

143	7.6	**303**	<1	**460**	1.7
144	<1	**304**	<1	**461**	<1
145	<1	**305**	<1	**462**	2.0
146	4	**306**	1.3	**463**	2.1
147	1.8	**307**	1.3	**464**	3.5
148	<1	**308**	<1	**465**	1.5
150	13	**309**	<1	**466**	1.8
151	<1	**310**	1.5	**467**	1.3
152	<1	**311**	<1	**468**	<1
153	<1	**312**	1.9	**469**	2.2
154	<1	**313**	<1	**470**	<1
155	<1	**314**	<1	**471**	2.3
156	<1	**315**	<1	**472**	1.2
157	2.5	**316**	<1	**473**	4.1
158	<1	**317**	<1	**474**	17
159	<1	**318**	1.5	**475**	7.0
730	20	**731**	>200	**732**	38.0
733	19	**734**	>200	**735**	52.0
736	121	**737**	140	**738**	200
739	73	**740**	85	**741**	>200
742	>200	**743**	121	**744**	30.0
745	44	**746**	5.2	**747**	16
748	6.3				

[001336] Table 3. K_i for Examplified Compounds for Inhibition of Mcl-1 by TR-FRET assay

Example	K_i (nM)	Example	K_i (nM)	Example	K_i (nM)
476	<0.2	**558**	<0.2	**641**	<0.2
477	<0.2	**559**	<0.2	**642**	3
478	0.24	**560**	0.53	**643**	1.3
479	0.95	**561**	<0.2	**644**	<0.2
480	<0.2	**562**	0.97	**645**	3.3
481	<0.2	**563**	<0.2	**646**	0.3
482	<0.2	**564**	0.46	**647**	0.32
483	<0.2	**565**	<0.2	**648**	0.23
484	<0.2	**566**	<0.2	**649**	<0.2
485	0.35	**567**	9.6	**650**	<0.2
486	1.4	**568**	1.8	**651**	<0.2
487	0.23	**569**	0.49	**652**	0.28
488	39	**570**	<0.2	**653**	15
489	<0.2	**571**	<0.2	**654**	0.34
490	0.29	**572**	<0.2	**655**	1.6
491	<0.2	**573**	<0.2	**656**	<0.2

492	<0.2	**574**	2.4	**657**	<0.2
493	<0.2	**575**	<0.2	**658**	<0.2
494	0.3	**576**	<0.2	**659**	0.96
495	42	**577**	<0.2	**660**	<0.2
496	0.64	**578**	<0.2	**661**	0.23
497	1.3	**579**	<0.2	**662**	0.93
498	0.58	**580**	<0.2	**663**	0.52
499	0.21	**581**	3.7	**664**	0.64
500	<0.2	**582**	0.28	**665**	<0.2
501	0.68	**583**	0.73	**666**	7.2
502	2.9	**584**	<0.2	**667**	<0.2
503	3.7	**585**	<0.2	**668**	7.6
504	0.23	**586**	2.6	**669**	1.0
505	1.3	**587**	<0.2	**670**	<0.2
506	<0.2	**588**	1.4	**671**	0.32
507	0.72	**589**	1.7	**672**	0.43
508	2.4	**590**	<0.2	**673**	0.31
509	1.6	**591**	<0.2	**674**	2.1
510	<0.2	**592**	<0.2	**675**	28
511	<0.2	**593**	<0.2	**676**	0.56
512	<0.2	**594**	<0.2	**677**	<0.2
513	<0.2	**595**	<0.2	**678**	0.22
514	<0.2	**596**	<0.2	**679**	3.1
515	<0.2	**598**	<0.2	**680**	0.33
516	<0.2	**599**	<0.2	**681**	5.5
517	0.36	**600**	<0.2	**682**	<0.2
518	<0.2	**602**	5.9	**683**	0.21
519	0.46	**603**	0.89	**684**	0.6
520	<0.2	**604**	0.73	**685**	3.2
521	<0.2	**605**	0.45	**686**	<0.2
522	0.32	**606**	0.47	**687**	<0.2
523	0.50	**607**	<0.2	**688**	0.22
524	0.28	**608**	0.91	**689**	2.1
525	0.41	**609**	0.26	**690**	0.26
526	<0.2	**610**	<0.2	**691**	<0.2
527	0.36	**611**	1.1	**692**	<0.2
528	<0.2	**612**	1.2	**693**	<0.2
529	<0.2	**613**	1.9	**694**	<0.2
530	<0.2	**614**	<0.2	**695**	0.57
531	0.48	**615**	9.6	**696**	1.1
532	0.20	**616**	<0.2	**697**	<0.2
533	0.69	**617**	<0.2	**698**	1.8
534	<0.2	**618**	3.8	**699**	1.2
535	<0.2	**619**	0.26	**700**	0.73
536	<0.2	**620**	<0.2	**709**	<0.2

537	<0.2	**621**	<0.2	**710**	<0.2
538	<0.2	**622**	0.76	**711**	<0.2
539	<0.2	**623**	<0.2	**712**	<0.2
540	<0.2	**624**	9.6	**713**	<0.2
541	0.53	**625**	0.22	**714**	<0.2
542	0.48	**626**	<0.2	**715**	<0.2
543	2.9	**627**	<0.2	**716**	<0.2
544	<0.2	**628**	<0.2	**717**	<0.2
545	0.39	**629**	<0.2	**718**	<0.2
546	0.38	**630**	<0.2	**719**	<0.2
547	10	**631**	<0.2	**720**	0.51
548	0.94	**632**	<0.2	**721**	<0.2
549	0.34	**633**	<0.2	**722**	3.1
550	0.52	**634**	<0.2	**723**	<0.2
551	0.3	**635**	<0.2	**724**	<0.2
552	<0.2	**636**	0.5	**725**	<0.2
553	<0.2	**637**	1.3	**726**	<0.2
554	0.26	**638**	1.7	**727**	<0.2
555	0.26	**639**	4.2	**728**	<0.2
556	<0.2	**640**	<0.2	**729**	<0.2
557	<0.2				

[001337] Among other things, these data demonstrate the utility of representative compounds as selective inhibitors of the activity of Mcl-l protein to bind peptides from relevant BH3 domains.

Cellular Viability of Human Tumor Cell Lines

[001338] Human cancer cell lines ALMC-1, ALMC-2, K562, H929, and OPM-2 were cultured in media supplemented with 10% fetal bovine serum (FBS). To evaluate compound effect on cellular proliferation, cells were plated at 1,000 cells/well in 96-well tissue culture plates in a total volume of 90 μL medium supplemented with 10% FBS (Sigma, Saint Louis, MO). 24 hours later, 10 μL of compound (in a 2-fold serial dilution) is added to the cells for a top concentration of 50 μM and a final DMSO concentration < 1%. After 72 hours, 50 μL of Cell TiterGlo (Promega, Madison, Wisconsin, USA) reagent is added to each well and plates are incubated at room temperature, in the dark, for 30 minutes. Luminescence is measured on a BioTek Cytation 3. Luminescence values are imported into a template in XLFit (Guildford, Surrey, UK) that uses a four-parameter fit to generate an IC_{50} value for each compound dilution series on the plate.

[001339] Table 4. GI_{50} (in μM) for representative compounds on cellular proliferation of H929 human cancer cell lines

Example	GI_{50} (μM)	Example	GI_{50} (μM)	Example	GI_{50} (μM)
2	8.3	**264**	0.56	**496**	1.2
3	6.6	**265**	1.5	**497**	1.7
4	8.7	**267**	3.1	**498**	1.9
7	13	**268**	0.41	**499**	0.74
11	9.9	**269**	0.76	**500**	0.33
12	8.3	**270**	0.31	**501**	1.2
13	4.5	**271**	0.26	**502**	<0.2
14	3.2	**272**	0.21	**503**	<0.2
15	11	**273**	4.1	**504**	1.0
16	2.9	**274**	2.2	**505**	3.2
19	4.1	**275**	0.37	**506**	1.3
20	6.5	**276**	0.29	**507**	1.4
21	4.9	**277**	1.4	**508**	0.45
23	4.9	**278**	1.5	**509**	0.39
26	0.83	**279**	3.3	**510**	0.24
28	3.7	**280**	2.2	**511**	0.3
30	5.4	**281**	1.4	**512**	0.22
31	1.8	**282**	2.4	**513**	5.3
32	7.6	**283**	1.2	**514**	<0.2
33	0.65	**284**	1.5	**515**	0.61
36	2.6	**285**	5.3	**516**	0.33
37	1.8	**286**	0.51	**517**	0.76
39	0.92	**287**	1.6	**518**	0.81
41	1.2	**288**	8.4	**519**	0.99
43	9.4	**289**	5.2	**520**	<0.2
44	14	**290**	5.3	**521**	0.61
45	3.8	**291**	1	**522**	0.75
48	0.8	**292**	0.69	**523**	0.89
49	2.6	**293**	0.81	**524**	0.22
50	0.71	**294**	2	**525**	0.33
51	1.5	**295**	<0.2	**526**	<0.2
52	0.47	**296**	0.24	**527**	0.26
53	0.5	**297**	7.9	**528**	0.87
54	0.32	**298**	0.29	**529**	0.52
55	5.7	**299**	2.3	**530**	0.23
56	0.81	**300**	5.9	**531**	0.38
57	1.7	**301**	8.3	**532**	0.39
58	3	**302**	<0.2	**533**	1.3
59	0.28	**304**	0.37	**534**	0.52
61	8.2	**305**	6.2	**535**	0.28
62	11	**306**	0.6	**536**	<0.2

63	0.27	**307**	3.5	**537**	<0.2
64	5.6	**308**	0.41	**538**	<0.2
65	5.5	**309**	0.53	**539**	<0.2
66	6.4	**310**	8.9	**540**	<0.2
67	8.5	**311**	3.4	**541**	1.7
68	0.35	**312**	5.7	**542**	3.3
69	<0.2	**313**	<0.2	**543**	1.8
70	2.4	**314**	0.93	**544**	0.32
71	3.3	**315**	2.8	**545**	0.56
72	4.7	**316**	0.47	**546**	0.42
74	2.6	**317**	0.72	**548**	0.61
75	1.1	**318**	0.82	**549**	0.34
76	<0.2	**321**	1.4	**550**	1.2
77	<0.2	**322**	1.8	**552**	4.6
78	<0.2	**323**	1.5	**553**	2.8
79	1.5	**324**	0.61	**555**	1.3
80	0.25	**325**	0.29	**556**	0.28
81	2.9	**326**	0.59	**557**	0.82
82	4.8	**327**	3.6	**558**	0.31
83	1.1	**328**	0.69	**559**	0.43
84	1.2	**329**	1.1	**560**	0.27
88	0.29	**330**	2.3	**561**	0.51
89	1.3	**331**	2.3	**562**	1.2
92	0.9	**332**	0.67	**563**	1.5
93	7.5	**333**	1.1	**564**	0.59
94	1.5	**334**	1.2	**565**	<0.2
95	10	**335**	0.91	**566**	0.41
96	4.7	**336**	0.25	**567**	0.93
97	3.4	**337**	0.54	**568**	0.28
98	6.6	**338**	2	**569**	0.47
99	2.1	**339**	0.32	**570**	0.56
100	5.8	**340**	1.8	**571**	<0.2
101	2.1	**341**	0.92	**572**	0.3
102	4.9	**342**	0.23	**573**	<0.2
103	0.48	**343**	3.6	**574**	0.27
104	0.57	**344**	1.3	**575**	0.74
105	0.27	**345**	1.8	**576**	0.35
106	0.79	**346**	1.6	**577**	0.23
108	0.88	**347**	1.9	**578**	0.39
109	0.71	**348**	1.3	**579**	0.24
110	0.79	**349**	0.78	**580**	0.96
111	2.6	**350**	0.3	**581**	0.25
112	5.3	**352**	5.1	**582**	0.22
113	0.33	**353**	2.9	**583**	<0.2
114	0.84	**354**	0.58	**584**	1

115	5.1	**355**	0.73	**585**	1.5
116	9.7	**356**	0.65	**586**	0.4
117	0.39	**357**	2	**587**	<0.2
118	0.82	**358**	2.3	**588**	1.4
119	2.9	**359**	0.29	**589**	1.1
120	12	**360**	2.5	**590**	0.67
122	11	**361**	0.29	**591**	2.8
123	6.9	**362**	0.97	**592**	0.88
124	1.9	**363**	1.4	**593**	<0.2
125	7.6	**364**	0.54	**594**	0.23
126	5.1	**365**	2.0	**595**	<0.2
128	0.41	**366**	0.44	**596**	1.3
129	0.55	**367**	0.4	**597**	0.69
130	2.4	**368**	0.62	**598**	1.9
131	1.9	**370**	4.5	**599**	<0.2
132	0.84	**371**	0.3	**600**	2.5
133	1.4	**372**	2.0	**602**	0.43
134	11	**373**	1.2	**603**	<0.2
137	0.46	**374**	1.5	**605**	0.49
138	4.8	**375**	2.5	**606**	0.6
140	7.6	**376**	0.75	**607**	<0.2
141	9.5	**377**	0.63	**608**	304
142	7.4	**378**	0.41	**609**	0.34
144	6.5	**379**	0.56	**610**	0.4
145	0.36	**380**	2.5	**612**	7.6
146	2.4	**381**	0.25	**614**	0.69
147	4.3	**382**	0.75	**615**	0.37
148	0.65	**383**	1.5	**616**	0.34
150	5.1	**384**	0.91	**617**	0.44
151	2.1	**385**	0.51	**618**	0.36
152	0.85	**386**	3.1	**619**	0.47
153	0.41	**387**	3.6	**620**	7.6
154	1.3	**388**	0.33	**621**	0.39
155	1.4	**389**	1.5	**622**	0.92
156	0.26	**390**	0.34	**623**	<0.2
157	6.4	**391**	0.37	**624**	0.43
158	0.48	**392**	0.95	**625**	0.42
159	0.29	**393**	1.2	**626**	4.4
160	0.69	**394**	0.27	**627**	<0.2
161	0.48	**395**	0.86	**628**	0.44
162	0.26	**396**	<0.2	**629**	0.56
163	0.26	**397**	0.34	**630**	9
164	0.92	**398**	0.2	**631**	0.3
165	1.2	**399**	0.21	**632**	0.22
166	1.4	**400**	0.43	**633**	<0.2

167	4.1	**401**	0.28	**634**	0.28
168	1	**402**	1.1	**635**	<0.2
169	2.6	**403**	<0.2	**636**	0.98
170	2.6	**405**	0.46	**637**	0.53
171	1.5	**407**	0.49	**638**	0.6
172	0.32	**408**	3.2	**639**	0.9
173	3.3	**409**	2.8	**640**	8.1
174	6.3	**410**	4	**641**	0.35
175	0.34	**412**	0.45	**642**	0.79
176	0.41	**414**	1.4	**643**	0.34
177	0.27	**415**	0.51	**644**	1.9
178	<0.2	**416**	<0.2	**645**	3.7
179	4.7	**417**	0.34	**646**	0.24
180	1.5	**418**	0.9	**647**	1.1
181	2	**419**	1.1	**648**	0.31
182	1.5	**420**	0.28	**649**	<0.2
183	0.36	**422**	0.83	**650**	0.21
184	0.77	**423**	1.7	**651**	0.29
185	2.9	**424**	1.3	**652**	0.37
186	<0.2	**425**	1.4	**653**	1.9
187	<0.2	**426**	0.25	**654**	0.34
188	2.7	**427**	0.49	**655**	0.34
189	0.92	**428**	0.92	**656**	0.25
190	2.2	**429**	0.97	**657**	0.61
191	3.2	**430**	1.4	**658**	0.25
192	<0.2	**431**	2.9	**659**	0.93
194	2.3	**432**	0.21	**660**	0.33
195	1.8	**433**	0.44	**661**	2.4
196	3.4	**434**	0.89	**662**	1.9
197	0.67	**435**	0.57	**663**	<0.2
198	0.61	**436**	0.51	**664**	0.58
201	<0.2	**437**	1.2	**665**	0.28
203	3.9	**438**	2.8	**667**	8.2
204	1	**439**	<0.2	**668**	1.5
206	3.2	**440**	4.5	**669**	7.6
207	0.75	**441**	4.6	**670**	<0.2
208	1.6	**442**	0.23	**671**	0.89
209	3.5	**443**	0.25	**672**	0.84
210	1.5	**444**	0.22	**673**	0.23
211	11	**445**	0.82	**674**	0.21
212	3.4	**447**	0.34	**675**	4.8
213	<0.2	**448**	0.36	**676**	1.1
214	0.38	**449**	1.2	**677**	<0.2
215	0.43	**450**	1.1	**678**	<0.2
218	<0.2	**451**	<0.2	**679**	0.94

219	1.2	**452**	0.38	**680**	0.61
220	2	**453**	0.33	**681**	0.94
221	0.45	**454**	2.1	**682**	0.34
222	3	**455**	0.22	**683**	0.25
223	5	**456**	<0.2	**684**	0.52
224	2.5	**457**	<0.2	**685**	1.4
225	3.3	**458**	0.29	**686**	0.52
226	2.6	**459**	0.51	**687**	0.33
227	1.3	**460**	0.42	**688**	0.43
228	0.78	**461**	<0.2	**689**	1.7
229	9.3	**462**	0.99	**690**	0.33
230	0.89	**463**	0.29	**691**	<0.2
231	2.7	**464**	0.48	**692**	0.39
232	4	**465**	0.69	**693**	0.21
233	1.4	**466**	0.3	**694**	0.32
234	1.6	**467**	1.3	**695**	0.28
235	0.24	**468**	0.26	**696**	1.4
236	1.1	**469**	3.3	**697**	2
237	7.6	**470**	<0.2	**698**	0.62
238	0.34	**471**	0.36	**699**	0.35
239	1.8	**472**	1.7	**700**	0.38
240	1.9	**474**	1.2	**709**	<0.2
241	0.42	**475**	0.25	**710**	<0.2
242	1.3	**476**	<0.2	**711**	<0.2
244	0.4	**477**	<0.2	**712**	<0.2
245	0.9	**478**	0.56	**713**	<0.2
246	5.3	**479**	1.5	**714**	<0.2
247	<0.2	**480**	0.25	**715**	<0.2
248	0.57	**481**	0.24	**716**	0.55
249	0.49	**482**	0.34	**717**	<0.2
250	0.48	**483**	0.28	**718**	0.41
251	0.25	**484**	0.31	**719**	0.64
252	2	**485**	0.41	**720**	0.22
253	1.1	**486**	2.9	**721**	<0.2
254	0.58	**487**	0.28	**722**	<0.2
256	0.27	**488**	8.7	**723**	<0.2
257	0.47	**489**	<0.2	**724**	0.33
258	3.6	**490**	0.81	**725**	<0.2
259	3.5	**491**	0.28	**726**	0.26
260	0.55	**492**	0.36	**727**	0.5
261	0.53	**493**	<0.2	**728**	0.71
262	0.45	**494**	0.45	**729**	0.26
263	0.27				

Apoptosis Assay protocol (Caspase 3/7 Glo)

[001340] Induction of apoptosis was measured by quantifying caspase 3/7 activity using the commercially available Caspase-Glo reagent (Promega, Madison, Wisconsin, USA). This assay relies on the cleavage of a proluminescent substrate by activated caspases, which is then detected on the BioTek Cytation 3. 5000 cells in 90 μL of media (+ 5% FBS) are plated in each well of a white 96-well plate and incubated overnight at 37°C in a tissue culture incubator. The following day, compound is diluted in a 10-pt, 2-fold serial dilution scheme for a final top concentration of 50 μM. 10 μL of compound is added directly to the cell assay plate for a final volume of 100 μL. Columns 11 and 12 are reserved for treatment with DMSO to serve as control wells. Plates are incubated for 3 hours. 100 μL of Caspase-Glo reagent is added to each well and plates are incubated at room temperature, in the dark, for 30 minutes. Luminescence is measured on the Cytation 3. Luminescence values are imported into a template in XLFit (Guildford, Surrey, UK) that uses a four-parameter fit to generate an IC_{50} value for each compound dilution series on the plate.

[001341] Among other things, these data demonstrate the utility of representative compounds as inhibitors of cellular proliferation of human cancer cell lines and initiators of apoptosis via caspase 3 and 7 activation in a Mcl-l sensitive human cancer cell line.

[001342] While several embodiments of the present invention have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the functions and/or obtaining the results and/or one or more of the advantages described herein, and each of such variations and/or modifications is deemed to be within the scope of the present invention. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials, and/or configurations will depend upon the specific application or applications for which the teachings of the present invention is/are used. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto, the invention may be practiced otherwise than as specifically described and claimed. The present invention is directed to each individual feature, system, article, material, kit, and/or method described herein. In addition, any combination of two or more such features, systems, articles, materials, kits, and/or methods, if such features, systems, articles, materials, kits, and/or

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methods are not mutually inconsistent, is included within the scope of the present invention.

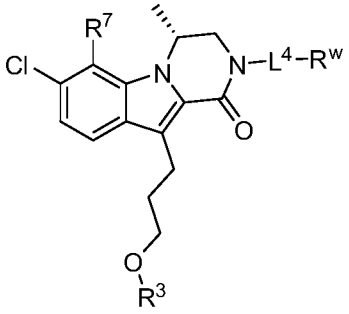
[001343] In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

[001344] It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country.

CLAIMS

The claims defining the invention are as follows:

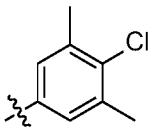
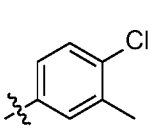
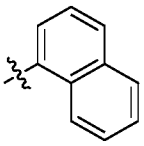
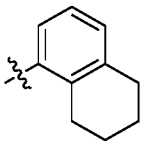
1 A compound having formula:



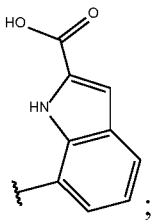
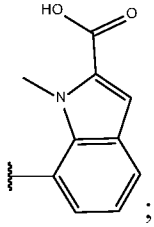
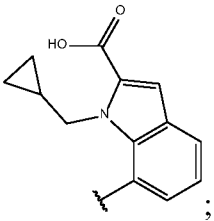
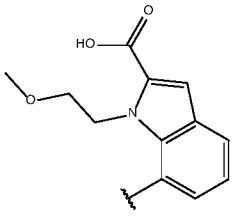
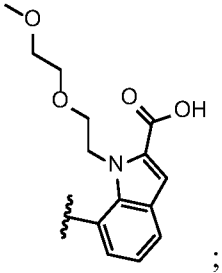
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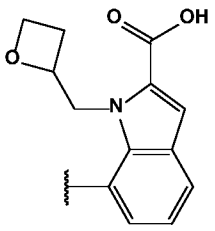
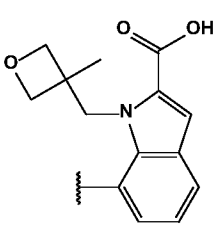
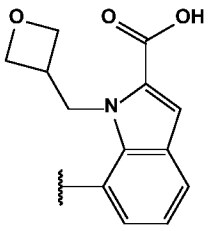
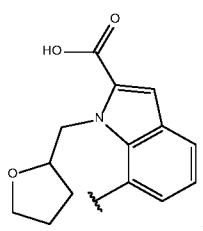
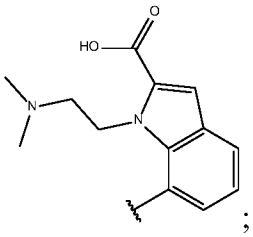
or a pharmaceutically acceptable salt thereof,

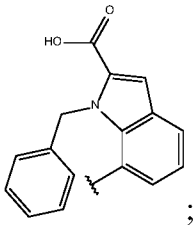
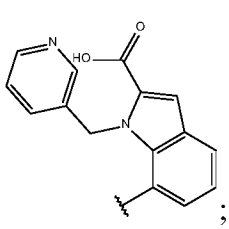
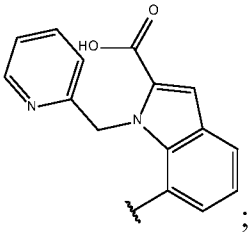
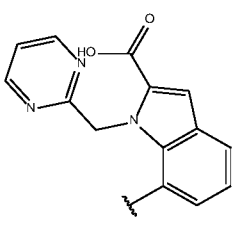
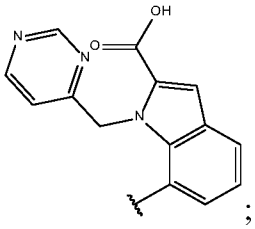
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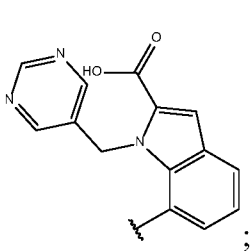
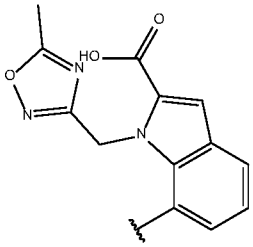
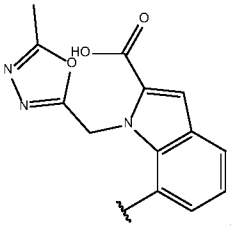
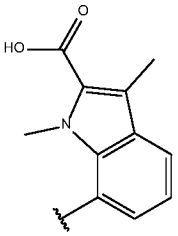
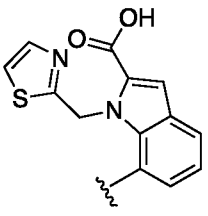
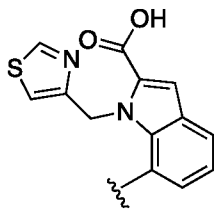
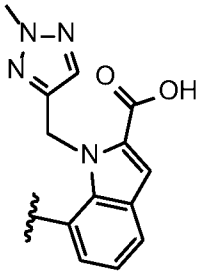
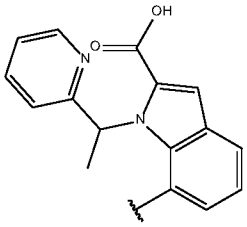
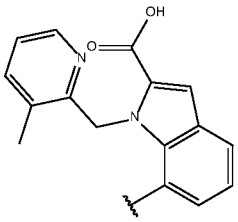
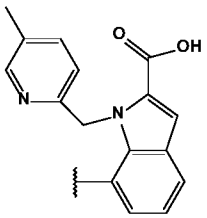
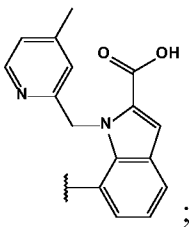
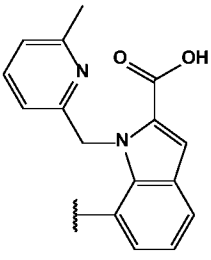
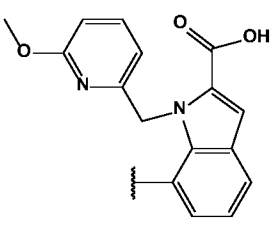
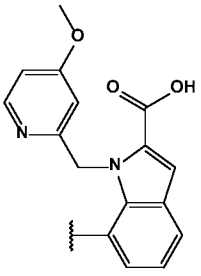
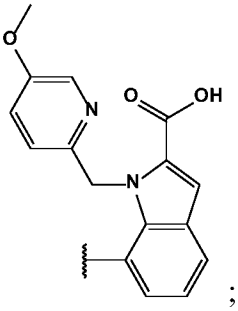
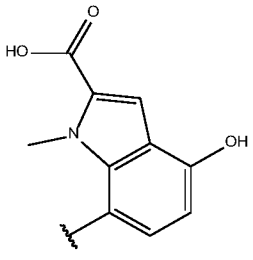
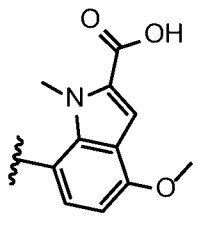
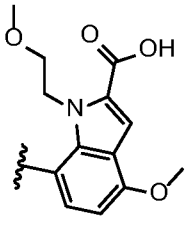
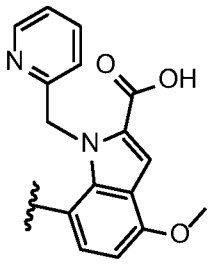
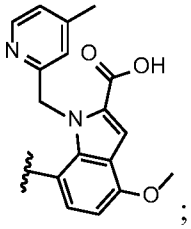
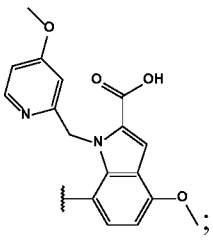
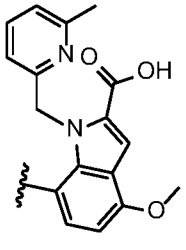
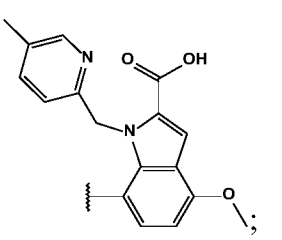
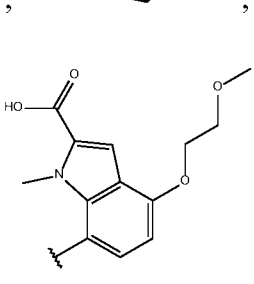
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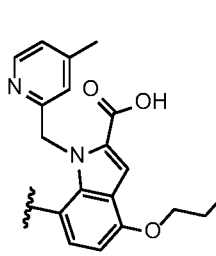
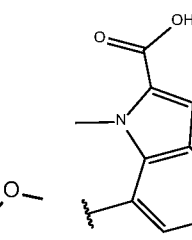
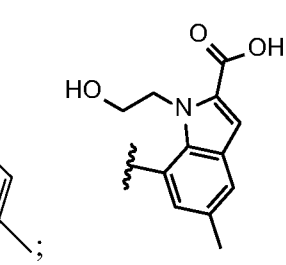
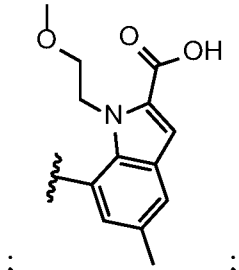
L^4-R^w is

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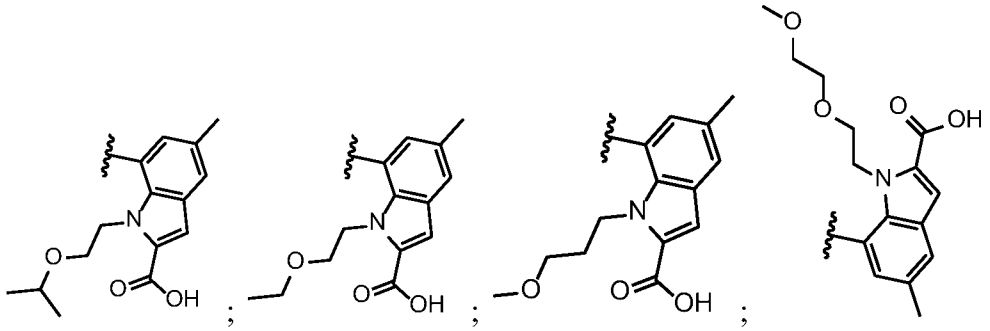
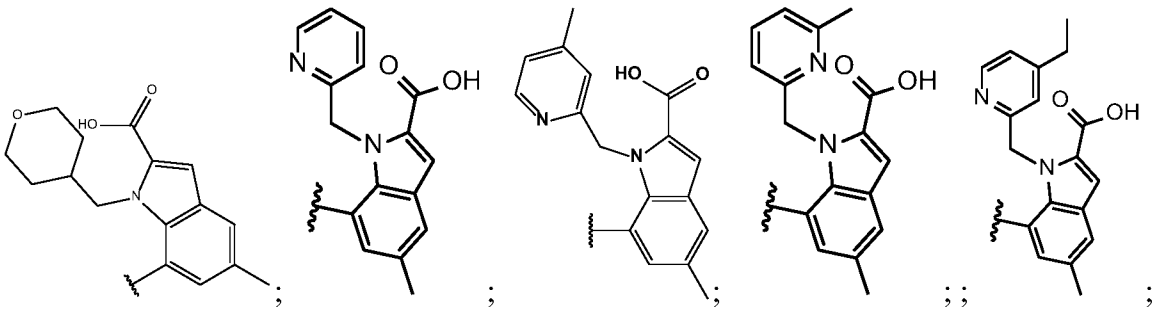
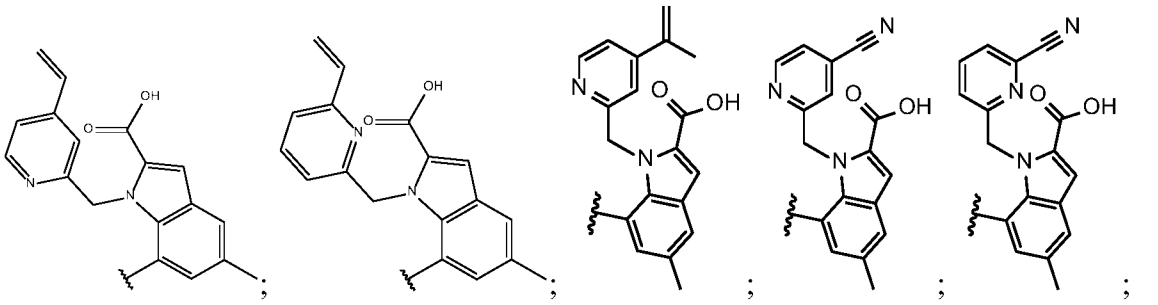
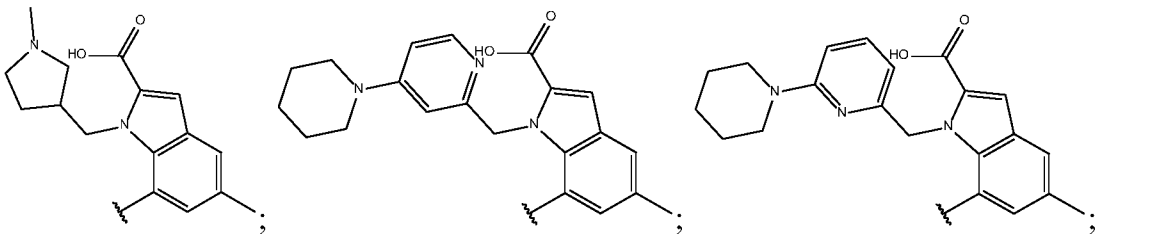
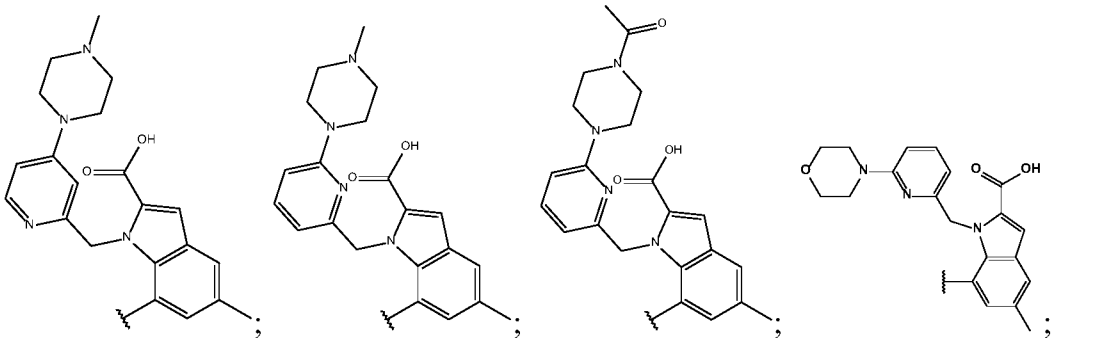
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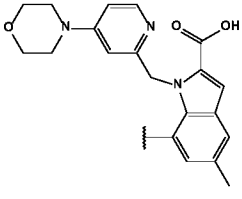
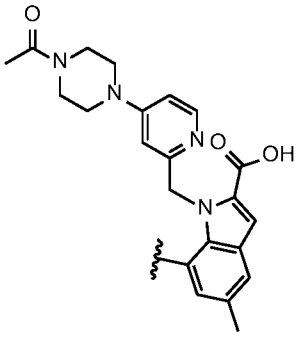
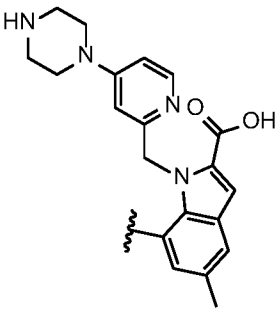
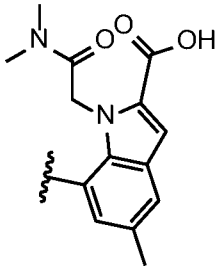
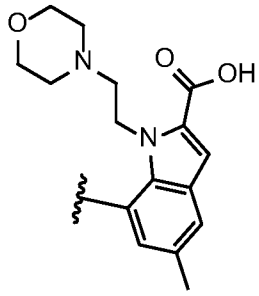
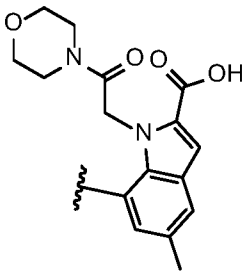
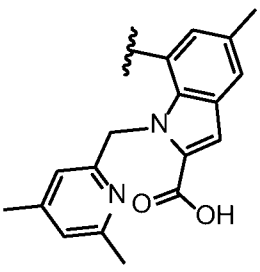
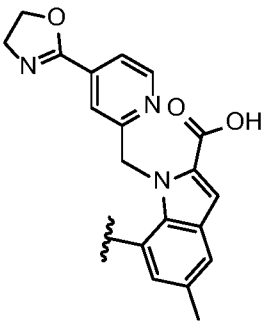
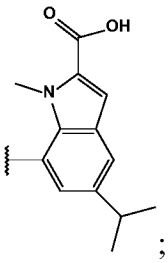
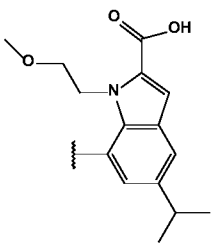
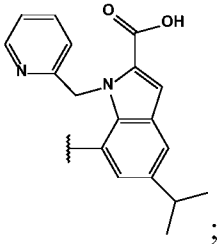
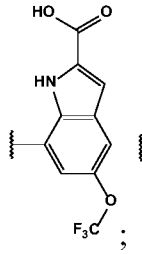
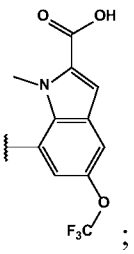
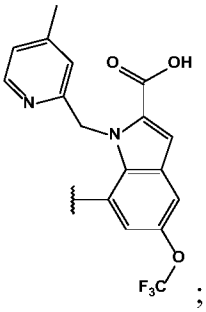
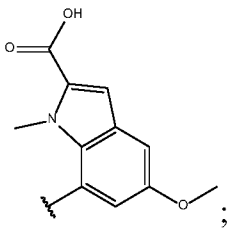
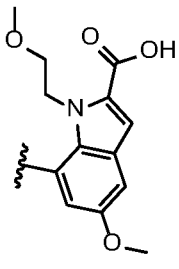
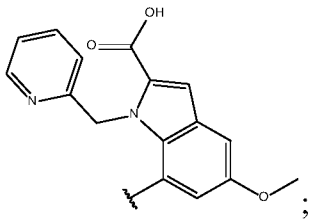
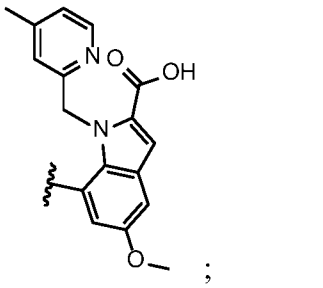
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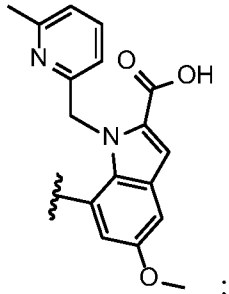
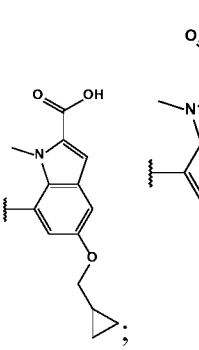
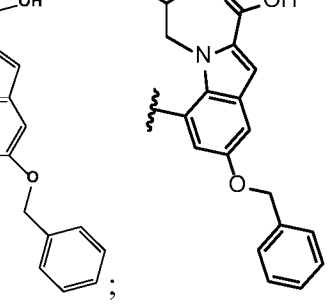
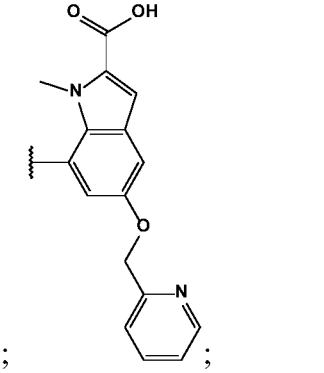







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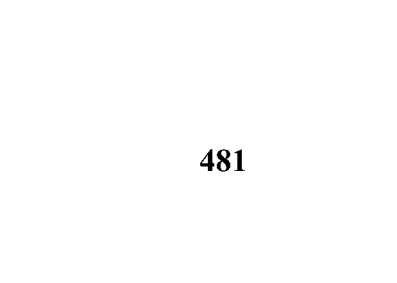
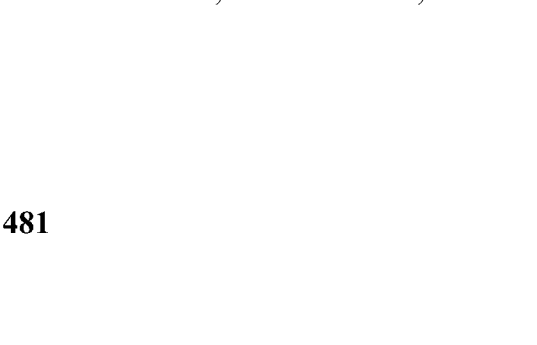
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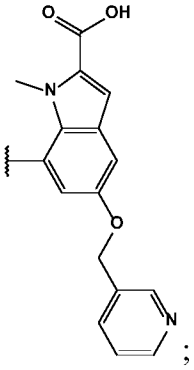
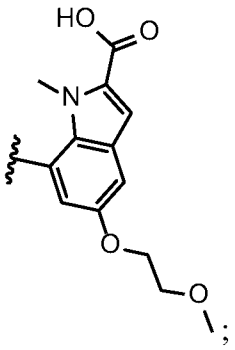
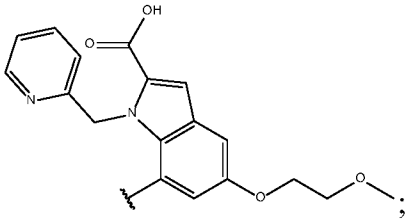
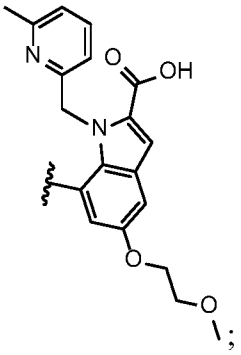
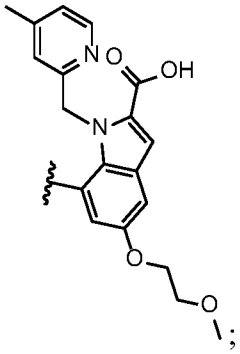
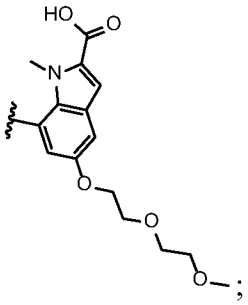
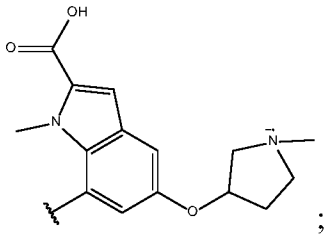
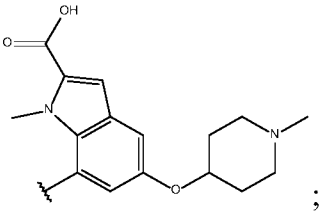
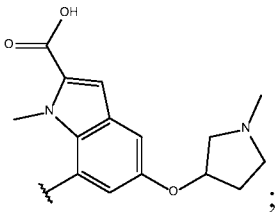
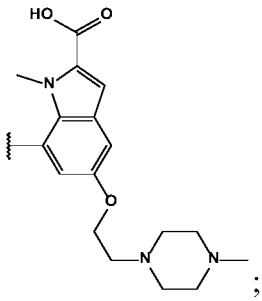
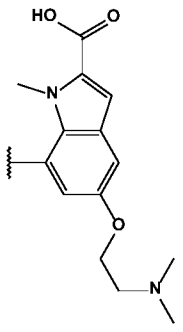
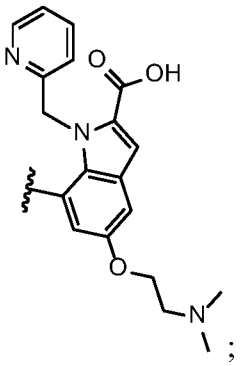
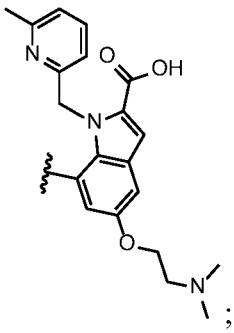
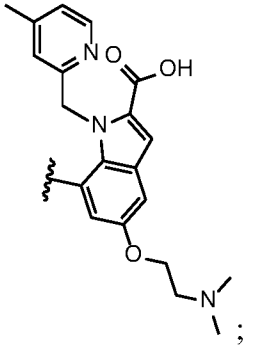
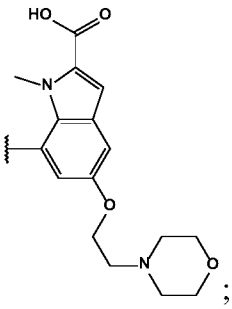
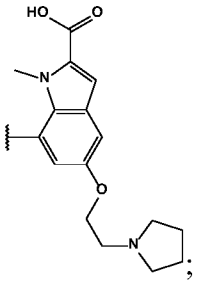
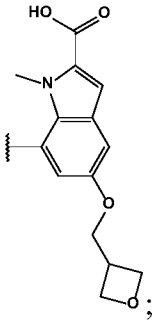
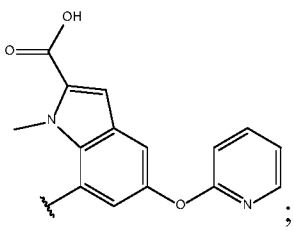
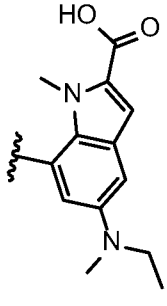
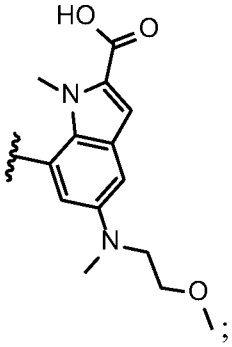
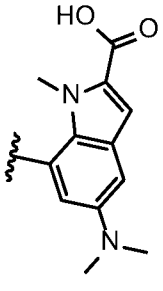
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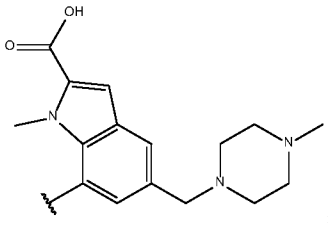
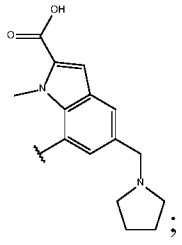
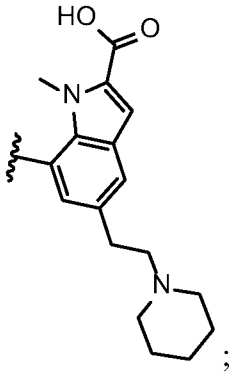
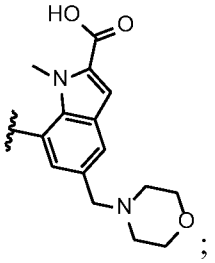
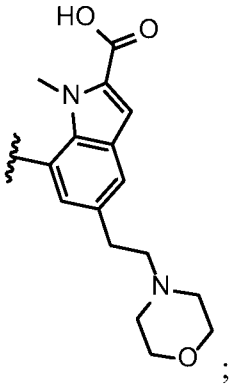
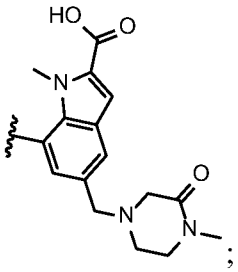
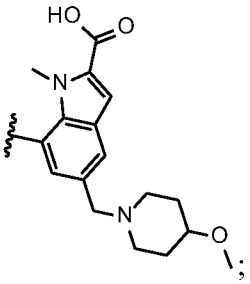
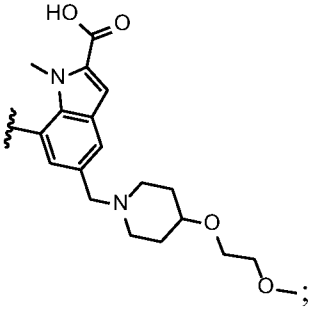
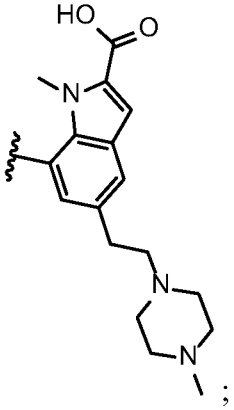
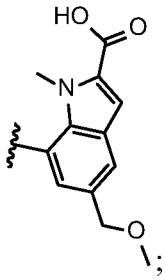
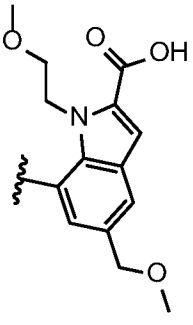
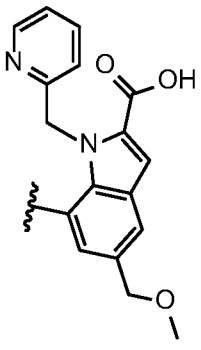
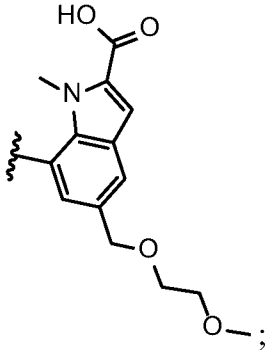
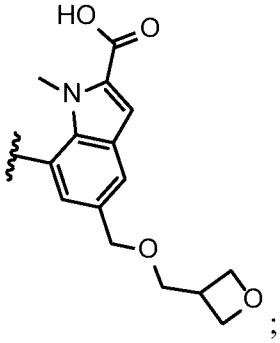
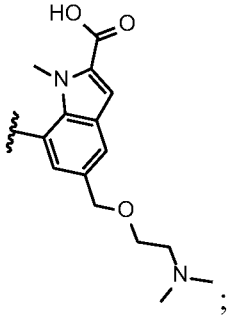
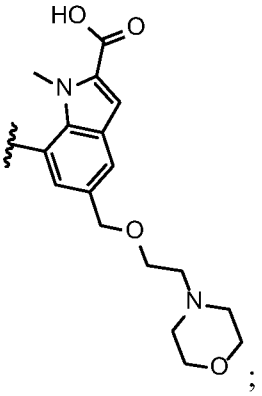
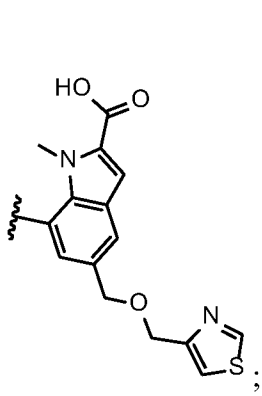
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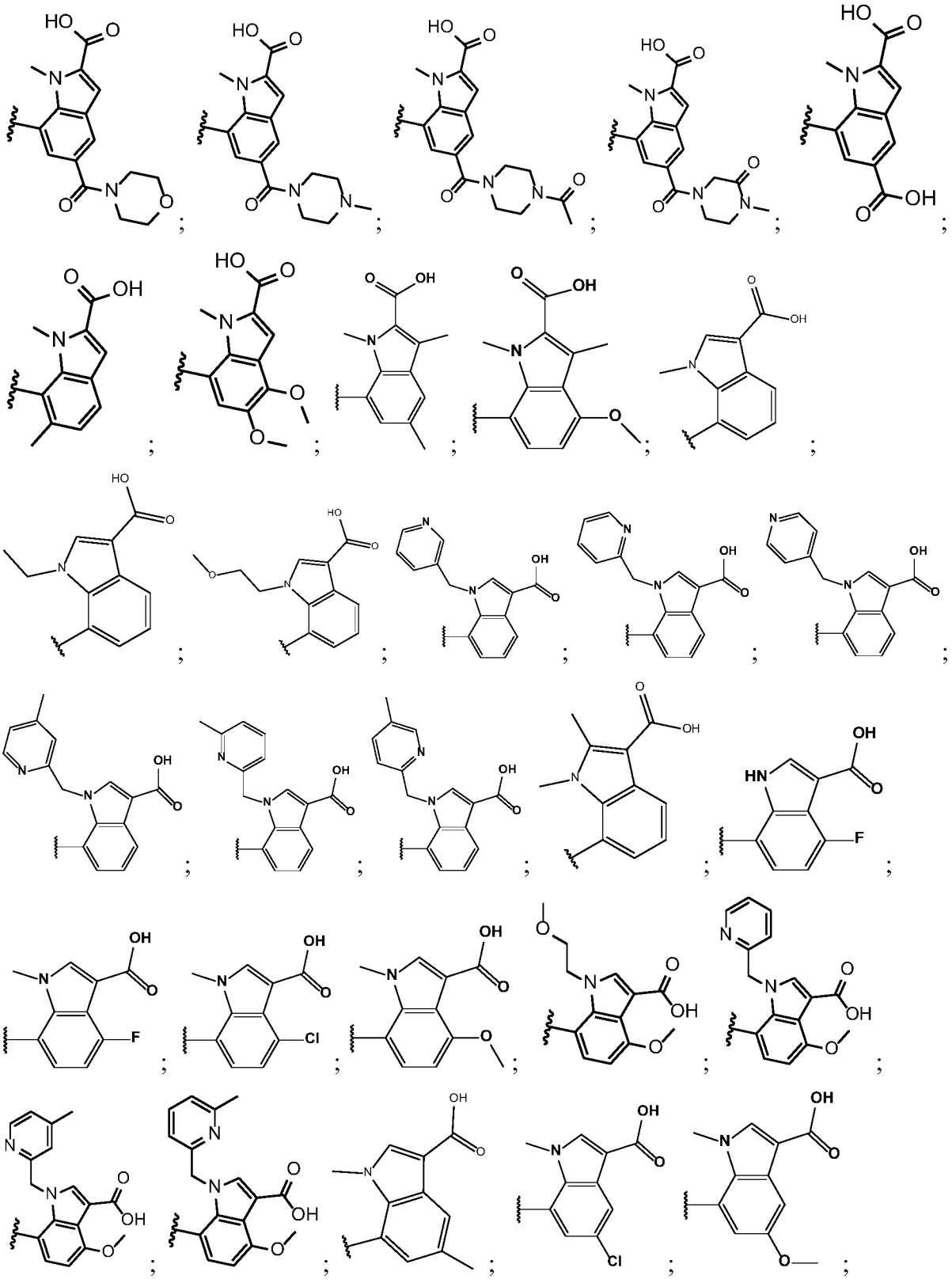
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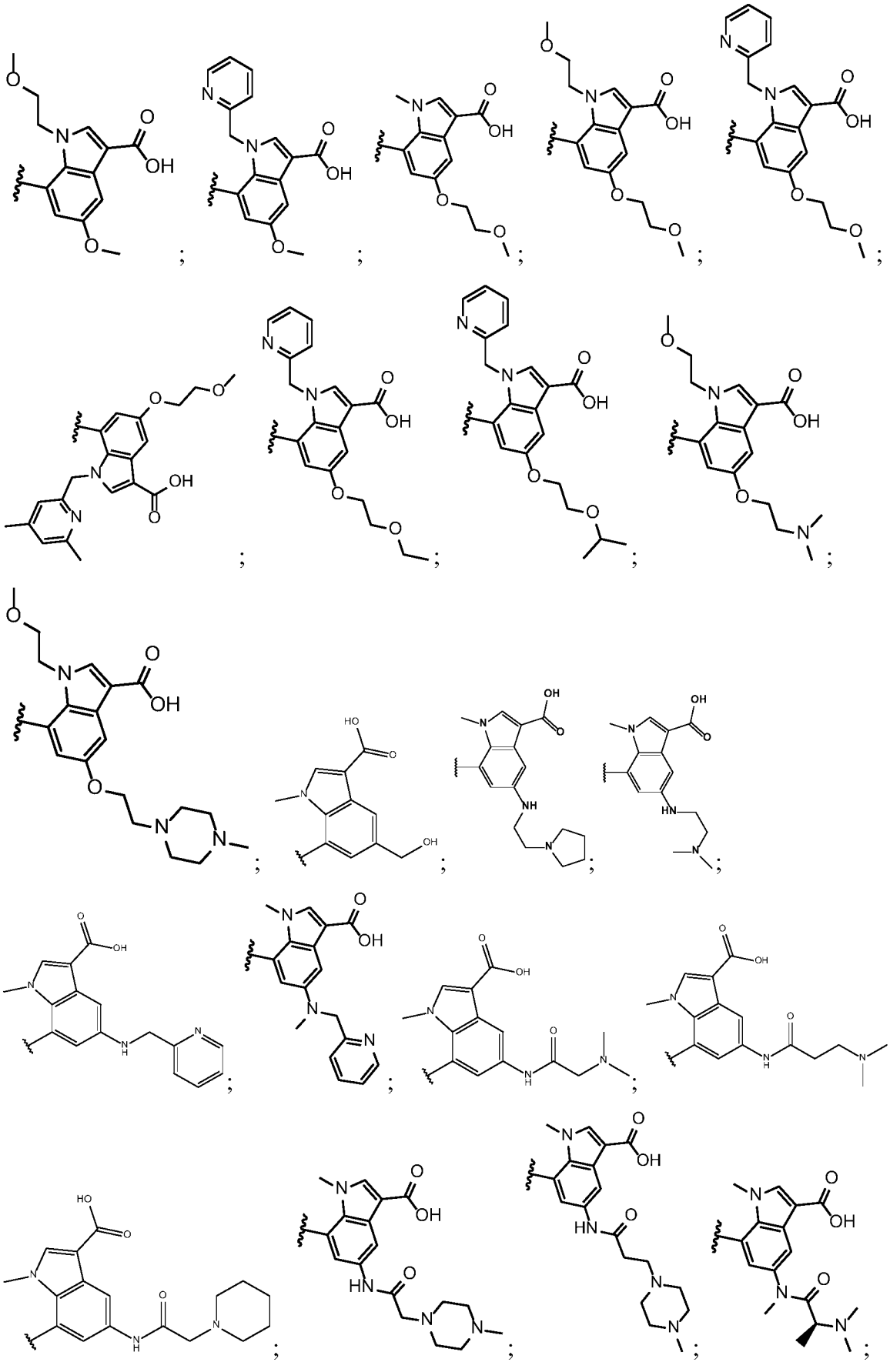
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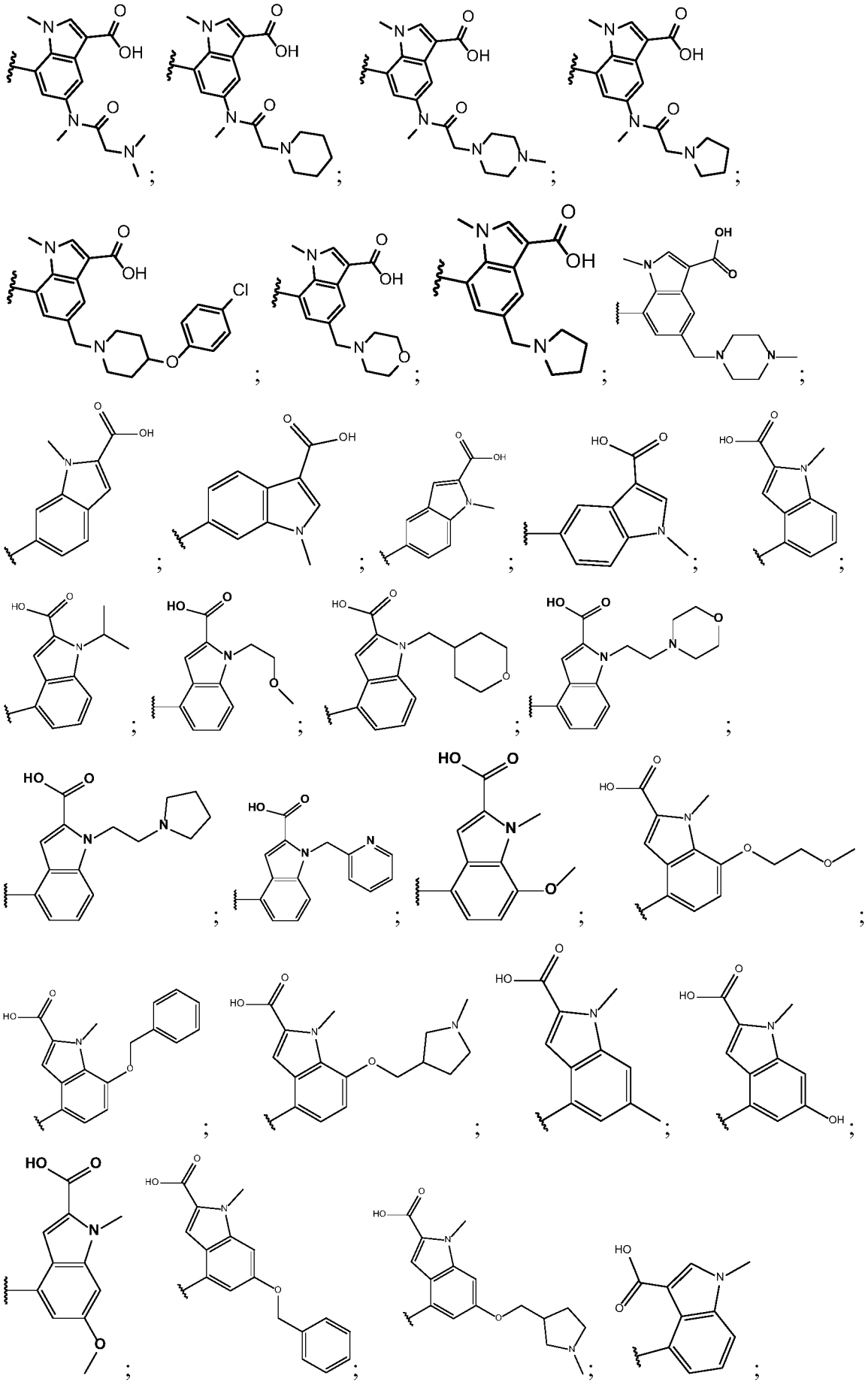
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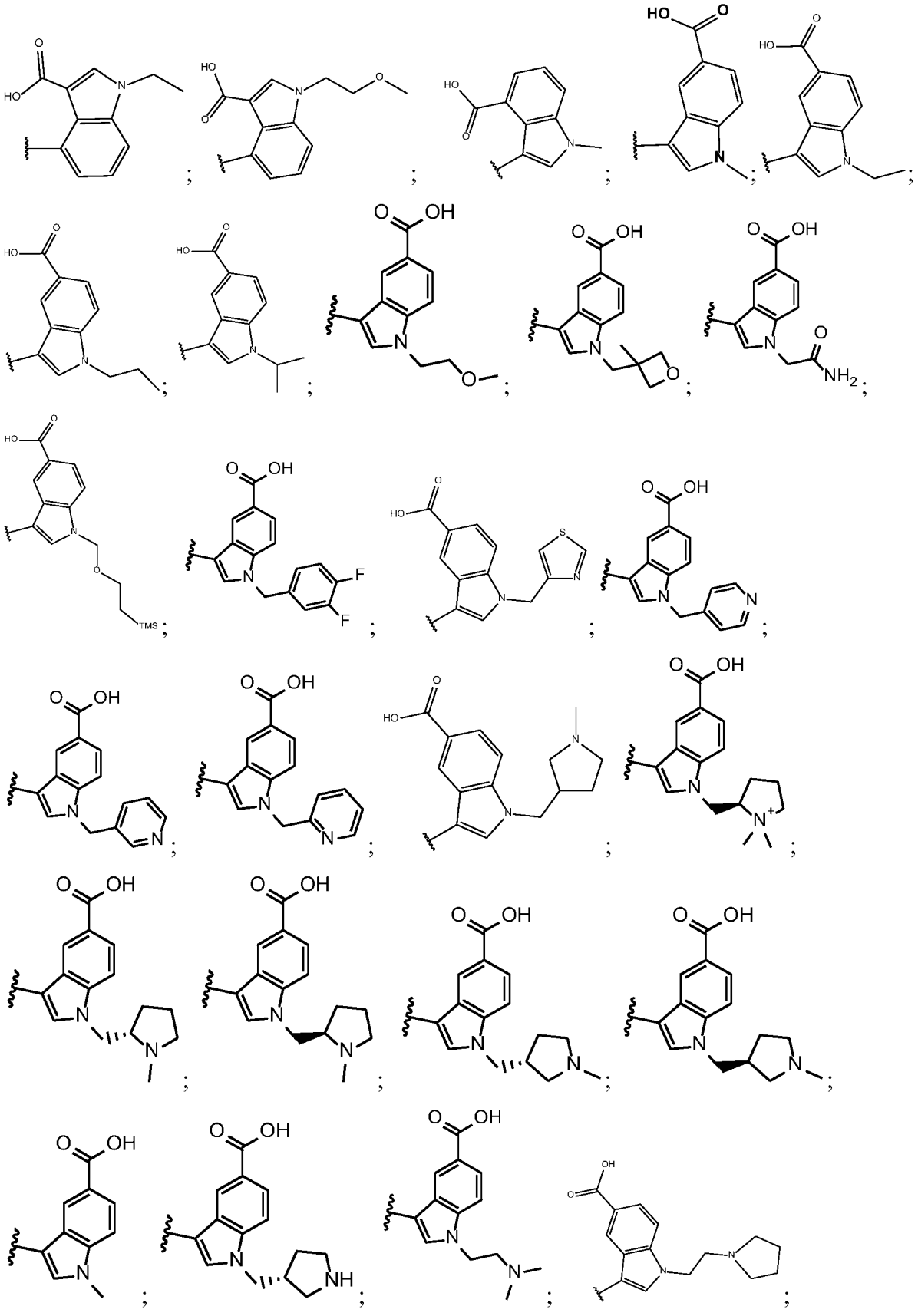
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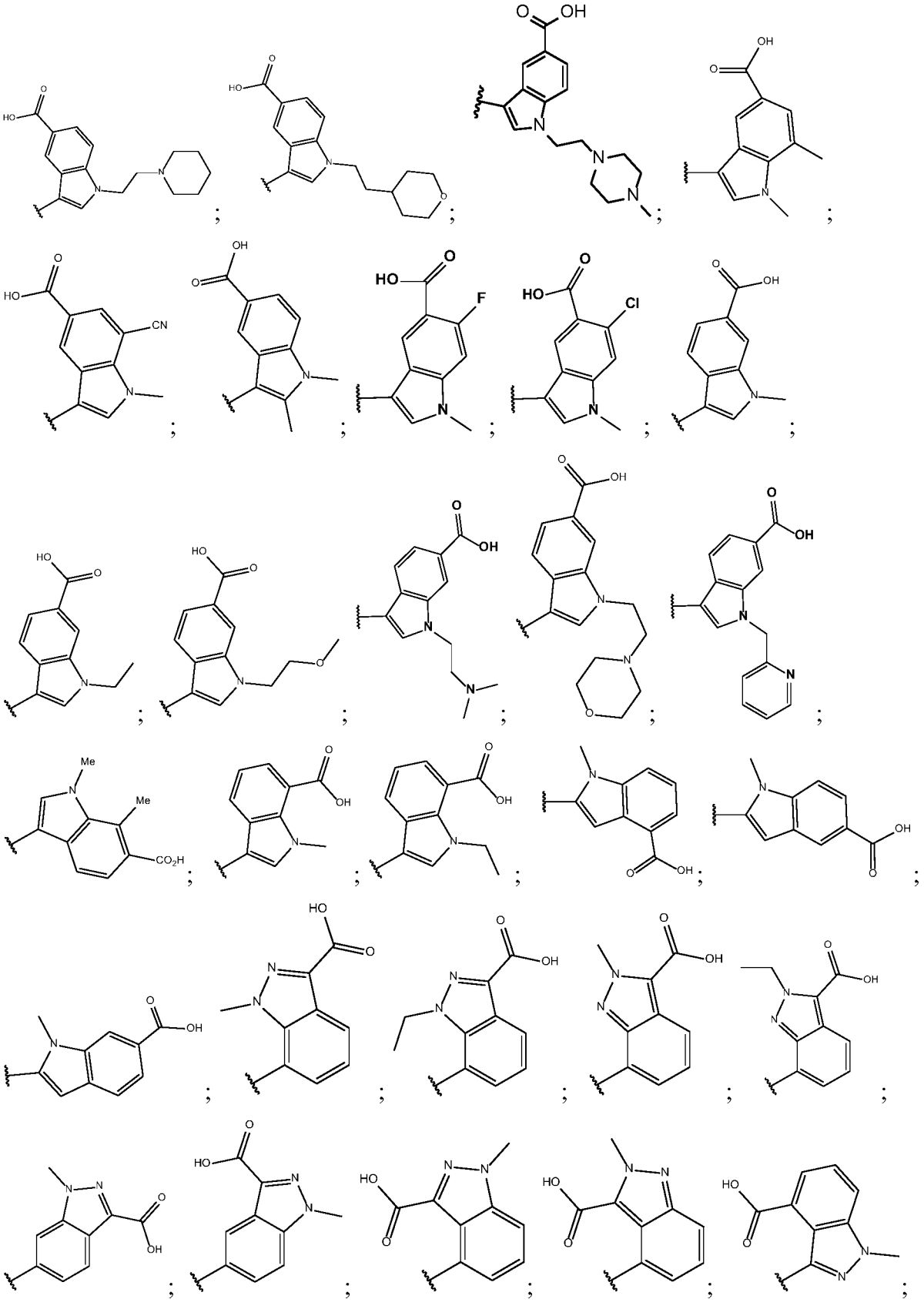
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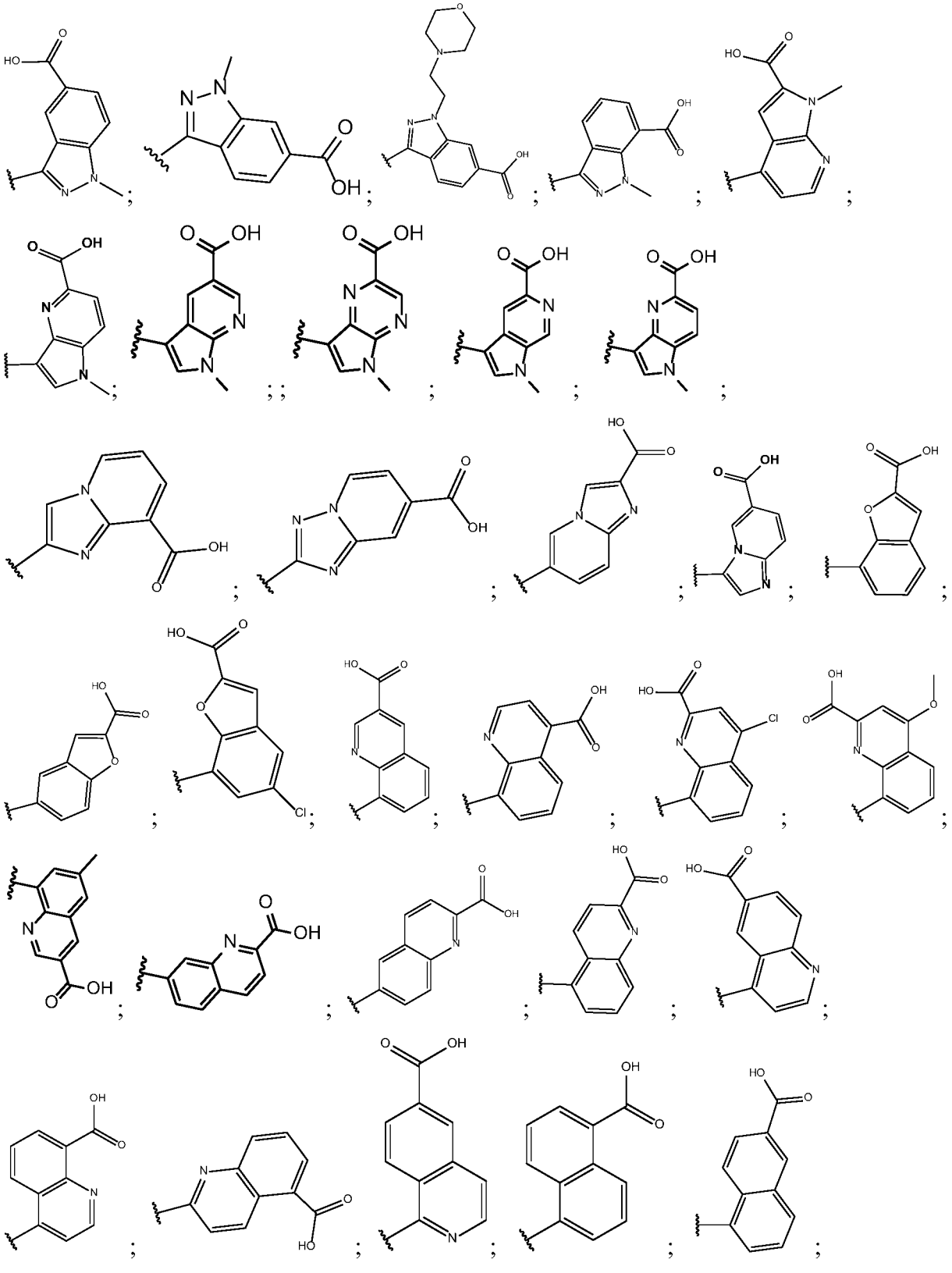


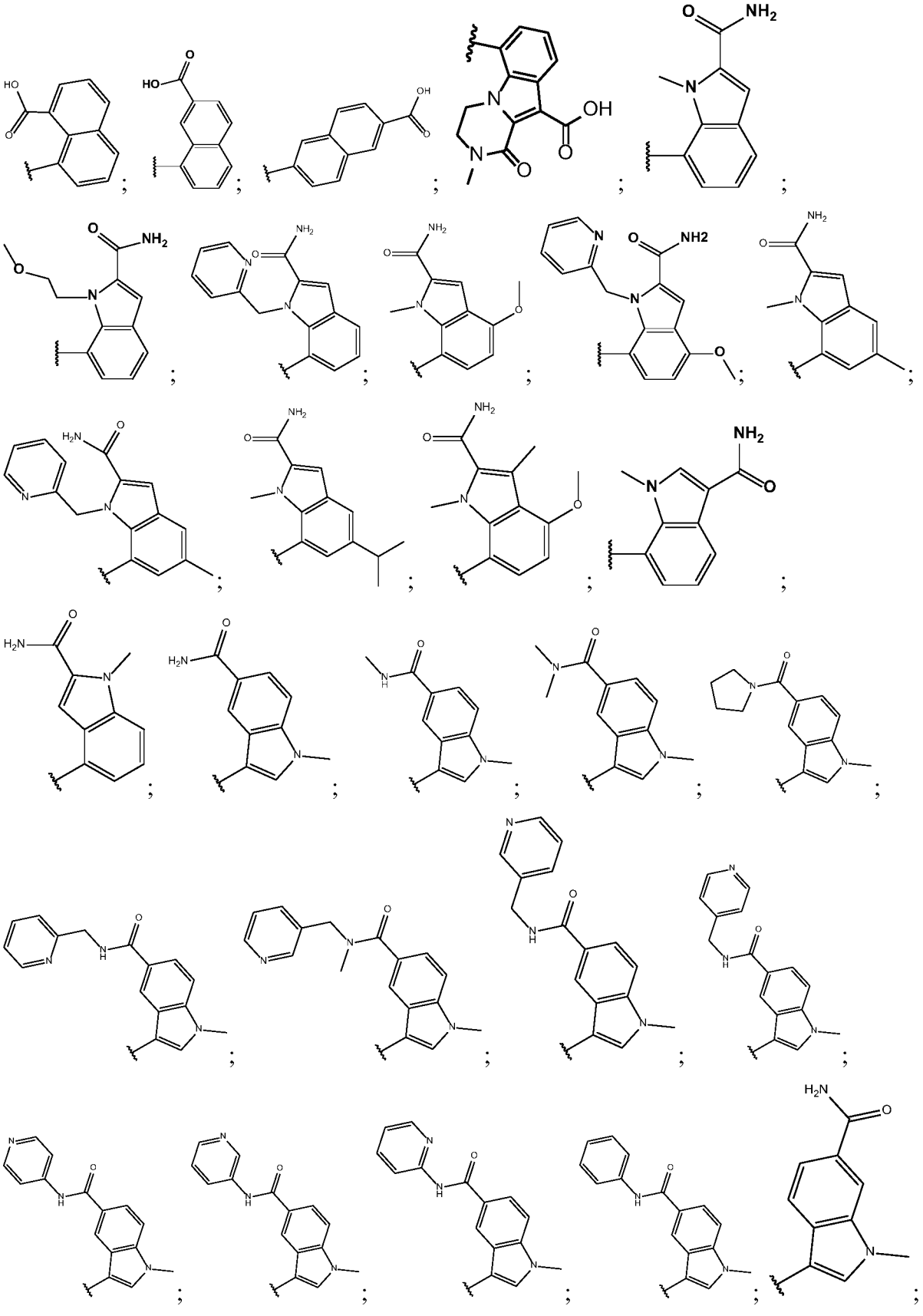


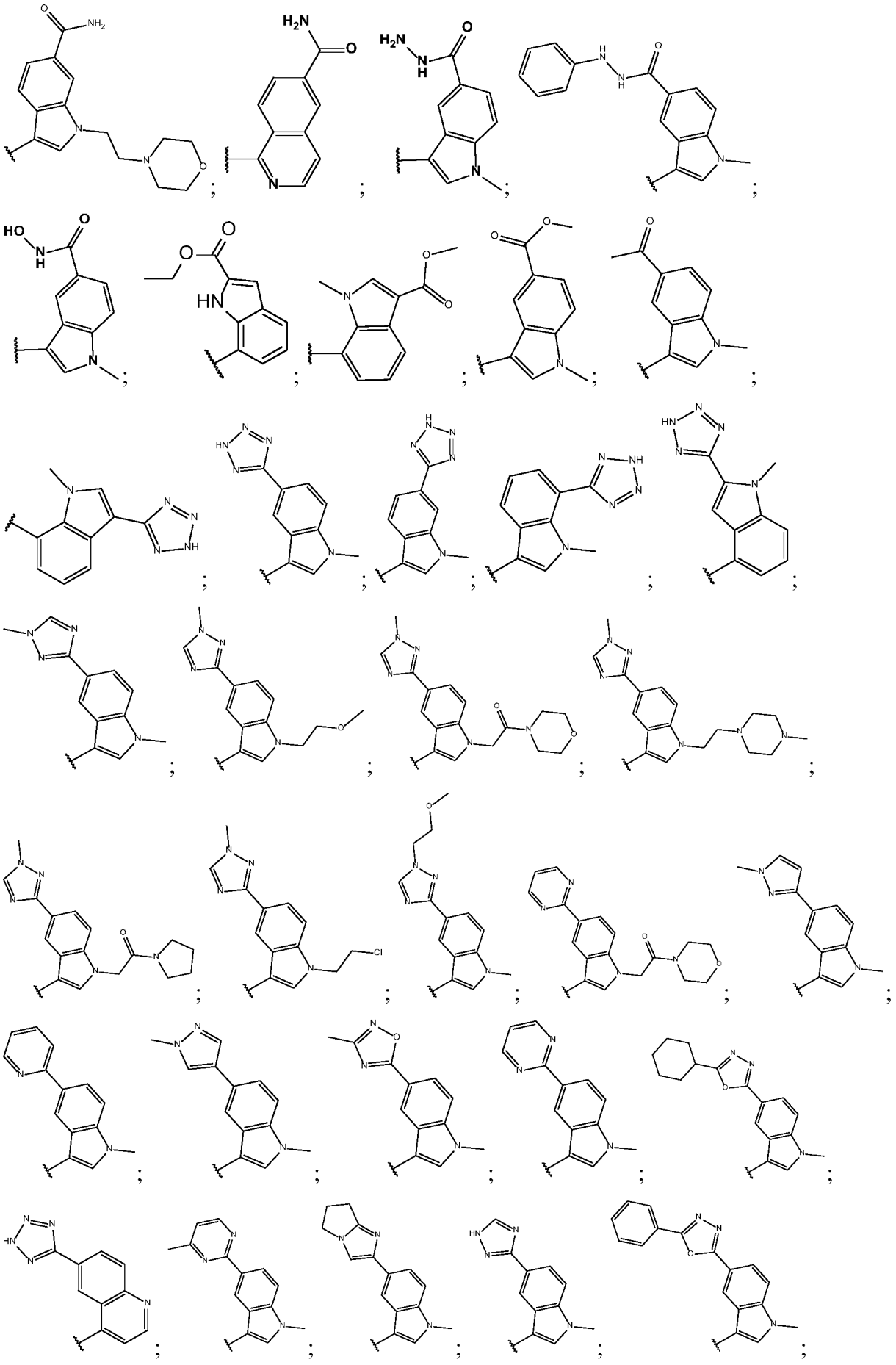


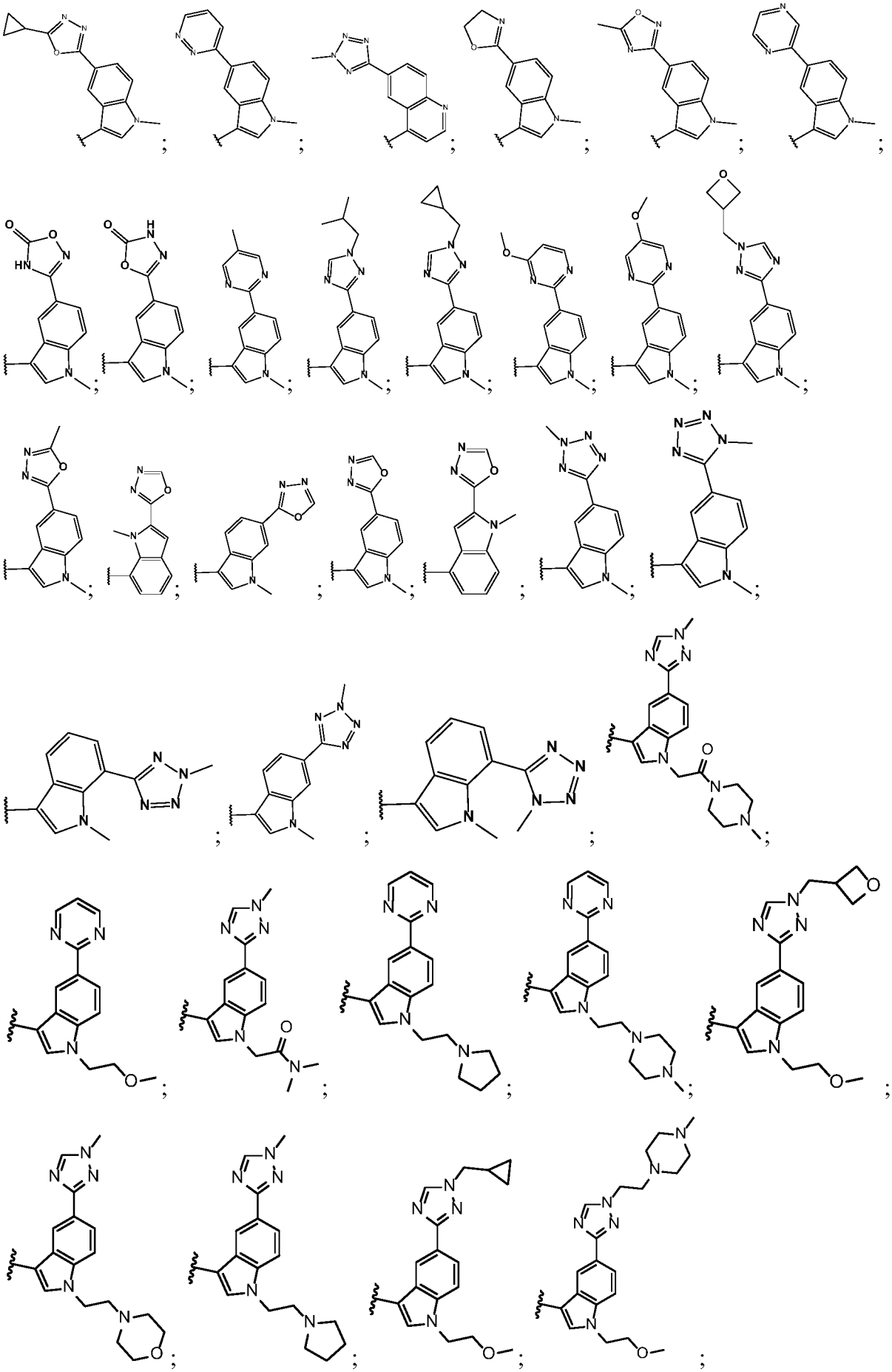


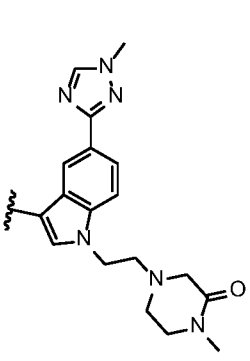
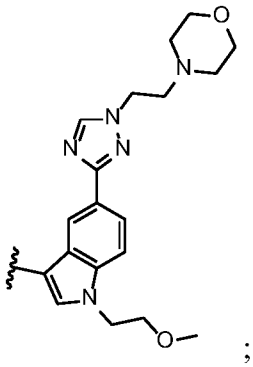
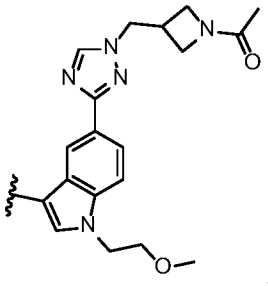
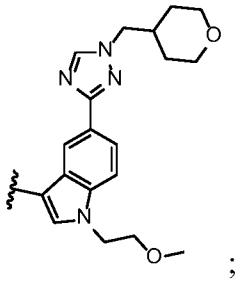
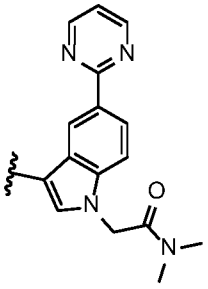
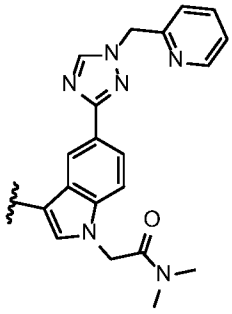
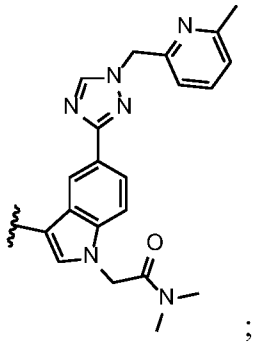
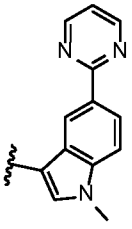
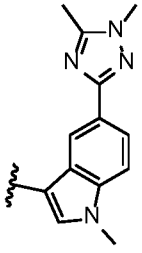
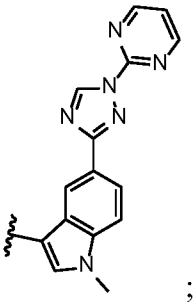
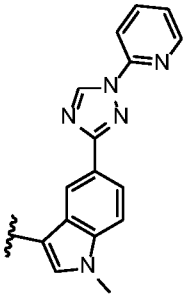
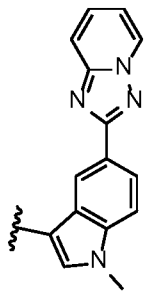
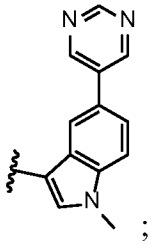
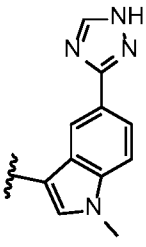
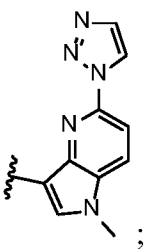
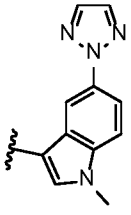
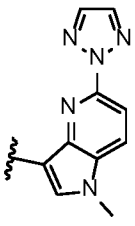
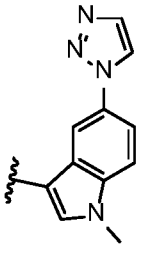
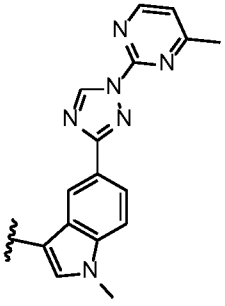
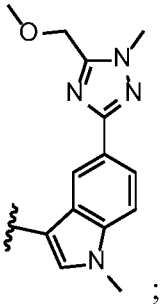
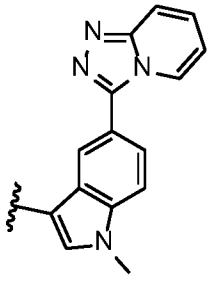
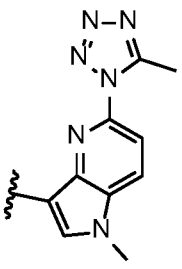
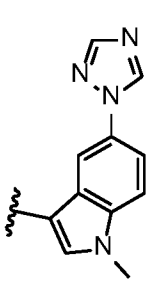
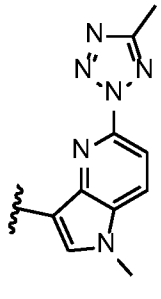
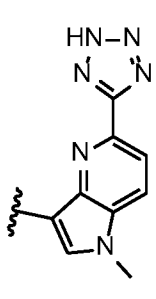
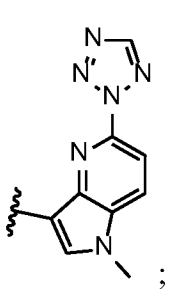
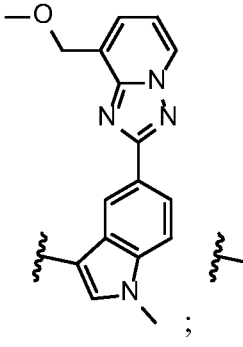
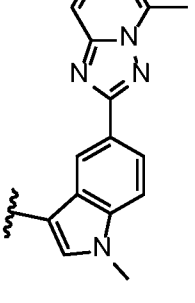











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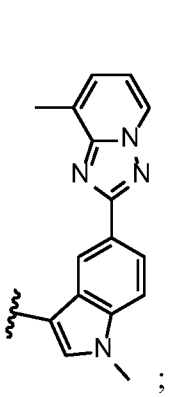
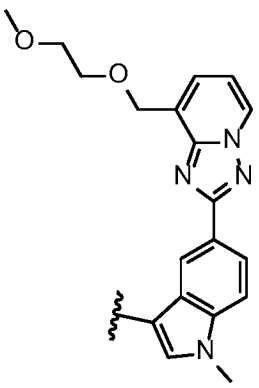
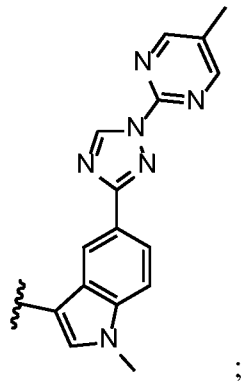
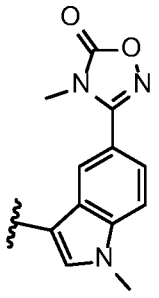
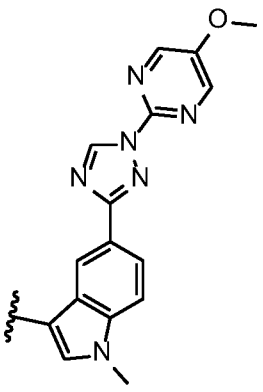
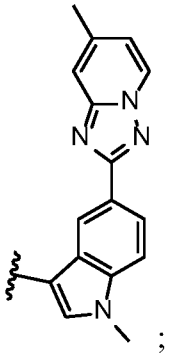
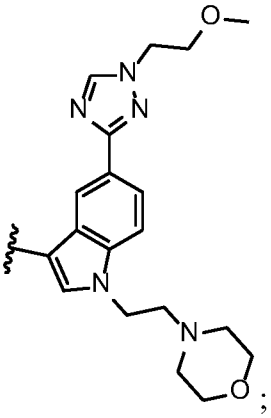
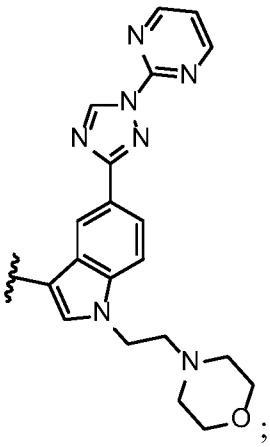
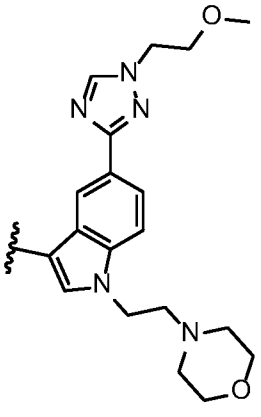
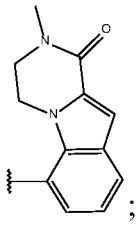
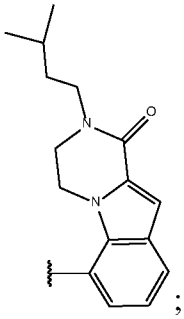
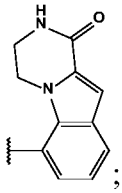
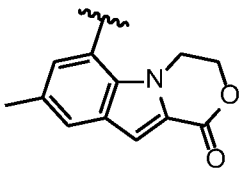
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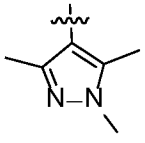
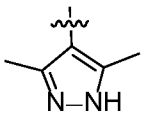
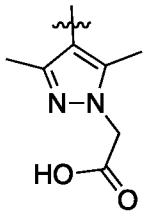
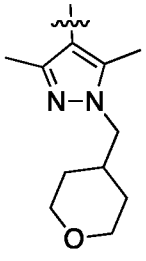
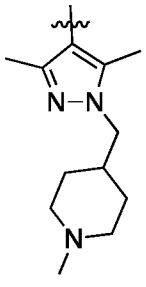
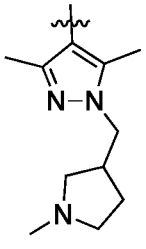
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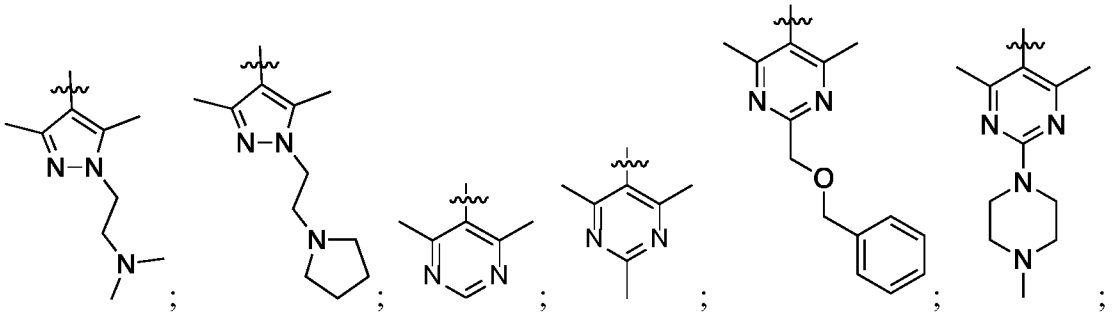
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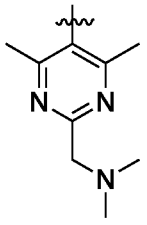
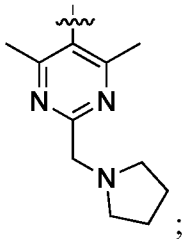
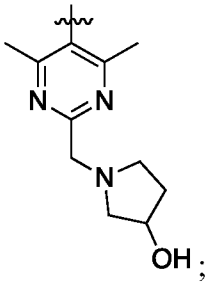
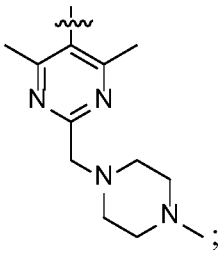
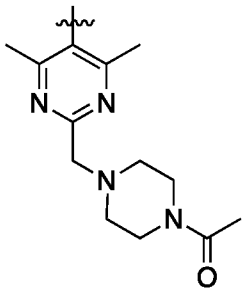
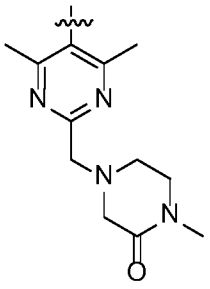
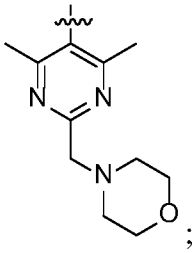
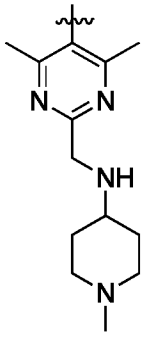
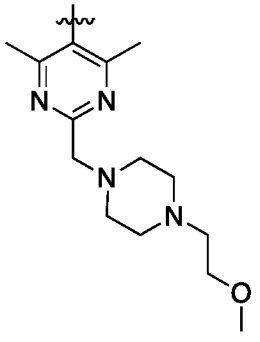
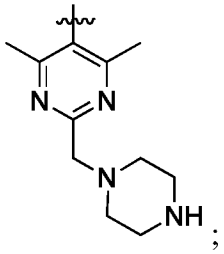
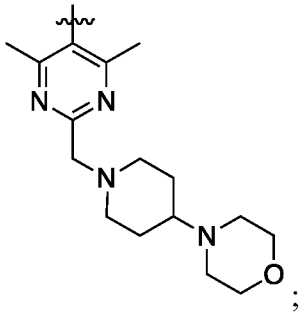
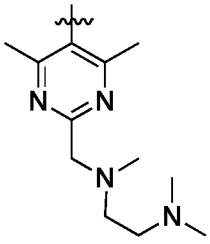
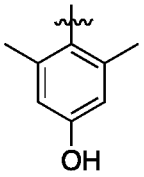
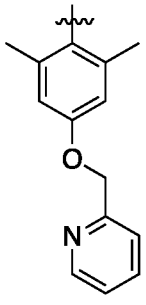
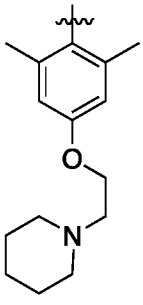
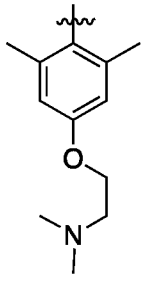
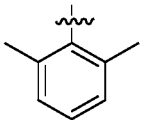

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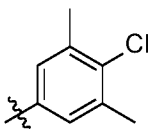
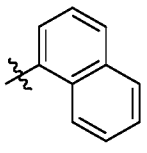
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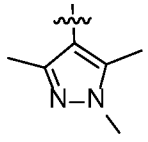
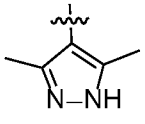
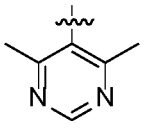
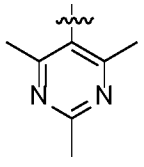
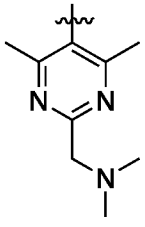
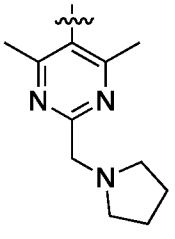
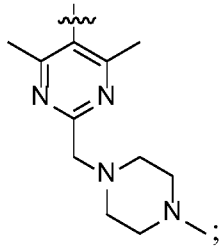
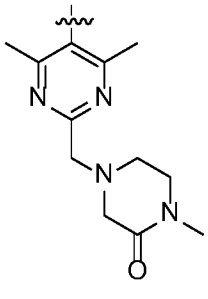
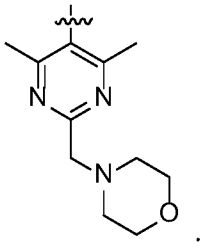
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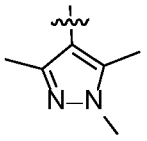
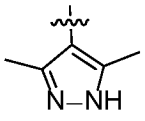
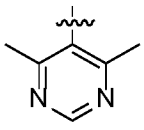
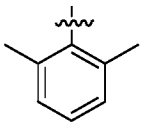
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from


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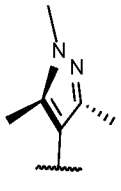
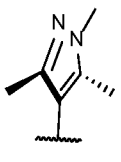
3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^7 is selected from:


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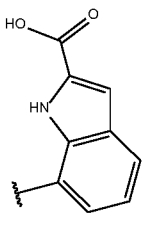
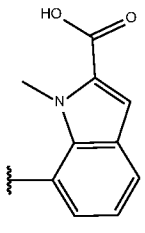
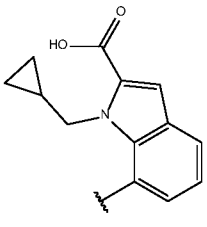
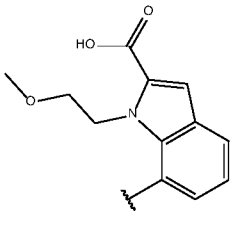
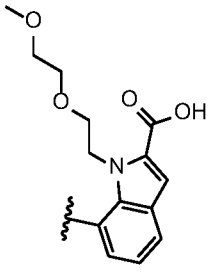
4. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^7 is selected from:

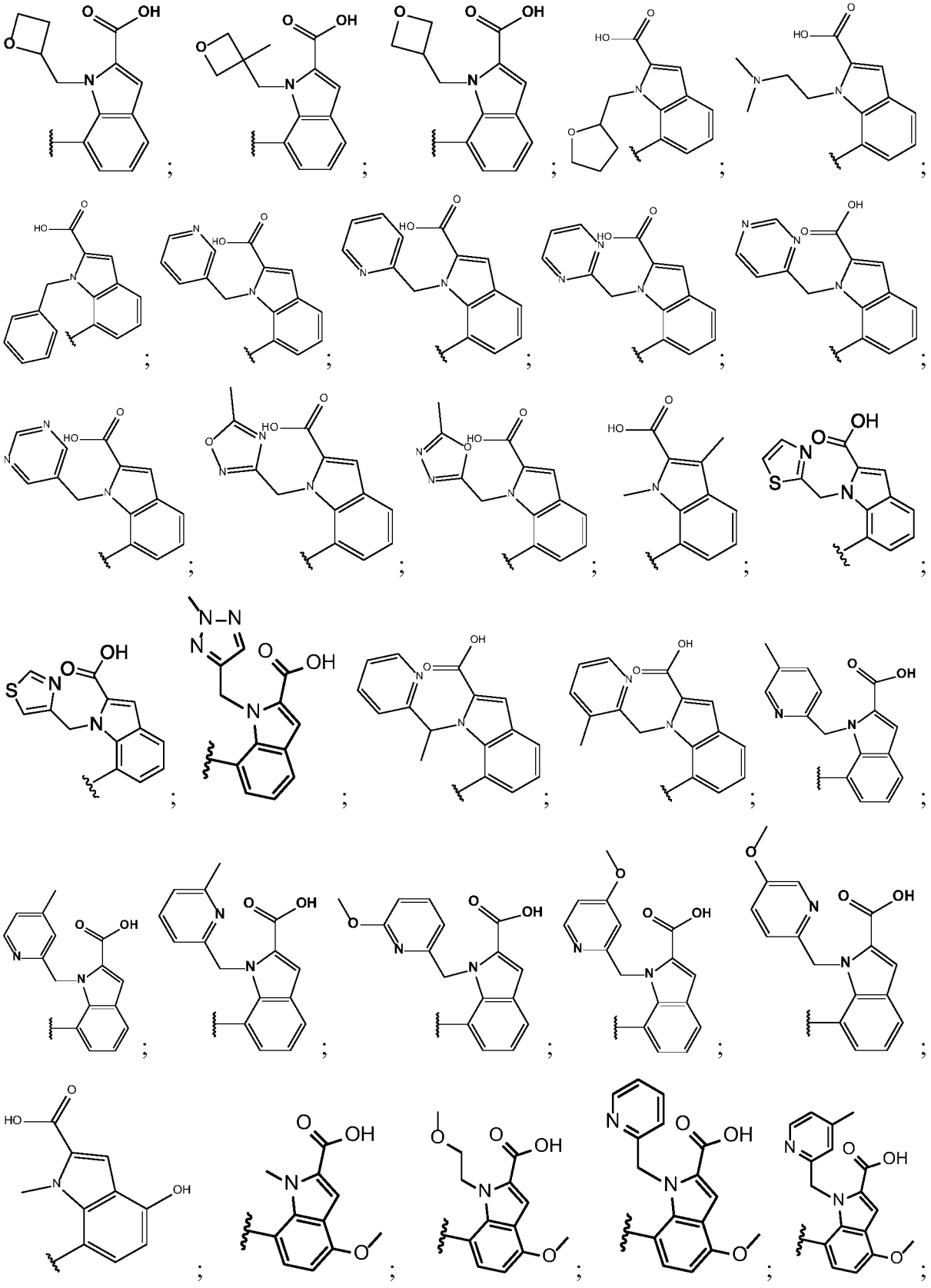

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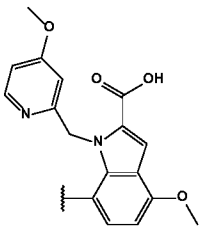
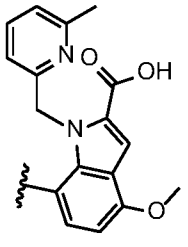
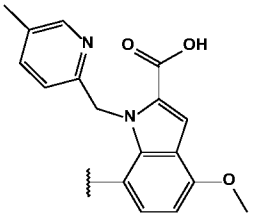
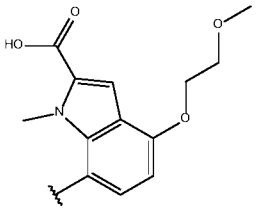
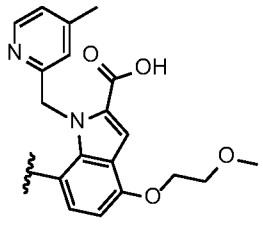
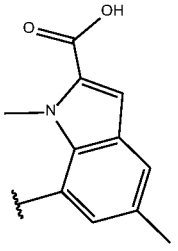
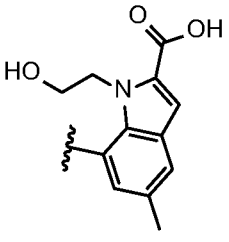
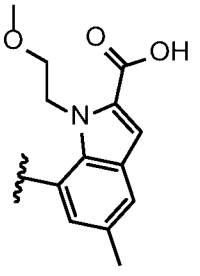
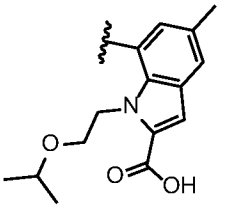
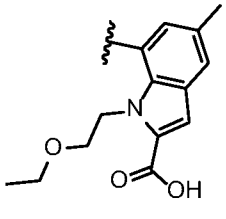
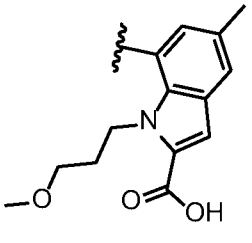
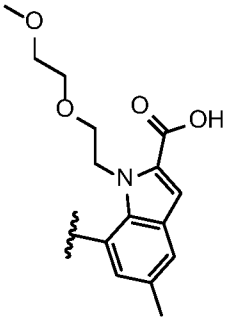
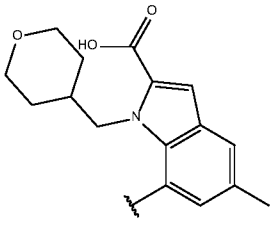
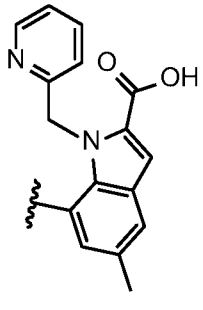
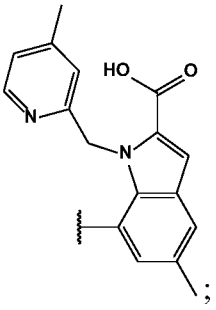
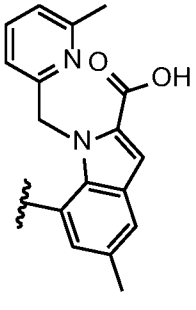
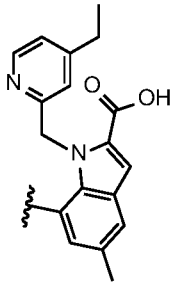
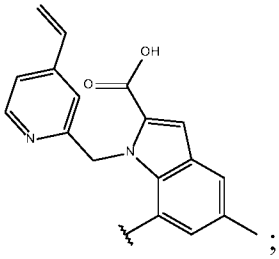
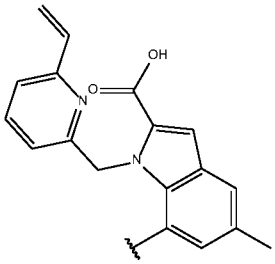
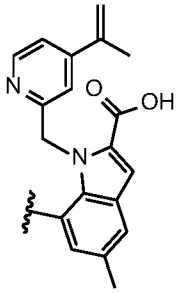
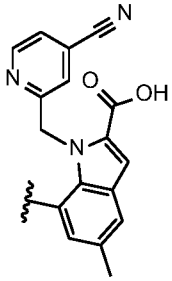
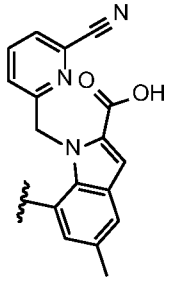
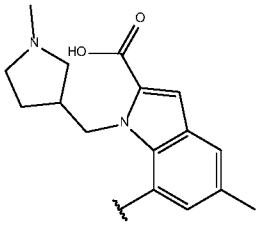
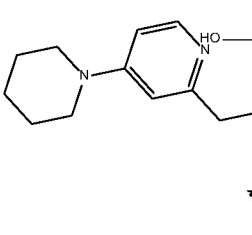
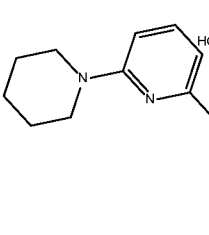
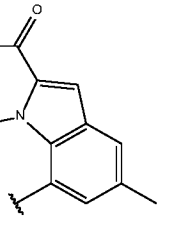
5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R^7 is


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6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein L^4-R^w is


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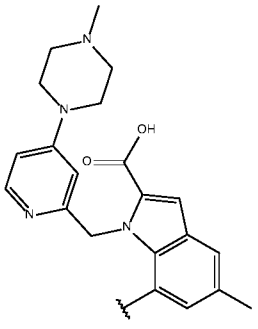
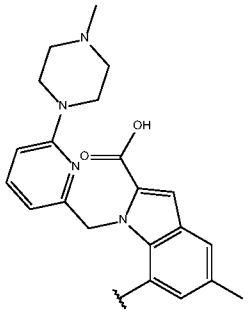
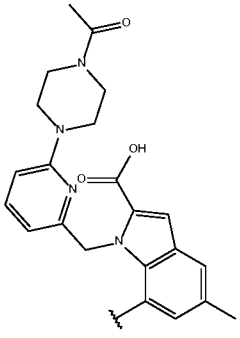
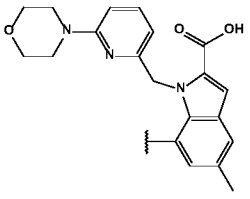
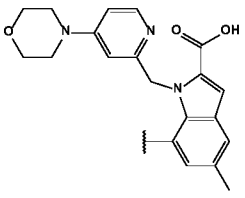
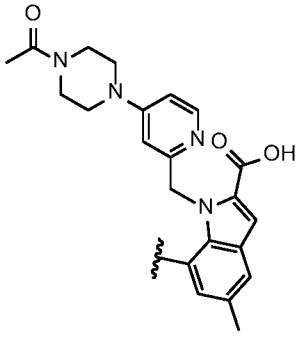
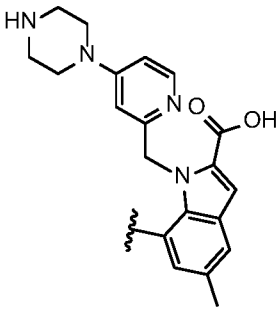
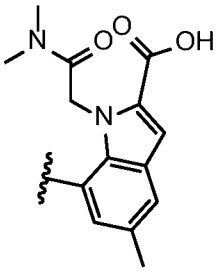
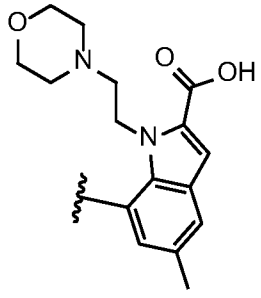
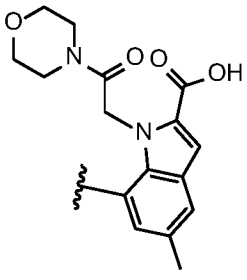
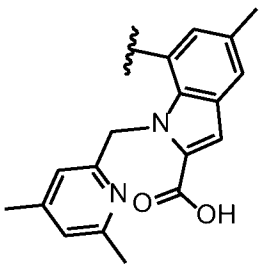
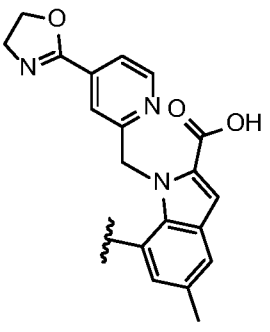
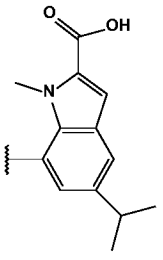
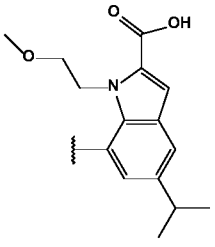
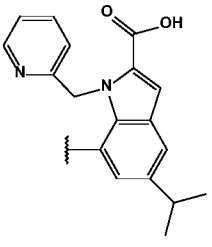
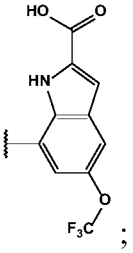
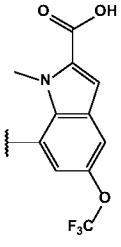
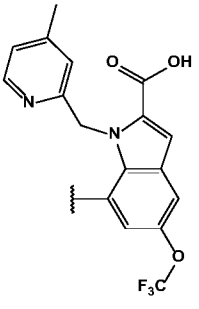
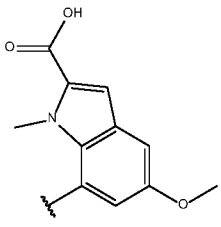
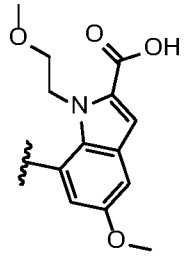
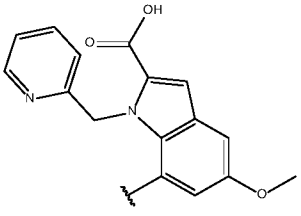
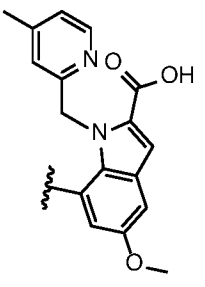


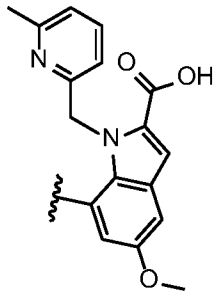
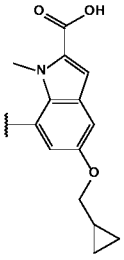
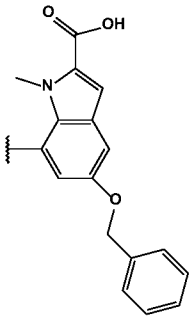
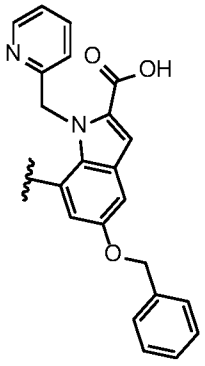
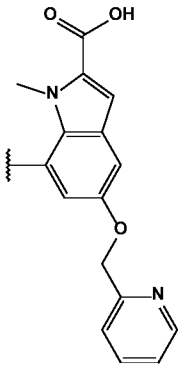
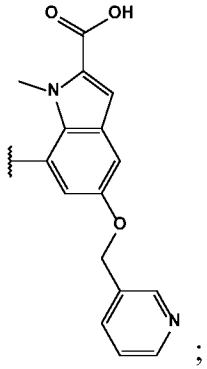
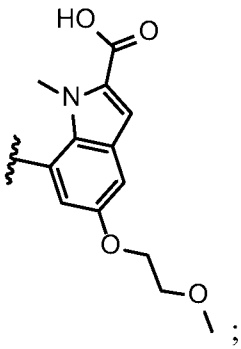
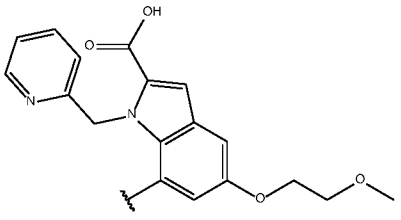
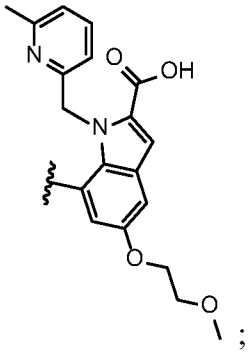
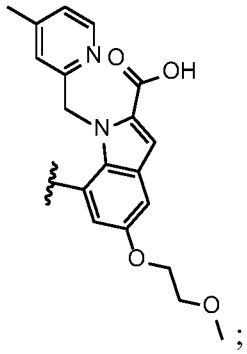
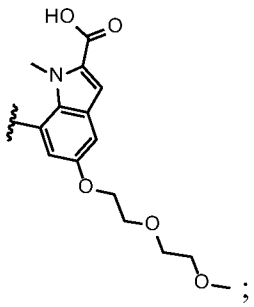
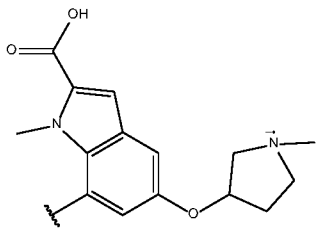
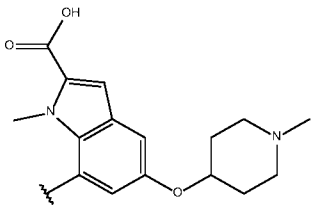
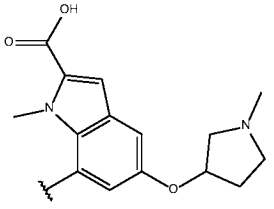
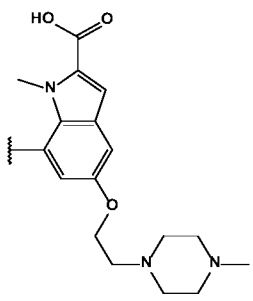
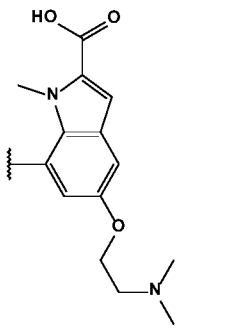
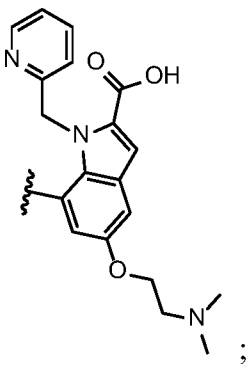

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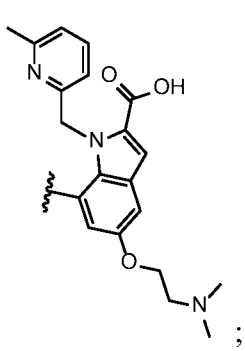
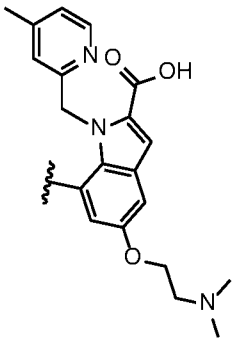
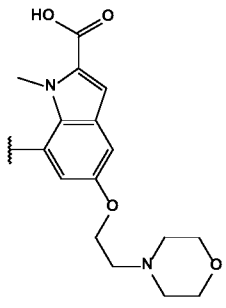
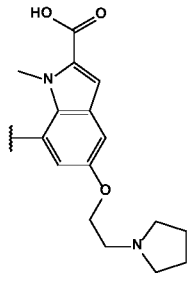
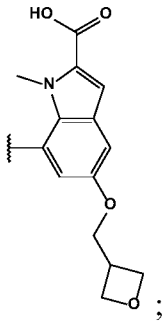
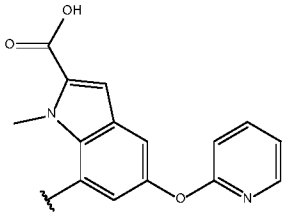
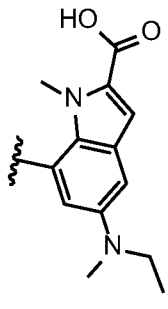
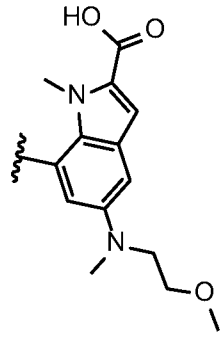
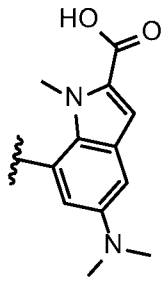
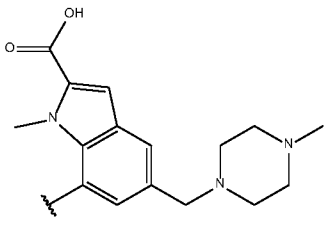
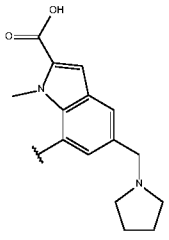
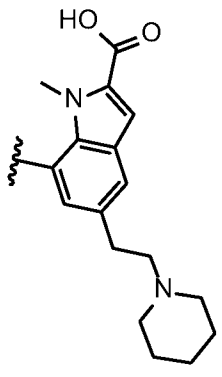
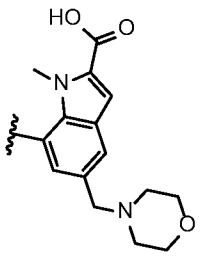
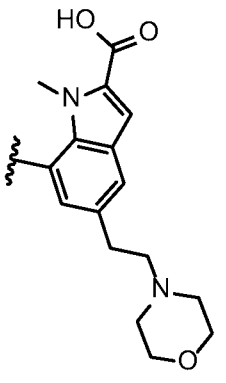
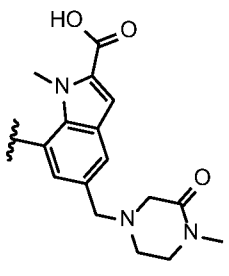
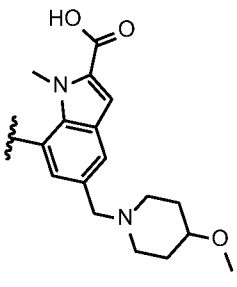
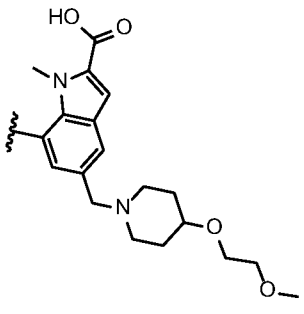
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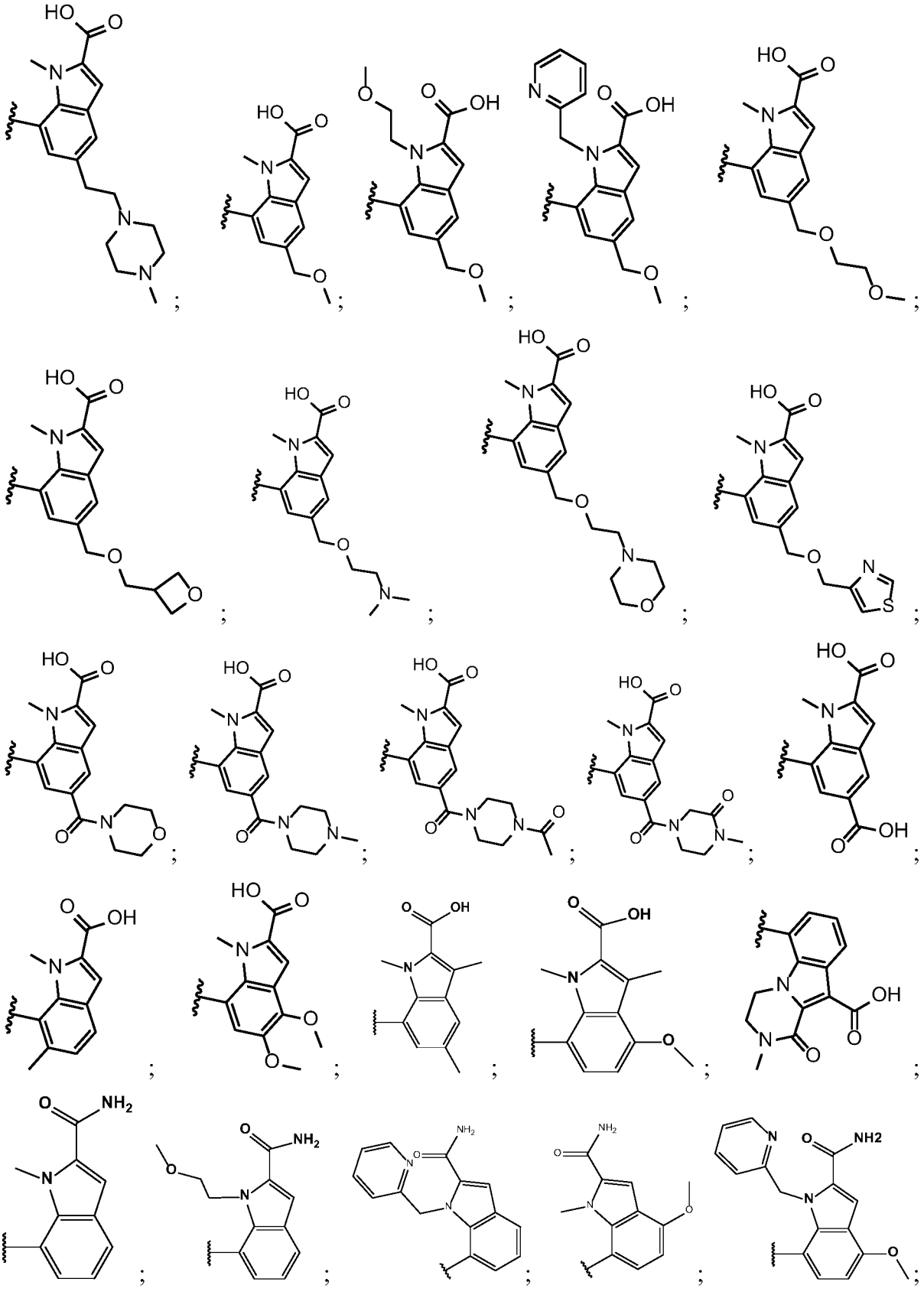
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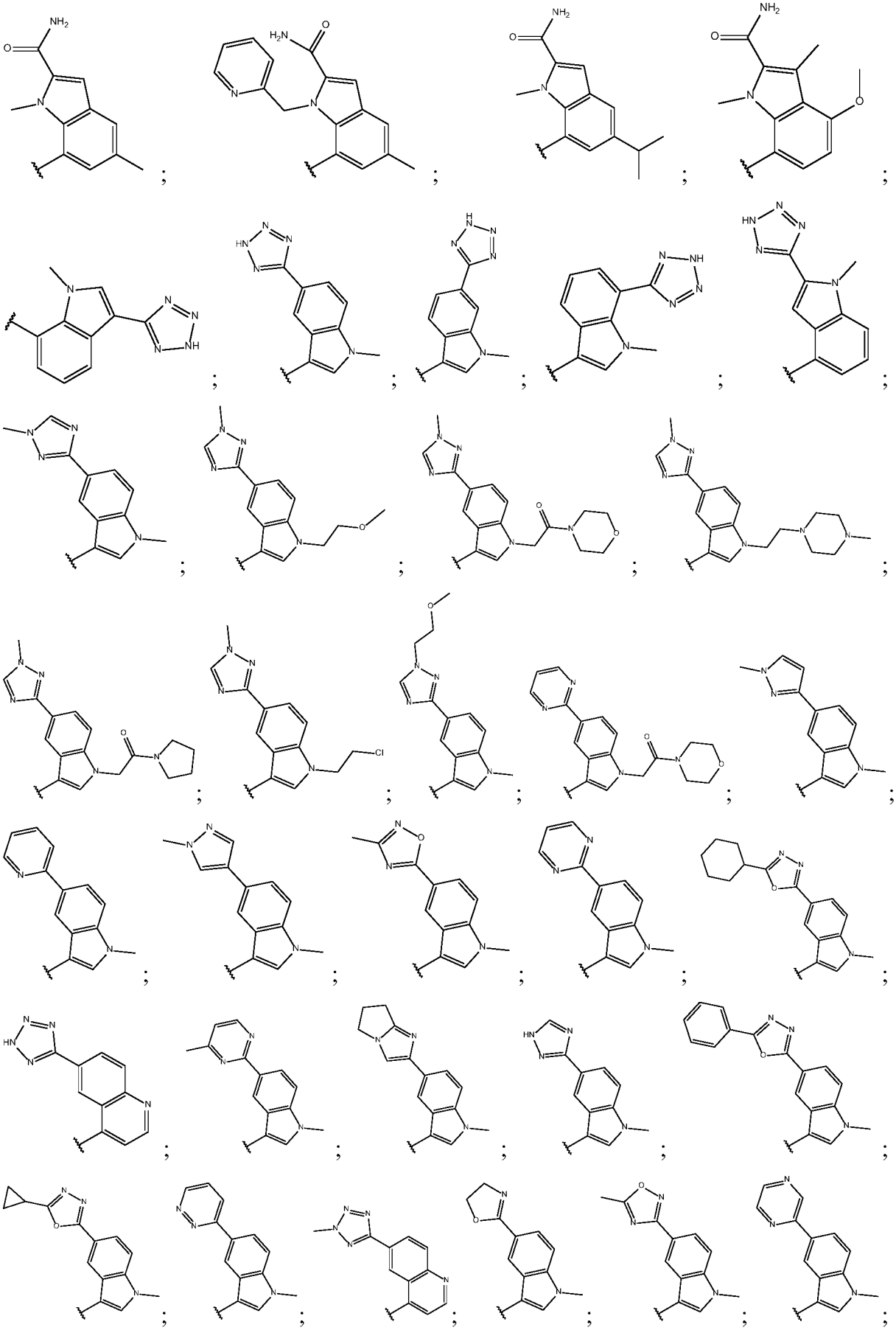
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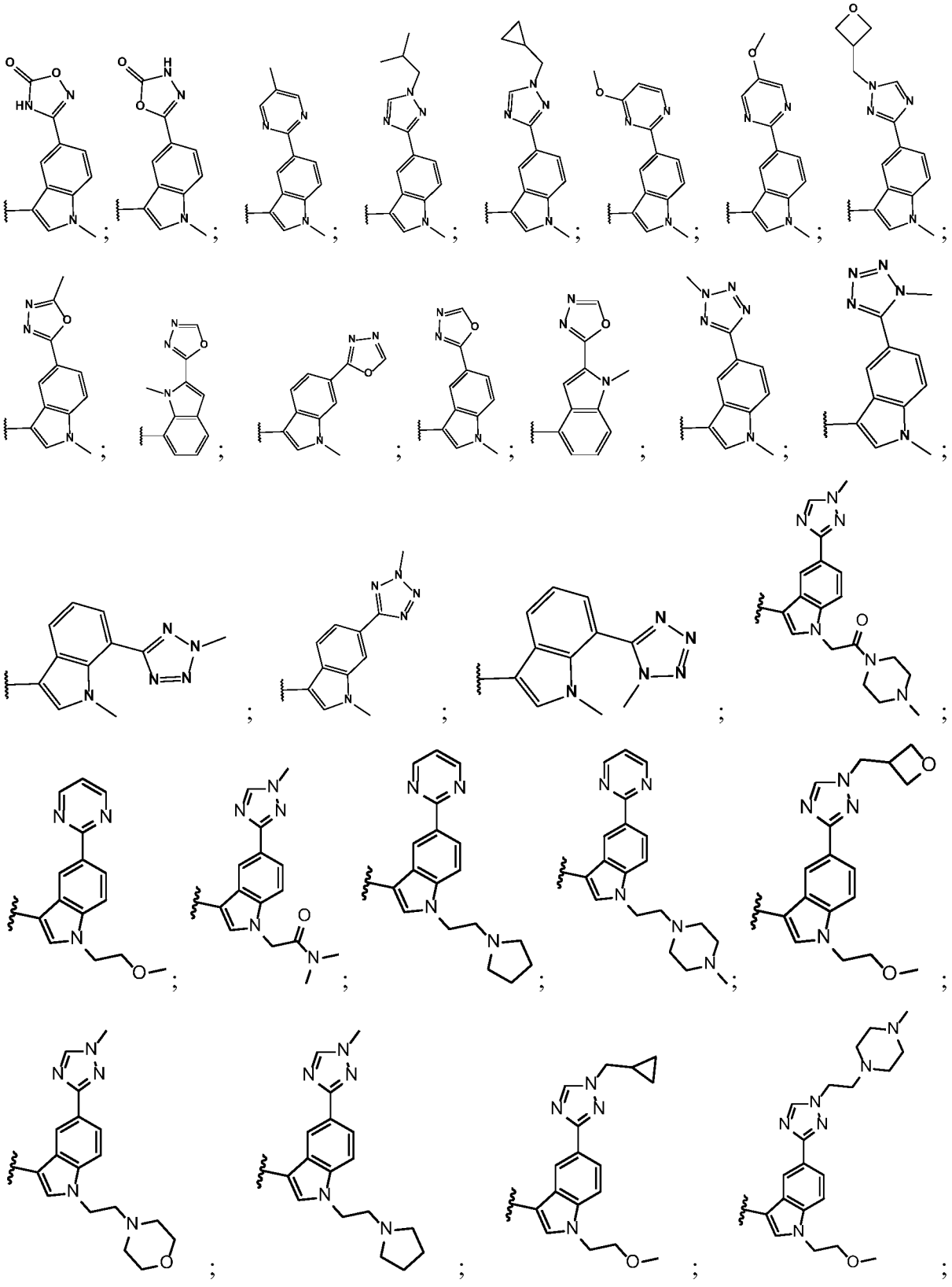

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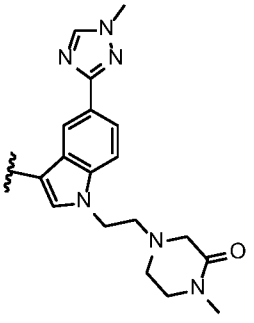
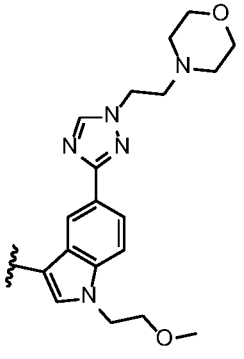
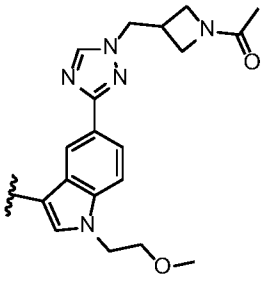
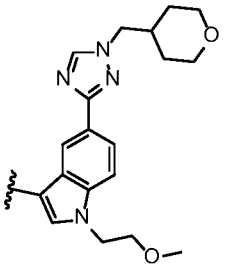
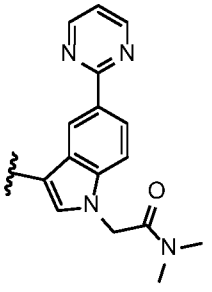
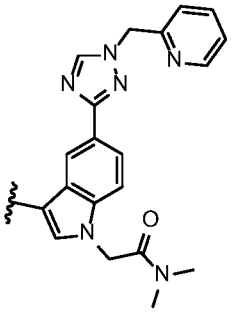
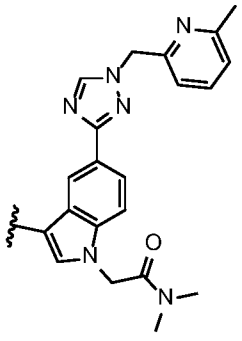
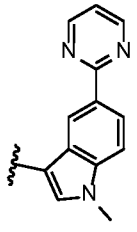
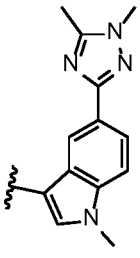
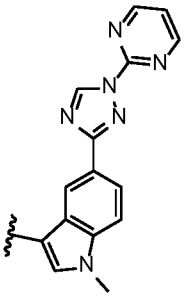
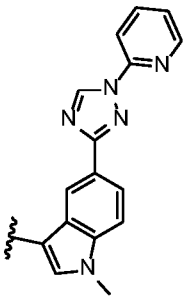
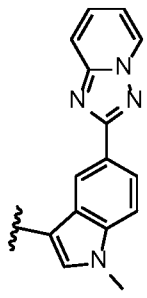
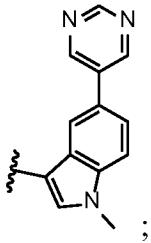
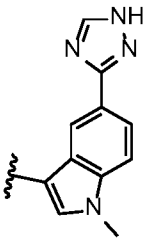
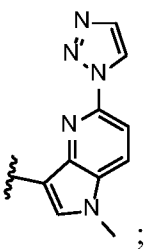
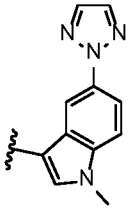
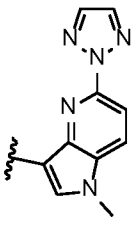
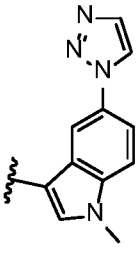
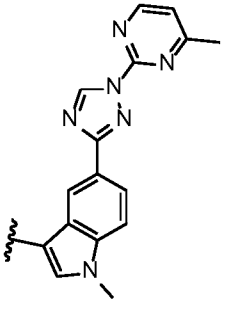
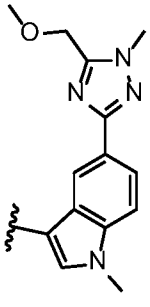
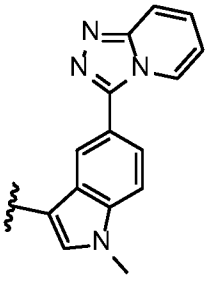
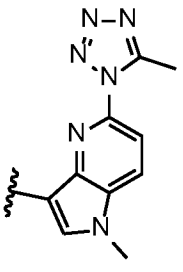
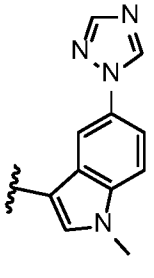
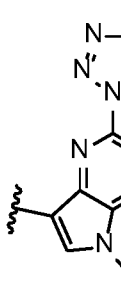
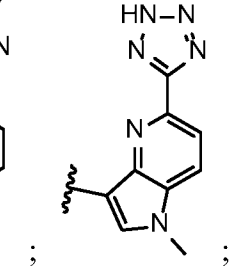
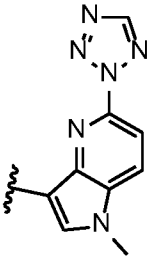
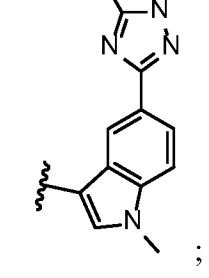
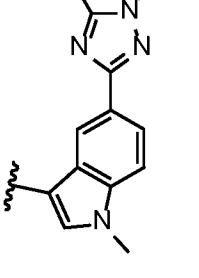

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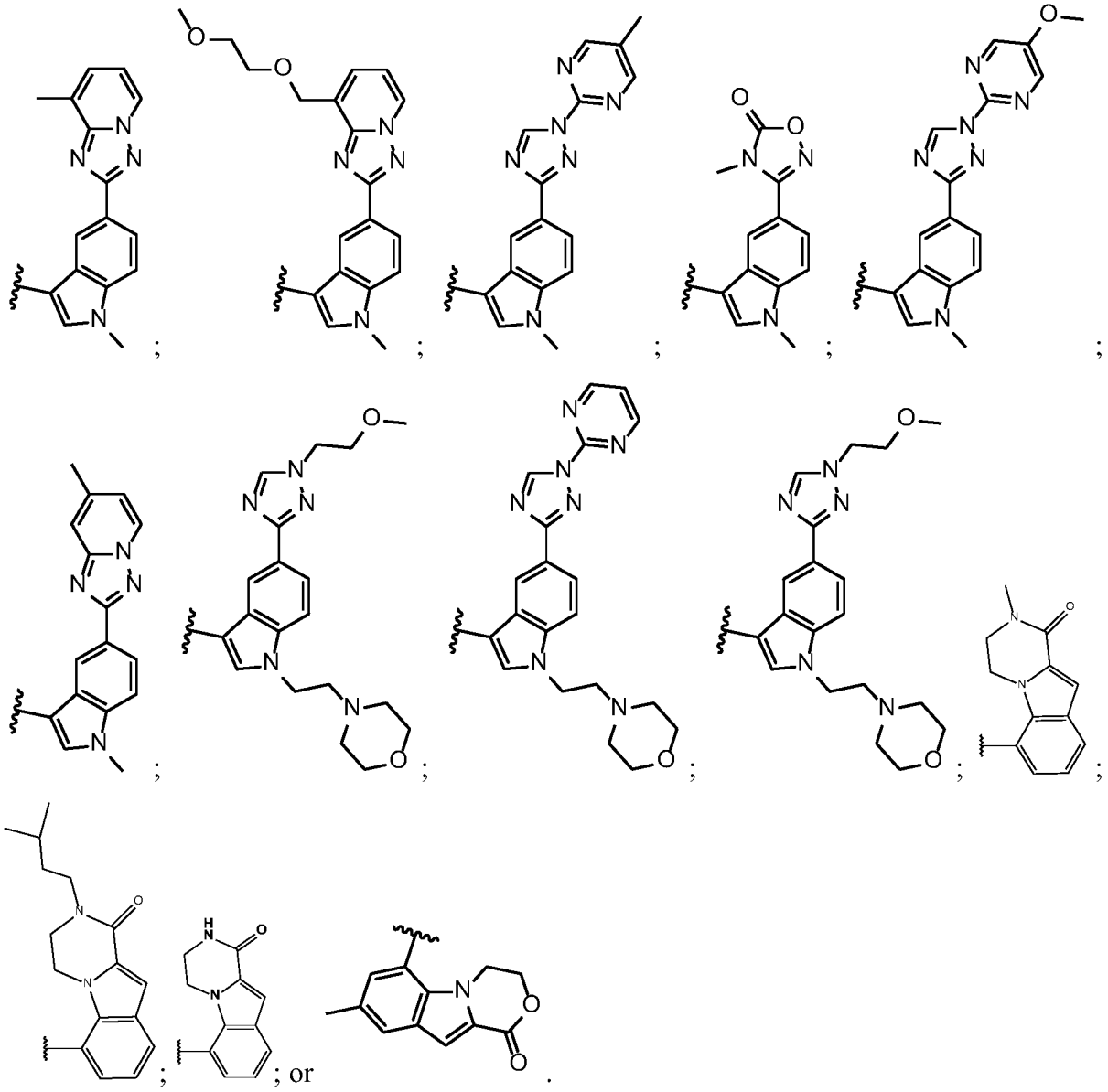
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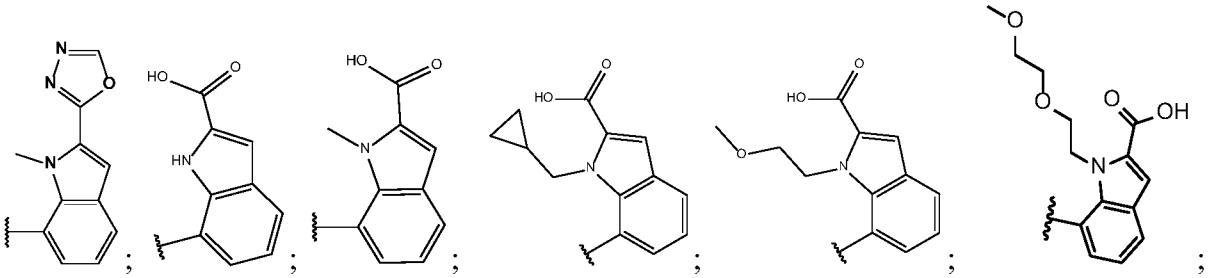
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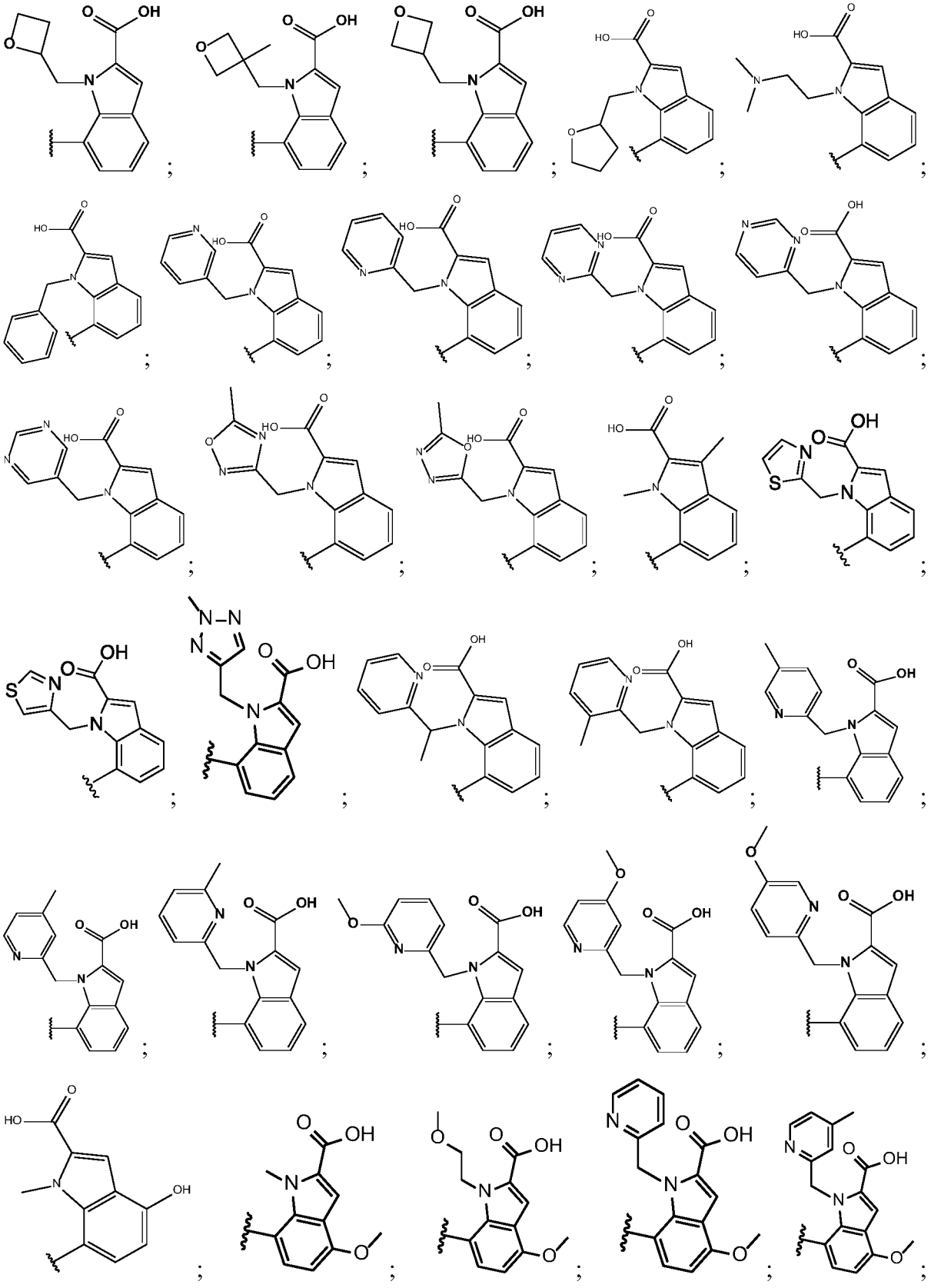
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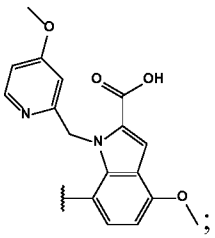
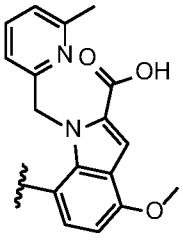
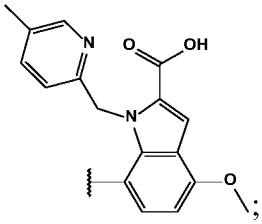
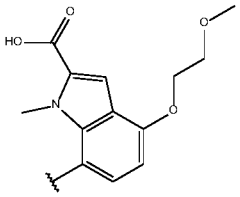
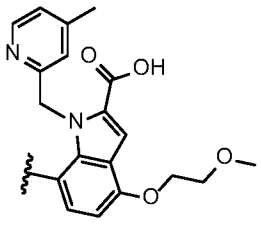
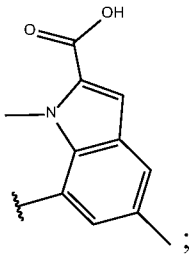
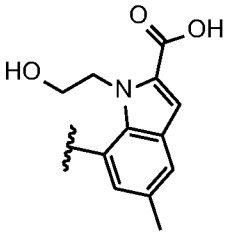
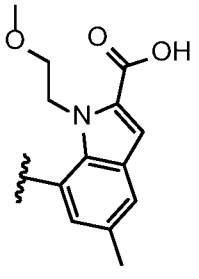
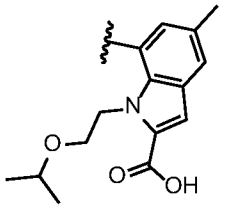
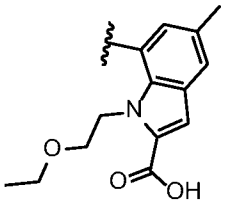
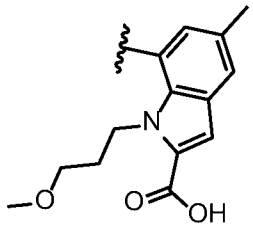
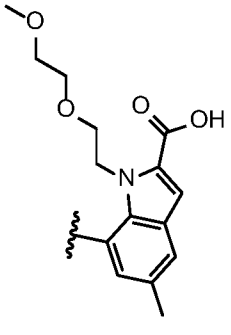
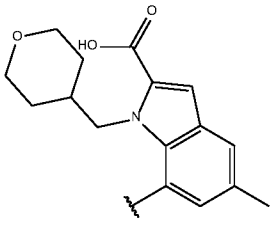
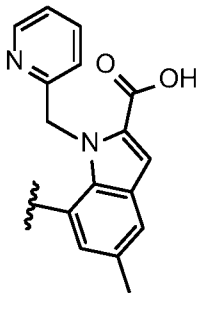
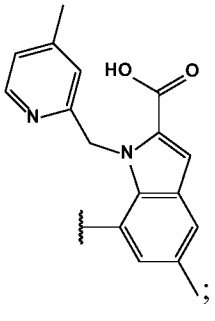
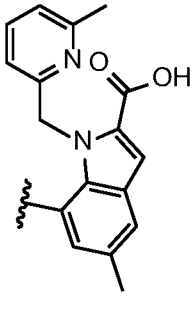
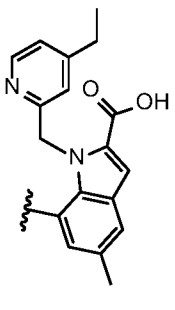
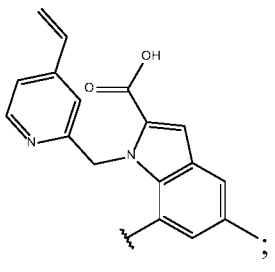
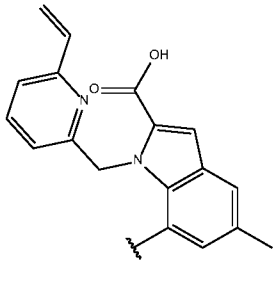
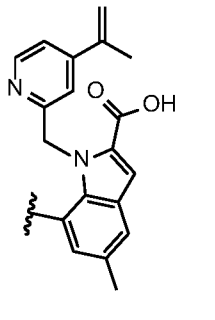
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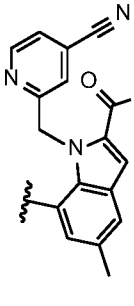
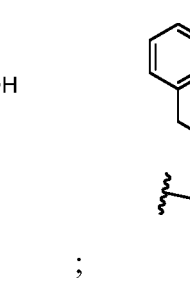
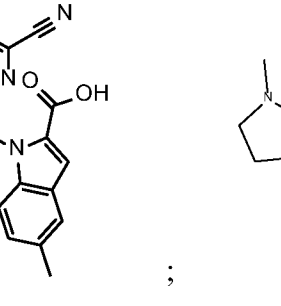
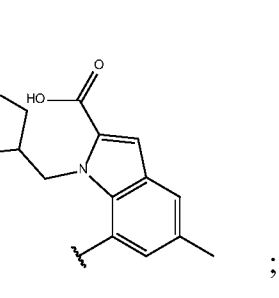


7. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein L^4-R^w is






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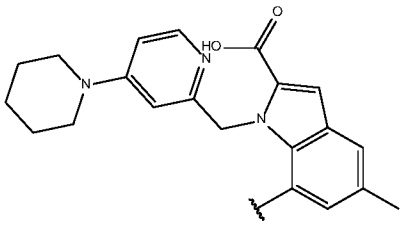
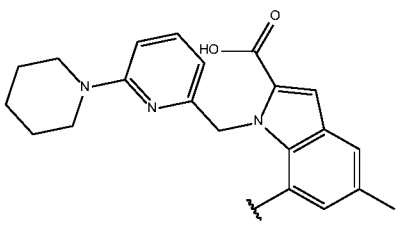
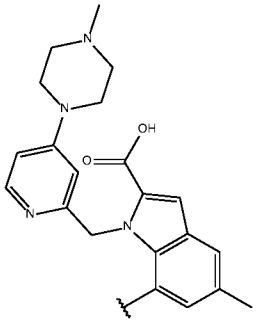
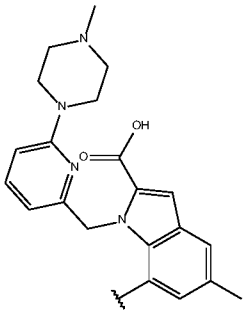
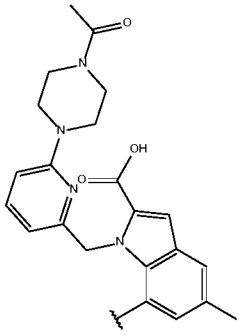
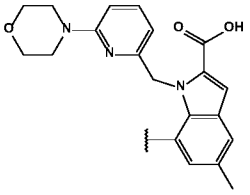
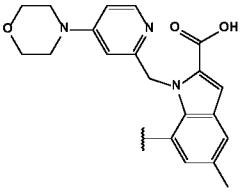
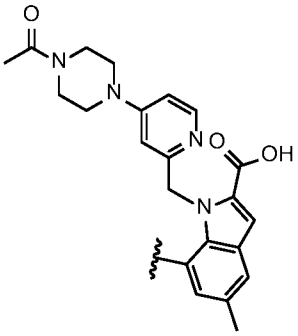
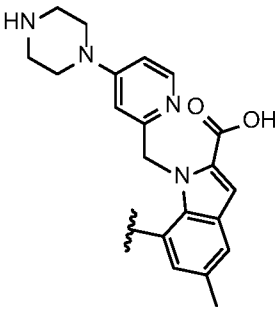
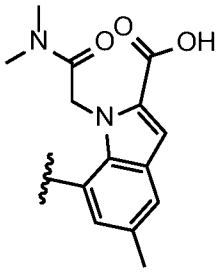
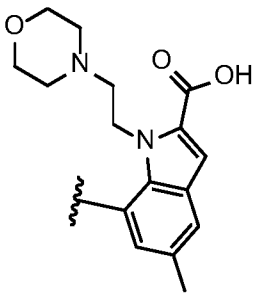
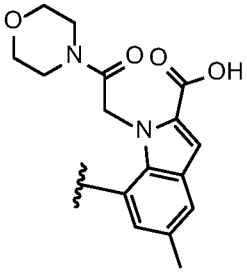
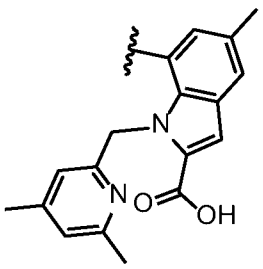
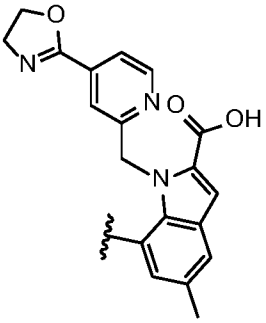
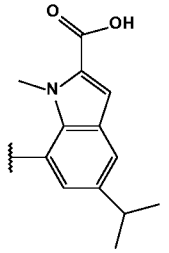
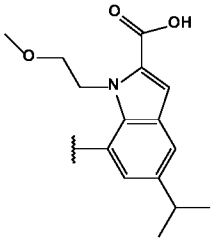
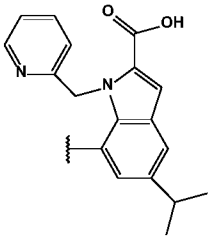
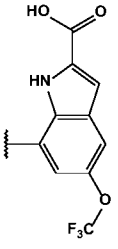
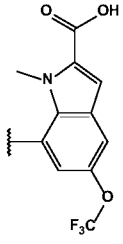
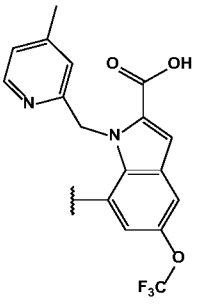
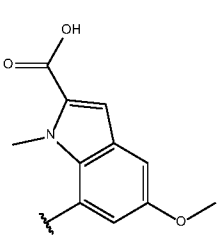
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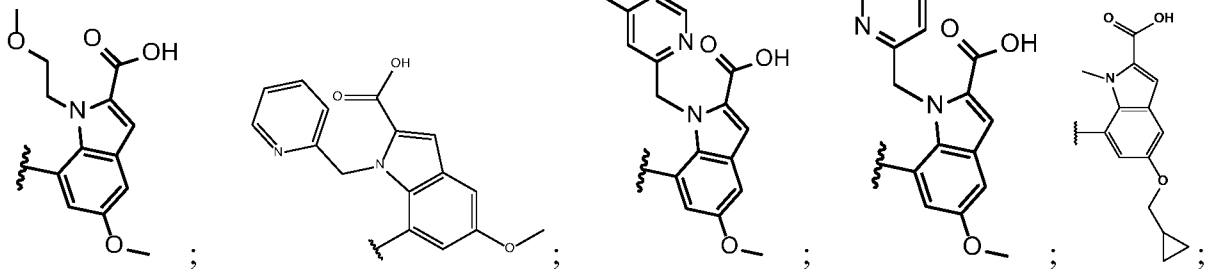
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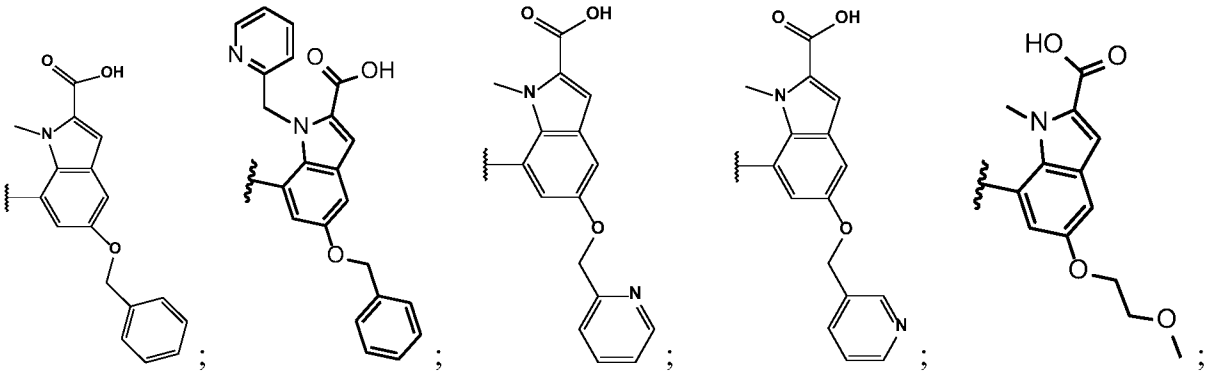
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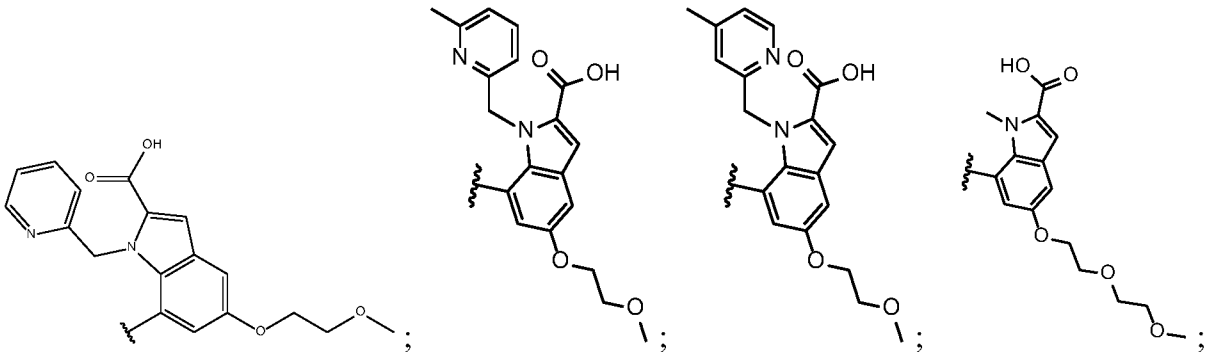
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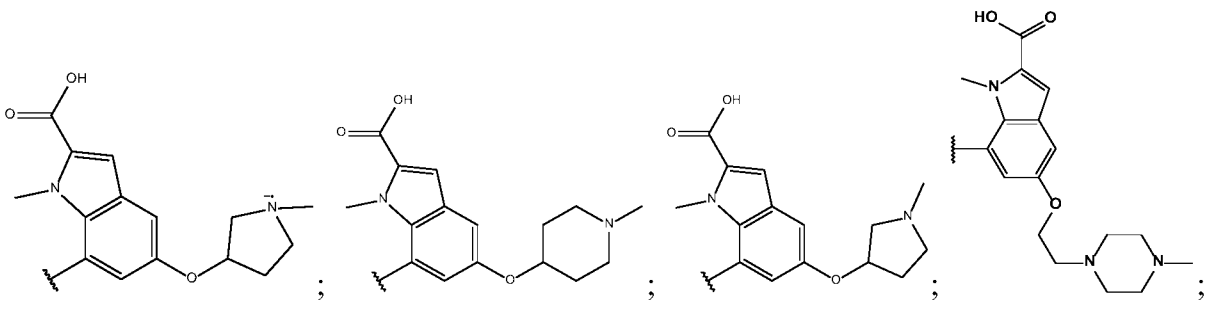
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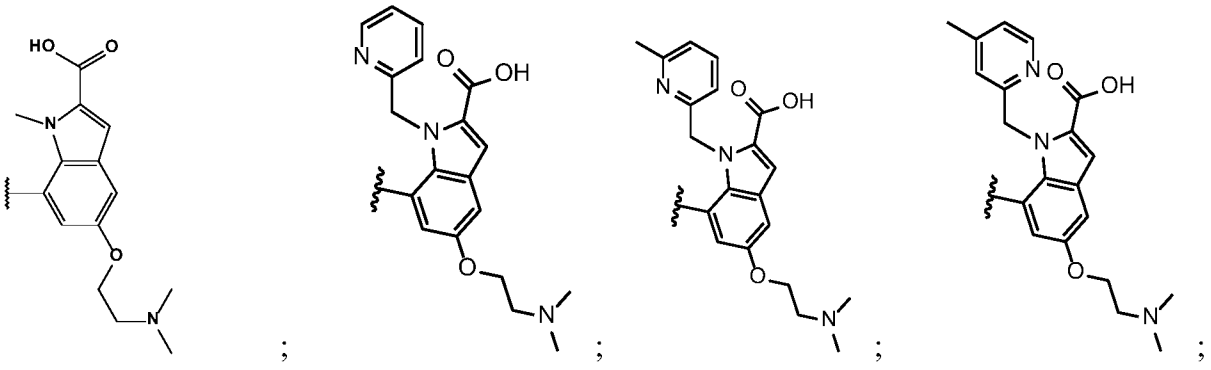

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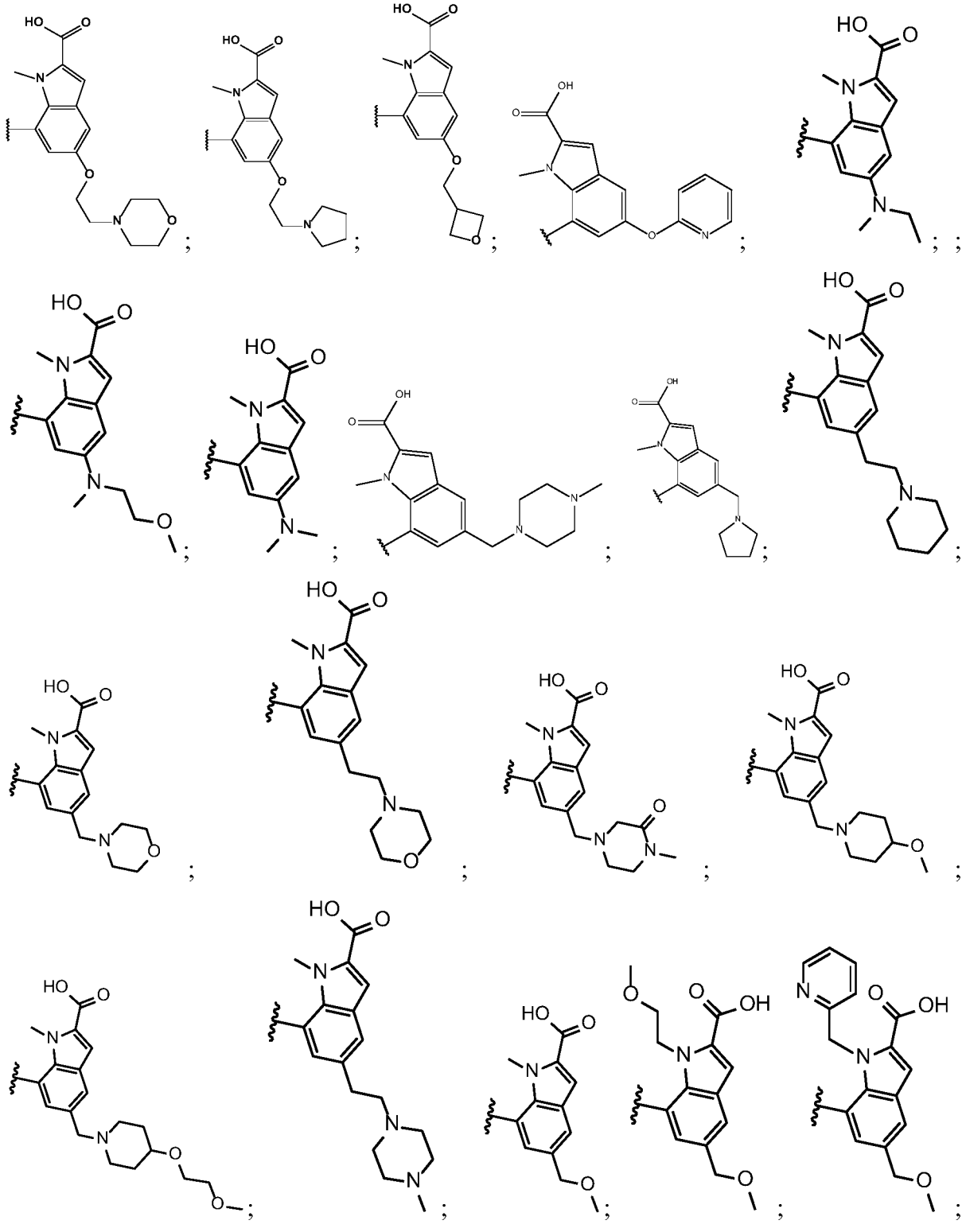


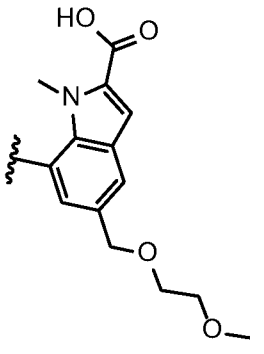
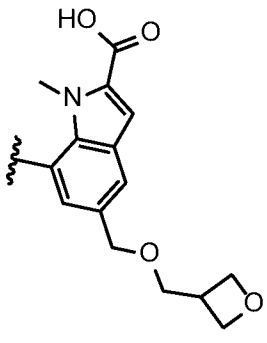
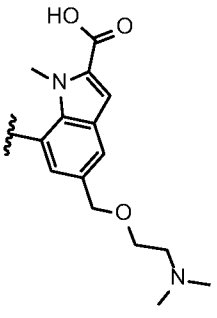
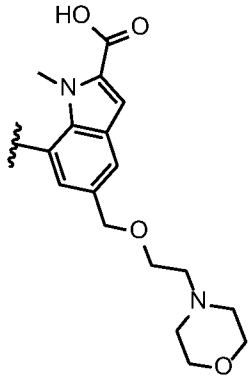
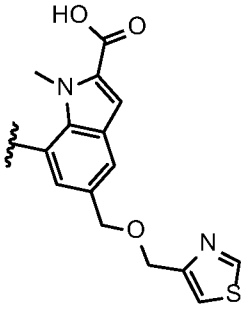
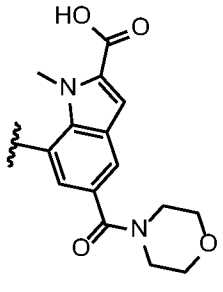
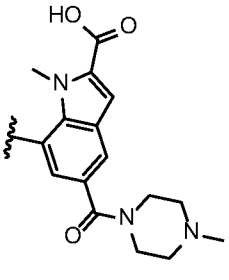
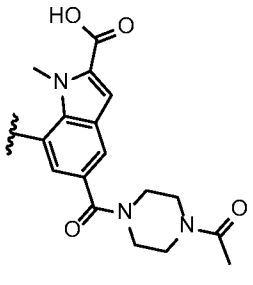
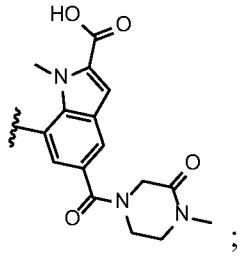
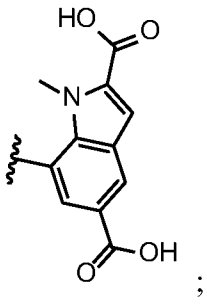
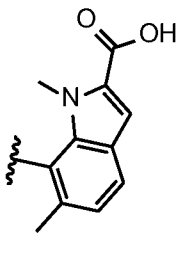
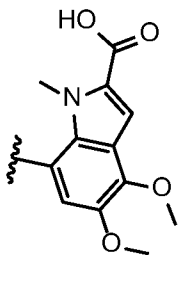
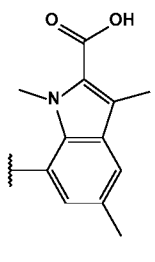
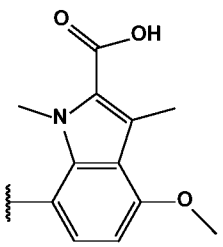
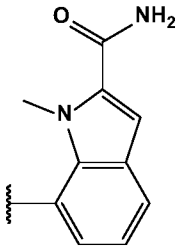
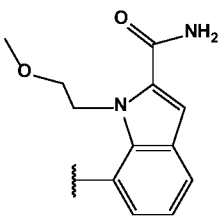
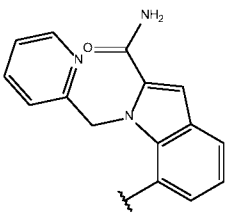
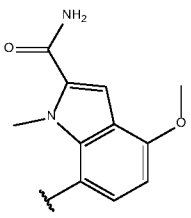
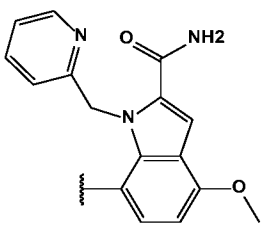
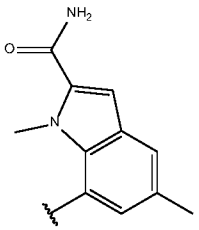
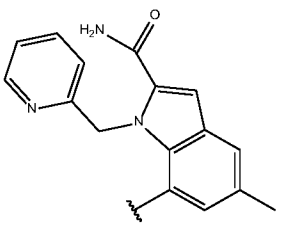
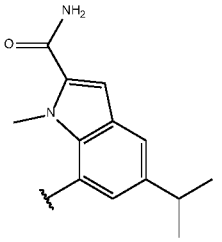
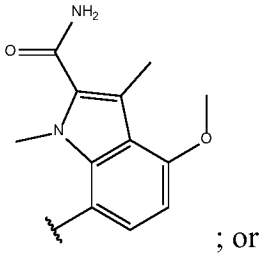
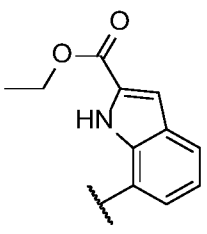




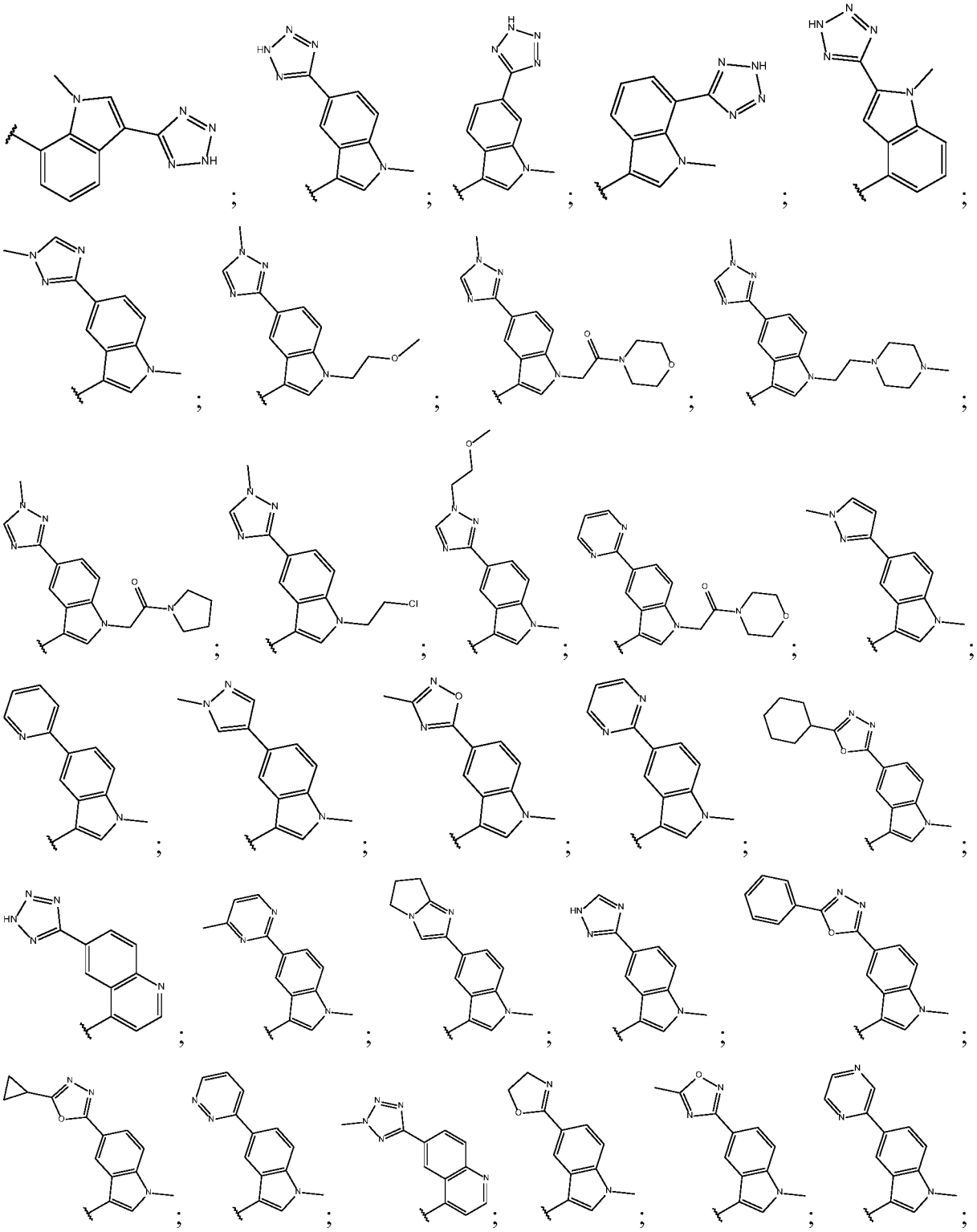


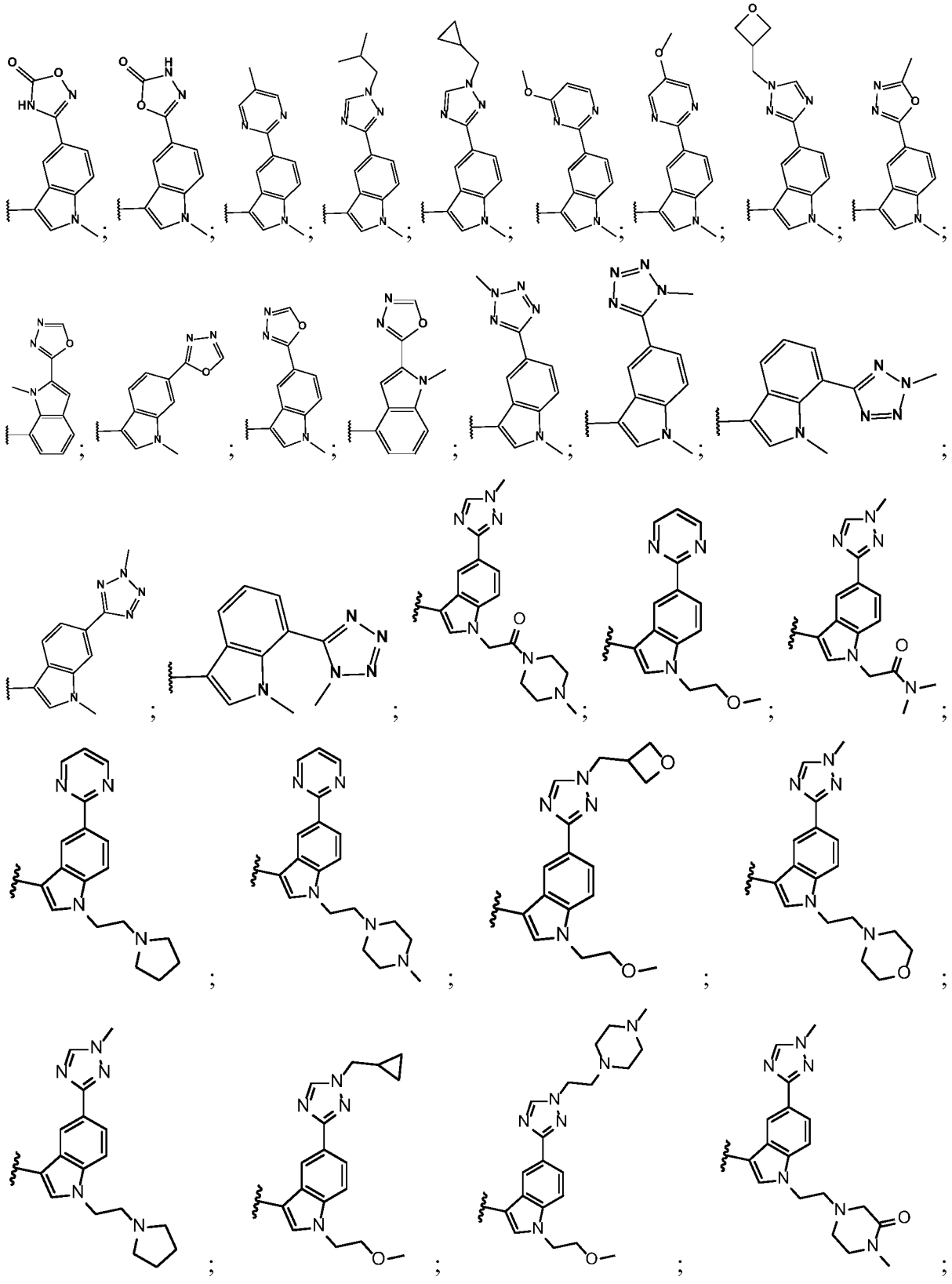


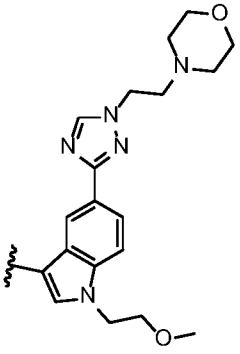
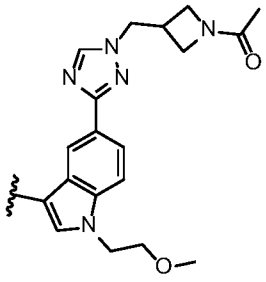
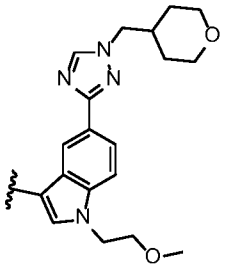
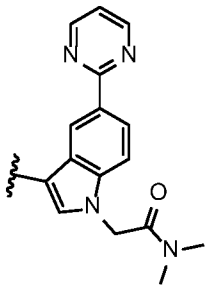
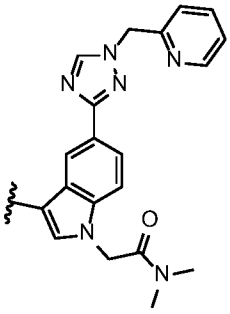
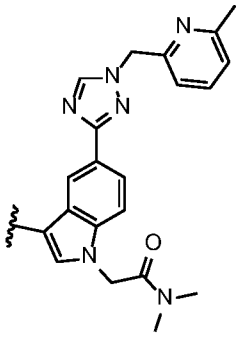
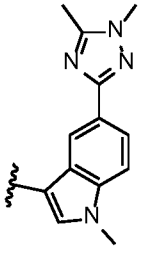
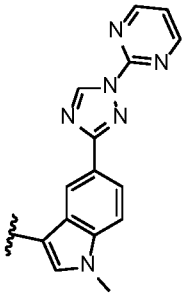
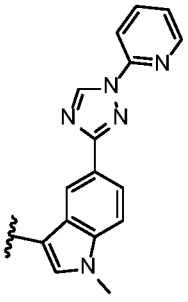
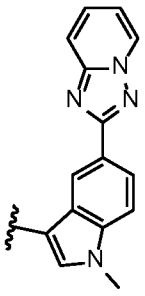
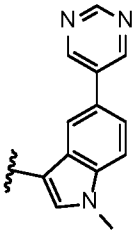
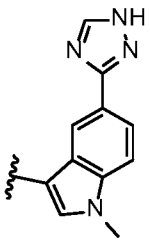
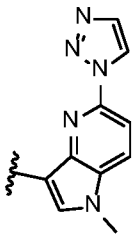
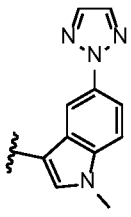
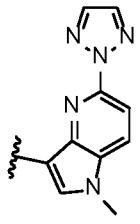
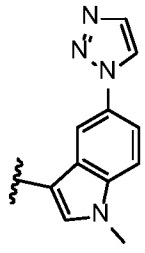
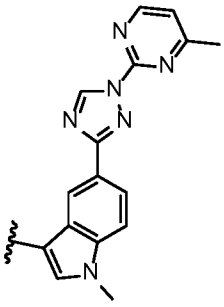
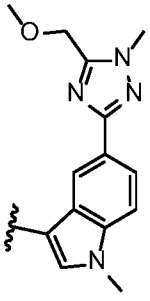
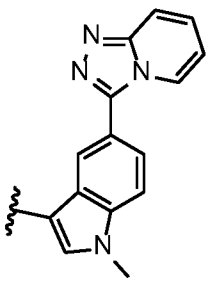
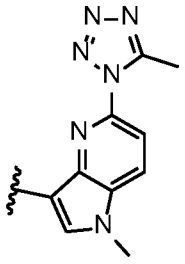
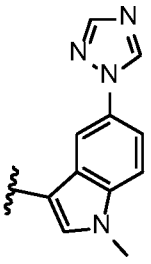
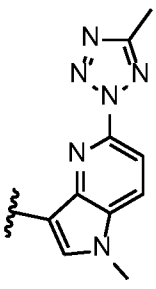


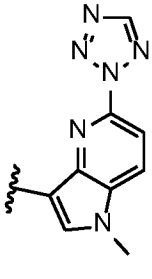
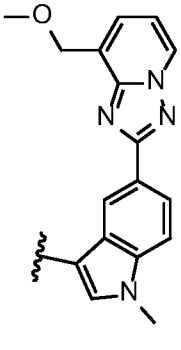
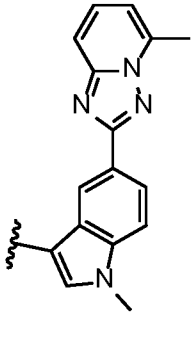
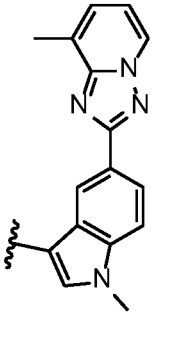

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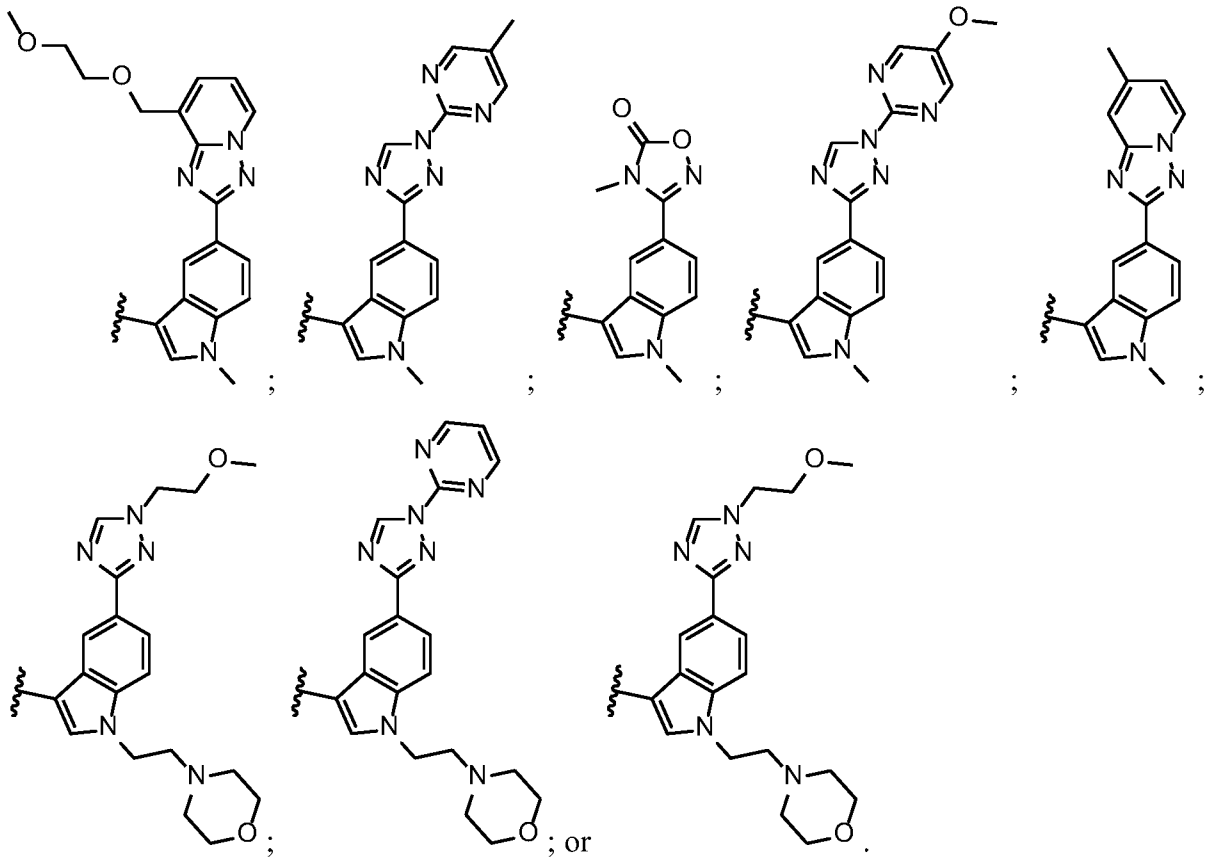
8. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein L^4-R^W is



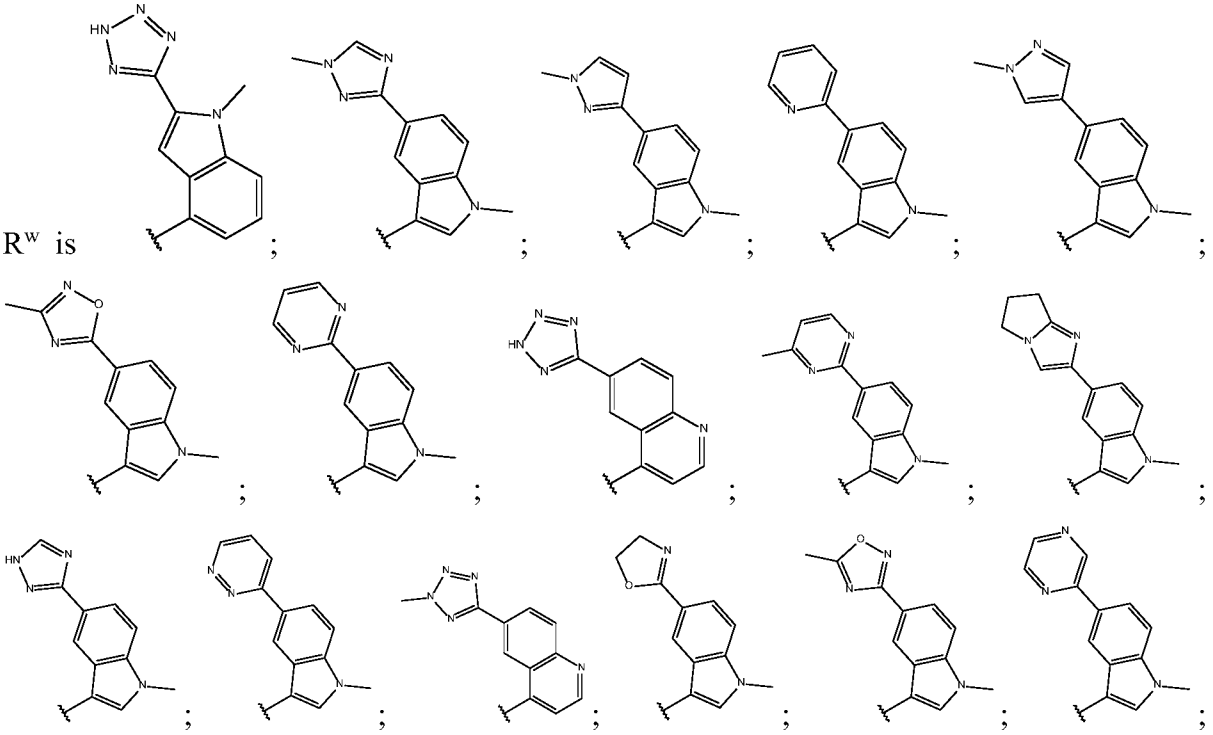


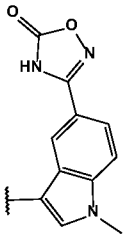
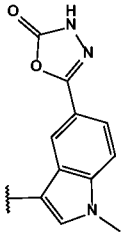
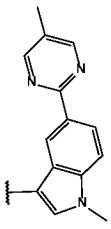
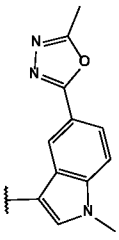
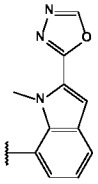
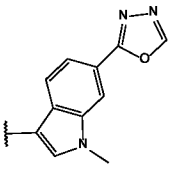
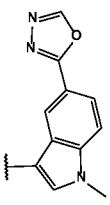
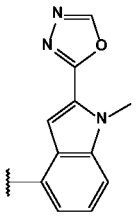
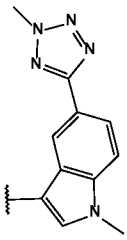
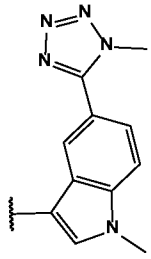
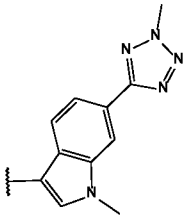
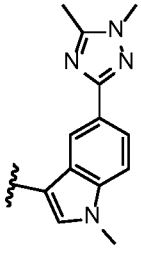
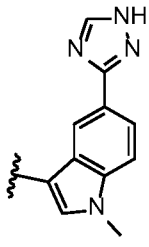
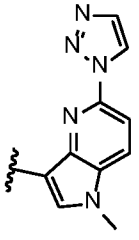
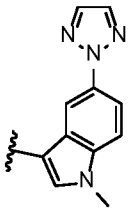
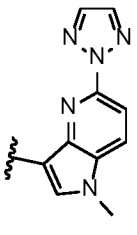
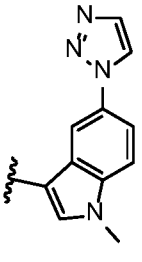
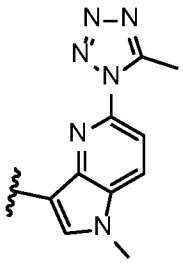
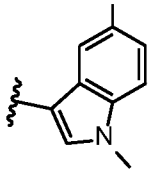
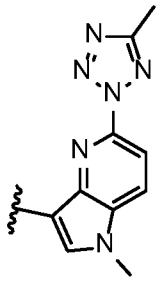
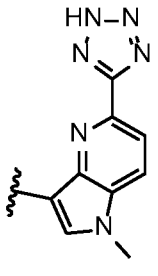
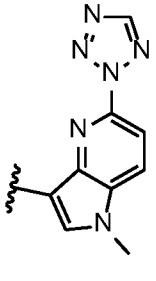

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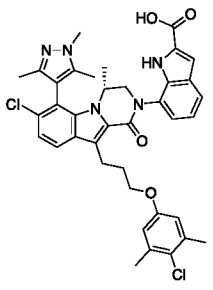
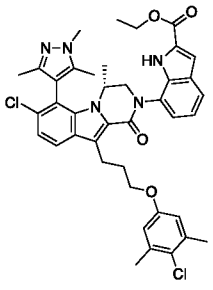
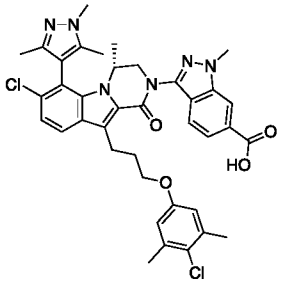
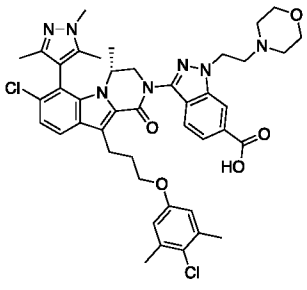
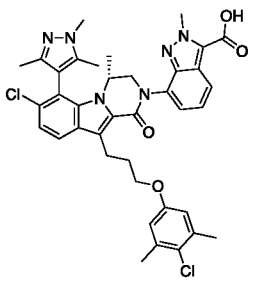
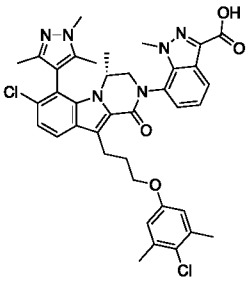
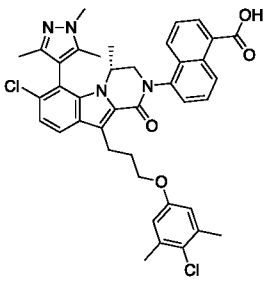
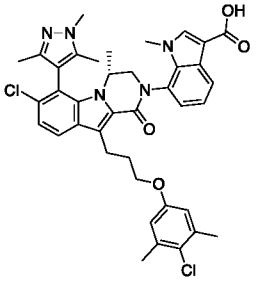


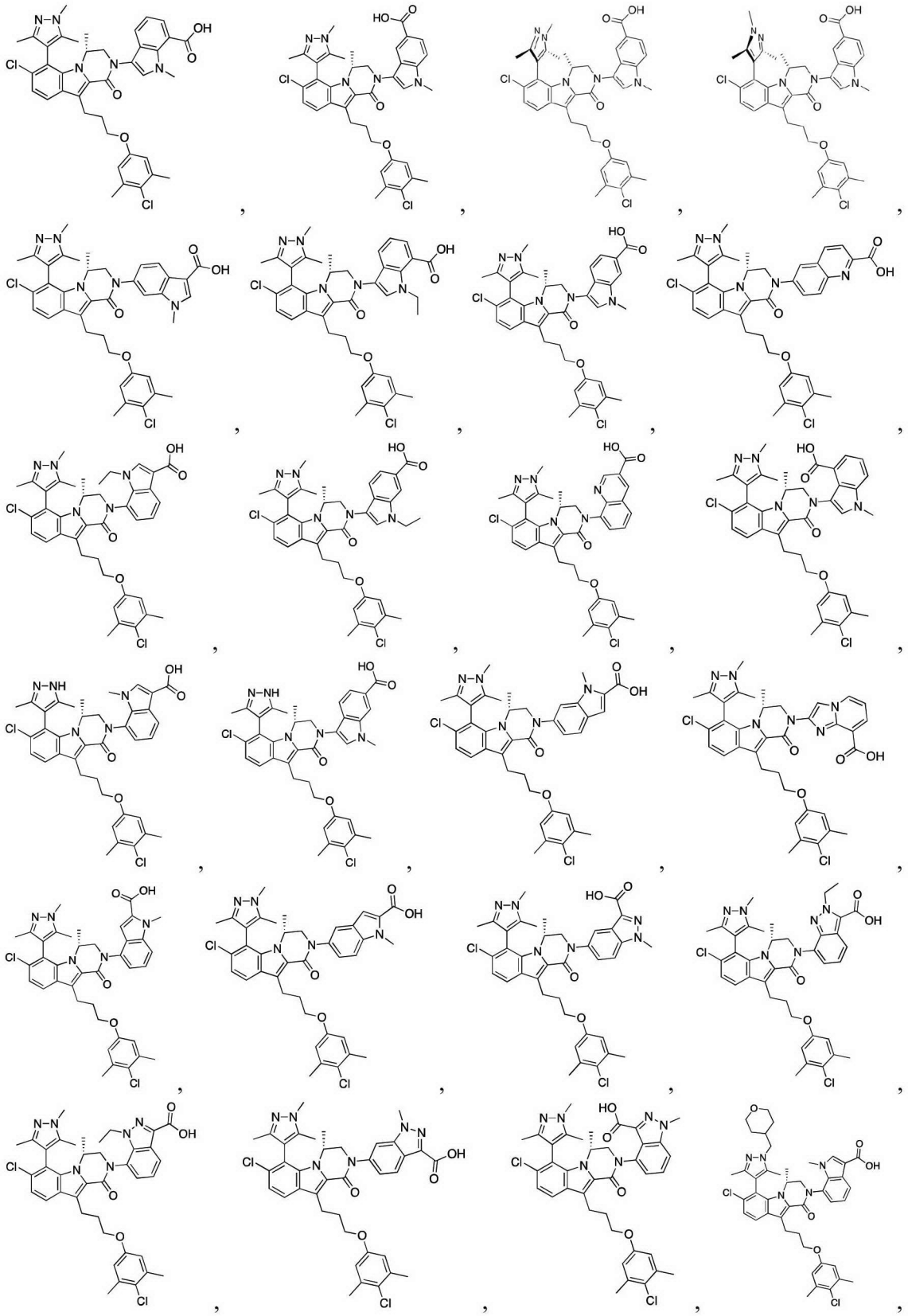
9. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein L^4-R^W is

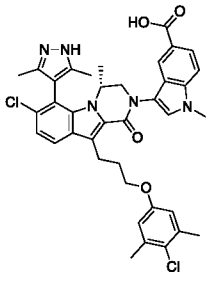
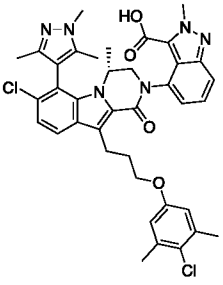
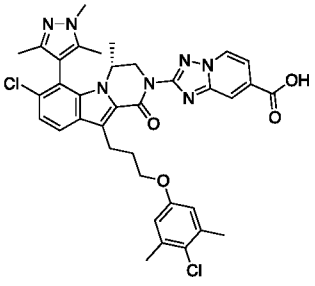
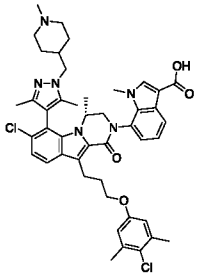
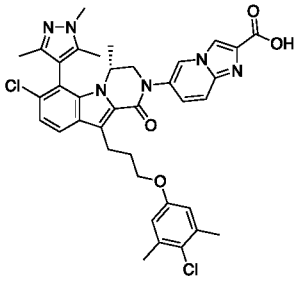
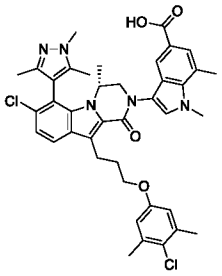
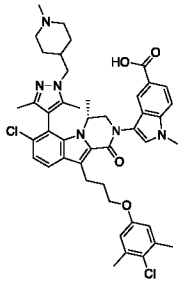
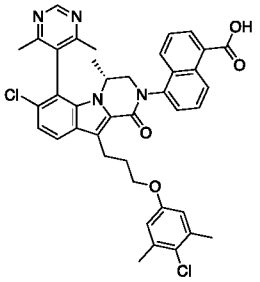
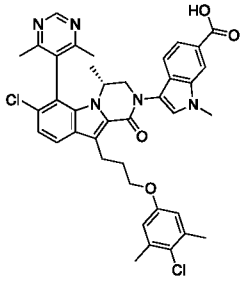
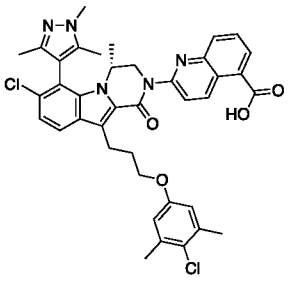
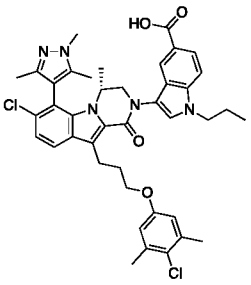
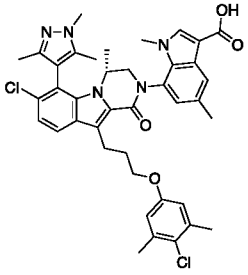
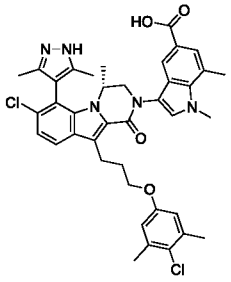
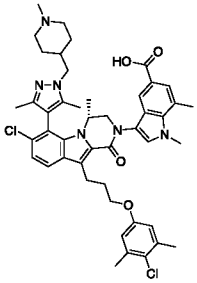
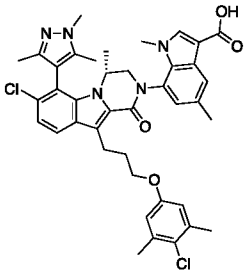
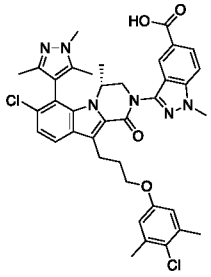
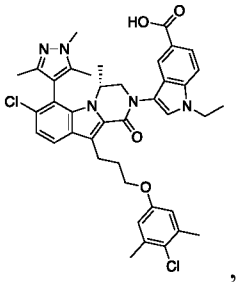
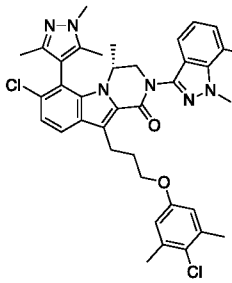
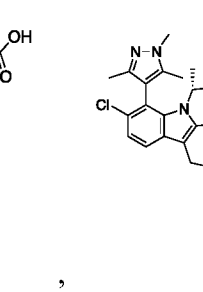
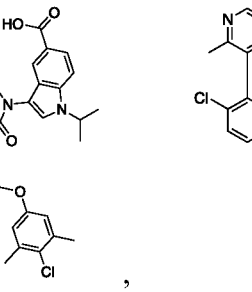
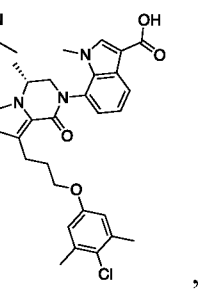
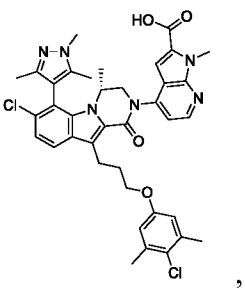
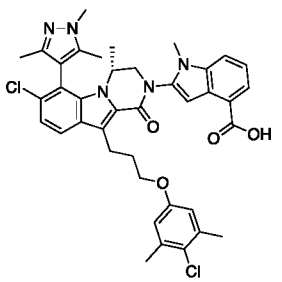
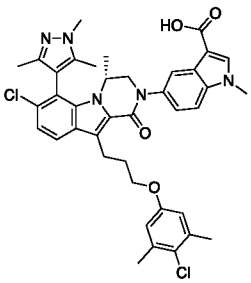
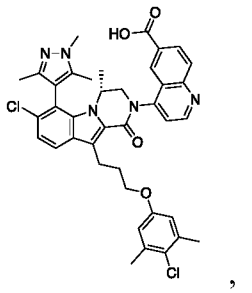
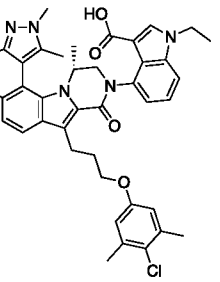



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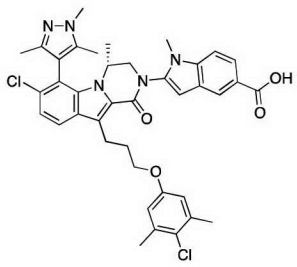
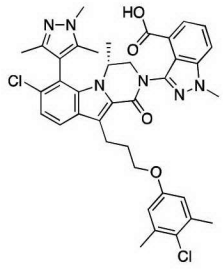
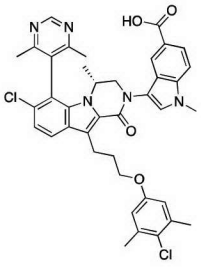
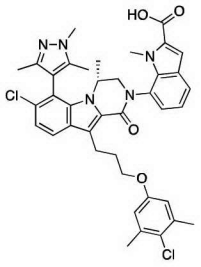
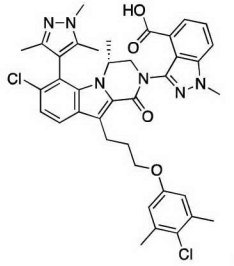
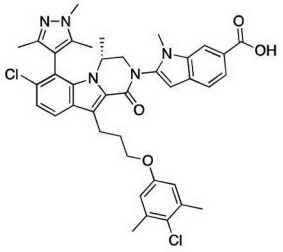
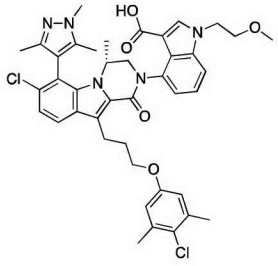
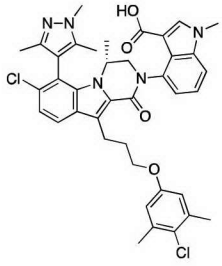
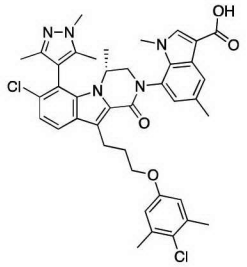
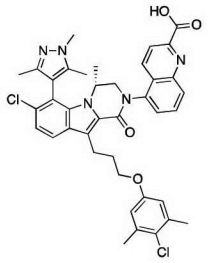
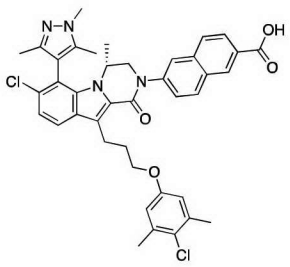
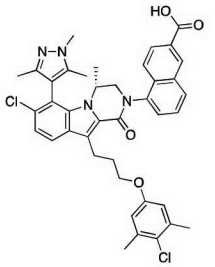
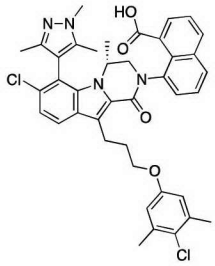
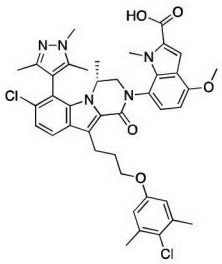
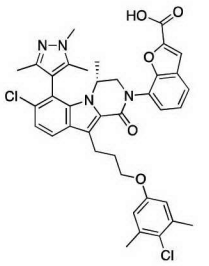
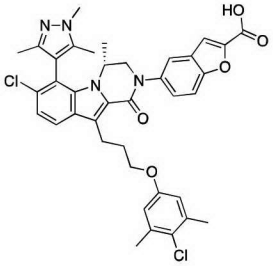
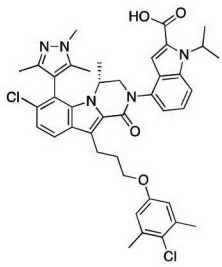
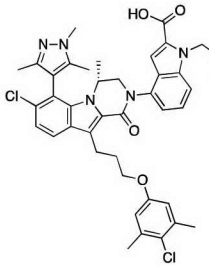
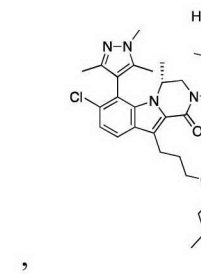
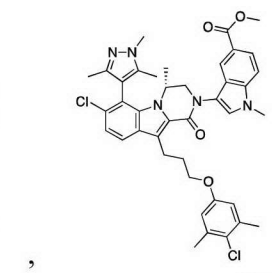
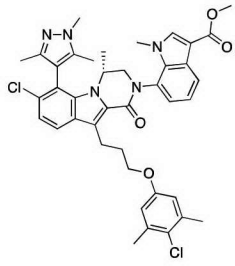
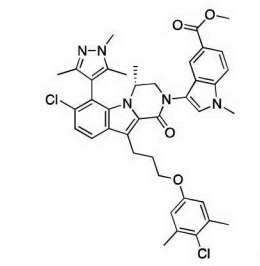
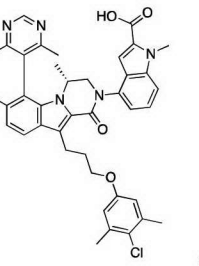
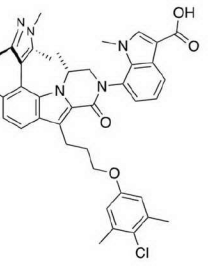

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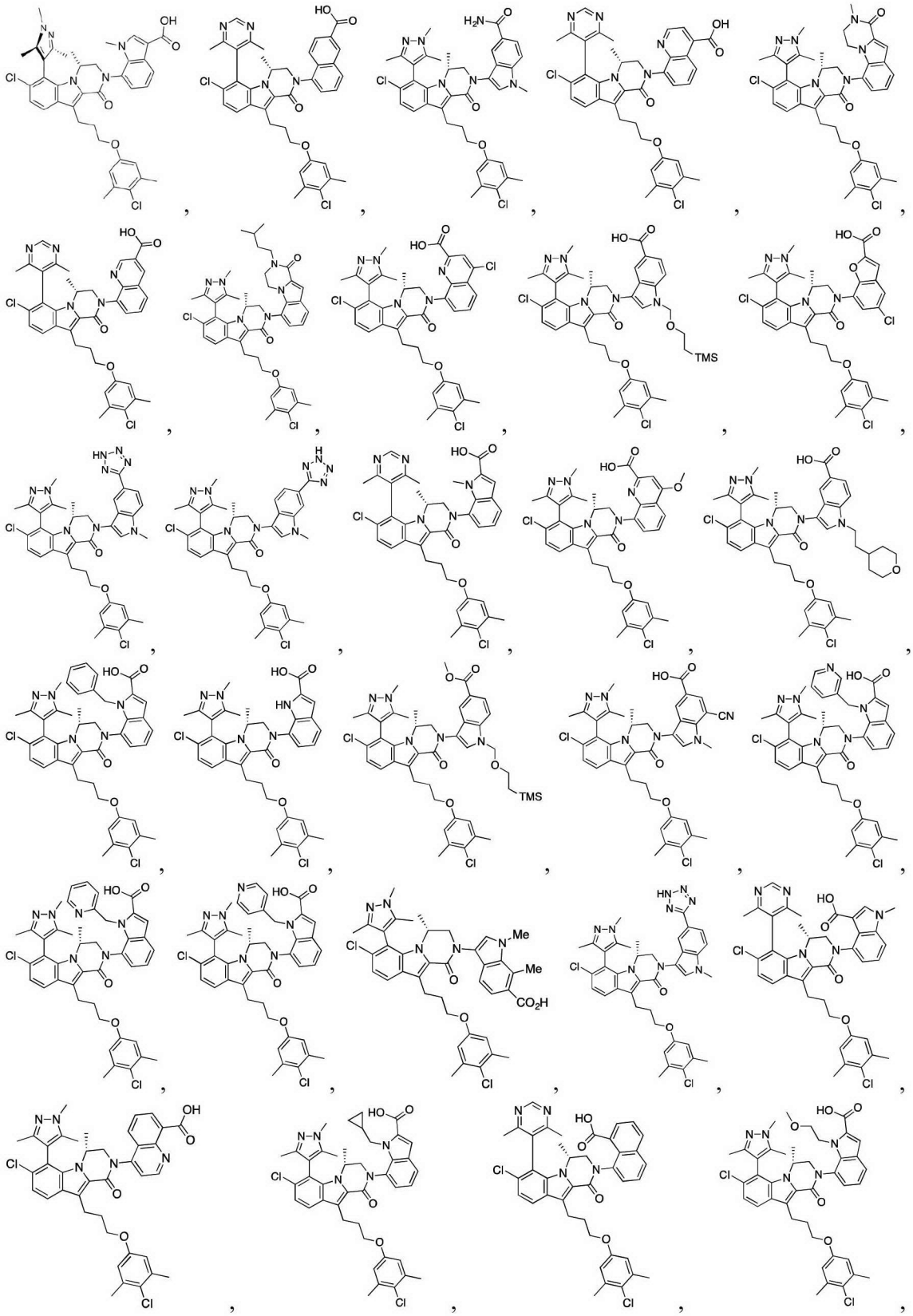

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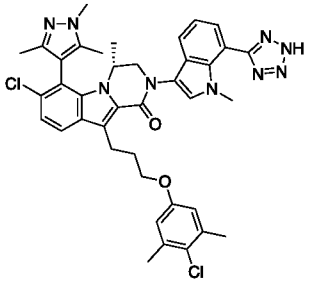
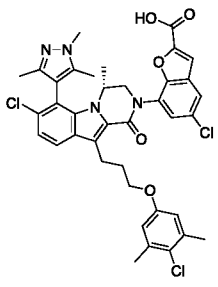
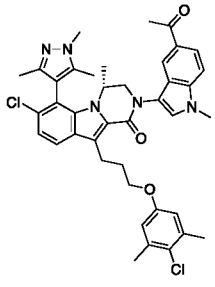
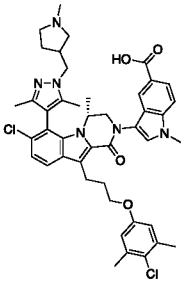
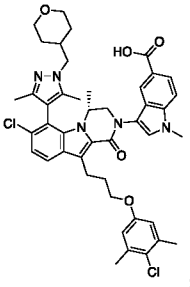
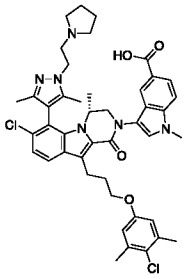
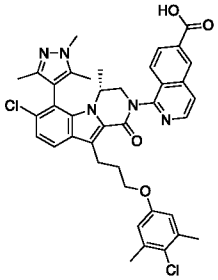
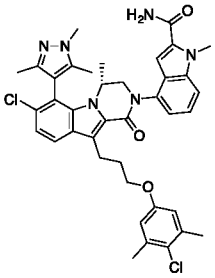
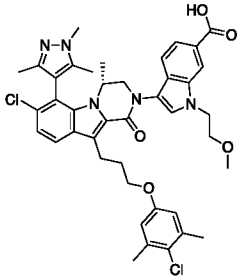
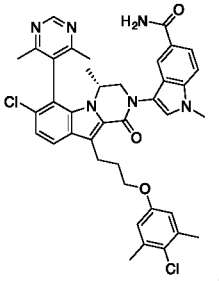
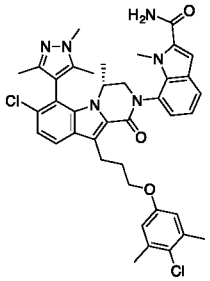
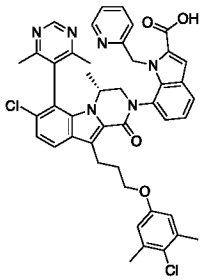
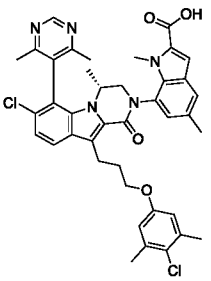
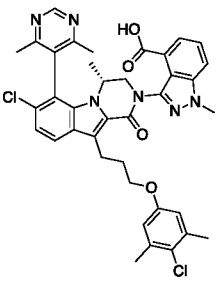
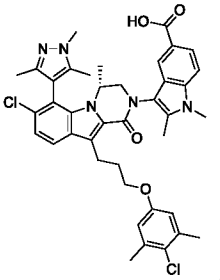
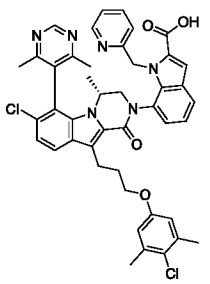
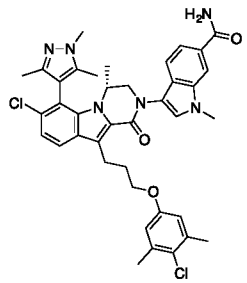
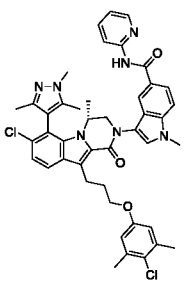
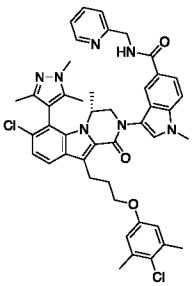
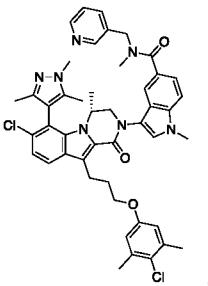
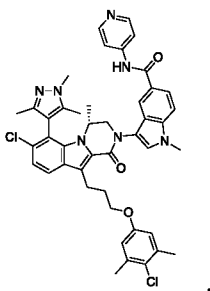
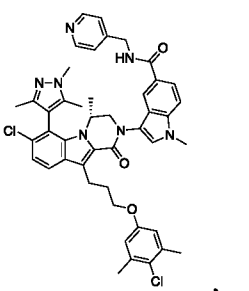
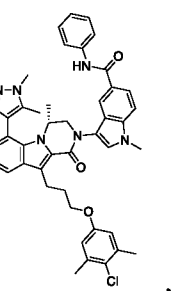
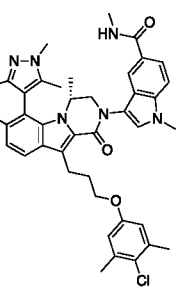
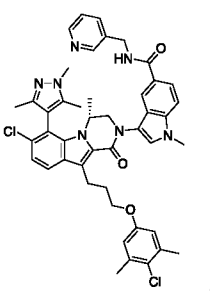
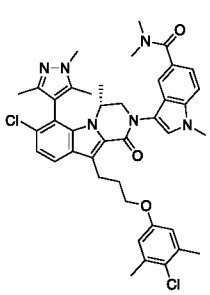
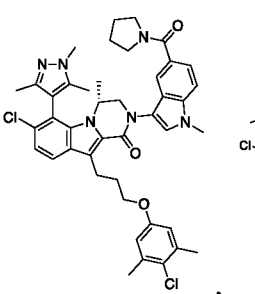
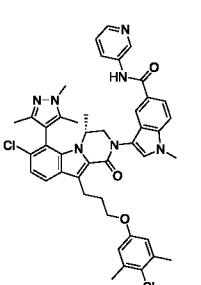
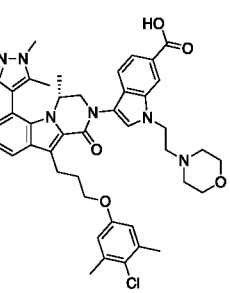
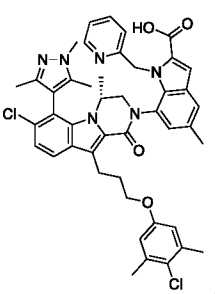
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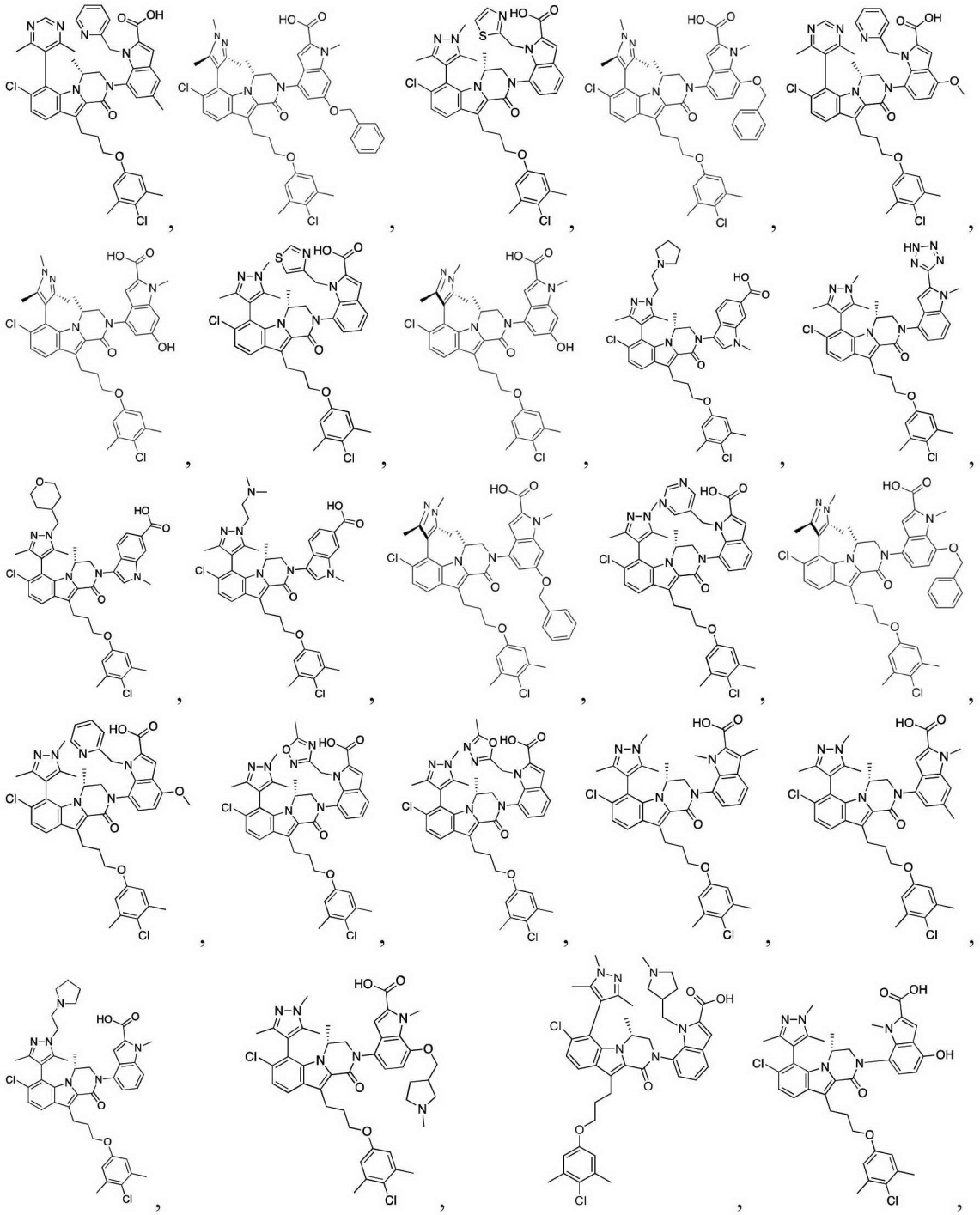
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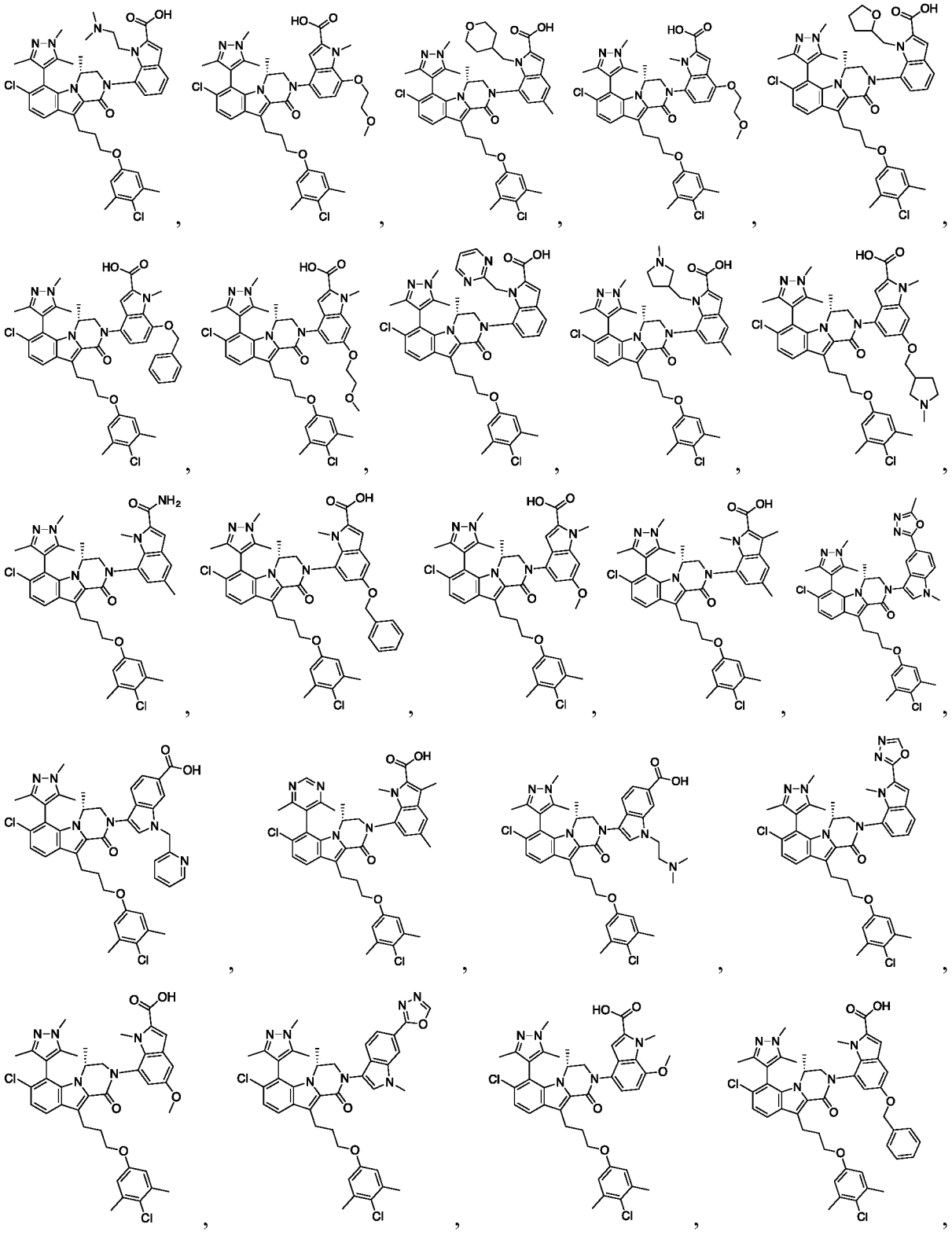
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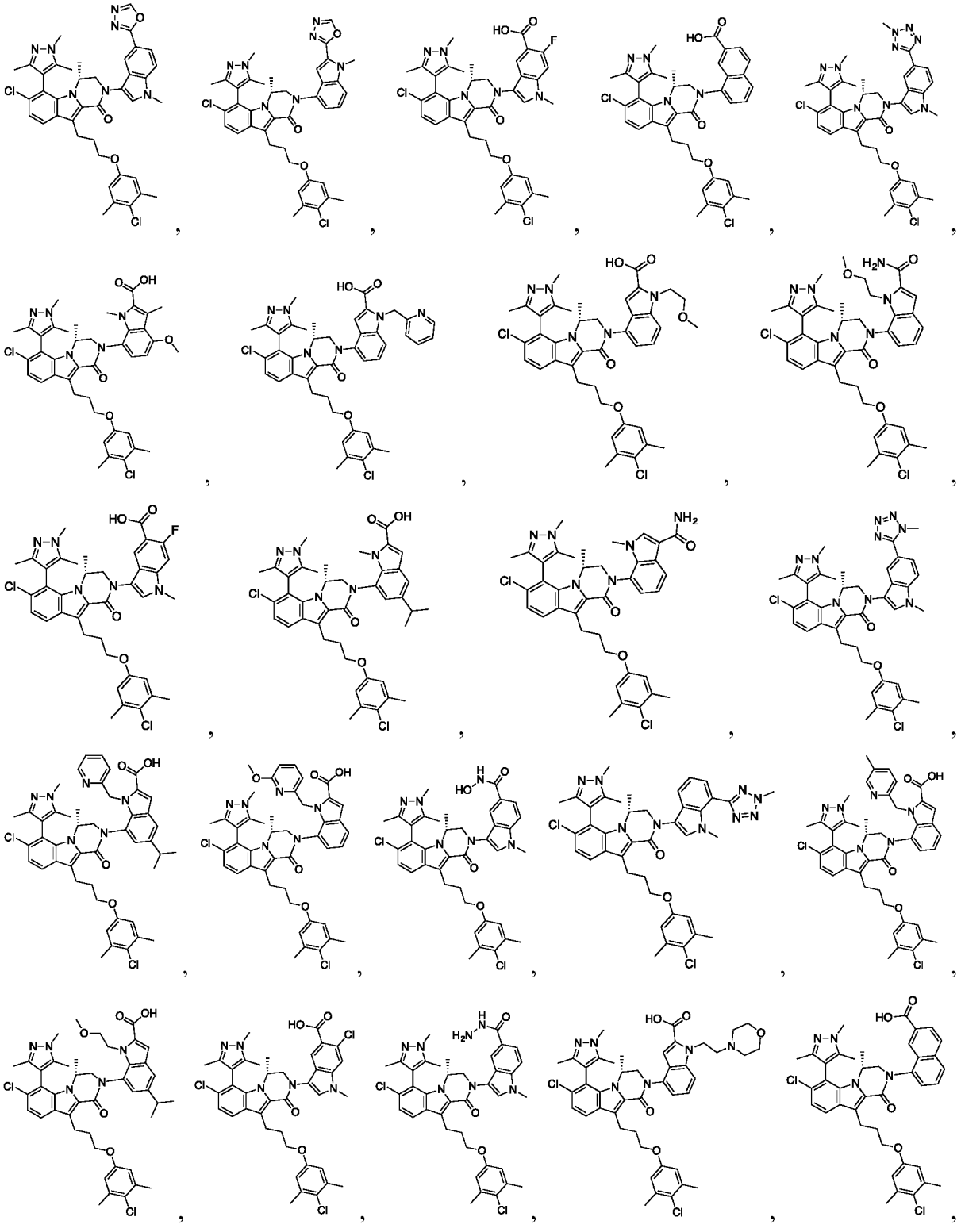
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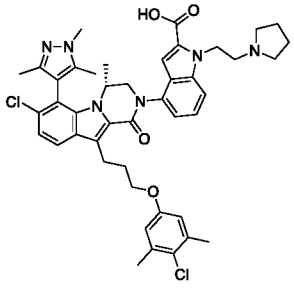
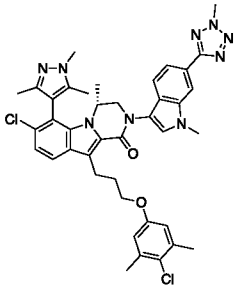
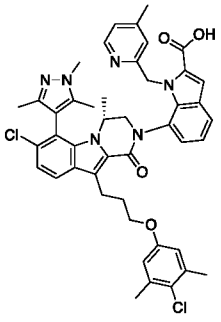
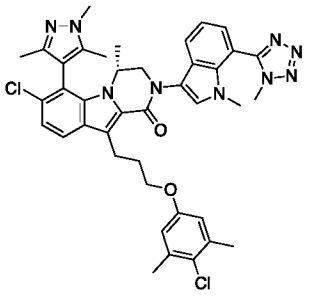
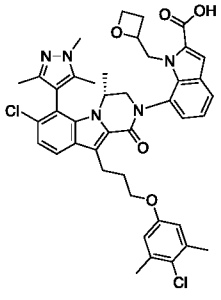
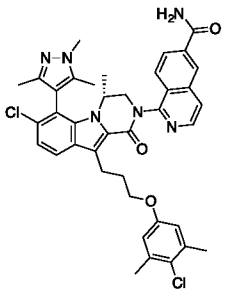
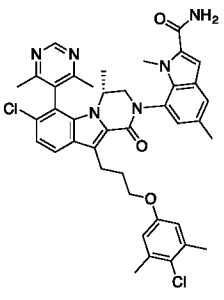
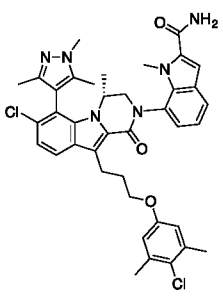
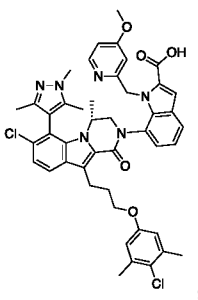
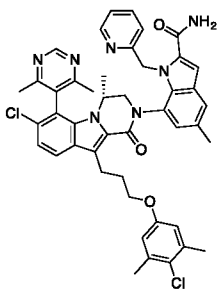
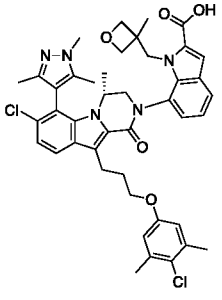
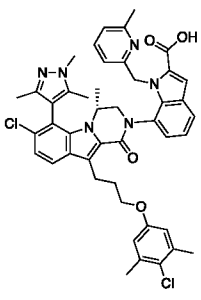
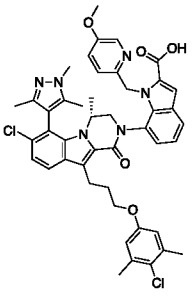
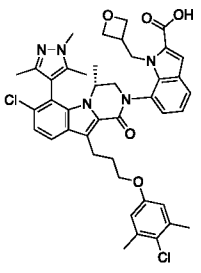
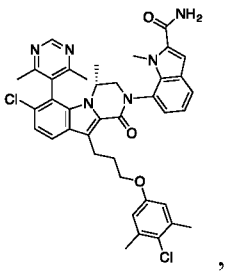
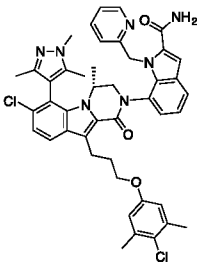
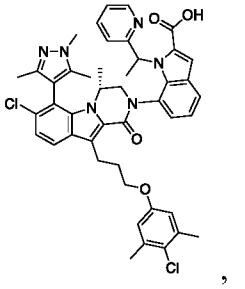
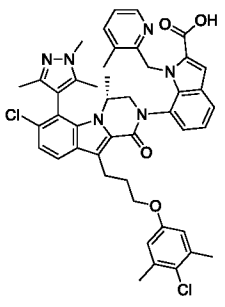
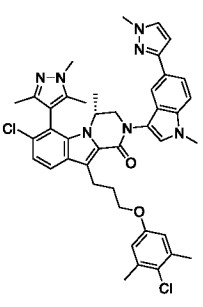
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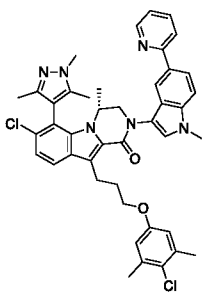
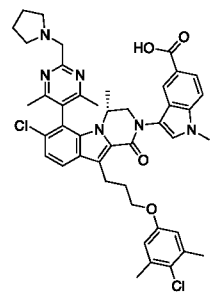
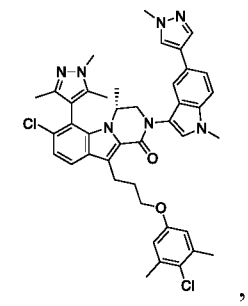
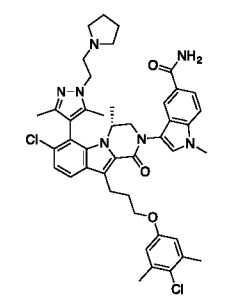
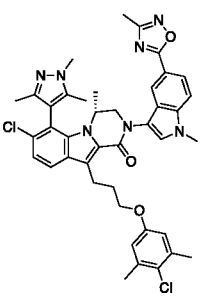

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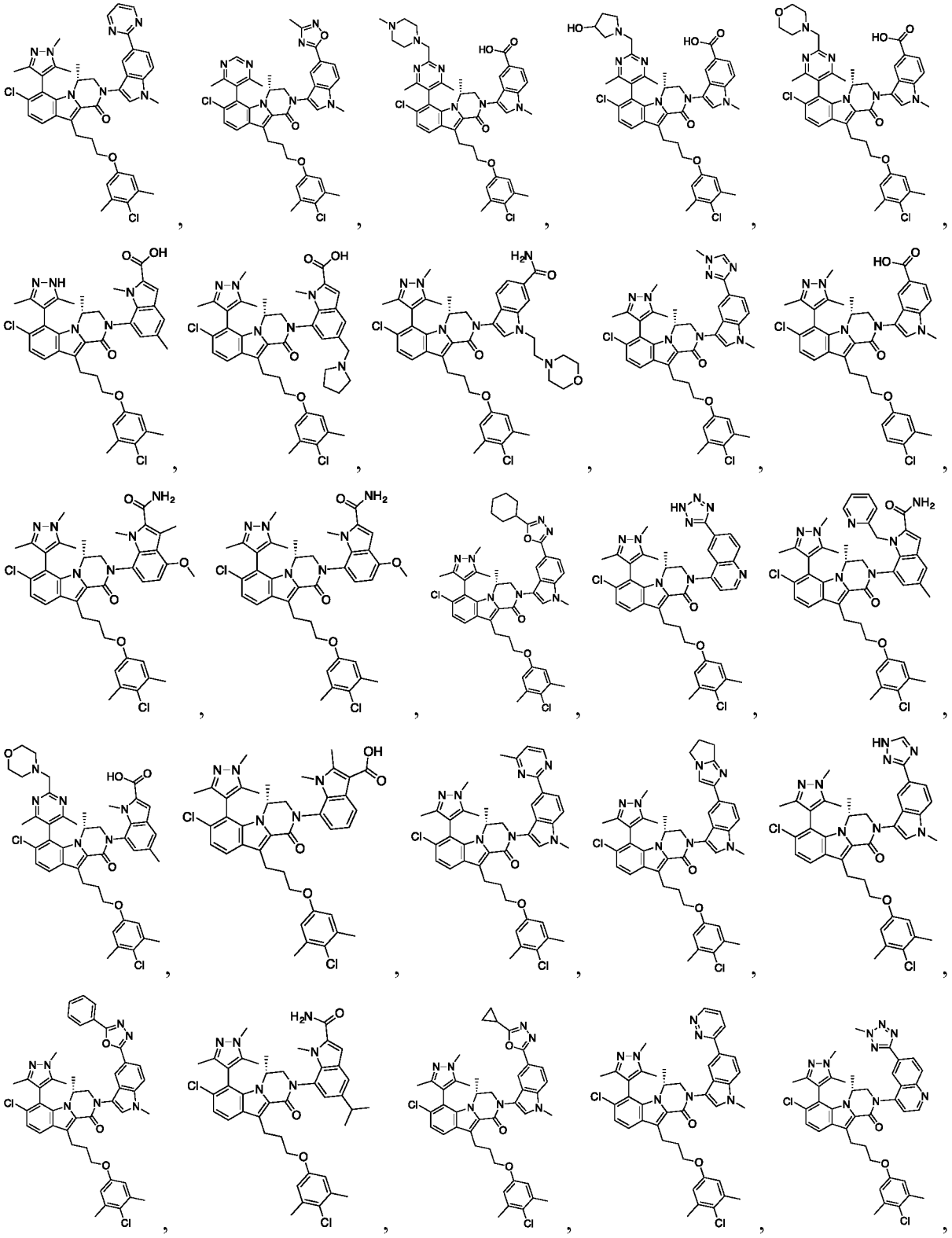
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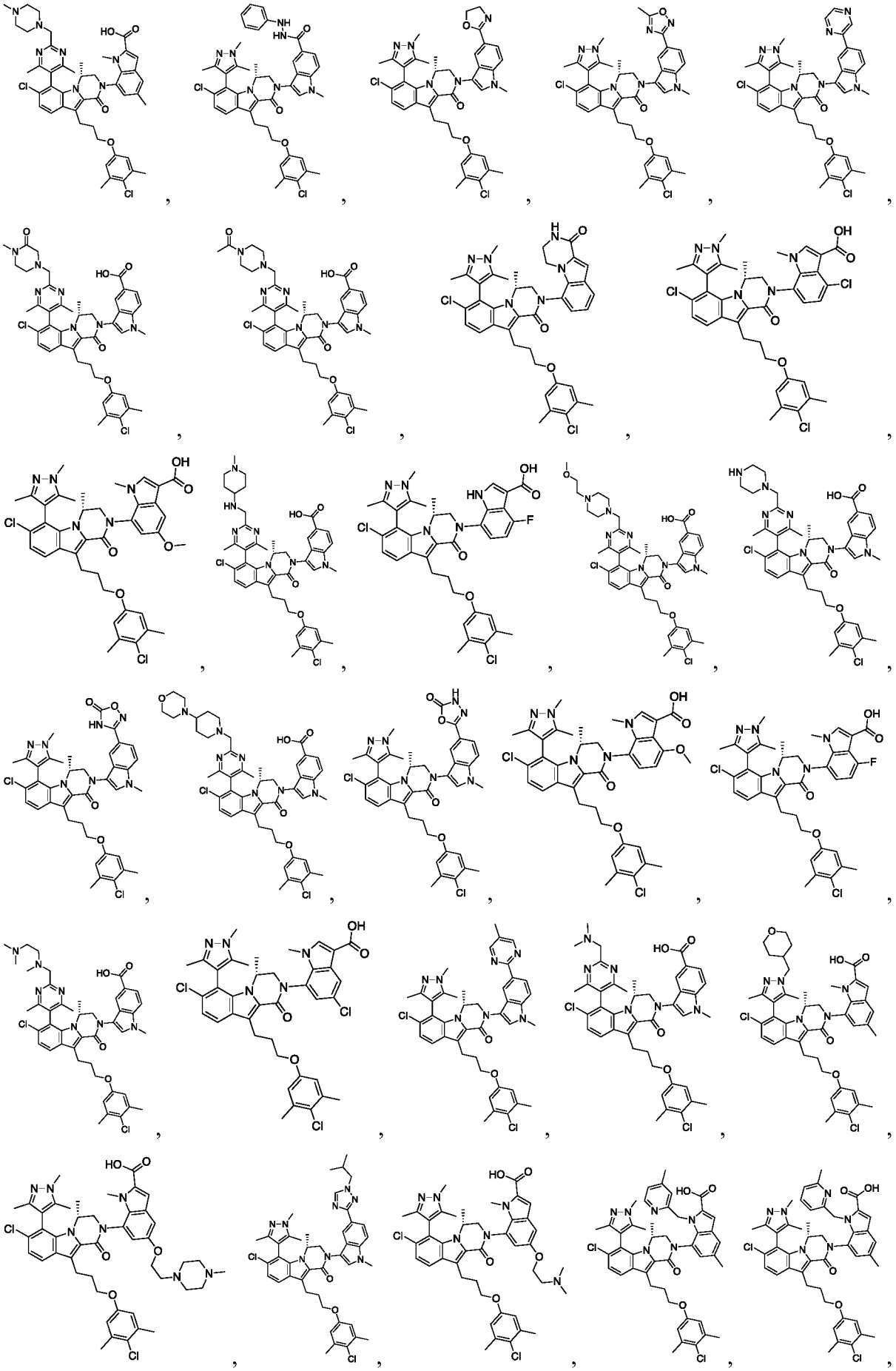
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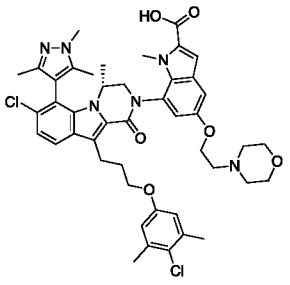
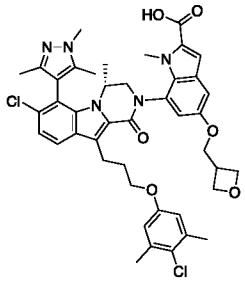
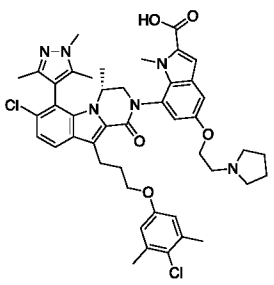
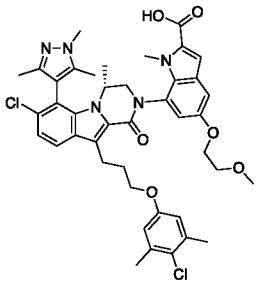
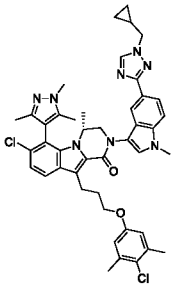
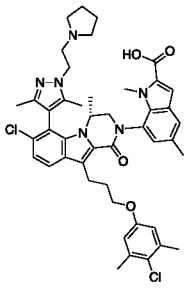
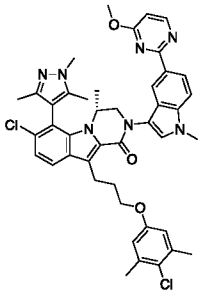
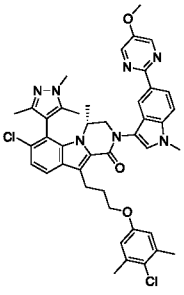
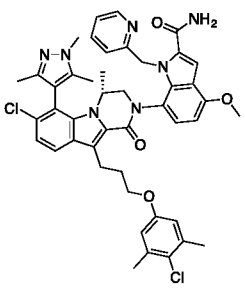
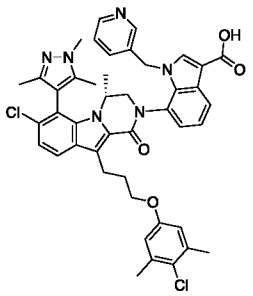
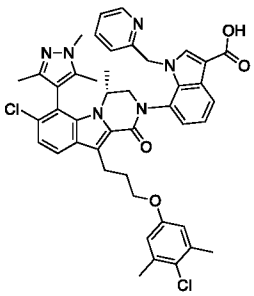
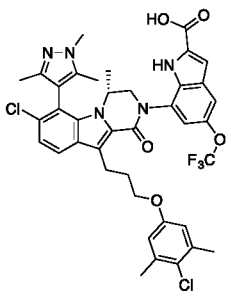
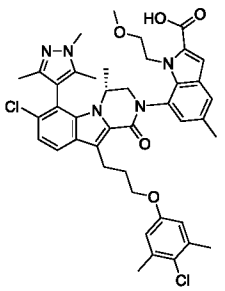
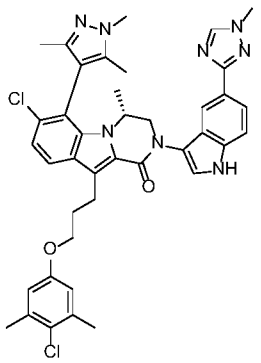
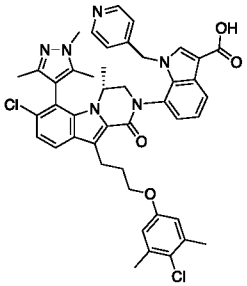
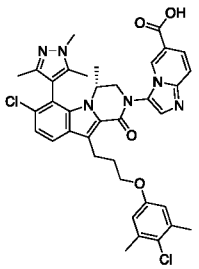
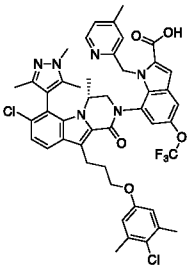
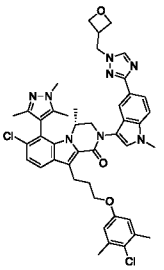
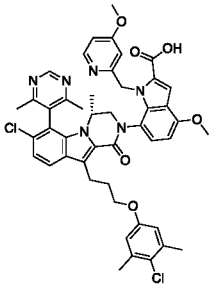
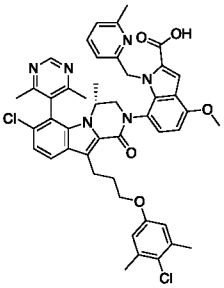
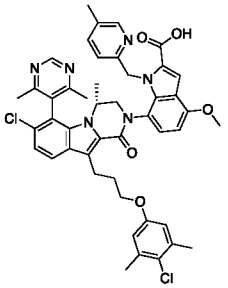
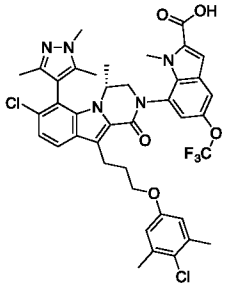
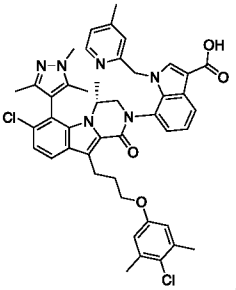
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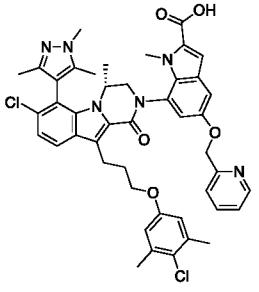
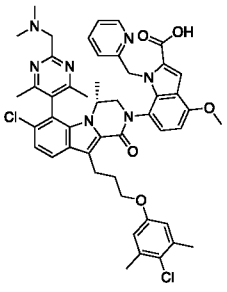
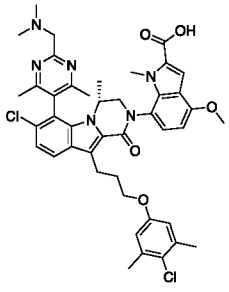
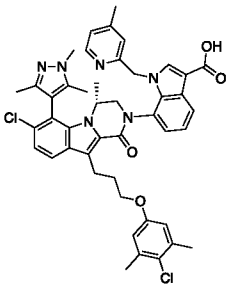
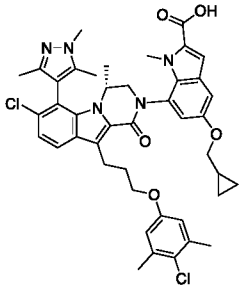
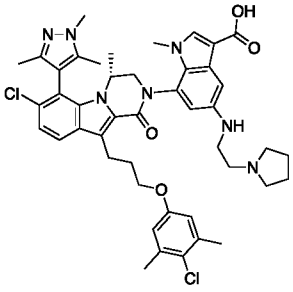
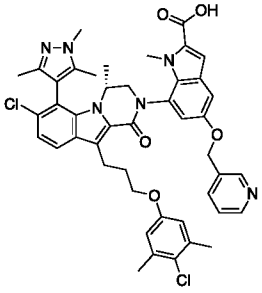
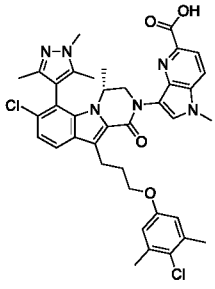
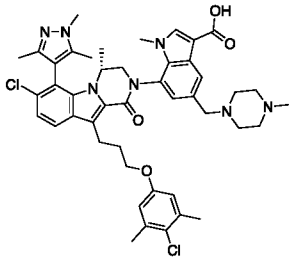
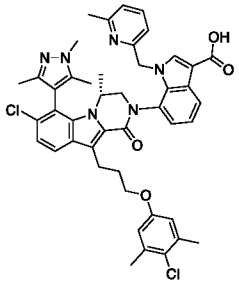
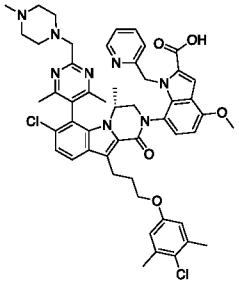
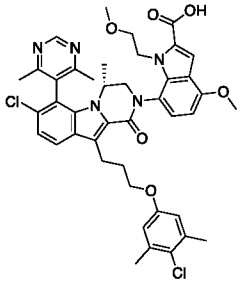
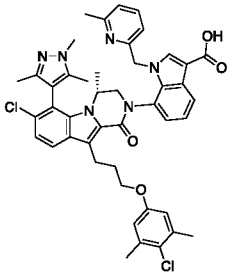
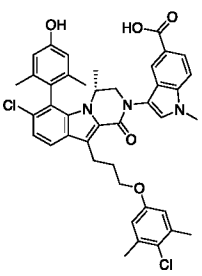
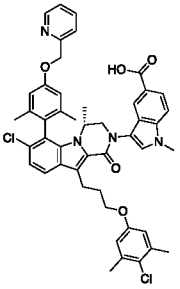
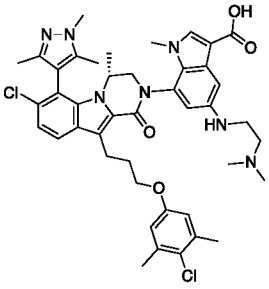
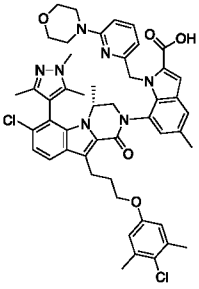
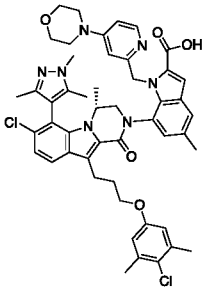
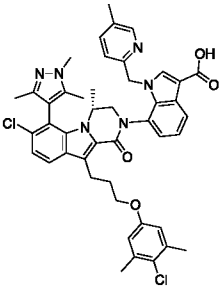
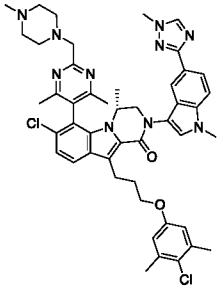
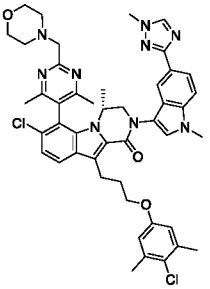
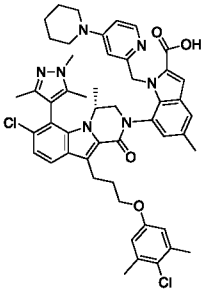
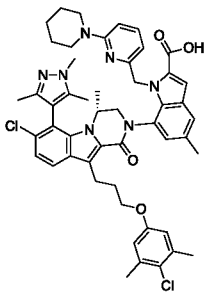
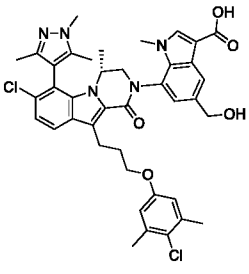
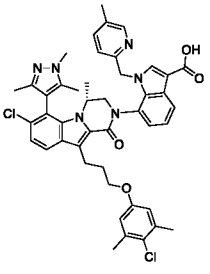
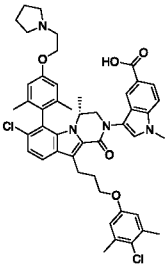
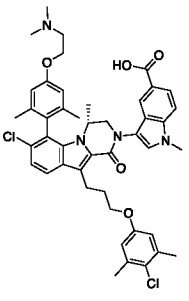
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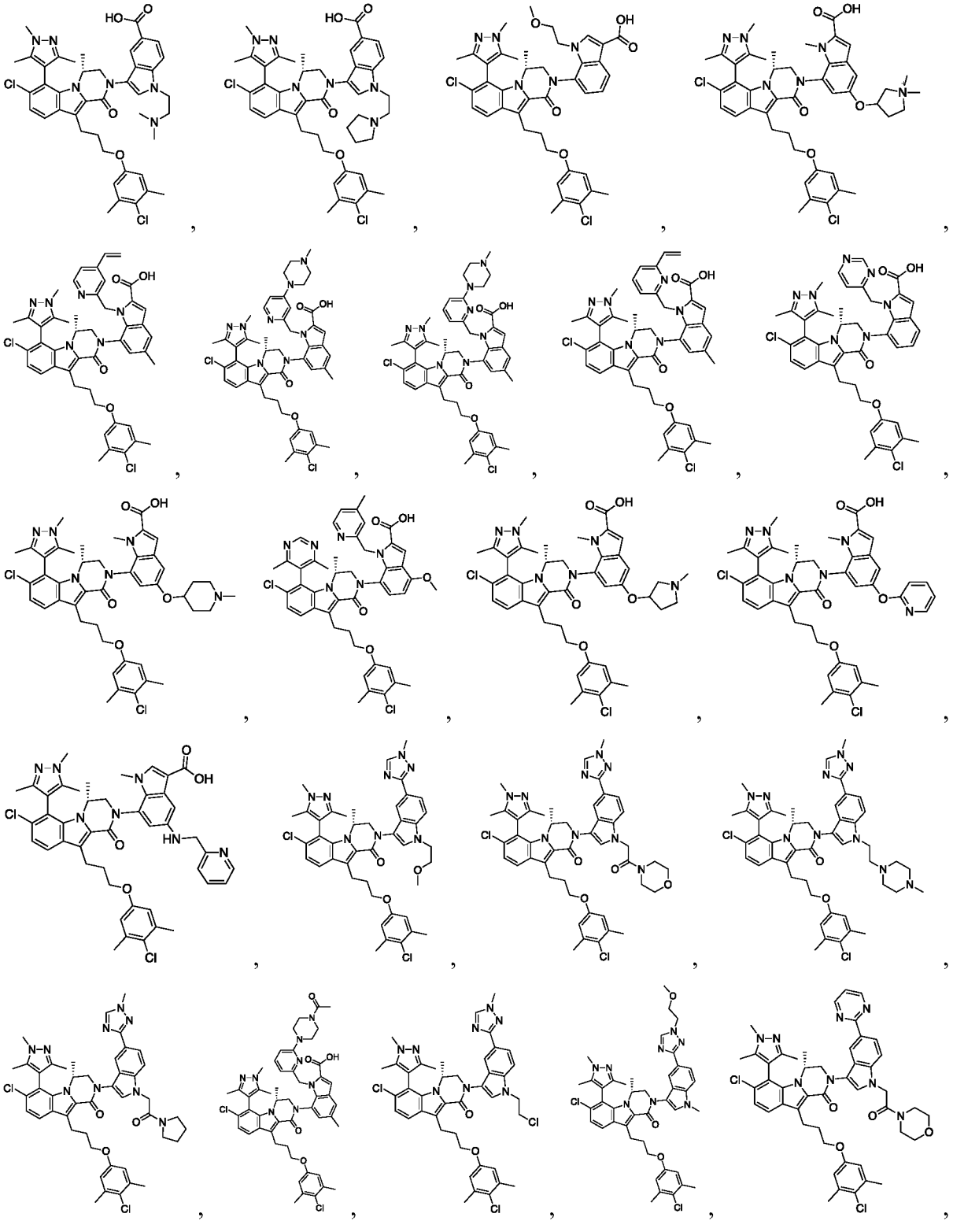
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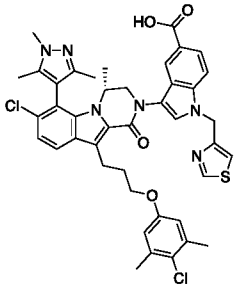
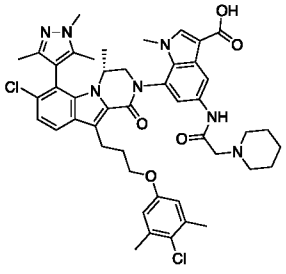
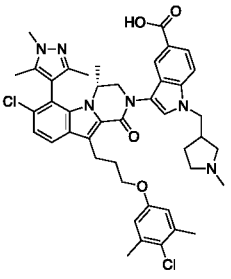
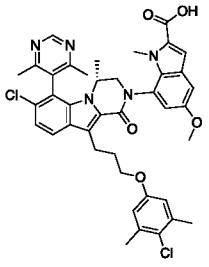
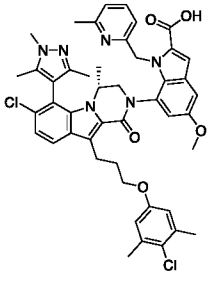
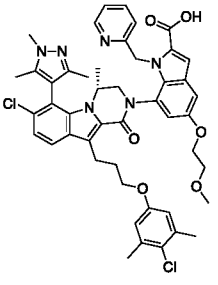
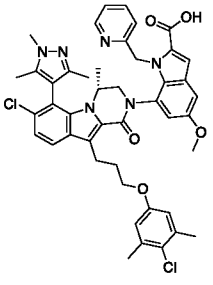
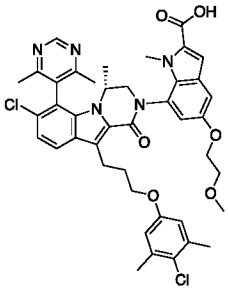
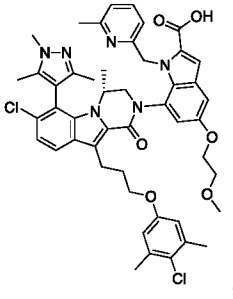
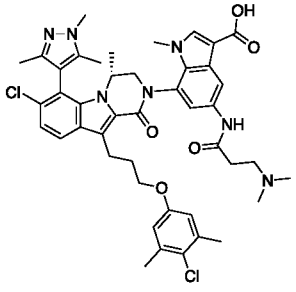
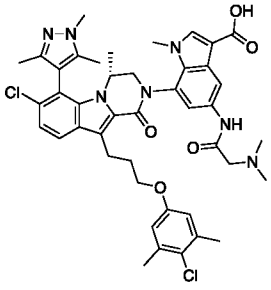
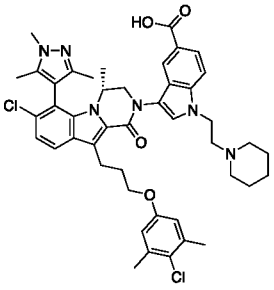
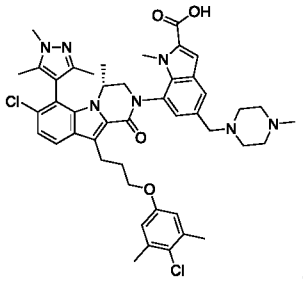
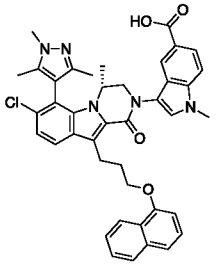
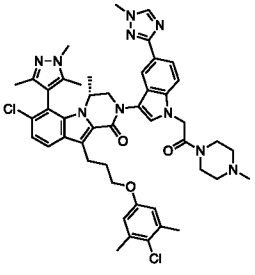
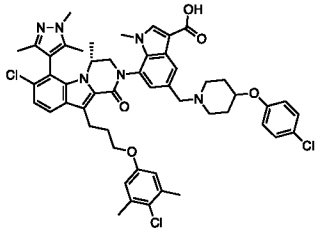
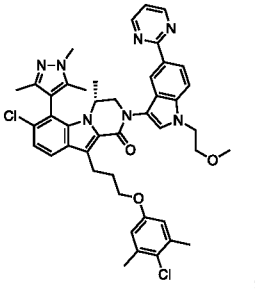
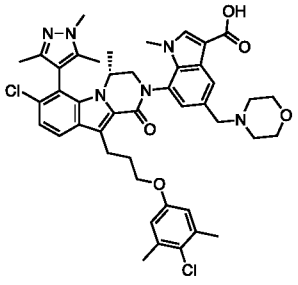
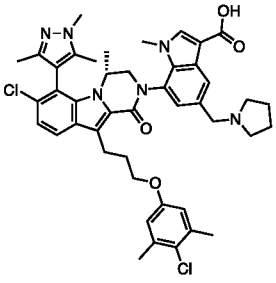
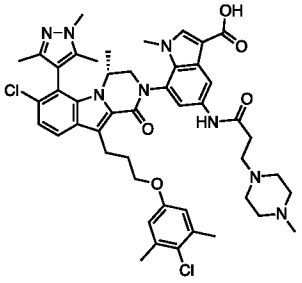
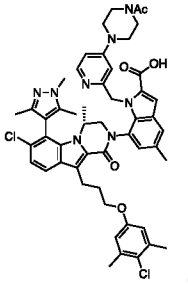
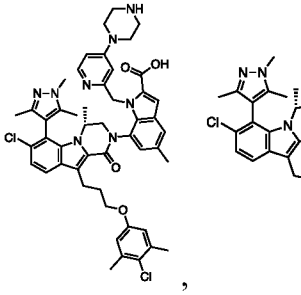
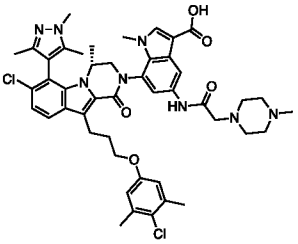
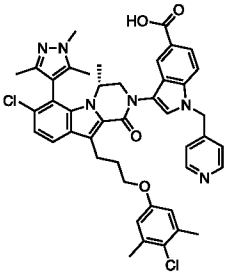
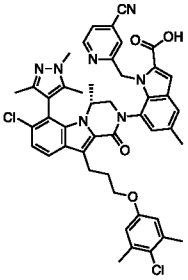
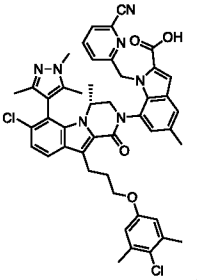


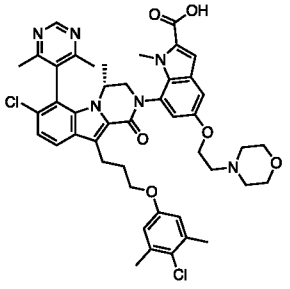
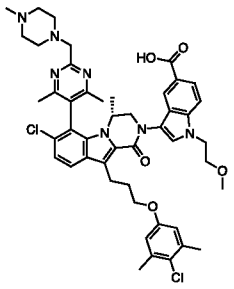
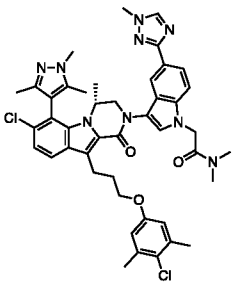
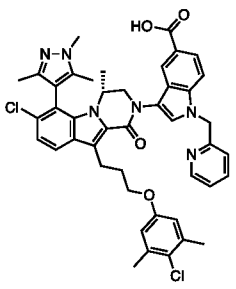
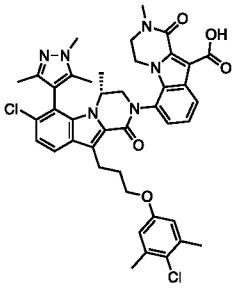
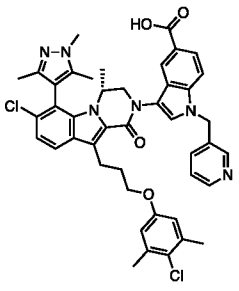
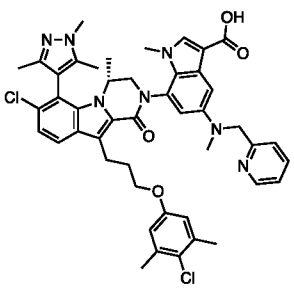
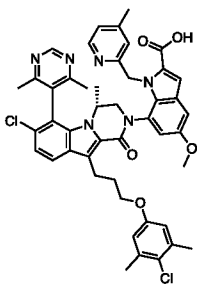
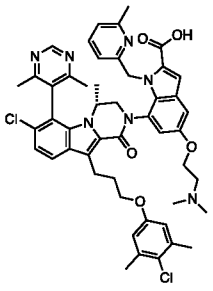
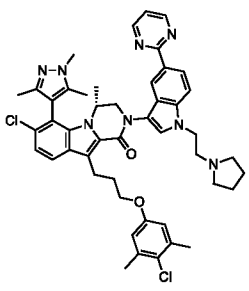
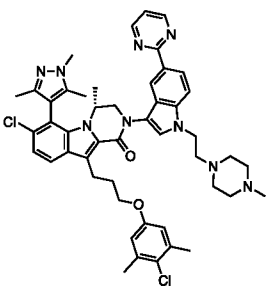
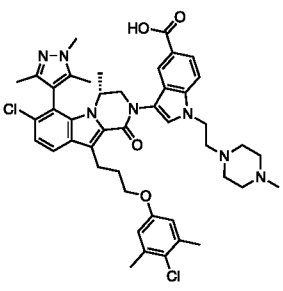
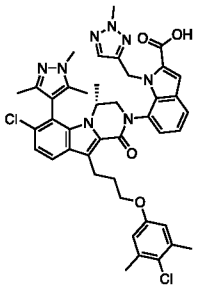
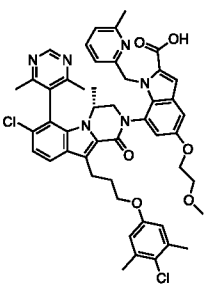
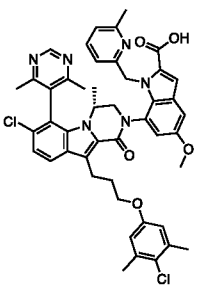
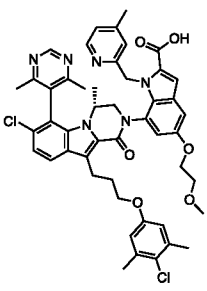
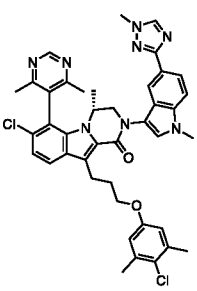
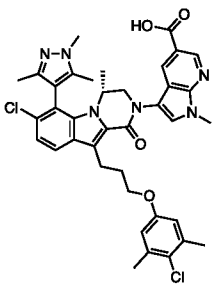
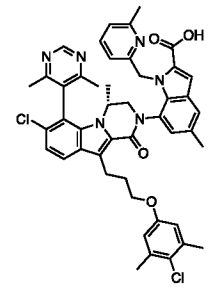
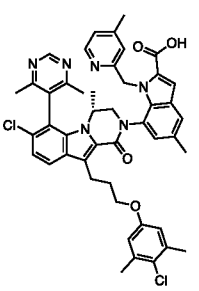
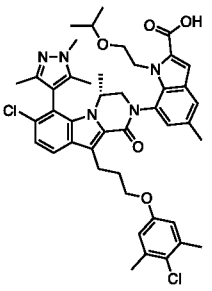
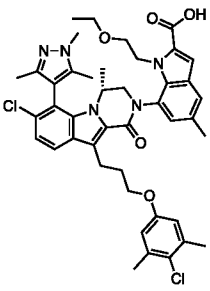
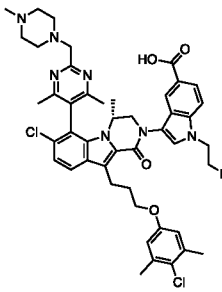
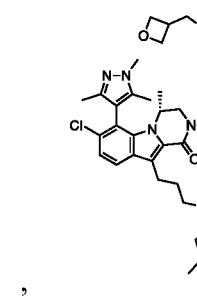
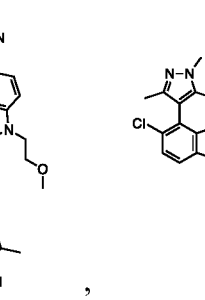
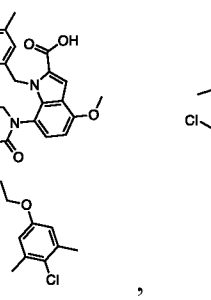
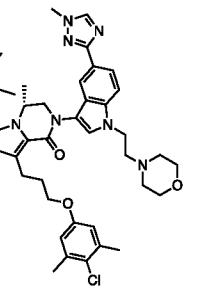



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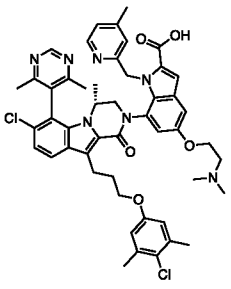
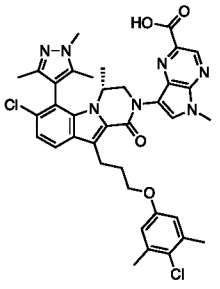
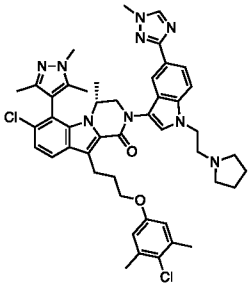
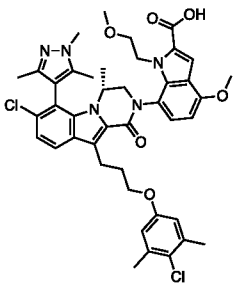
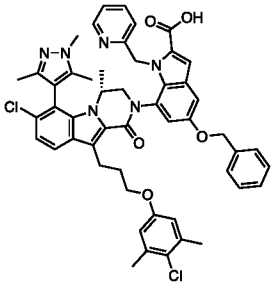
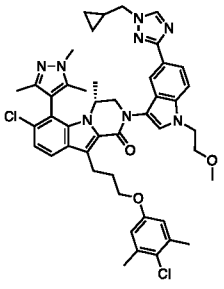
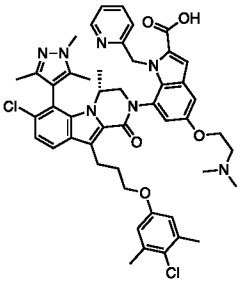
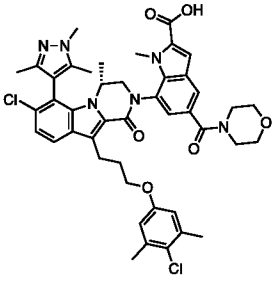
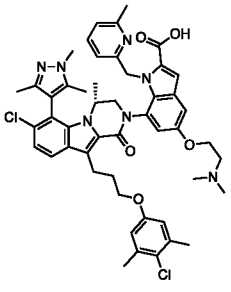
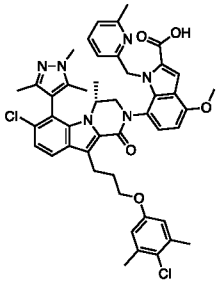
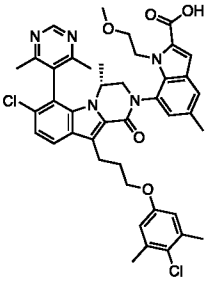
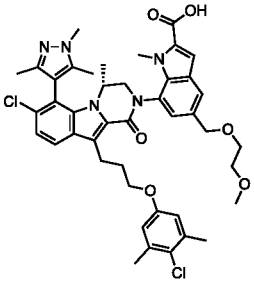
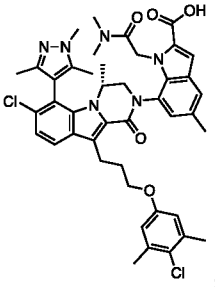
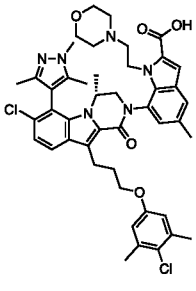
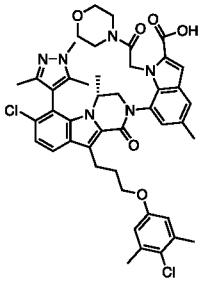
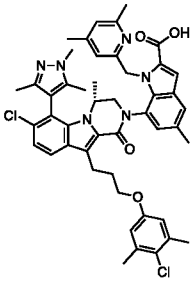
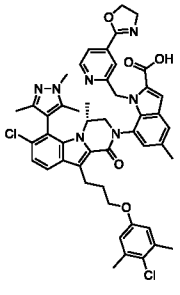
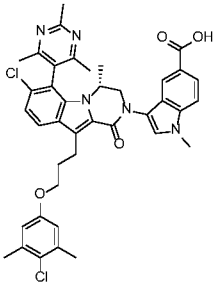
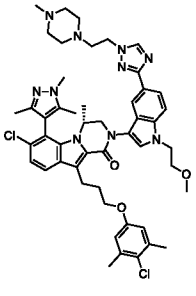
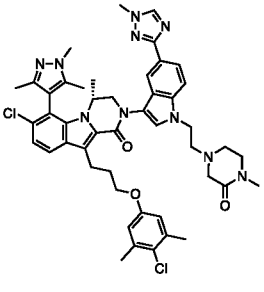
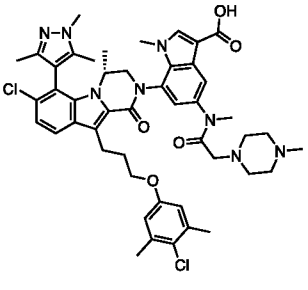
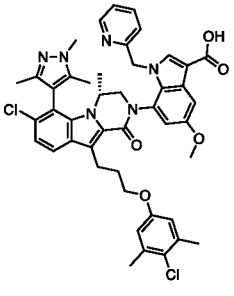
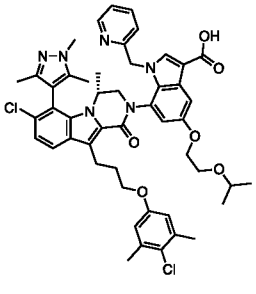
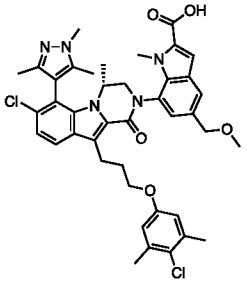
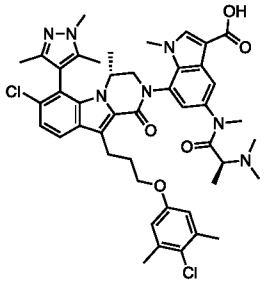
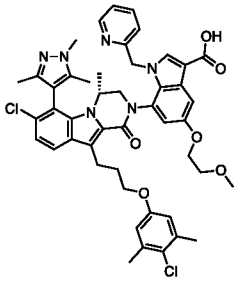

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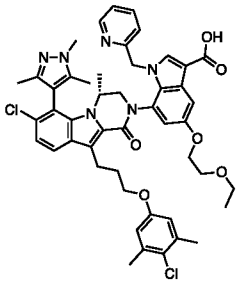
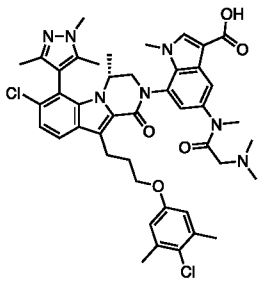
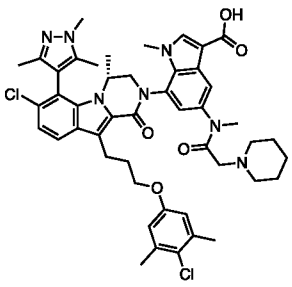
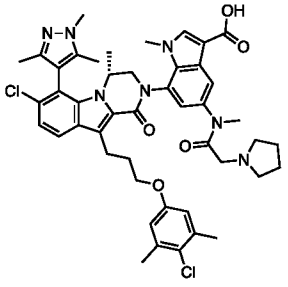
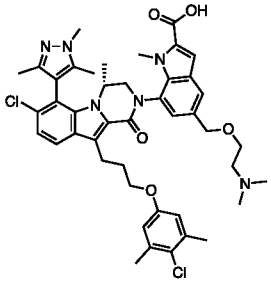
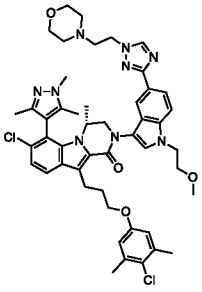
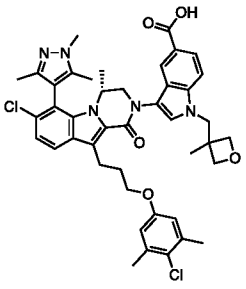
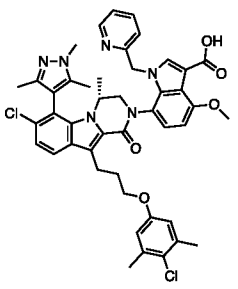
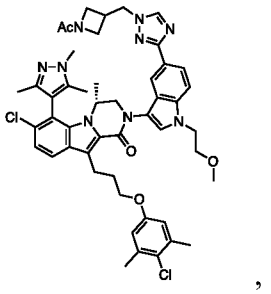
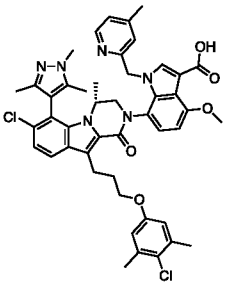
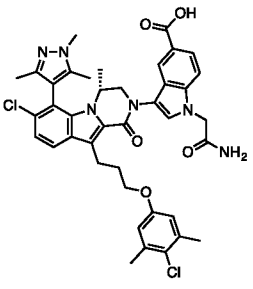
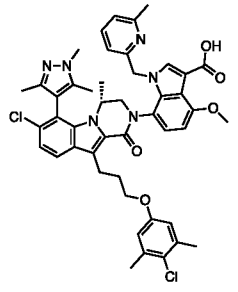
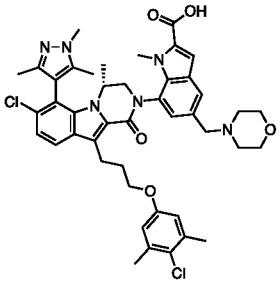
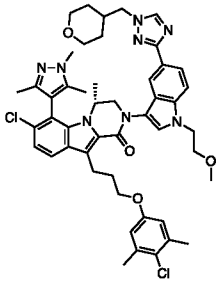
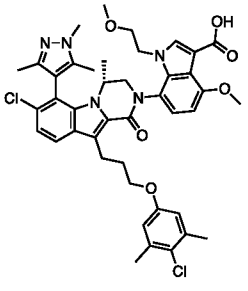
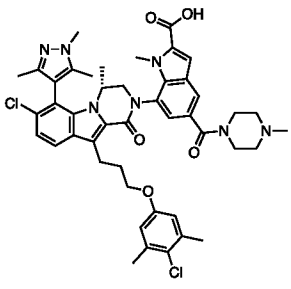
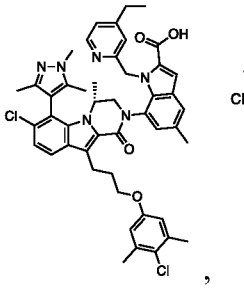
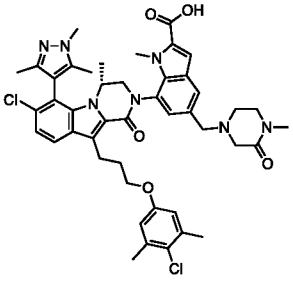
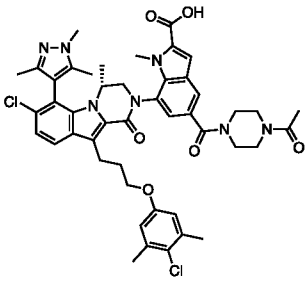
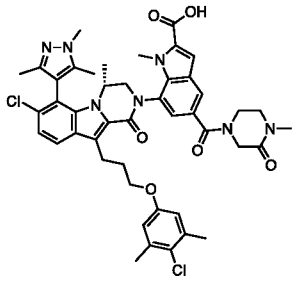
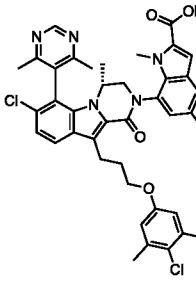
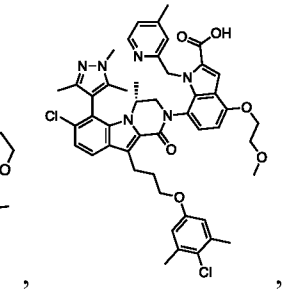
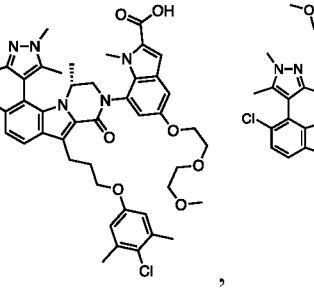
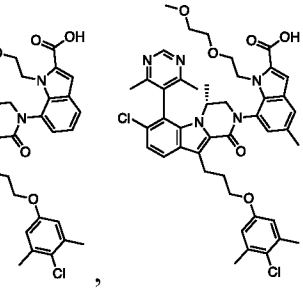



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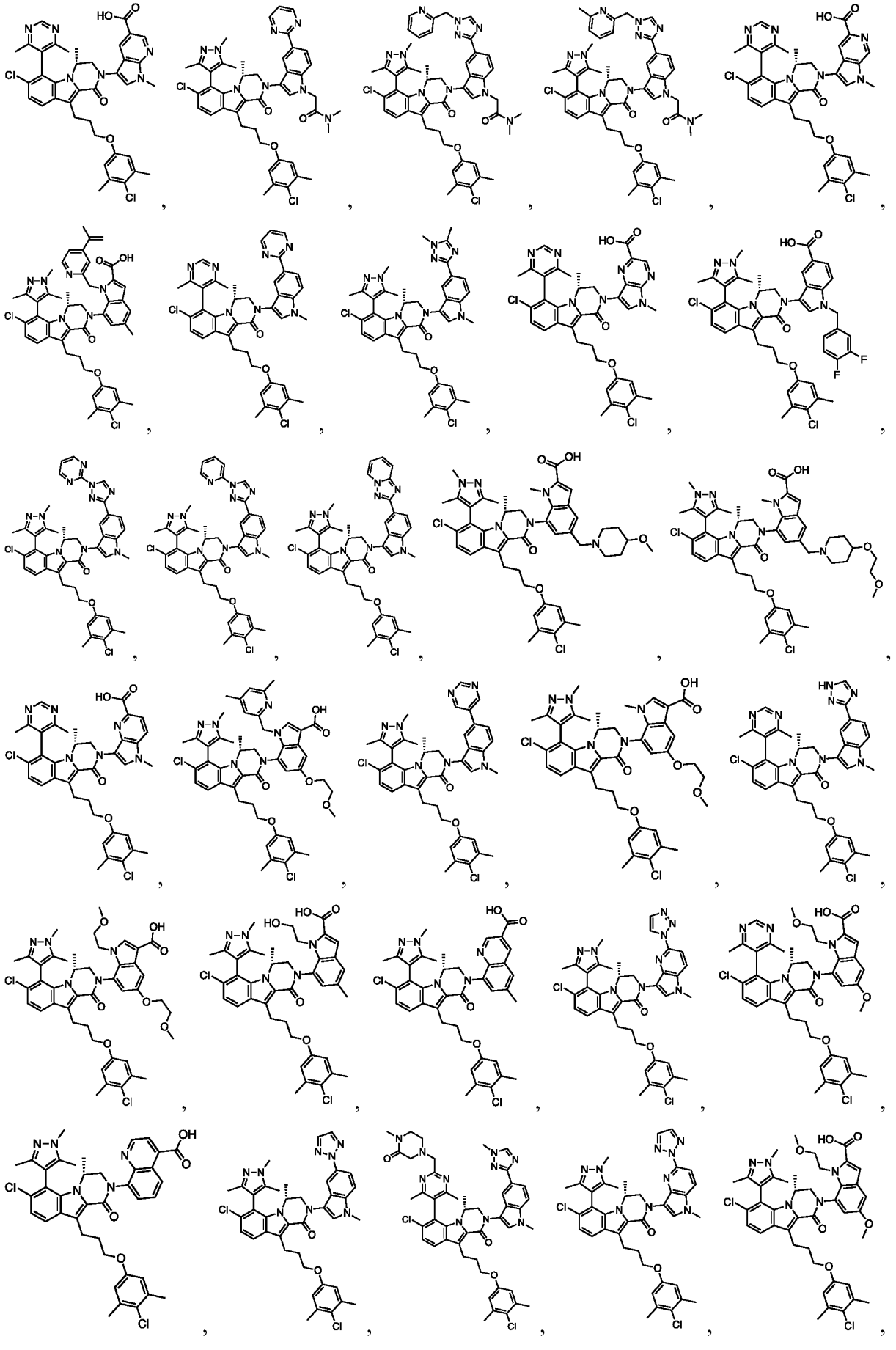
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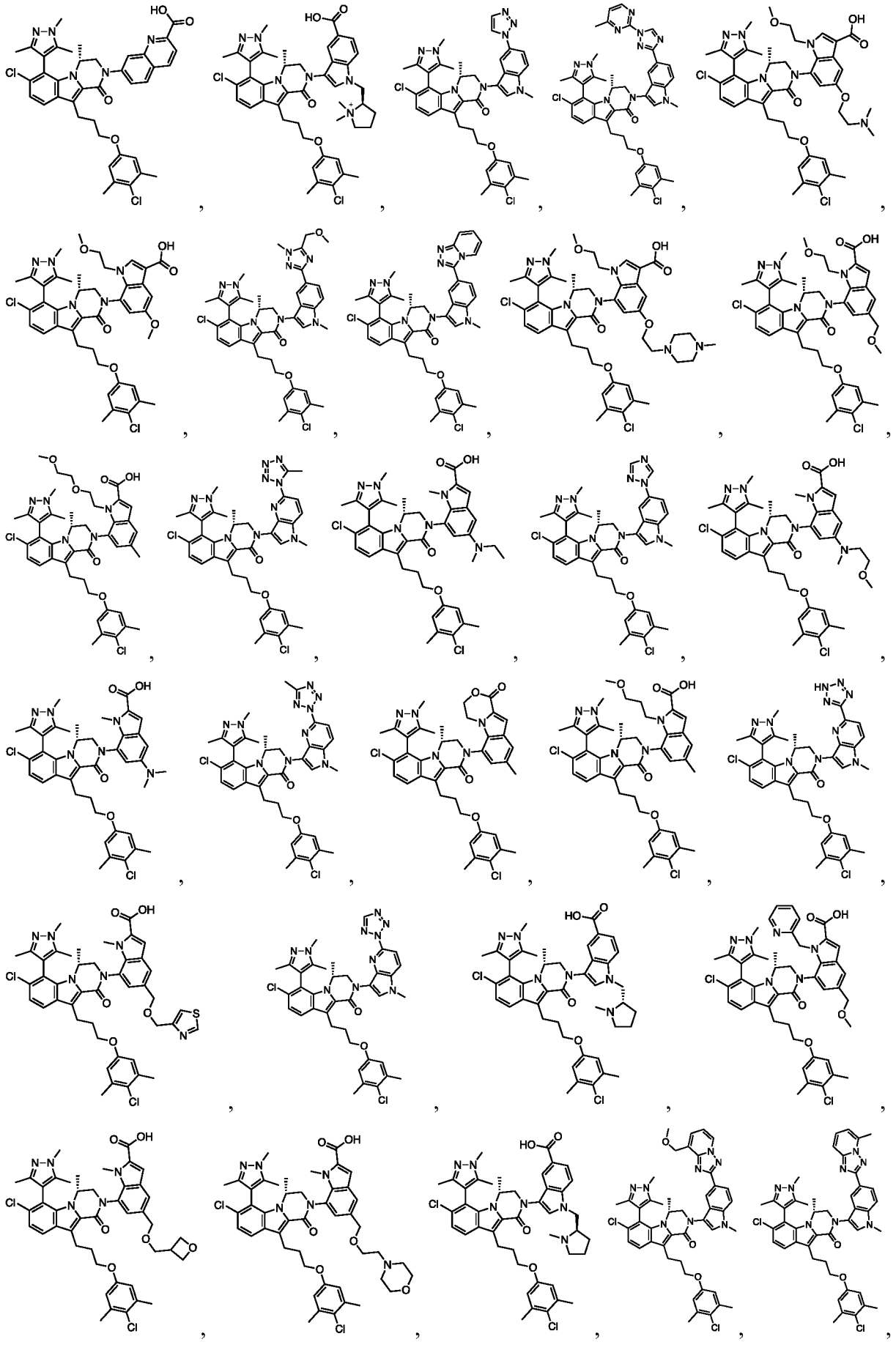
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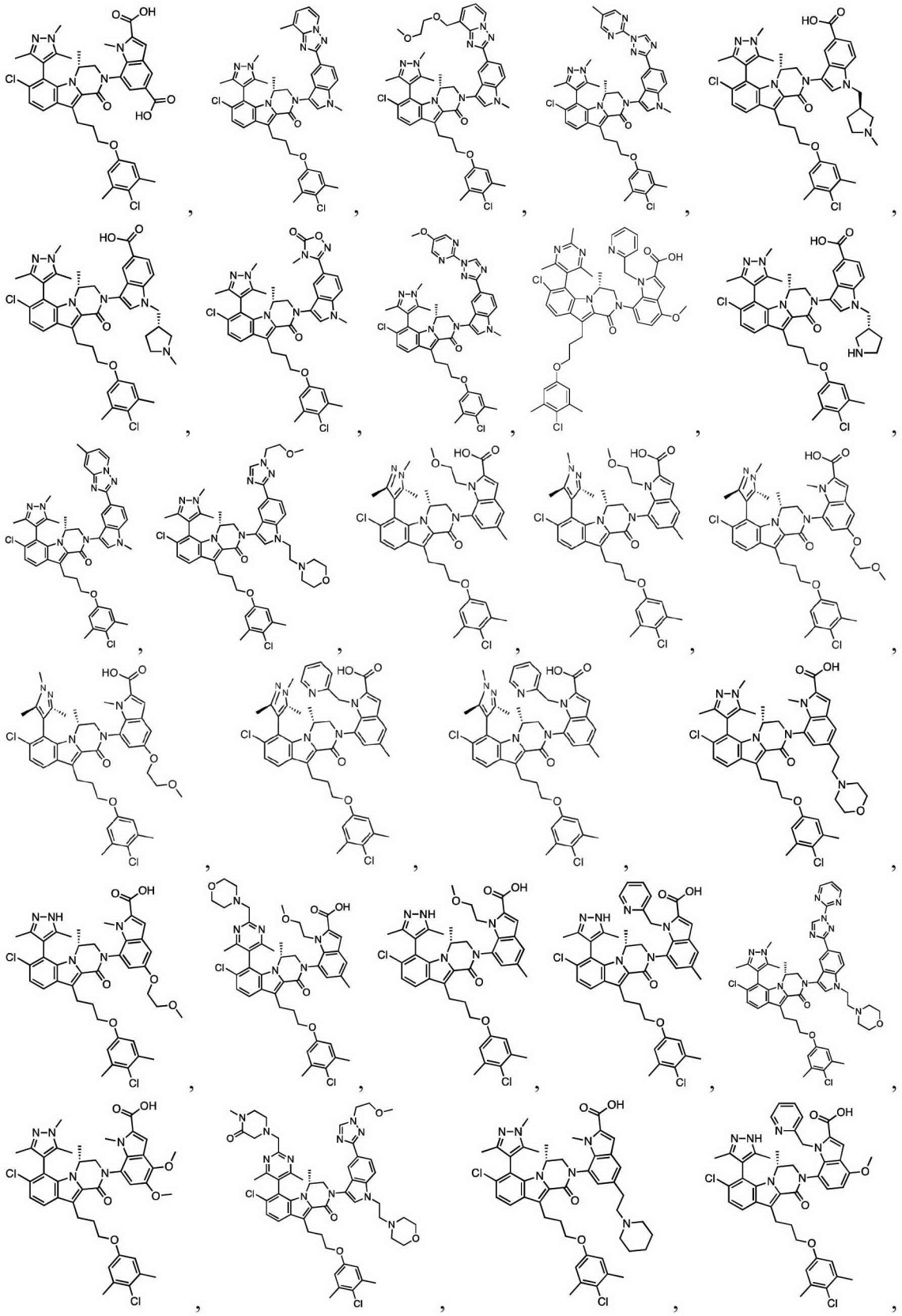
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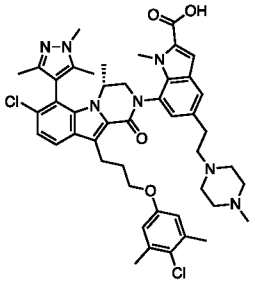
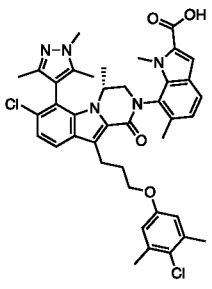
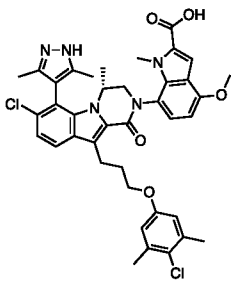
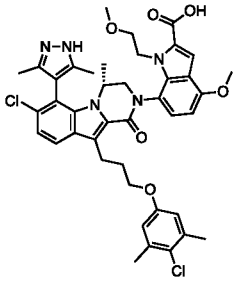
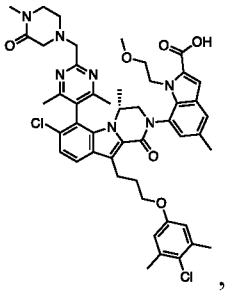
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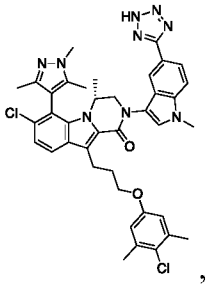
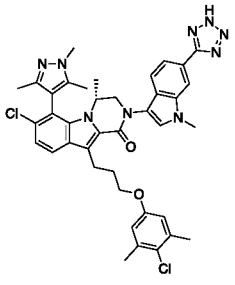
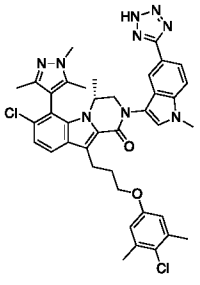
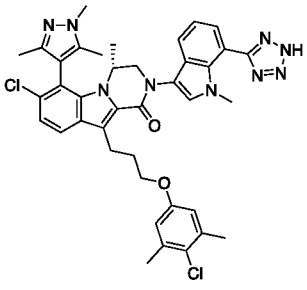
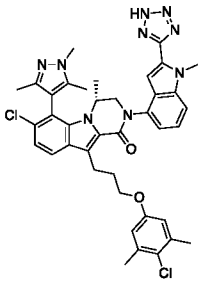
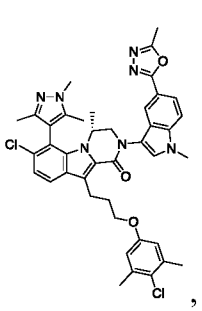
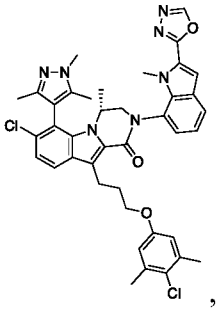
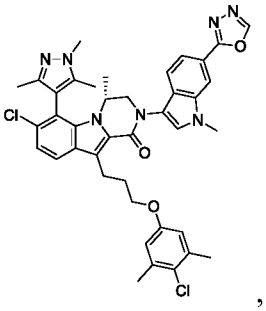
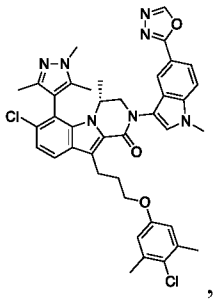
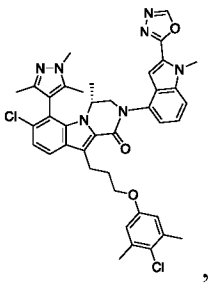
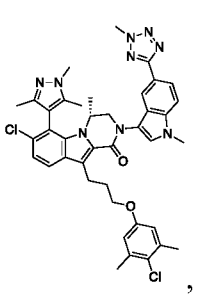
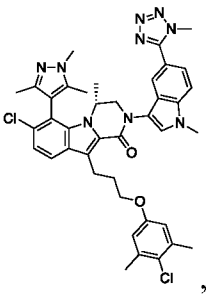
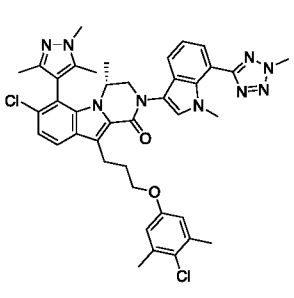
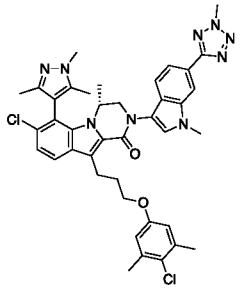


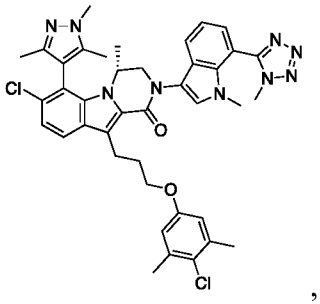
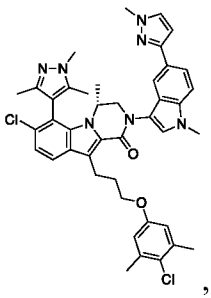
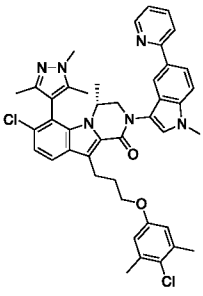
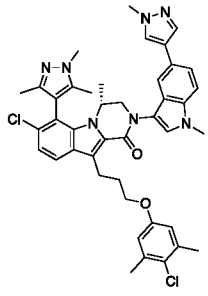
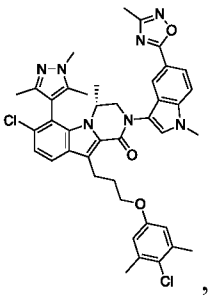
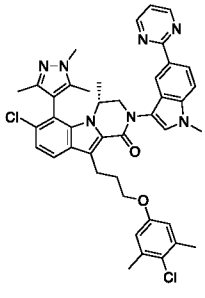
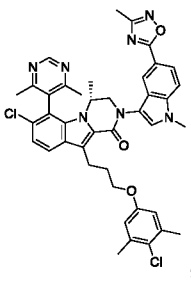
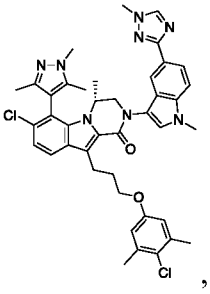
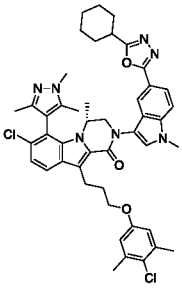
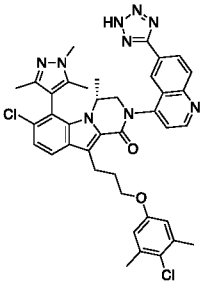
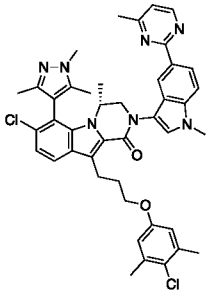
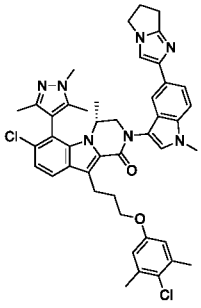
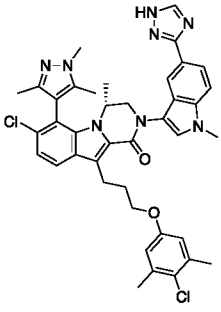
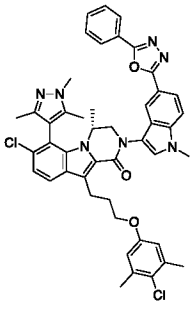
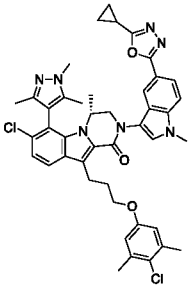
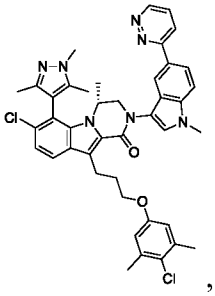
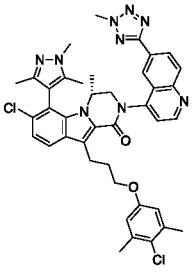
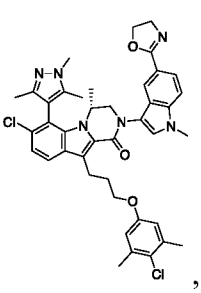
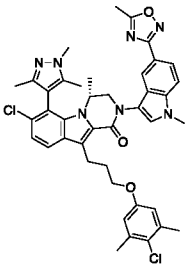
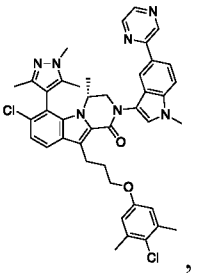
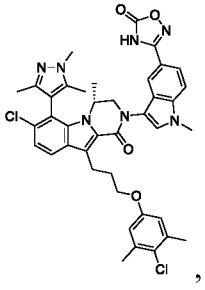
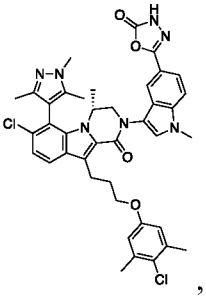
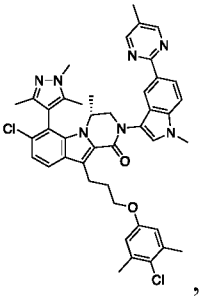
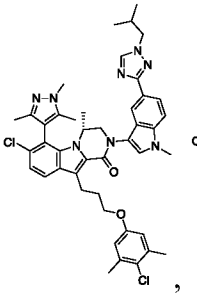
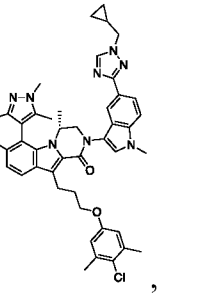



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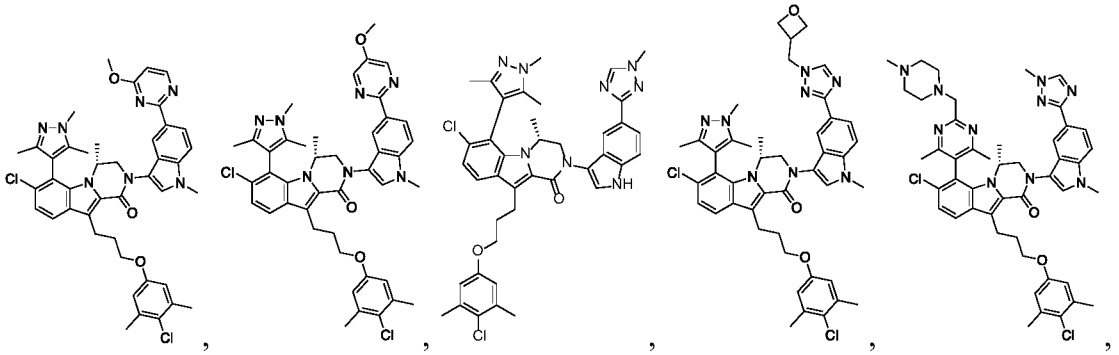
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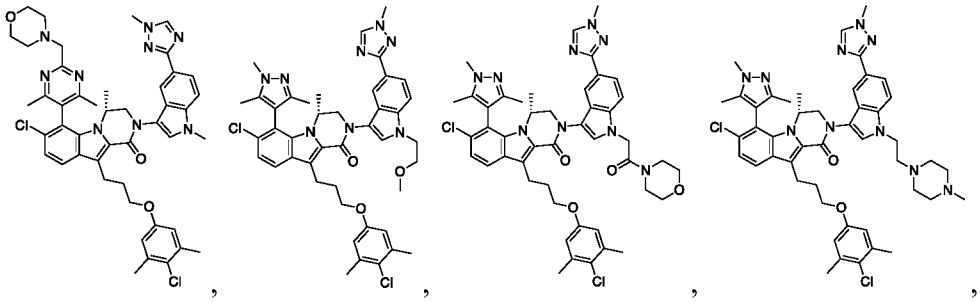
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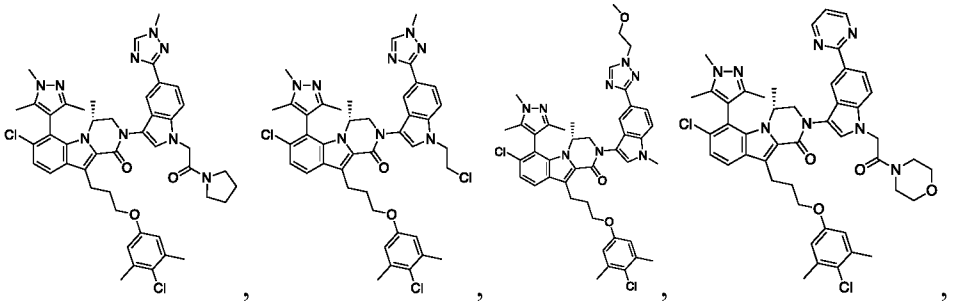
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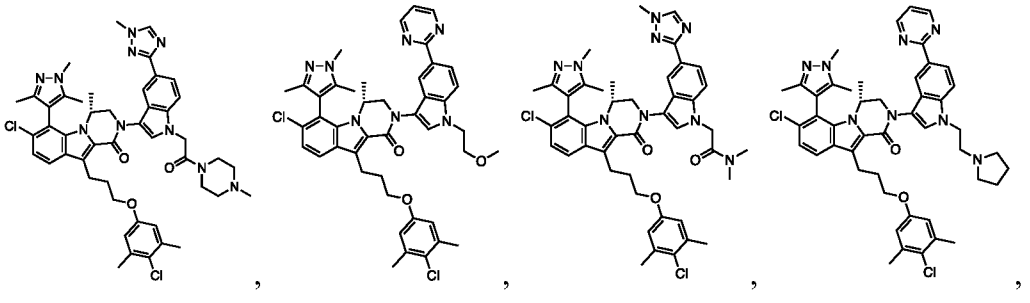
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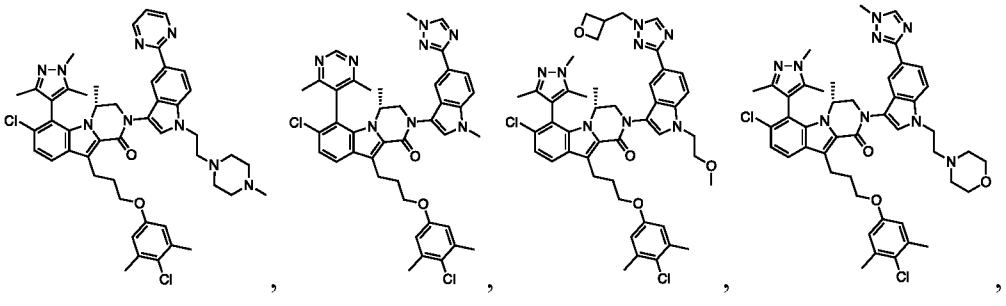
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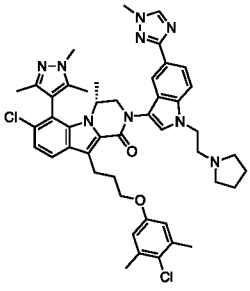
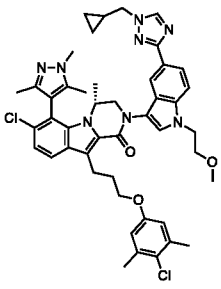
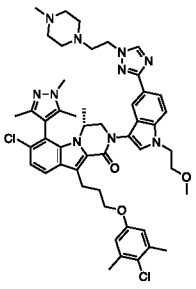
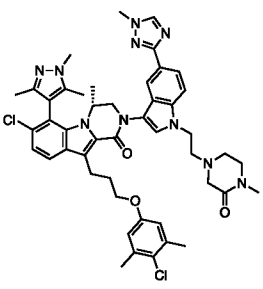
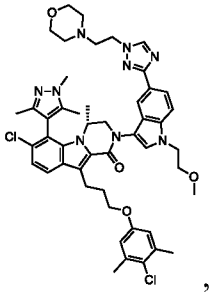
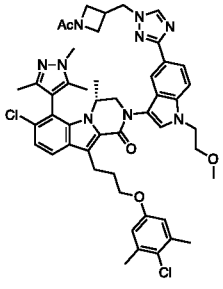
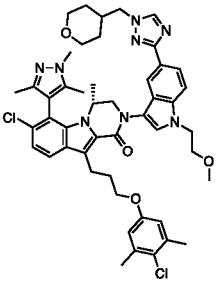
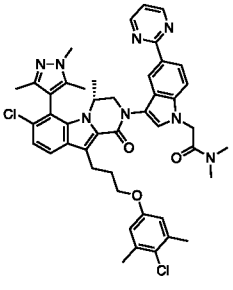
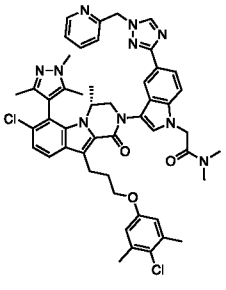
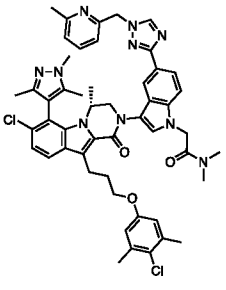
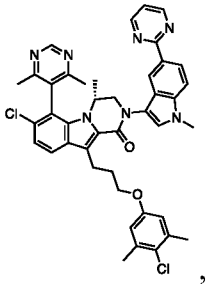
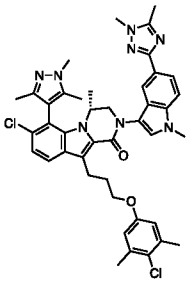
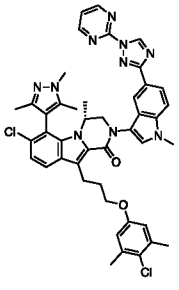
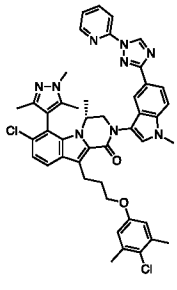
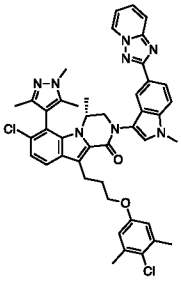
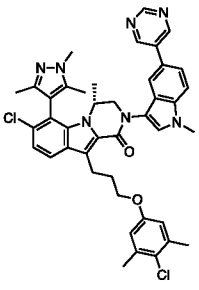
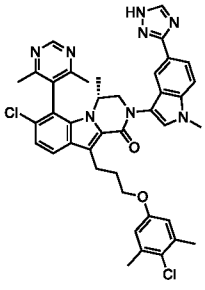
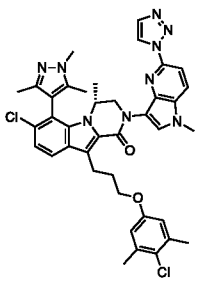
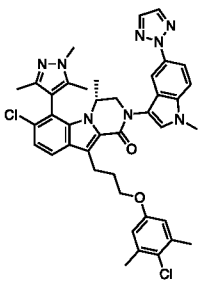
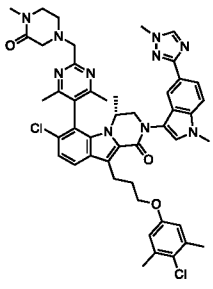
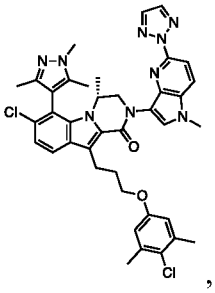
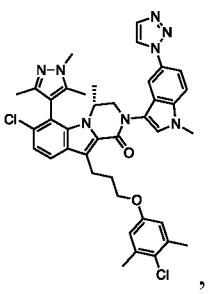
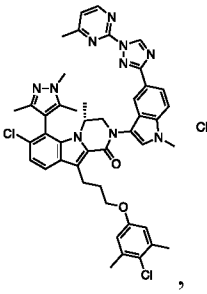
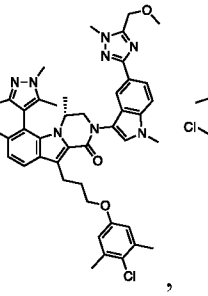
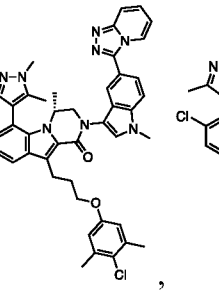
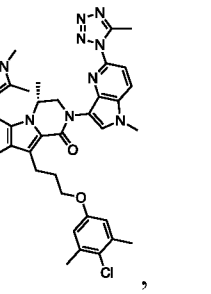
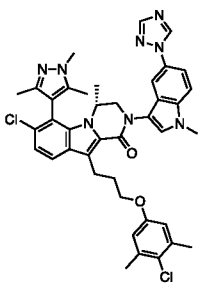
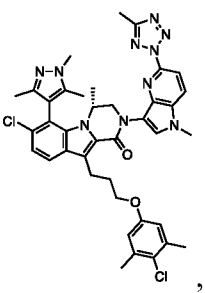
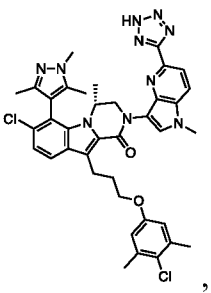
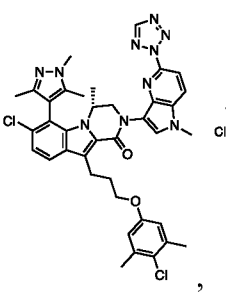
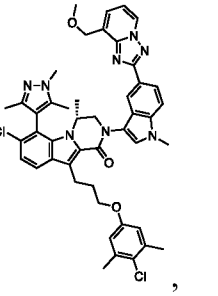











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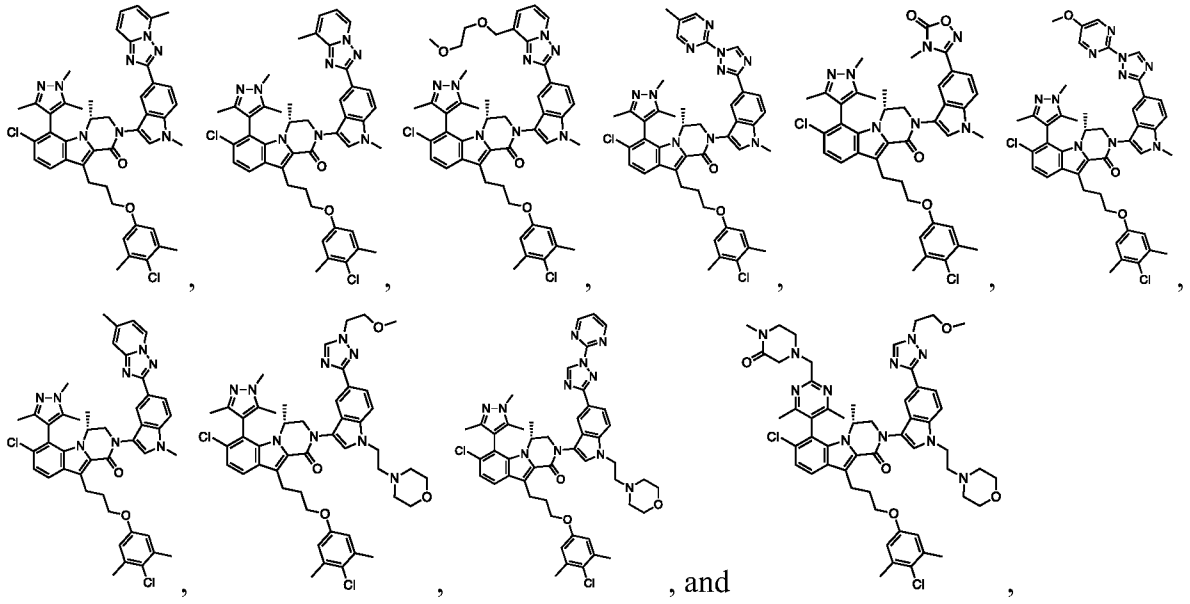
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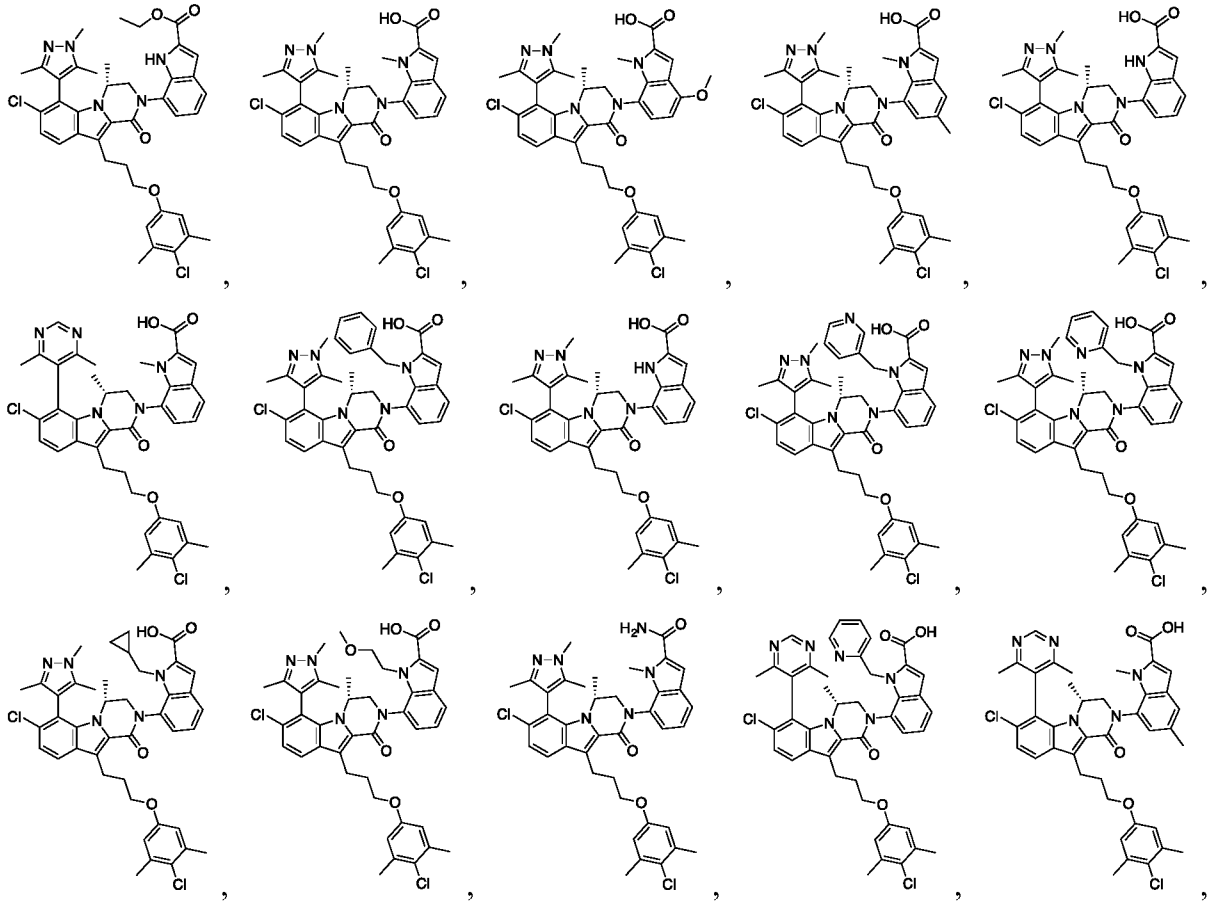
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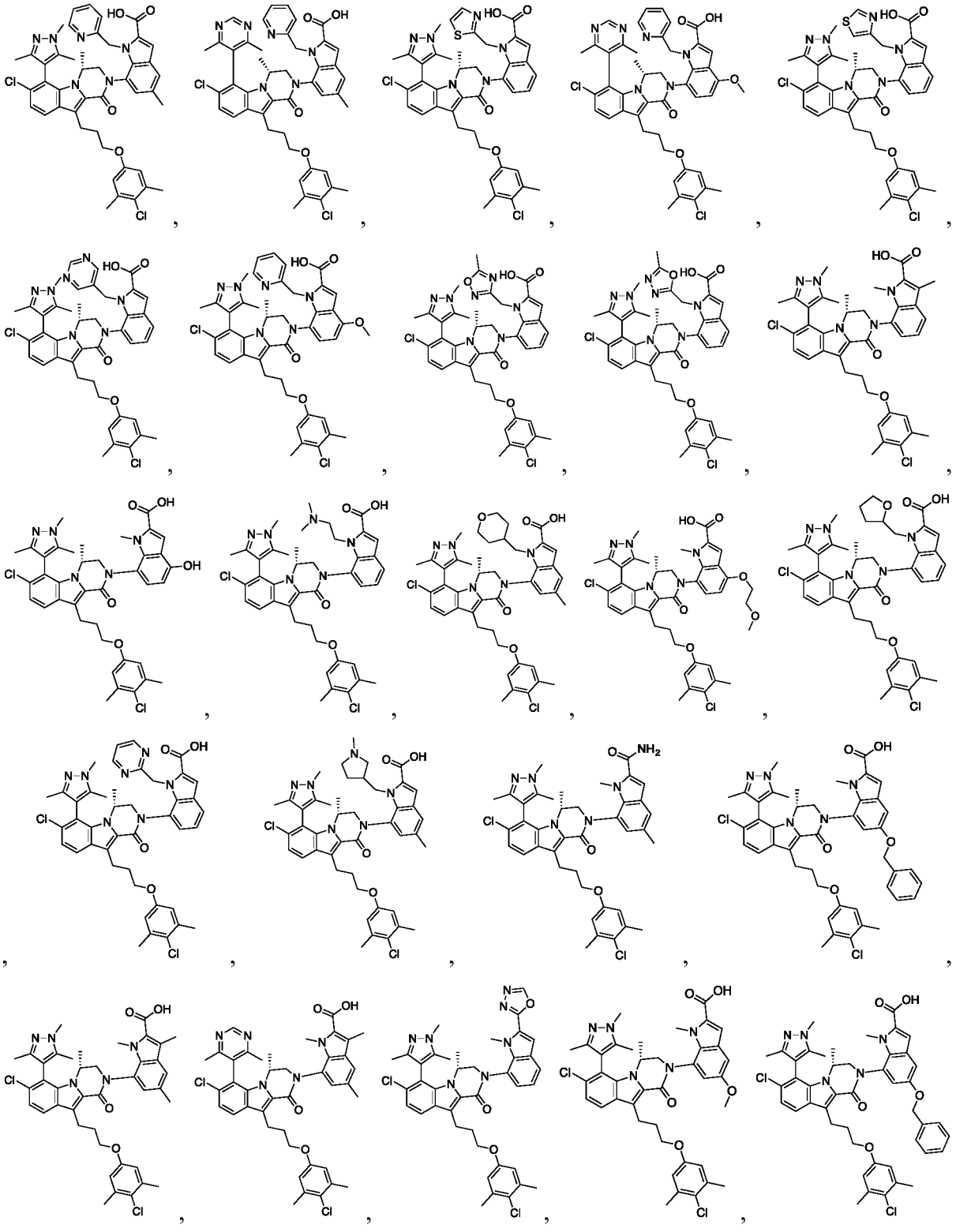


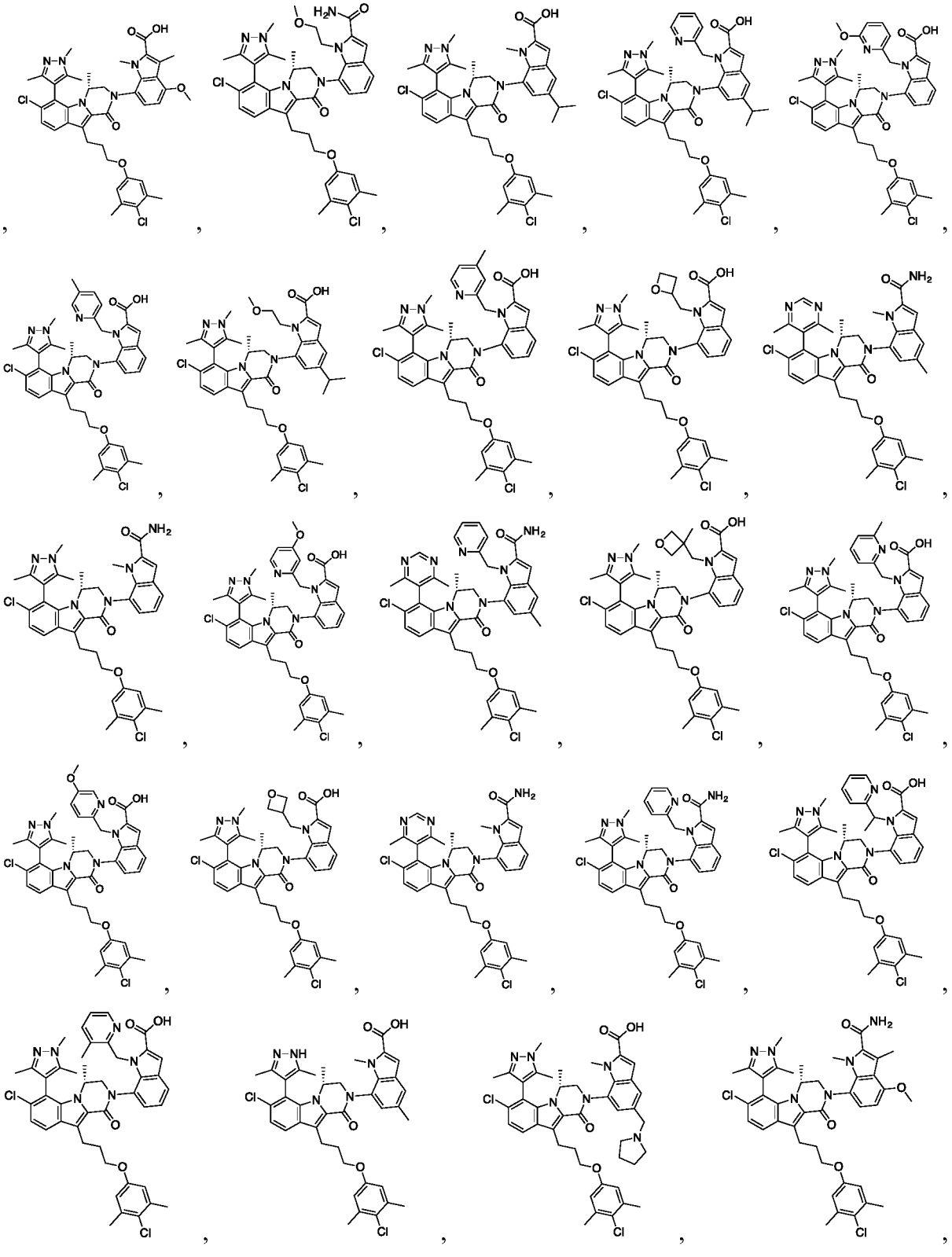
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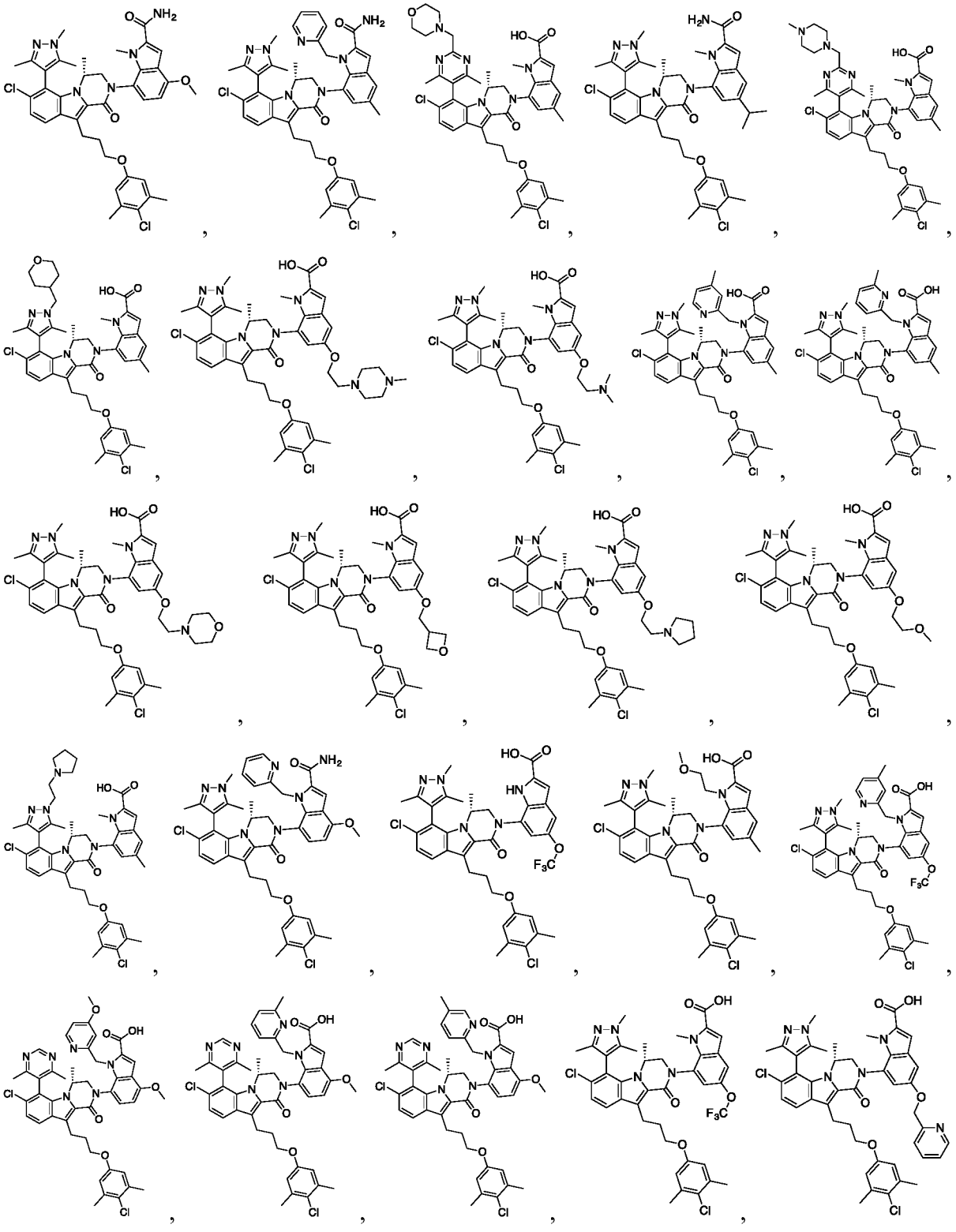
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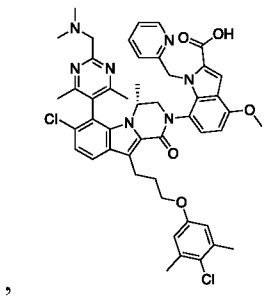
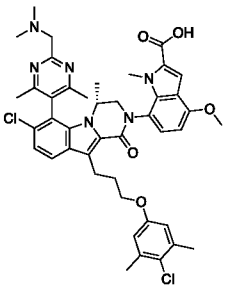
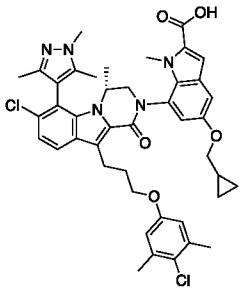
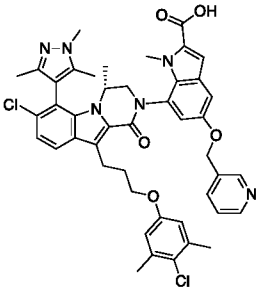
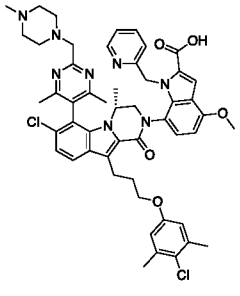
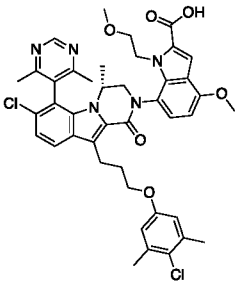
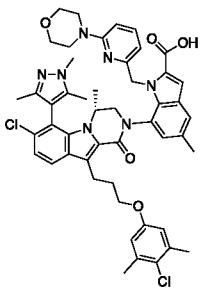
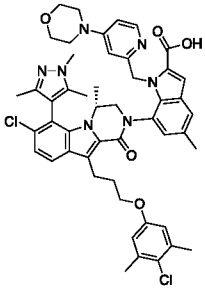
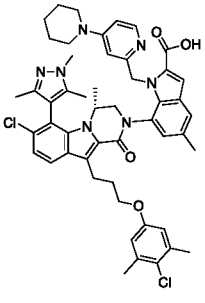
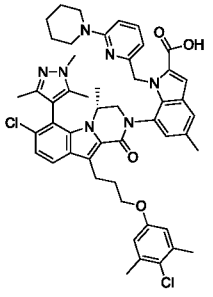
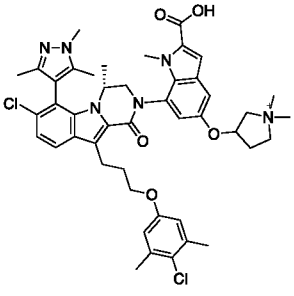
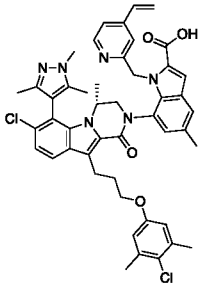
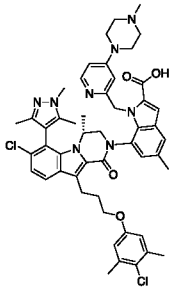
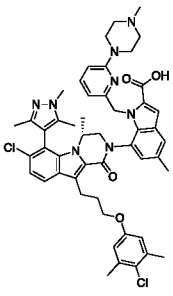
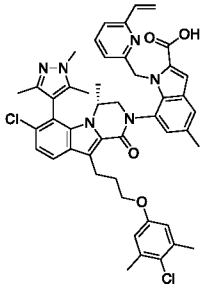
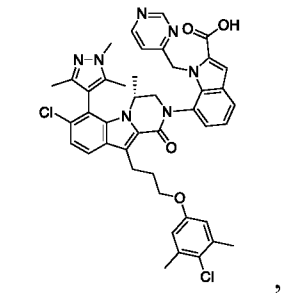
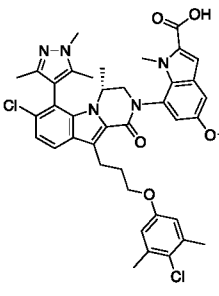
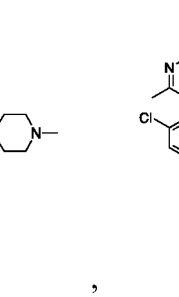
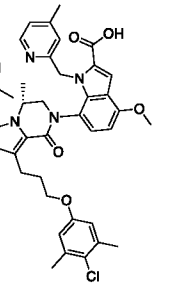
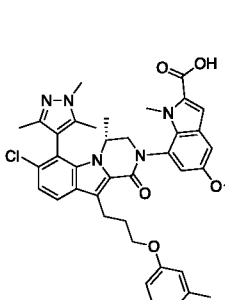
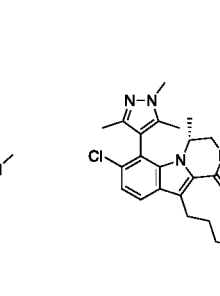
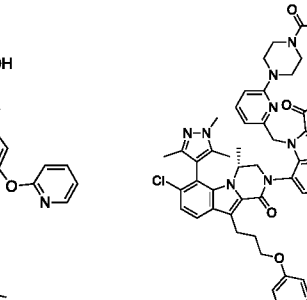
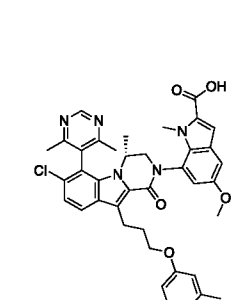
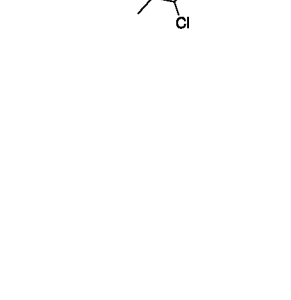
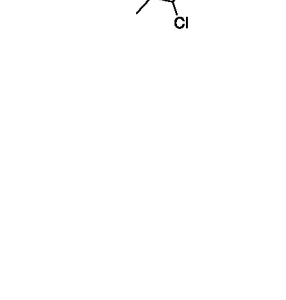
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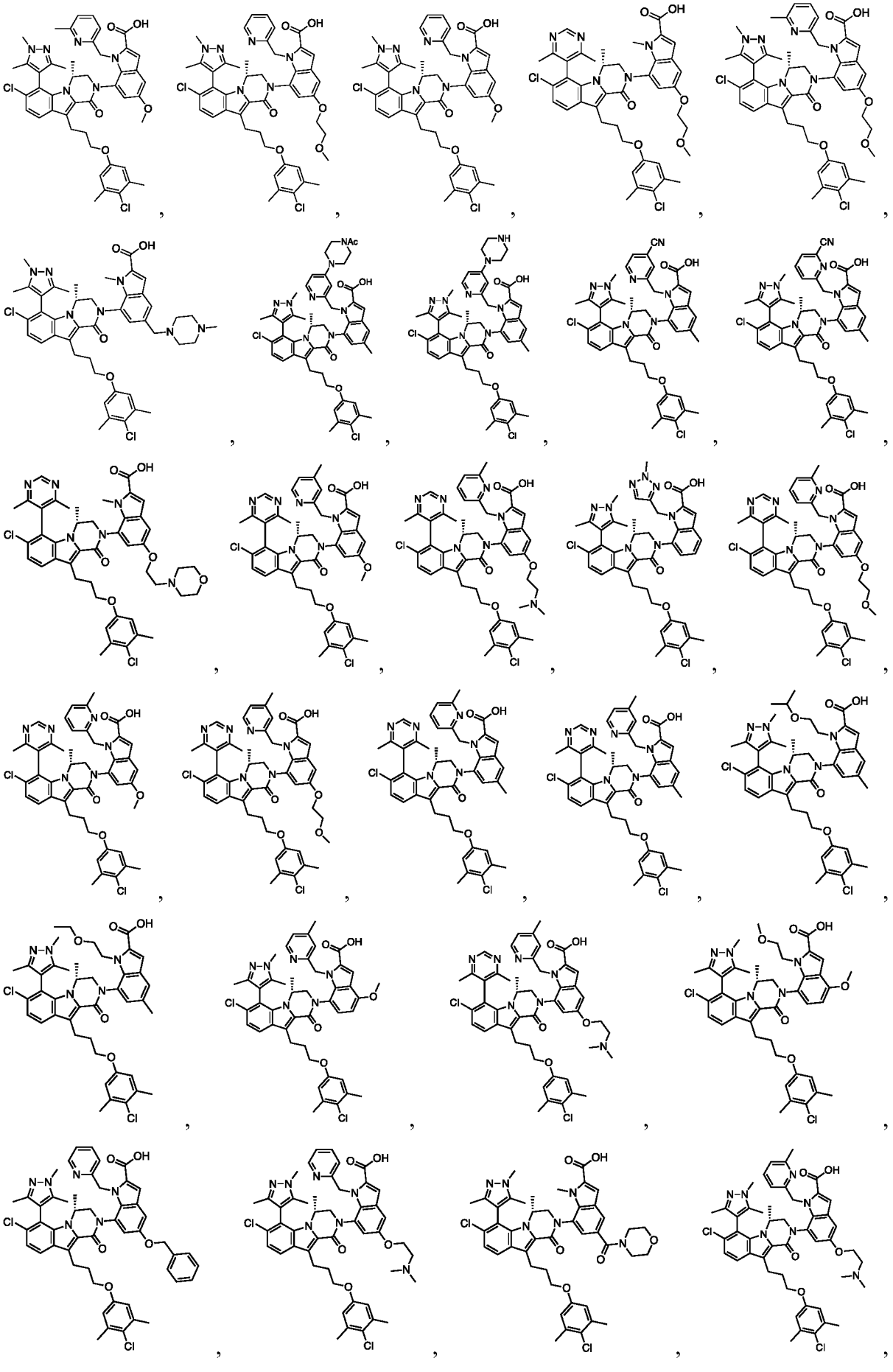


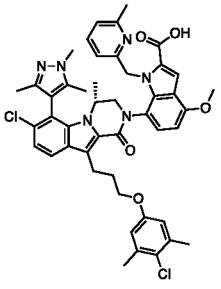
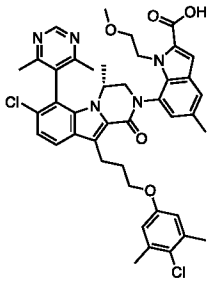
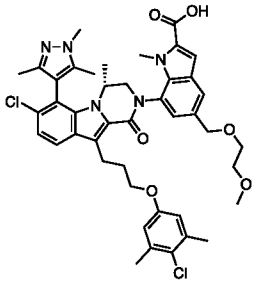
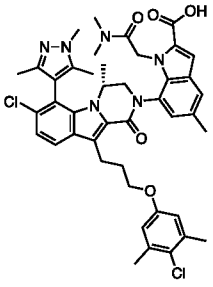
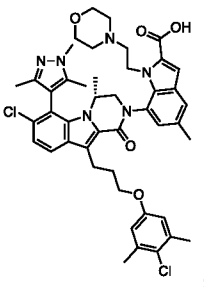
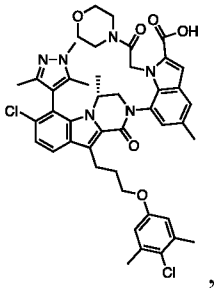
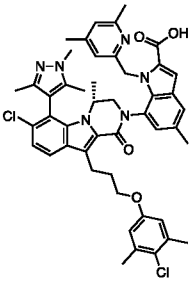
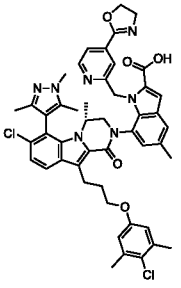
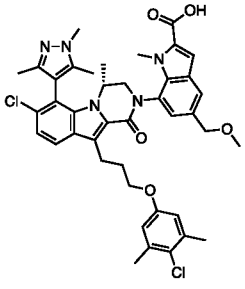
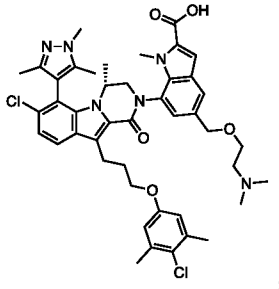
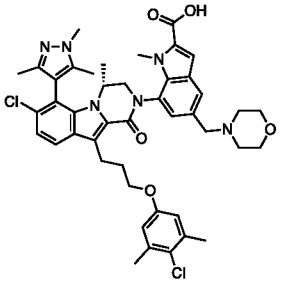
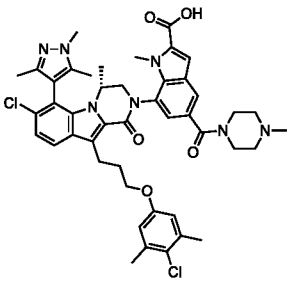
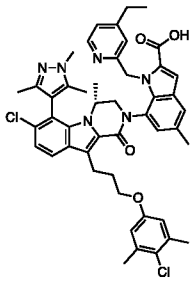
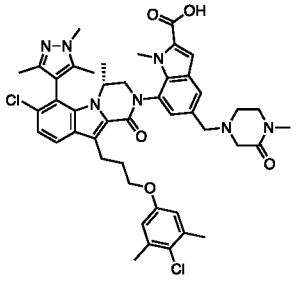
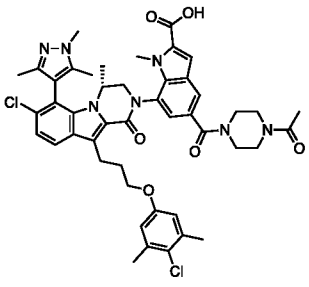
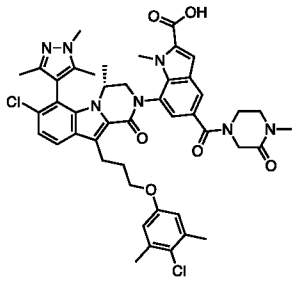
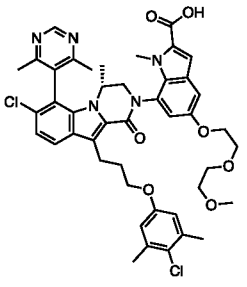
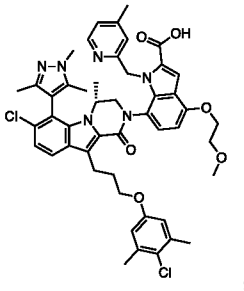
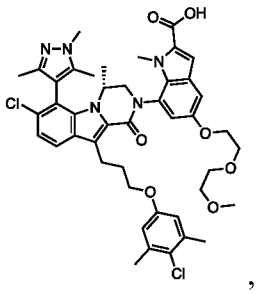
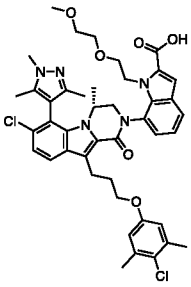
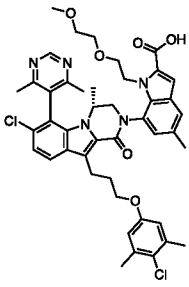
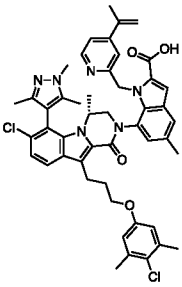
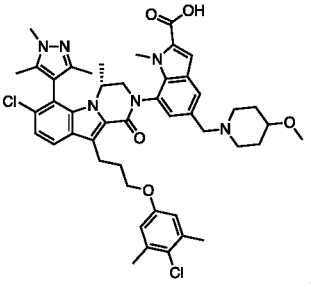
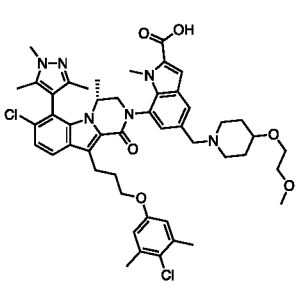
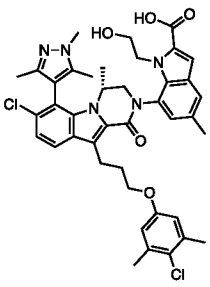
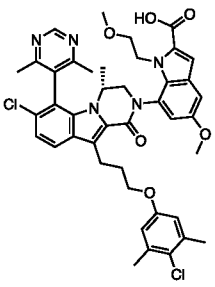
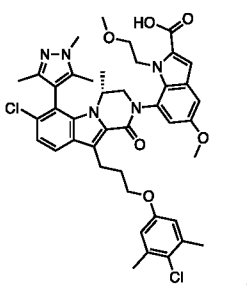


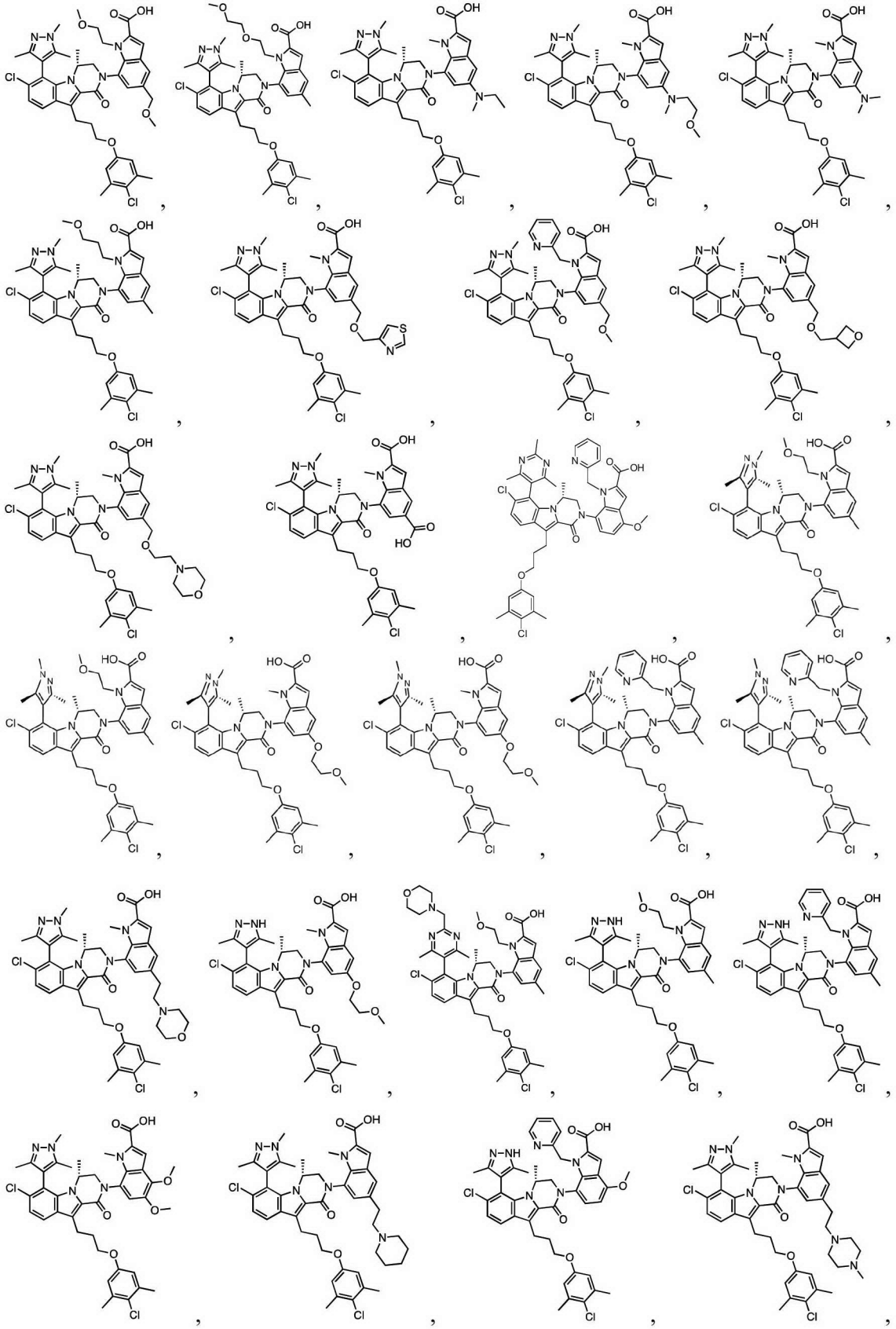

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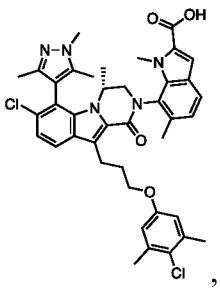
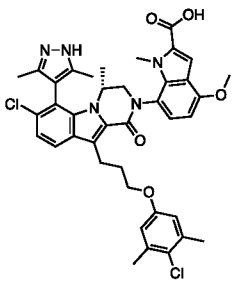
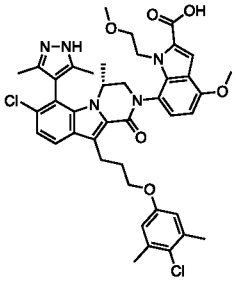
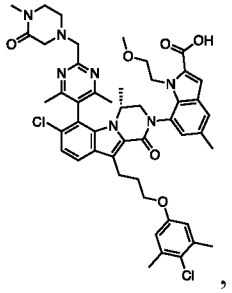
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or a pharmaceutically acceptable salt thereof.

13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein the compound has a K_i value less than about 1 μM for inhibition of Mcl-1.

14. A pharmaceutical composition comprised of a compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

15. The pharmaceutical composition of claim 14, further comprising one or more additional therapeutically active agents.

16. A method of modulating the activity of the Bcl-2 family of proteins comprising administering to a mammalian patient in need thereof a therapeutically effective amount of at least one compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, and, optionally, an additional therapeutic agent.

17. A method for treating diseases or disorders associated with the expression or over-expression of Mcl-1, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein:
the diseases or disorders are selected from the group consisting of acoustic neuroma, acute leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia (monocytic, myeloblastic, adenocarcinoma, adrenocortical cancer, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute T-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, bone cancer, brain cancer, brain stem glioma, breast cancer, bronchogenic carcinoma, cervical cancer, cholangiocarcinoma, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myeloogeneous leukemia, colon cancer, colorectal cancer,

craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, duodenal cancer, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fallopian tube carcinoma, fibrosarcoma, follicular lymphoma, gastric carcinoma, germ cell testicular cancer, gestational trophobalstic disease, glioblastoma, gall bladder cancer, head and neck cancer, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, liposarcoma, lung cancer both small cell lung cancer and non-small cell lung cancer, lymphagioendothelio-sarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma, including Diffuse Large B-celllymphoma, follicular lymphoma, Hodgkin's lymphoma and non-Hodgkin's lymphoma, malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, leukemia, lymphoma, medullary carcinoma, medulloblastoma, melanoma (cutaneous or intraocular), meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, parathyroid cancer, peripheral T -cell lymphoma, pinealoma, pituitary adenoma, polycythemia vera, prostate cancer including hormone-insensitive (refractory) prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small intestine cancer, solid tumors (carcinomas and sarcomas), small cell lung cancer, spinal axis tumors, spleen cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, testicular cancer (including germ cell testicular cancer), thyroid cancer, urethra cancer, uterine cancer, Waldenstram's macroglobulinemia, testicular tumors, vaginal cancer, vulva cancer, Wilms' tumor, embryonal rhabdomyosarcoma, pediatric acute lymphoblastic leukemia, pediatric acute myelogenous leukemia, pediatric alveolar rhabdomyosarcoma, pediatric anaplastic ependymoma, pediatric anaplastic large cell lymphoma, pediatric anaplastic medulloblastoma, pediatric atypical teratoidlrhabdoid tumor of the central nervous system, pediatric biphenotypic acute leukemia, pediatric Burkitts lymphoma, pediatric cancers of Ewing's family of tumors such as primitive neuroectodermal rumors, pediatric diffuse anaplastic Wilm's tumor, pediatric favorable histology Wilm's tumor, pediatric glioblastoma, pediatric medulloblastoma, pediatric neuroblastoma, pediatric neuroblastoma-derived myelocytomatosis, pediatric pre-B-cell

cancers (such as leukemia), pediatric psteosarcoma, pediatric rhabdoid kidney tumor, pediatric rhabdomyosarcoma, and pediatric T-cell cancers such as lymphoma and skin cancer.

18. A method for preventing, inhibiting, or treating the progression or onset of diseases or disorders associated with the expression or over-expression of anti-apoptotic Bcl-2 family protein members, particularly Mcl-1 protein, comprising administering to a mammalian patient in need of prevention, inhibition, or treatment a therapeutically effective amount of at least one compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, and, optionally, an additional therapeutic agent wherein:

(a) the diseases or disorders are selected from the group consisting of acoustic neuroma, acute leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia (monocytic, myeloblastic, adenocarcinoma, adrenocortical cancer, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute T-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, bone cancer, brain cancer, brain stem glioma, breast cancer, bronchogenic carcinoma, cervical cancer, cholangiocarcinoma, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myleogeneous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, duodenal cancer, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fallopian tube carcinoma, fibrosarcoma, follicular lymphoma, gastric carcinoma, germ cell testicular cancer, gestational trophobalstic disease, glioblastoma, gall bladder cancer, head and neck cancer, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, liposarcoma, lung cancer both small cell lung cancer and non-small cell lung cancer, lymphagioendothelio-sarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma, including Diffuse Large B-celllymphoma, follicular lymphoma, Hodgkin's lymphoma and non-Hodgkin's lymphoma, malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, leukemia, lymphoma, medullary carcinoma, medulloblastoma, melanoma (cutaneous or intraocular), meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer,

papillary adenocarcinomas, papillary carcinoma, parathyroid cancer, peripheral T -cell lymphoma, pinealoma, pituitary adenoma, polycythemia vera, prostate cancer including hormone-insensitive (refractory) prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small intestine cancer, solid tumors (carcinomas and sarcomas), small cell lung cancer, spinal axis tumors, spleen cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, testicular cancer (including germ cell testicular cancer), thyroid cancer, urethra cancer, uterine cancer, Waldenstram's macroglobulinemia, testicular tumors, vaginal cancer, vulva cancer, Wilms' tumor, embryonal rhabdomyosarcoma, pediatric acute lymphoblastic leukemia, pediatric acute myelogenous leukemia, pediatric alveolar rhabdomyosarcoma, pediatric anaplastic ependymoma, pediatric anaplastic large cell lymphoma, pediatric anaplastic medulloblastoma, pediatric atypical teratoidlrhabdoid tumor of the central nervous system, pediatric biphenotypic acute leukemia, pediatric Burkitts lymphoma, pediatric cancers of Ewing's family of tumors such as primitive neuroectodermal rumors, pediatric diffuse anaplastic Wilm's tumor, pediatric favorable histology Wilm's tumor, pediatric glioblastoma, pediatric medulloblastoma, pediatric neuroblastoma, pediatric neuroblastoma-derived myelocytomatosis, pediatric pre-B-cell cancers (such as leukemia), pediatric psteosarcoma, pediatric rhabdoid kidney tumor, pediatric rhabdomyosarcoma, and pediatric T-cell cancers such as lymphoma and skin cancer; and

(b) the additional therapeutic agent is selected from the group of anti-cancer agents consisting of alkylating agents, angiogenesis inhibitors, antibodies, antimetabolites, antimitotics, antiproliferatives, aurora kinase inhibitors, Bcl-2 family protein (for example, Bcl-xL, Bcl-2, Bcl-w) inhibitors, Bcr-Abl kinase inhibitors, biologic response modifiers, cyclin-dependent kinase inhibitors, cell cycle inhibitors, cyclooxygenase-2 inhibitors, leukemia viral oncogene homolog (ErbB2) receptor inhibitors, growth factor inhibitors, heat shock protein (HSP)-90 inhibitors, histone deacetylase (HDAC) inhibitors inhibitors, hormonal therapies, inhibitors of apoptosis proteins (lAPs), immunologicals, intercalating antibiotics, kinase inhibitors, mammalian target of rapamycin inhibitors, mitogen-activated extracellular signal-regulated kinase inhibitors, microRNA's, small inhibitory ribonucleic acids (siRNAs), non-steroidal anti-inflammatory drugs (NSAID's), poly ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitors, platinum chemotherapeutics, polo-like kinase inhibitors, proteasome inhibitors, purine analogs, pyrimidine analogs, receptor tyrosine kinase inhibitors, retinoids/deltoids plant alkaloids and topoisomerase inhibitors.

19. Use of a compound according to any one of claims 1-13, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating diseases or disorders associated with the expression or over-expression of Mcl-1, wherein:
the diseases or disorders are selected from the group consisting of acoustic neuroma, acute leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia (monocytic, myeloblastic, adenocarcinoma, adrenocortical cancer, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute T-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, bone cancer, brain cancer, brain stem glioma, breast cancer, bronchogenic carcinoma, cervical cancer, cholangiocarcinoma, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myleogeneous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, duodenal cancer, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fallopian tube carcinoma, fibrosarcoma, follicular lymphoma, gastric carcinoma, germ cell testicular cancer, gestational trophobalstic disease, glioblastoma, gall bladder cancer, head and neck cancer, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, liposarcoma, lung cancer both small cell lung cancer and non-small cell lung cancer, lymphagioendothelio-sarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma, including Diffuse Large B-celllymphoma, follicular lymphoma, Hodgkin's lymphoma and non-Hodgkin's lymphoma, malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, leukemia, lymphoma, medullary carcinoma, medulloblastoma, melanoma (cutaneous or intraocular), meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, parathyroid cancer, peripheral T -cell lymphoma, pinealoma, pituitary adenoma, polycythemia vera, prostate cancer including hormone-insensitive (refractory) prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small intestine cancer, solid tumors (carcinomas and sarcomas), small cell lung cancer, spinal axis tumors, spleen cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, testicular cancer (including

germ cell testicular cancer), thyroid cancer, urethra cancer, uterine cancer, Waldenstram's macroglobulinemia, testicular tumors, vaginal cancer, vulva cancer, Wilms' tumor, embryonal rhabdomyosarcoma, pediatric acute lymphoblastic leukemia, pediatric acute myelogenous leukemia, pediatric alveolar rhabdomyosarcoma, pediatric anaplastic ependymoma, pediatric anaplastic large cell lymphoma, pediatric anaplastic medulloblastoma, pediatric atypical teratoidlrhabdoid tumor of the central nervous system, pediatric biphenotypic acute leukemia, pediatric Burkitts lymphoma, pediatric cancers of Ewing's family of tumors such as primitive neuroectodermal rumors, pediatric diffuse anaplastic Wilm's tumor, pediatric favorable histology Wilm's tumor, pediatric glioblastoma, pediatric medulloblastoma, pediatric neuroblastoma, pediatric neuroblastoma-derived myelocytomatosis, pediatric pre-B-cell cancers (such as leukemia), pediatric psteosarcoma, pediatric rhabdoid kidney tumor, pediatric rhabdomyosarcoma, and pediatric T-cell cancers such as lymphoma and skin cancer.

20. Use of a compound according to any one of claims 1-13, or a pharmaceutically acceptable salt thereof, and, optionally, an additional therapeutic agent, in the manufacture of a medicament for preventing, inhibiting, or treating the progression or onset of diseases or disorders associated with the expression or over-expression of anti-apoptotic Bcl-2 family protein members, wherein:

(a) the diseases or disorders are selected from the group consisting of acoustic neuroma, acute leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia (monocytic, myeloblastic, adenocarcinoma, adrenocortical cancer, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute T-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, bone cancer, brain cancer, brain stem glioma, breast cancer, bronchogenic carcinoma, cervical cancer, cholangiocarcinoma, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myleogeneous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, duodenal cancer, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fallopian tube carcinoma, fibrosarcoma, follicular lymphoma, gastric carcinoma, germ cell testicular cancer, gestational trophobalstic disease, glioblastoma, gall bladder cancer, head and neck cancer, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer,

leiomyosarcoma, liposarcoma, lung cancer both small cell lung cancer and non-small cell lung cancer, lymphagioendothelio-sarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma, including Diffuse Large B-celllymphoma, follicular lymphoma, Hodgkin's lymphoma and non-Hodgkin's lymphoma, malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, leukemia, lymphoma, medullary carcinoma, medulloblastoma, melanoma (cutaneous or intraocular), meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, parathyroid cancer, peripheral T -cell lymphoma, pinealoma, pituitary adenoma, polycythemia vera, prostate cancer including hormone-insensitive (refractory) prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small intestine cancer, solid tumors (carcinomas and sarcomas), small cell lung cancer, spinal axis tumors, spleen cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, testicular cancer (including germ cell testicular cancer), thyroid cancer, urethra cancer, uterine cancer, Waldenstram's macroglobulinemia, testicular tumors, vaginal cancer, vulva cancer, Wilms' tumor, embryonal rhabdomyosarcoma, pediatric acute lymphoblastic leukemia, pediatric acute myelogenous leukemia, pediatric alveolar rhabdomyosarcoma, pediatric anaplastic ependymoma, pediatric anaplastic large cell lymphoma, pediatric anaplastic medulloblastoma, pediatric atypical teratoidlrhabdoid tumor of the central nervous system, pediatric biphenotypic acute leukemia, pediatric Burkitts lymphoma, pediatric cancers of Ewing's family of tumors such as primitive neuroectodermal rumors, pediatric diffuse anaplastic Wilm's tumor, pediatric favorable histology Wilm's tumor, pediatric glioblastoma, pediatric medulloblastoma, pediatric neuroblastoma, pediatric neuroblastoma-derived myelocytomatosis, pediatric pre-B-cell cancers (such as leukemia), pediatric psteosarcoma, pediatric rhabdoid kidney tumor, pediatric rhabdomyosarcoma, and pediatric T-cell cancers such as lymphoma and skin cancer; and

(b) the additional therapeutic agent is selected from the group of anti-cancer agents consisting of alkylating agents, angiogenesis inhibitors, antibodies, antimetabolites, antimitotics, antiproliferatives, aurora kinase inhibitors, Bcl-2 family protein (for example, Bcl-xL, Bcl-2, Bcl-w) inhibitors, Bcr-Abl kinase inhibitors, biologic response modifiers, cyclin-dependent kinase inhibitors, cell cycle inhibitors, cyclooxygenase-2 inhibitors, leukemia viral oncogene homolog (ErbB2) receptor inhibitors, growth factor inhibitors, heat

shock protein (HSP)-90 inhibitors, histone deacetylase (HDAC) inhibitors inhibitors, hormonal therapies, inhibitors of apoptosis proteins (lAPs), immunologicals, intercalating antibiotics, kinase inhibitors, mammalian target of rapamycin inhibitors, mitogen-activated extracellular signal-regulated kinase inhibitors, microRNA's, small inhibitory ribonucleic acids (siRNAs), non-steroidal anti-inflammatory drugs (NSAID's), poly ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitors, platinum chemotherapeutics, polo-like kinase inhibitors, proteasome inhibitors, purine analogs, pyrimidine analogs, receptor tyrosine kinase inhibitors, retinoids/deltoids plant alkaloids and topoisomerase inhibitors.