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(54) Title: TETRACYCLIC DERIVATIVES AS KRAS INHIBITORS

(57) Abstract: Provided are certain tetracyclic derivatives that inhibit certain K-Ras proteins and are therefore useful for the treatment of cancers mediated by such proteins. Also provided are pharmaceutical compositions containing such compounds and processes for preparing such compounds.

TETRACYCLIC DERIVATIVES AS KRAS INHIBITORS

Field of the disclosure

The present disclosure provides certain tetracyclic derivatives that inhibit certain K-Ras proteins and are therefore useful for the treatment of cancers mediated by such proteins. Also provided are pharmaceutical compositions containing such compounds and processes for preparing such compounds.

Background

Kirsten Rat Sarcoma 2 Viral Oncogene Homolog (KRAS) gene is a prevalent oncogene that encodes a small GTPase transductor protein called K-Ras. K-Ras can serve as a molecular switch by cyling between active GTP-bound and inactive GDP-bound forms (see Science 2001;294:1299–304.). K-Ras signaling is activated by RAS guanine nucleotide exchange factors (GEFs), e.g., Son of Sevenless homologue (SOS) protein, that facilitate the GDP to GTP exchange of K-Ras (see Curr Biol 2005;15:563–74.). The interaction between K-Ras and GTPase-activating proteins (GAPs) such as p120GAP and neurofibromin, potentiates K-Ras intrinsic GTPase activity and accelerates GTP hydrolysis and diminishes K-Ras signaling (see Curr. Biol. 2005;15:563–74.).

K-Ras plays a crucial role in the regulation of cell proliferation, differentiation and survival by signaling through several major downstream pathways, including the MAPK, the PI3K and the Ral-GEFs pathways (see Lung Cancer 2018;124: 53–64), among them the MAPK pathway is the best characterized (see Mol. Cell Biol.1995;15:6443–6453.). K-Ras-GTP binds to and activates RAF kinases, which phosphorylates MEK and subsequently phosphorylates ERK. Phospho-ERK can further activate downstream cytosolic proteins, which then translocate to the nucleus to drive the expression of diverse genes, propagating the growth signal.

PI3K pathway is also involved in RAS-mediated tumorigenesis (see Cell 2007;129:957–968.). Upon activation by K-Ras-GTP, PI3K phosphorylates PIP2 to form PIP3, activates PDK1 and then phosphorylates AKT. pAKT yields phosphorylation of several physiological substrates, e.g., mTOR, FOXO and NF-κB that promote metabolism, cell-cycle progression, resistance to apoptosis, cell survival and migration. The Ral-GEFs signaling pathway plays a key role in RAS-mediated oncogenesis as well (see Proc. Natl. Acad. Sci. U. S. A. 1994; 91:11089–11093.). The K-Ras effector, RALGDS, stimulates the RAS family RAL-A/B small GTPases for the subsequent signaling

cascades. RALGDS can also promote the JNK pathway to stimulate transcription of pro-survival and cell-cycle progression genes for cell proliferation and survival.

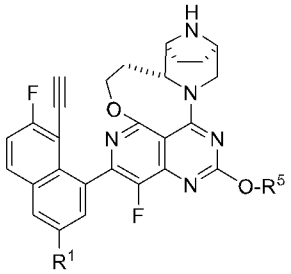
KRAS gene is the most frequently mutated oncogene in human cancer. KRAS mutations are associated with poor clinical outcome and found at high frequency in pancreatic cancer (~90%), colorectal cancer (~44%) and non-small-cell lung cancer (NSCLC) (~29%) (see Cancer Discov. 2021;11:1–16). KRAS mutations are also present in breast cancer, liver cancer, biliary tract malignancies, endometrial cancer, cervical cancer, bladder cancer and myeloid leukemia. The most common KRAS mutations are observed at residues G12 (77%), G13 (10%), and Q61 (6%), and the most predominant KRAS variant in human malignancies is G12D (35%), followed by G12V (29%), G12C (21%), G12A (7%), G12R (5%), and G12S (3%) (see Cancer Discov. 2021;11:1-16). These mutations perturbate GTP hydrolysis of K-Ras by interfering with GAP binding/stimulation and/or reducing K-Ras intrinsic GTPase activity, resulting in constitutive activation of the protein and K-Ras signaling.

Targeting KRAS signaling has been a long pursuit in drug discovery. Among KRAS mutants, K-Ras G12C offers special opportunity, because it harbors a non-native cysteine residue, which can act as nucleophile and therefore can be targeted by covelent attachment. Besides AMG510, which is an approved drug for treating K-Ras G12C driven cancers, several other K-Ras G12C covelent inhibitors, including MRTX849, JNJ-74699157 and LY349944631, are in clinical trials for treating cancer patients with KRAS G12C mutation (see ACS Cent. Sci. 2020;6:1753-1761). These compounds ocuppy a dynamic pocket in the switch II region of K-Ras thereby irreversibly locking K-Ras G12C in inactive GDP-bound state. Since KRAS mutations, including G12C, enrich predominantly active-state protein in cancer cells, sufficient residual GTPase activity and nucleotide cycling are required for effective inhibition of K-Ras by inactive state-selective drugs (see Cell 2020; 183(4):850-859). Currently, there are no molecules in clinical trial that can inhibit K-Ras G12C by binding to its active GTP form or both GTP and GDP forms. Compared to K-ras G12C mutant, other prevalent K-Ras mutants, such as G12D, do not contain non-native cysteine residue and cycle through inactive state at extremely low rate, thus making non-G12C mutant-specific drug discovery more challenging.

Given the role of K-Ras mutants in human malignancy, there is still unmet medical need for development of new treatments for cancer patients with KRAS mutations. The present disclosure fulfills this and related needs.

Summary

In a first aspect, provided is a compound selected from Table IA, or a pharmaceutically acceptable salt thereof:



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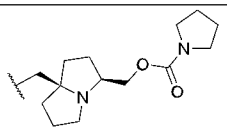
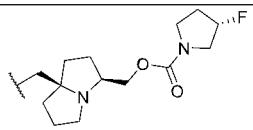
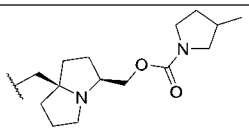
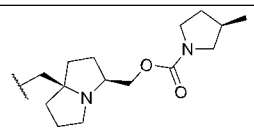
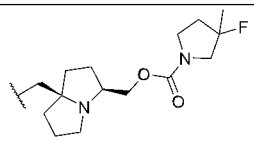
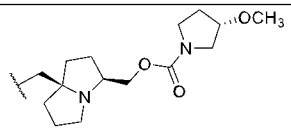
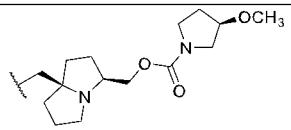
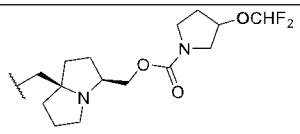
1.1	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl pyrrolidine-1-carboxylate
1.2	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl (S)-3-fluoropyrrolidine-1-carboxylate
1.3	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 3-methylpyrrolidine-1-carboxylate

Cpd #	R^1	R^5	Name
1.4	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl (R)-3-methylpyrrolidine-1-carboxylate
1.5	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 3-fluoro-3-methylpyrrolidine-1-carboxylate
1.6	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl (S)-3-methoxypyrrolidine-1-carboxylate
1.7	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl (R)-3-methoxypyrrolidine-1-carboxylate
1.8	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-

Cpd #	R^1	R^5	Name
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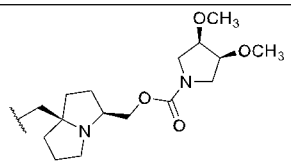
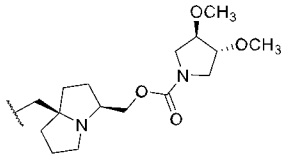
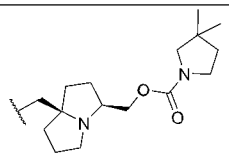
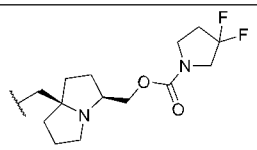
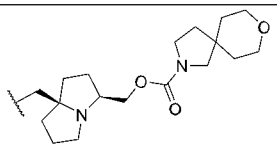
1.9	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl (3S,4R)-3,4-dimethoxypyrrolidine-1-carboxylate
1.10	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl (3R,4R)-3,4-dimethoxypyrrolidine-1-carboxylate
1.11	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 3,3-dimethylpyrrolidine-1-carboxylate
1.12	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 3,3-difluoropyrrolidine-1-carboxylate
1.13	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-

Cpd #	R^1	R^5	Name
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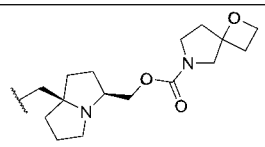
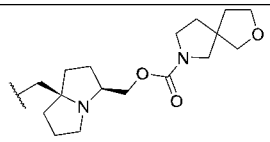
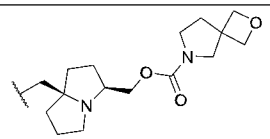
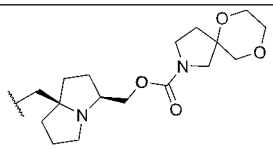
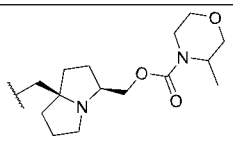
1.14	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 1-oxa-6-azaspiro[3.4]octane-6-carboxylate
1.15	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-7-azaspiro[4.4]nonane-7-carboxylate
1.16	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-6-azaspiro[3.4]octane-6-carboxylate
1.17	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 6,9-dioxa-2-azaspiro[4.5]decane-2-carboxylate
1.18	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-

Cpd #	R^1	R^5	Name
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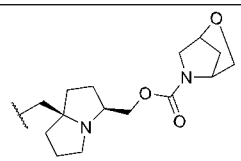
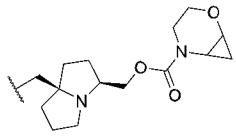
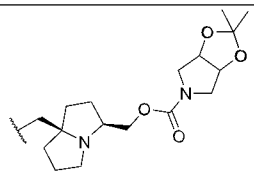
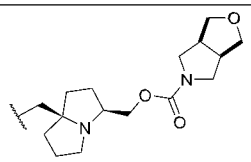
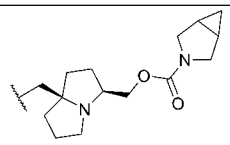
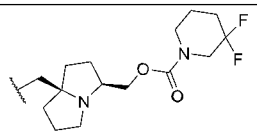
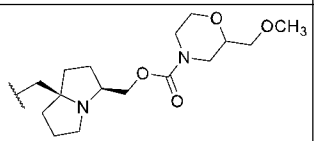
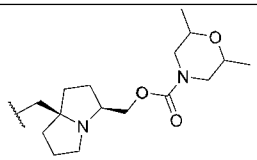
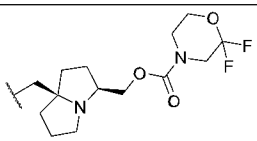
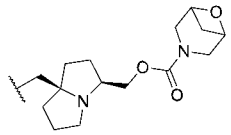
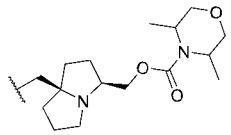
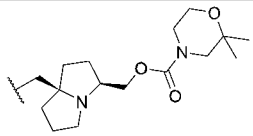
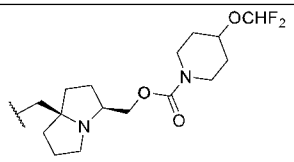
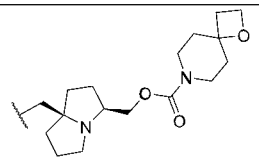
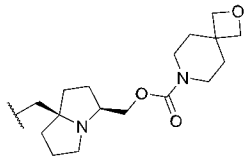
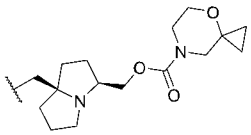
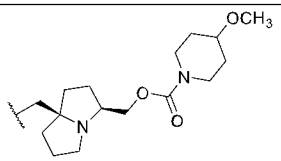
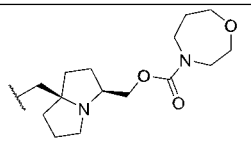
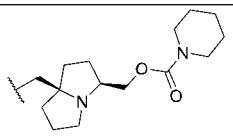
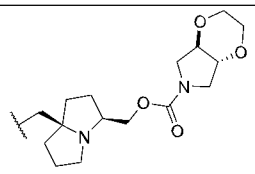
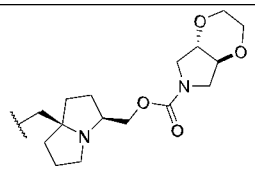
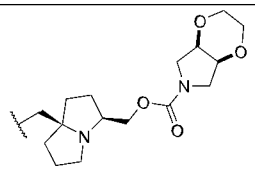
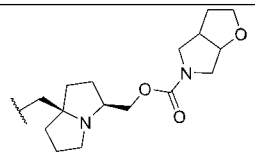
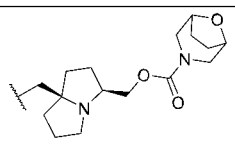
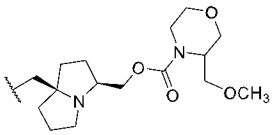
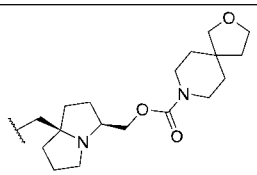
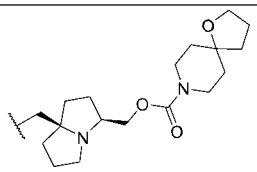
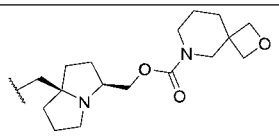
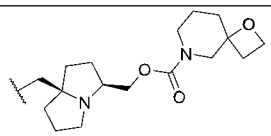
1.19	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate
1.20	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-5-azabicyclo[4.1.0]heptane-5-carboxylate
1.21	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 2,2-dimethyltetrahydro-5H-[1,3]dioxolo[4,5-c]pyrrole-5-carboxylate
1.22	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl (3aR,6aS)-tetrahydro-1H-furo[3,4-c]pyrrole-5(3H)-carboxylate

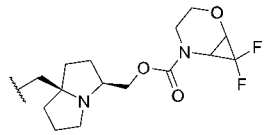
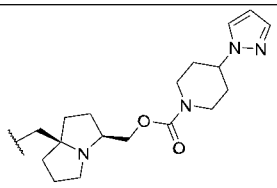
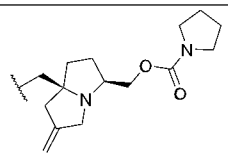
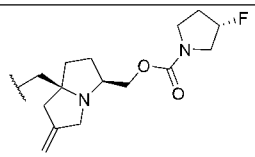
Cpd #	R^1	R^5	Name
1.23	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 3-azabicyclo[3.1.0]hexane-3-carboxylate
1.24	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 3,3-difluoropiperidine-1-carboxylate
1.25	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 2-(methoxymethyl)morpholine-4-carboxylate
1.26	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 2,6-dimethylmorpholine-4-carboxylate
1.27	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 2,2-difluoromorpholine-4-carboxylate

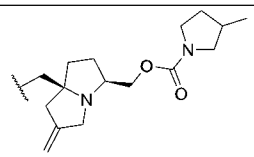
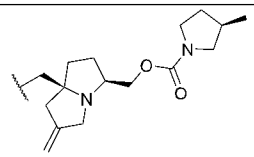
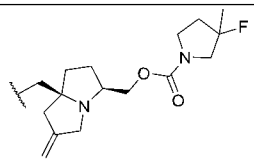
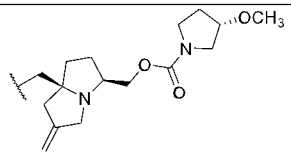
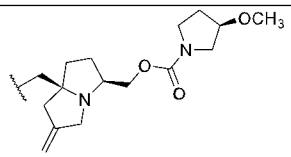
Cpd #	R^1	R^5	Name
1.28	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 6-oxa-3-azabicyclo[3.1.1]heptane-3-carboxylate
1.29	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 3,5-dimethylmorpholine-4-carboxylate
1.30	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 2,2-dimethylmorpholine-4-carboxylate
1.31	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 4-(difluoromethoxy)piperidine-1-carboxylate
1.32	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 1-oxa-7-azaspiro[3.5]nonane-7-carboxylate

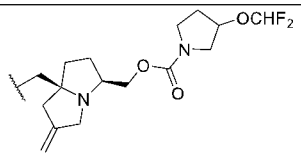
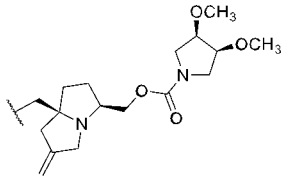
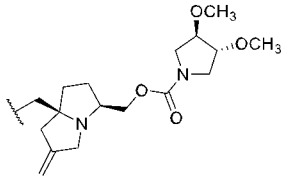
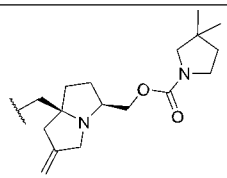
Cpd #	R^1	R^5	Name
1.33	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-7-azaspiro[3.5]nonane-7-carboxylate
1.34	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 4-oxa-7-azaspiro[2.5]octane-7-carboxylate
1.35	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 4-methoxypiperidine-1-carboxylate
1.36	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 1,4-oxazepane-4-carboxylate
1.37	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl piperidine-1-carboxylate

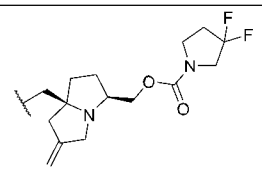
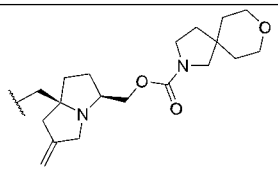
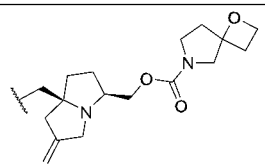
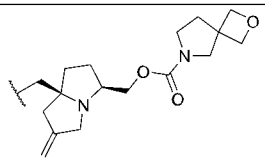
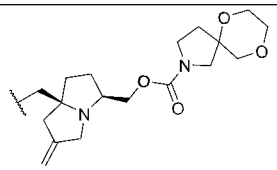
Cpd #	R^1	R^5	Name
1.38	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl (4aR,7aR)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate
1.39	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl (4aS,7aS)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate
1.40	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl (4aR,7aS)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate
1.41	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl hexahydro-5H-furo[2,3-c]pyrrole-5-carboxylate
1.42	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-

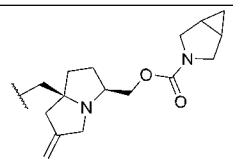
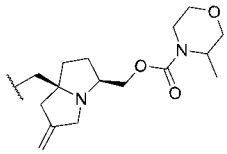
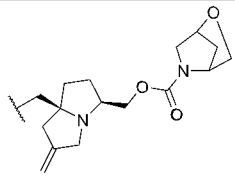
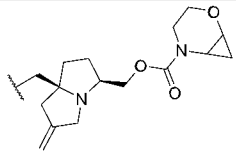
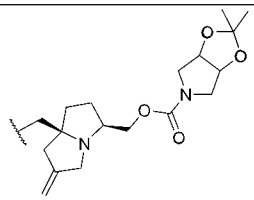
Cpd #	R^1	R^5	Name
			methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate
1.43	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 3-(methoxymethyl)morpholine-4-carboxylate
1.44	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-8-azaspiro[4.5]decane-8-carboxylate
1.45	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 1-oxa-8-azaspiro[4.5]decane-8-carboxylate
1.46	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-6-azaspiro[3.5]nonane-6-carboxylate
1.47	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-

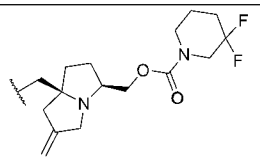
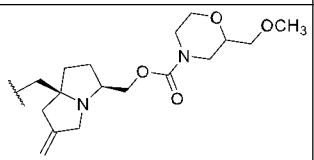
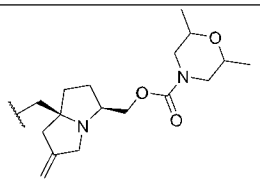
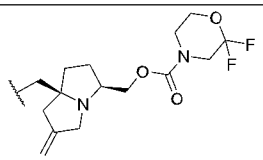
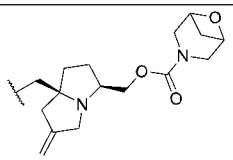
Cpd #	R^1	R^5	Name
			methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 1-oxa-6-azaspiro[3.5]nonane-6-carboxylate
1.48	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 7,7-difluoro-2-oxa-5-azabicyclo[4.1.0]heptane-5-carboxylate
1.49	H		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 4-(1H-pyrazol-1-yl)piperidine-1-carboxylate
1.50	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl pyrrolidine-1-carboxylate
1.51	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl (S)-3-fluoropyrrolidine-1-carboxylate

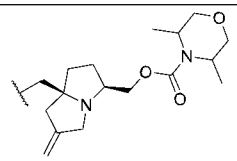
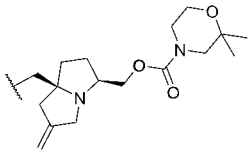
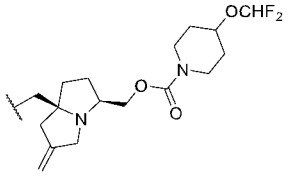
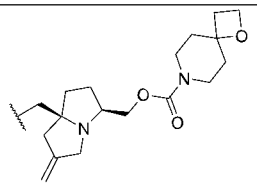
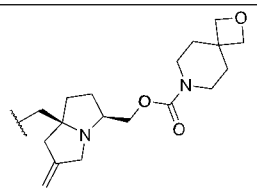
Cpd #	R^1	R^5	Name
1.52	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 3-methylpyrrolidine-1-carboxylate
1.53	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl (R)-3-methylpyrrolidine-1-carboxylate
1.54	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 3-fluoro-3-methylpyrrolidine-1-carboxylate
1.55	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl (S)-3-methoxypyrrolidine-1-carboxylate
1.56	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-

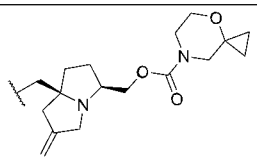
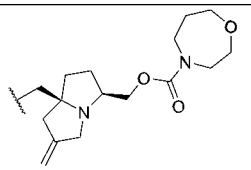
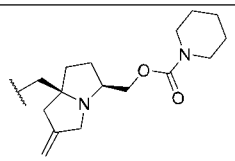
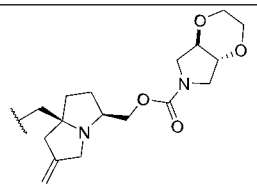
Cpd #	R^1	R^5	Name
			yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl (R)-3-methoxypyrrolidine-1-carboxylate
1.57	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 3-(difluoromethoxy)pyrrolidine-1-carboxylate
1.58	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl (3S,4R)-3,4-dimethoxypyrrolidine-1-carboxylate
1.59	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl (3R,4R)-3,4-dimethoxypyrrolidine-1-carboxylate
1.60	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 3,3-dimethylpyrrolidine-1-carboxylate

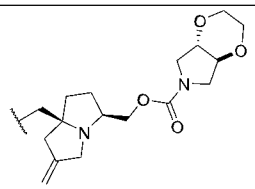
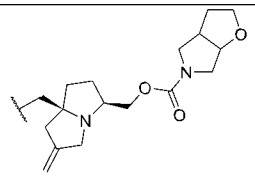
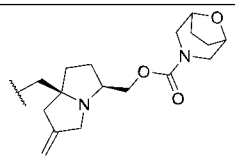
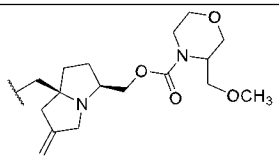
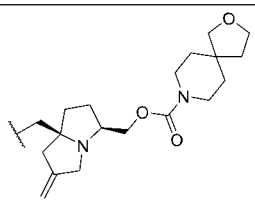
Cpd #	R^1	R^5	Name
1.61	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 3,3-difluoropyrrolidine-1-carboxylate
1.62	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 8-oxa-2-azaspiro[4.5]decane-2-carboxylate
1.63	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 1-oxa-6-azaspiro[3.4]octane-6-carboxylate
1.64	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-6-azaspiro[3.4]octane-6-carboxylate
1.65	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 6,9-dioxa-2-azaspiro[4.5]decane-2-carboxylate

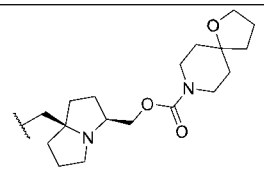
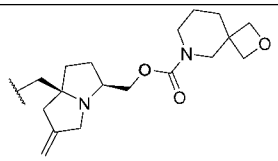
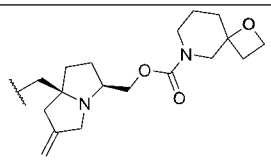
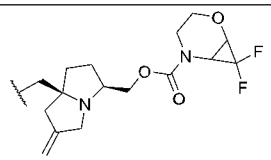
Cpd #	R^1	R^5	Name
1.66	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 3-azabicyclo[3.1.0]hexane-3-carboxylate
1.67	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 3-methylmorpholine-4-carboxylate
1.68	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate
1.69	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-5-azabicyclo[4.1.0]heptane-5-carboxylate
1.70	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-

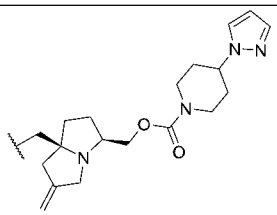
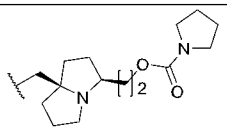
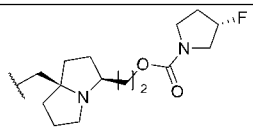
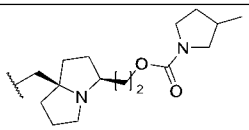
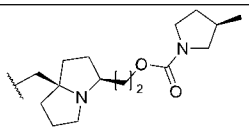
Cpd #	R^1	R^5	Name
			yl)methyl 2,2-dimethyltetrahydro-5H-[1,3]dioxolo[4,5-c]pyrrole-5-carboxylate
1.71	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 3,3-difluoropiperidine-1-carboxylate
1.72	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 2-(methoxymethyl)morpholine-4-carboxylate
1.73	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 2,6-dimethylmorpholine-4-carboxylate
1.74	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 2,2-difluoromorpholine-4-carboxylate
1.75	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-

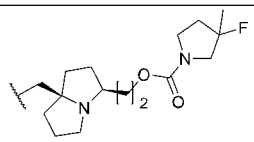
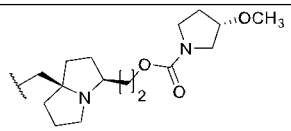
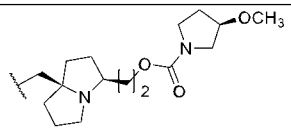
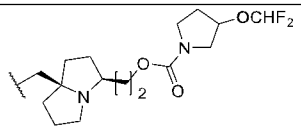
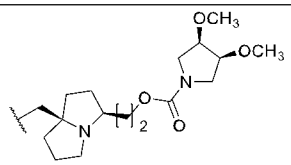
Cpd #	R^1	R^5	Name
			yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 6-oxa-3-azabicyclo[3.1.1]heptane-3-carboxylate
1.77	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 3,5-dimethylmorpholine-4-carboxylate
1.77	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 2,2-dimethylmorpholine-4-carboxylate
1.78	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 4-(difluoromethoxy)piperidine-1-carboxylate
1.79	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 1-oxa-7-azaspiro[3.5]nonane-7-carboxylate
1.80	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-

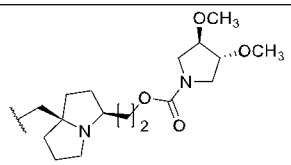
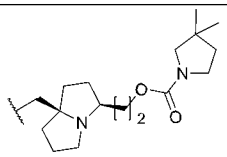
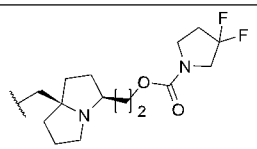
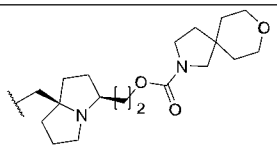
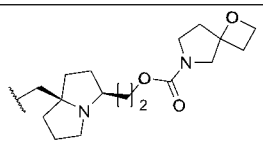
Cpd #	R^1	R^5	Name
			yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-7-azaspiro[3.5]nonane-7-carboxylate
1.81	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 4-oxa-7-azaspiro[2.5]octane-7-carboxylate
1.82	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 1,4-oxazepane-4-carboxylate
1.83	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl piperidine-1-carboxylate
1.84	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl (4aR,7aR)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate

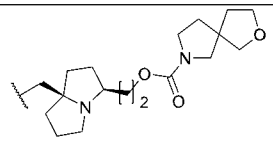
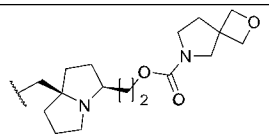
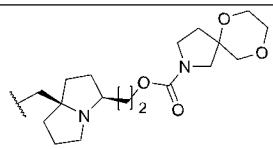
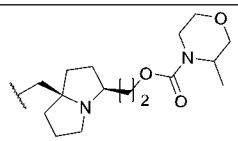
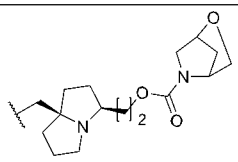
Cpd #	R^1	R^5	Name
1.85	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl (4aS,7aS)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate
1.86	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl hexahydro-5H-furo[2,3-c]pyrrole-5-carboxylate
1.87	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate
1.88	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 3-(methoxymethyl)morpholine-4-carboxylate
1.89	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-

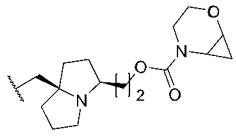
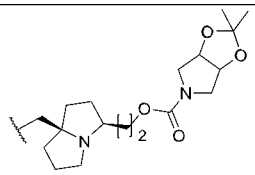
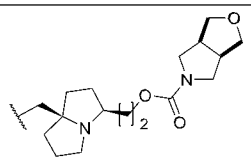
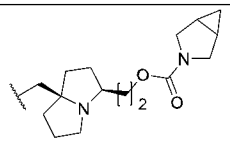
Cpd #	R^1	R^5	Name
			yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-8-azaspiro[4.5]decane-8-carboxylate
1.90	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 1-oxa-8-azaspiro[4.5]decane-8-carboxylate
1.91	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-6-azaspiro[3.5]nonane-6-carboxylate
1.92	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 1-oxa-6-azaspiro[3.5]nonane-6-carboxylate
1.93	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 7,7-difluoro-2-oxa-5-azabicyclo[4.1.0]heptane-5-carboxylate

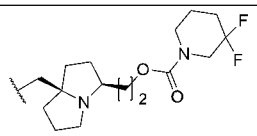
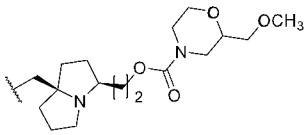
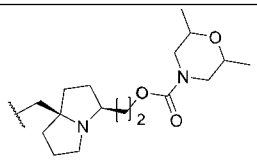
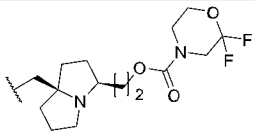
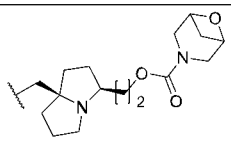
Cpd #	R^1	R^5	Name
1.94	H		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 4-(1H-pyrazol-1-yl)piperidine-1-carboxylate
1.95	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl pyrrolidine-1-carboxylate
1.96	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl (S)-3-fluoropyrrolidine-1-carboxylate
1.97	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 3-methylpyrrolidine-1-carboxylate
1.98	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl (R)-3-methylpyrrolidine-1-carboxylate

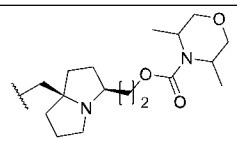
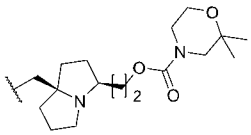
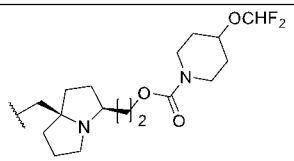
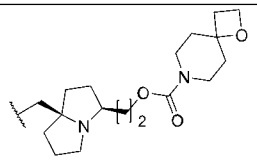
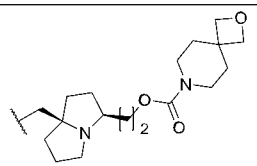
Cpd #	R^1	R^5	Name
1.99	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 3-fluoro-3-methylpyrrolidine-1-carboxylate
2.1	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl (S)-3-methoxypyrrolidine-1-carboxylate
2.2	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl (R)-3-methoxypyrrolidine-1-carboxylate
2.3	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 3-(difluoromethoxy)pyrrolidine-1-carboxylate
2.4	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-

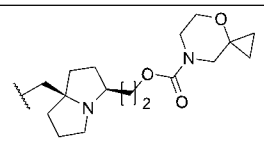
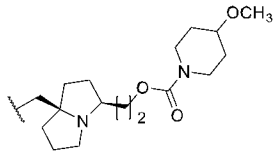
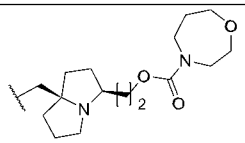
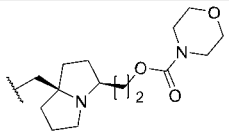
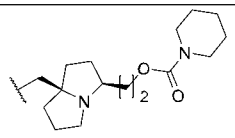
Cpd #	R^1	R^5	Name
			yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl (3S,4R)-3,4-dimethoxypyrrolidine-1-carboxylate
2.5	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl (3R,4R)-3,4-dimethoxypyrrolidine-1-carboxylate
2.6	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 3,3-dimethylpyrrolidine-1-carboxylate
2.7	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 3,3-difluoropyrrolidine-1-carboxylate
2.8	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 8-oxa-2-azaspiro[4.5]decane-2-carboxylate
2.9	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-

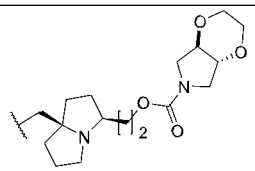
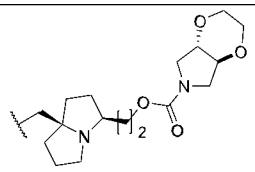
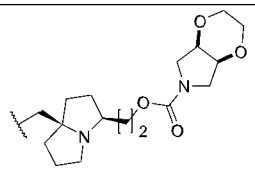
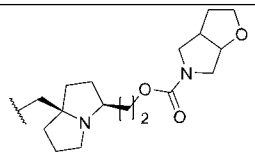
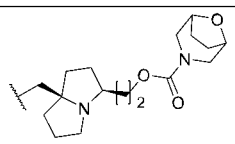
Cpd #	R^1	R^5	Name
			yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 1-oxa-6-azaspiro[3.4]octane-6-carboxylate
2.10	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-7-azaspiro[4.4]nonane-7-carboxylate
2.11	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-6-azaspiro[3.4]octane-6-carboxylate
2.12	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 6,9-dioxa-2-azaspiro[4.5]decane-2-carboxylate
2.13	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 3-methylmorpholine-4-carboxylate
2.14	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-

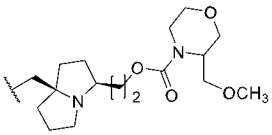
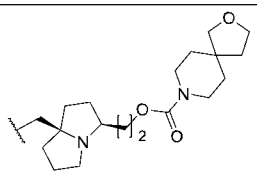
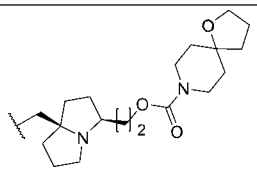
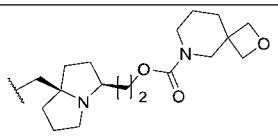
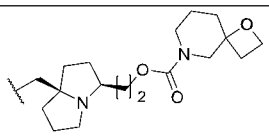
Cpd #	R^1	R^5	Name
			yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate
2.15	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-5-azabicyclo[4.1.0]heptane-5-carboxylate
2.16	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 2,2-dimethyltetrahydro-5H-[1,3]dioxolo[4,5-c]pyrrole-5-carboxylate
2.17	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl (3aR,6aS)-tetrahydro-1H-furo[3,4-c]pyrrole-5(3H)-carboxylate
2.18	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 3-azabicyclo[3.1.0]hexane-3-carboxylate

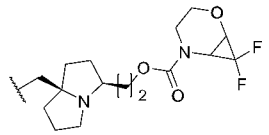
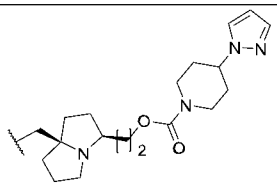
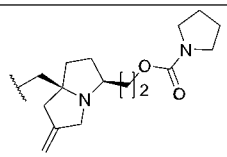
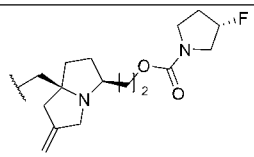
Cpd #	R^1	R^5	Name
2.19	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 3,3-difluoropiperidine-1-carboxylate
2.20	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 2-(methoxymethyl)morpholine-4-carboxylate
2.21	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 2,6-dimethylmorpholine-4-carboxylate
2.22	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 2,2-difluoromorpholine-4-carboxylate
2.23	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 6-oxa-3-azabicyclo[3.1.1]heptane-3-carboxylate

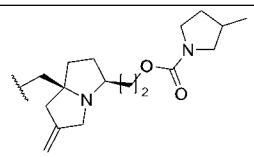
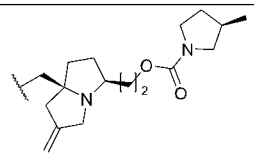
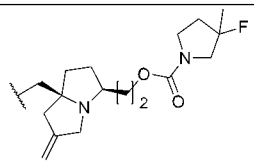
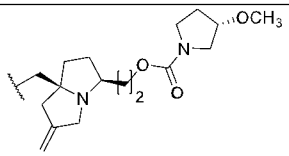
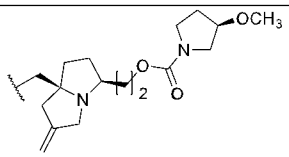
Cpd #	R^1	R^5	Name
2.24	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 3,5-dimethylmorpholine-4-carboxylate
2.25	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 2,2-dimethylmorpholine-4-carboxylate
2.26	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 4-(difluoromethoxy)piperidine-1-carboxylate
2.27	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 1-oxa-7-azaspiro[3.5]nonane-7-carboxylate
2.28	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-7-azaspiro[3.5]nonane-7-carboxylate

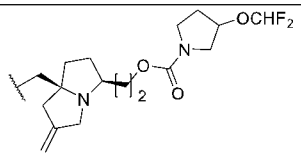
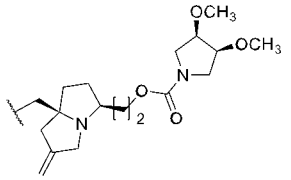
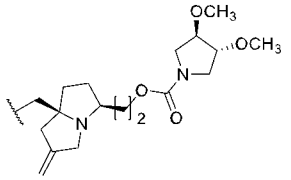
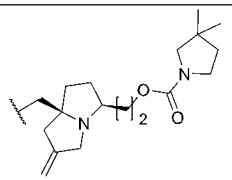
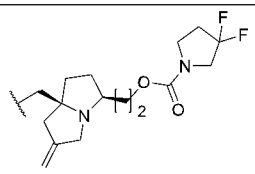
Cpd #	R^1	R^5	Name
2.29	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 4-oxa-7-azaspiro[2.5]octane-7-carboxylate
2.30	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 4-methoxypiperidine-1-carboxylate
2.31	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 1,4-oxazepane-4-carboxylate
2.32			2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl morpholine-4-carboxylate
2.33	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl piperidine-1-carboxylate

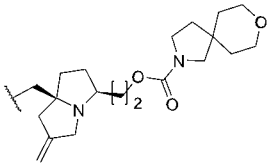
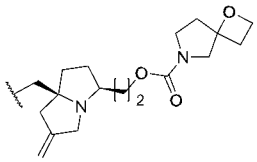
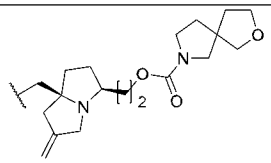
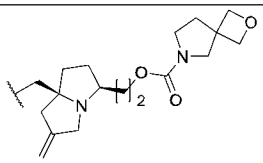
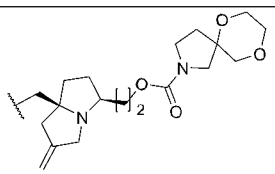
Cpd #	R^1	R^5	Name
2.34	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl (4aR,7aR)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate
2.35	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl (4aS,7aS)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate
2.36	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl (4aR,7aS)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate
2.37	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl hexahydro-5H-furo[2,3-c]pyrrole-5-carboxylate
2.38	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-

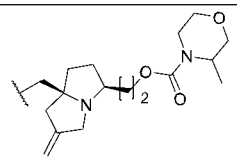
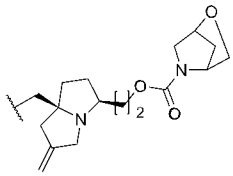
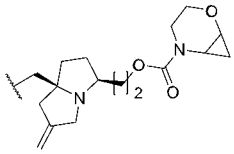
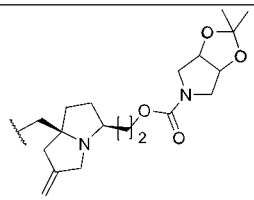
Cpd #	R^1	R^5	Name
			methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate
2.39	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 3-(methoxymethyl)morpholine-4-carboxylate
2.40	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-8-azaspiro[4.5]decane-8-carboxylate
2.41	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 1-oxa-8-azaspiro[4.5]decane-8-carboxylate
2.42	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-6-azaspiro[3.5]nonane-6-carboxylate
2.43	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-

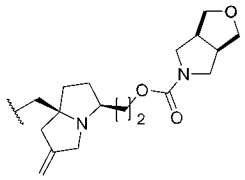
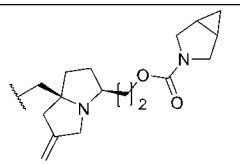
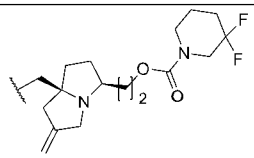
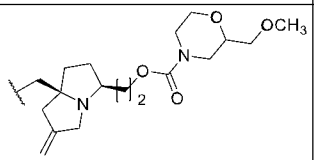
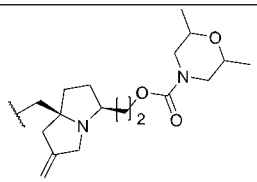
Cpd #	R^1	R^5	Name
			methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 1-oxa-6-azaspiro[3.5]nonane-6-carboxylate
2.44	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 7,7-difluoro-2-oxa-5-azabicyclo[4.1.0]heptane-5-carboxylate
2.45	H		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 4-(1H-pyrazol-1-yl)piperidine-1-carboxylate
2.46	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl pyrrolidine-1-carboxylate
2.47	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl (S)-3-fluoropyrrolidine-1-carboxylate

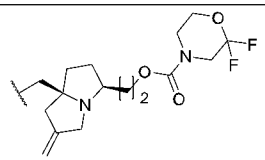
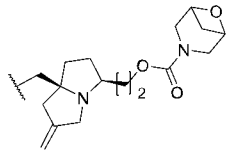
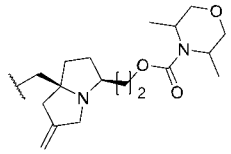
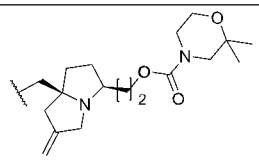
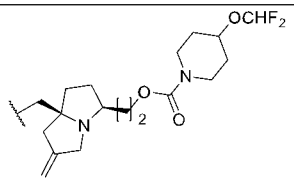
Cpd #	R^1	R^5	Name
2.48	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 3-methylpyrrolidine-1-carboxylate
2.49	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl (R)-3-methylpyrrolidine-1-carboxylate
2.50	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 3-fluoro-3-methylpyrrolidine-1-carboxylate
2.51	H		2((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl (S)-3-methoxypyrrolidine-1-carboxylate
2.52	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-

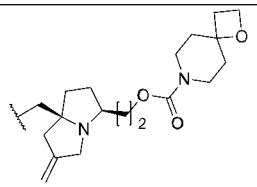
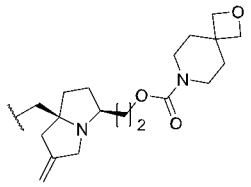
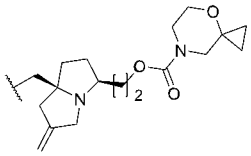
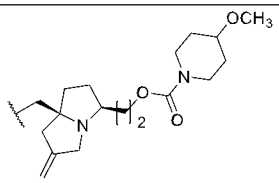
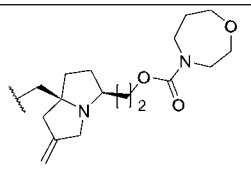
Cpd #	R^1	R^5	Name
			yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl (R)-3-methoxypyrrolidine-1-carboxylate
2.53	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 3-(difluoromethoxy)pyrrolidine-1-carboxylate
2.54	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl (3S,4R)-3,4-dimethoxypyrrolidine-1-carboxylate
2.55	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl (3R,4R)-3,4-dimethoxypyrrolidine-1-carboxylate
2.56	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 3,3-dimethylpyrrolidine-1-carboxylate
2.57	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-

Cpd #	R^1	R^5	Name
			yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 3,3-difluoropyrrolidine-1-carboxylate
2.58	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 8-oxa-2-azaspiro[4.5]decane-2-carboxylate
2.59	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 1-oxa-6-azaspiro[3.4]octane-6-carboxylate
2.60	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-7-azaspiro[4.4]nonane-7-carboxylate
2.61	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-6-azaspiro[3.4]octane-6-carboxylate
2.62	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-

Cpd #	R^1	R^5	Name
			yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 6,9-dioxa-2-azaspiro[4.5]decane-2-carboxylate
2.63	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 3-methylmorpholine-4-carboxylate
2.64	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate
2.65	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-5-azabicyclo[4.1.0]heptane-5-carboxylate
2.66	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 2,2-dimethyltetrahydro-5H-[1,3]dioxolo[4,5-c]pyrrole-5-carboxylate

Cpd #	R^1	R^5	Name
2.67	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl (3aR,6aS)-tetrahydro-1H-furo[3,4-c]pyrrole-5(3H)-carboxylate
2.68	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 3-azabicyclo[3.1.0]hexane-3-carboxylate
2.69	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 3,3-difluoropiperidine-1-carboxylate
2.70	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 2-(methoxymethyl)morpholine-4-carboxylate
2.71	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-

Cpd #	R^1	R^5	Name
			yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 2,6-dimethylmorpholine-4-carboxylate
2.72	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 2,2-difluoromorpholine-4-carboxylate
2.73	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 6-oxa-3-azabicyclo[3.1.1]heptane-3-carboxylate
2.74	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 3,5-dimethylmorpholine-4-carboxylate
2.75	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 2,2-dimethylmorpholine-4-carboxylate
2.76	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-

Cpd #	R^1	R^5	Name
			yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 4-(difluoromethoxy)piperidine-1-carboxylate
2.77	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 1-oxa-7-azaspiro[3.5]nonane-7-carboxylate
2.78	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-7-azaspiro[3.5]nonane-7-carboxylate
2.79	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 4-oxa-7-azaspiro[2.5]octane-7-carboxylate
2.80	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 4-methoxypiperidine-1-carboxylate
2.81	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-

Cpd #	R^1	R^5	Name
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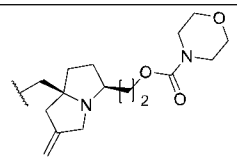
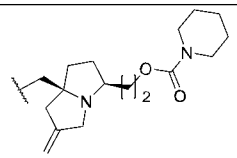
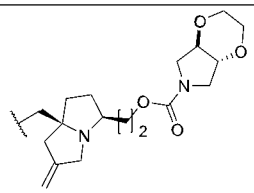
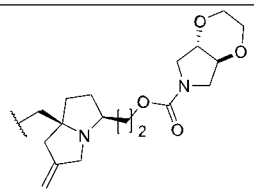
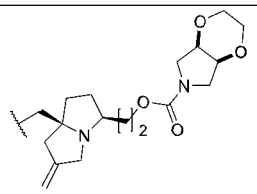
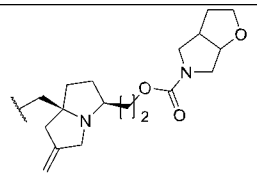
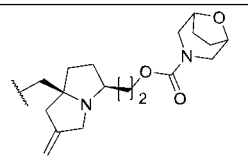
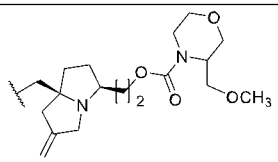
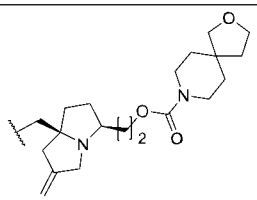
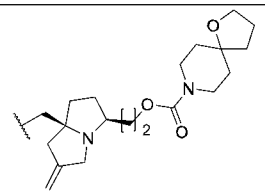
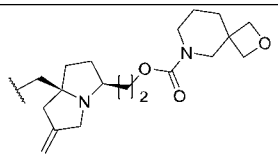
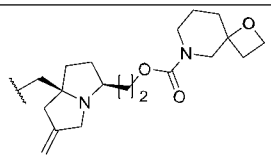
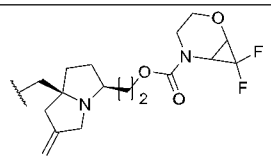
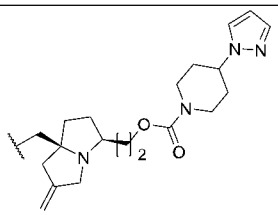
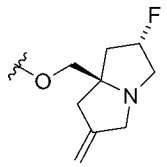
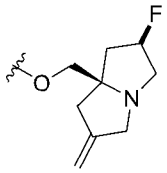
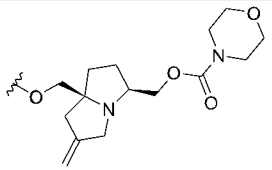
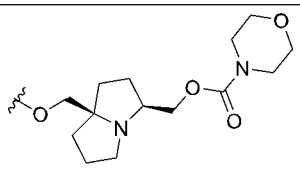
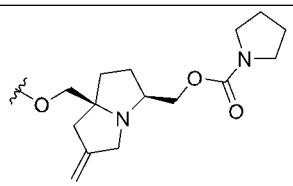
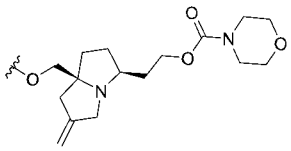
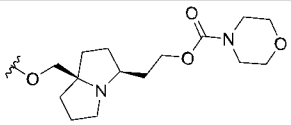
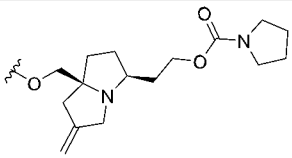
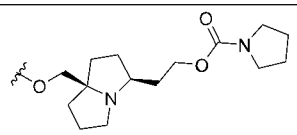
2.82			2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl morpholine-4-carboxylate
2.83	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl piperidine-1-carboxylate
2.84	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl (4aR,7aR)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate
2.85	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl (4aS,7aS)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate

Cpd #	R^1	R^5	Name
2.86	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl (4aR,7aS)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate
2.87	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl hexahydro-5H-furo[2,3-c]pyrrole-5-carboxylate
2.88	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate
2.89	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 3-(methoxymethyl)morpholine-4-carboxylate
2.90	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-

Cpd #	R^1	R^5	Name
			yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-8-azaspiro[4.5]decane-8-carboxylate
2.91	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 1-oxa-8-azaspiro[4.5]decane-8-carboxylate
2.92	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-6-azaspiro[3.5]nonane-6-carboxylate
2.93	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 1-oxa-6-azaspiro[3.5]nonane-6-carboxylate
2.94	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 7,7-difluoro-2-oxa-5-azabicyclo[4.1.0]heptane-5-carboxylate

Cpd #	R^1	R^5	Name
2.95	H		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 4-(1H-pyrazol-1-yl)piperidine-1-carboxylate
2.96	OH		5-ethynyl-6-fluoro-4-((6aR,7S,10R)-1-fluoro-13-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-2-yl)naphthalen-2-ol
2.97	OH		5-ethynyl-6-fluoro-4-((6aR,7S,10R)-1-fluoro-13-(((2R,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-2-yl)naphthalen-2-ol
2.98	OH		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl morpholine-4-carboxylate
2.99	OH		((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl morpholine-4-carboxylate

Cpd #	R^1	R^5	Name
3.1	OH		((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl pyrrolidine-1-carboxylate
3.2	OH		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl morpholine-4-carboxylate
3.3	OH		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl morpholine-4-carboxylate
3.4	OH		2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl pyrrolidine-1-carboxylate
3.5	OH		2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl pyrrolidine-1-carboxylate

In a second aspect, provided is a pharmaceutical composition comprising a compound selected from Table 1A above or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

In a third aspect, provided is a method of inhibiting K-Ras, in particular K-Ras G12D, in a cell, comprising contacting the cell with a compound selected from Table 1A above or a pharmaceutically acceptable salt thereof. In one embodiment of the third aspect, the contacting is in vitro. In another embodiment of the third aspect, the contacting is in vivo.

In a fourth aspect, provided is a method of inhibiting cell proliferation in vitro or in vivo, comprising contacting a cell with a compound selected from Table 1A above or a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof as disclosed herein. In one embodiment of the fourth aspect, the contacting is in vitro. In another embodiment of the fourth aspect, the contacting is in vivo.

In a fifth aspect, provided is a method of treating cancer in a patient, preferably the patient is in need of such treatment, which method comprises administering to the patient, preferably a patient in need of such treatment, a therapeutically effective amount of a compound selected from Table 1A above or a pharmaceutically acceptable salt thereof or a a pharmaceutical composition thereof as disclosed herein.

In a sixth aspect, provided is a method of treating cancer associated with K-Ras, in particular K-Ras G12D, in a patient, preferably the patient is in need of such treatment, which method comprises administering to the patient, preferably a patient in need of such treatment, a therapeutically effective amount of a compound selected from Table 1A above or a pharmaceutically acceptable salt thereof or a a pharmaceutical composition thereof as disclosed herein.

In a seventh aspect, provided is a compound selected from Table 1A above or a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof as disclosed herein for use as a medicament. In one embodiment, the medicament is useful for the treatment of cancer.

In an eighth aspect, provided is a compound selected from Table 1A above or a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof as disclosed herein for use as a therapy.

In a ninth aspect, provided is a compound selected from Table 1A above or a pharmaceutically acceptable salt thereof.

In a tenth aspect, provided is a compound selected from Table 1A above or a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof as disclosed herein for use in the treatment of cancers associated with KRas, in particular cancers associated with K-Ras G12D.

In an eleventh aspect, provided is a compound selected from Table 1A above or a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof as disclosed herein for use in inhibiting K-Ras, in particular K-Ras G12D.

In any of the aforementioned aspects involving the treatment of cancer, are further embodiments comprising a compound selected from Table 1A above or a pharmaceutically acceptable salt thereof in combination with at least one additional anticancer agent. When combination therapy is used, the agents can be administered simultaneously or sequentially.

Detailed Description

Definitions:

Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meaning:

A "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include:

acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as formic acid, acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or

salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an

organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine, and the like. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference in its entirety.

The compounds of Table 1A may also contain unnatural amounts of isotopes at one or more of the atoms that constitute such compounds. Unnatural amounts of an isotope may be defined as ranging from the amount found in nature to an amount 100% of the atom in question, that differ only in the presence of one or more isotopically enriched atoms. Exemplary isotopes that can be incorporated into a compound of Table 1A include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and $^{125}1$, respectively. Isotopically labeled compounds (e.g., those labeled with ^{3}H and ^{14}C) can be useful in compound or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes can be useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements). In some embodiments, in compounds of Table 1A one or more hydrogen atoms are replaced by ^{2}H or ^{3}H, or one or more carbon atoms are replaced by ^{13}C- or ^{14}C-enriched carbon. Positron emitting isotopes such as ^{15}O, ^{13}N, ^{11}C, and ^{15}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Isotopically labeled compounds can generally be prepared by following procedures analogous to those disclosed in the Schemes or in the Examples herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

A "pharmaceutically acceptable carrier or excipient" means a carrier or an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier or an excipient that is acceptable for veterinary use as well as human pharmaceutical use.

"A pharmaceutically acceptable carrier/excipient" as used in the specification and claims includes both one and more than one such excipient.

The term "disease" as used herein is intended to be generally synonymous, and is used interchangeably with, the terms "disorder," "syndrome," and "condition" (as in medical condition),

in that all reflect an abnormal condition of the human or animal body or of one of its parts that impairs normal functioning, is typically manifested by distinguishing signs and symptoms, and causes the human or animal to have a reduced duration or quality of life.

The term "combination therapy" means the administration of two or more therapeutic agents to treat a disease or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each active ingredient. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

The term "patient" is generally synonymous with the term "subject" and includes all mammals including humans. Examples of patients include humans, livestock such as cows, goats, sheep, pigs, and rabbits, and companion animals such as dogs, cats, rabbits, and horses. Preferably, the patient is a human.

"Treating" or "treatment" of a disease includes:

(1) preventing the disease, i.e., causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease;

(2) inhibiting the disease, i.e., delaying, arresting (i.e., stabilizing), or reducing the development or severity of the disease or its clinical symptoms; or

(3) relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

In one embodiment, treating or treatment of a disease includes inhibiting the disease, i.e., delaying, arresting or reducing the development or severity of the disease or its clinical symptoms; or relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

A "therapeutically effective amount" means the amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof that, when administered to a patient for treating a disease, is sufficient to affect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated. The therapeutically effective amount of a K-ras inhibitor disclosed herein can be administered to the patient in a single dosage form or multiples thereof. For example, 600 mg dose of a K-ras inhibitor can be administered in a single 600 mg tablet or two 300 mg tablets.

The terms "inhibiting" and "reducing," or any variation of these terms in relation of K-Ras G12D, includes any measurable decrease or complete inhibition to achieve a desired result. For example, there may be a decrease of about, at most about, or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or more, or any range derivable therein, reduction of K-Ras G12D GTPase activity; a decrease of K-Ras G12D GTP binding affinity or an increase of G12D GDP binding affinity; an increase of GTP off rate or a decrease of GDP off rate; a decrease of signaling transduction molecules levels downstream in the K-Ras pathway, e.g., a decrease in pERK level; and/or a decrease of K-Ras complex binding to downstream signaling molecules compared to normal.

General Synthesis

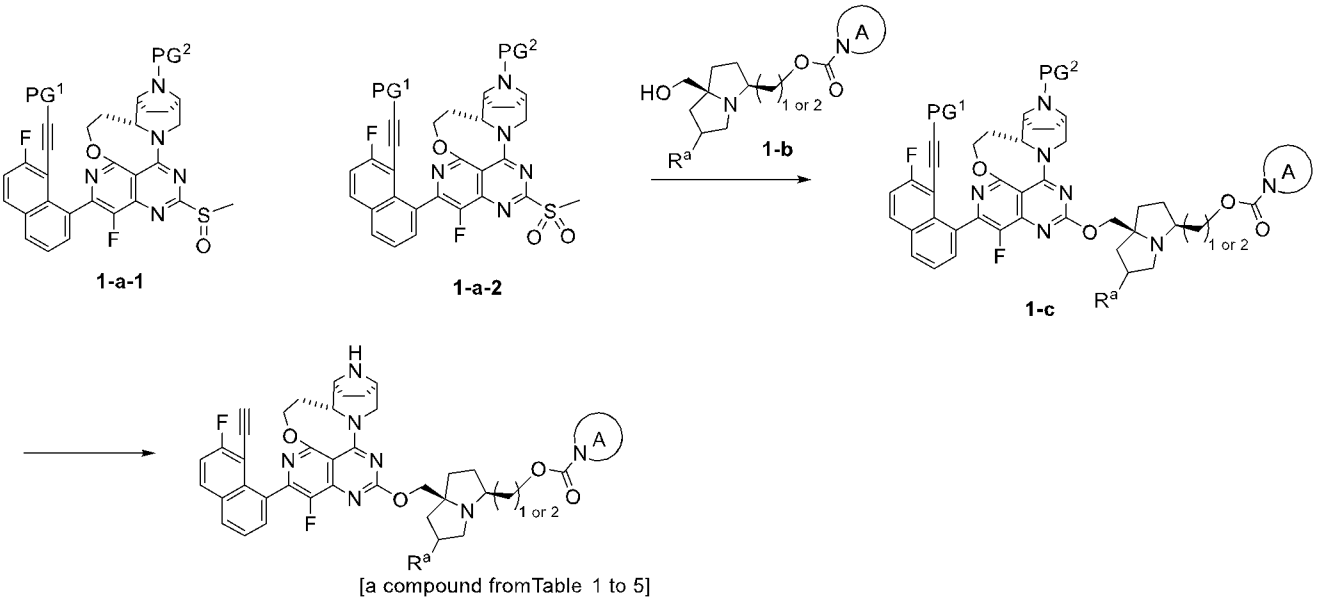
Compounds of Table 1A can be made by the methods depicted in the reaction schemes shown below.

The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.), Bachem (Torrance, Calif.), or Sigma (St. Louis, Mo.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition) and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of Table 1A can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art reading this disclosure. The starting materials and the intermediates, and the final products of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from about –78 °C to about 150 °C, such as from about 0 °C to about 125 °C and further such as at about room (or ambient) temperature, e.g., about 20 °C.

Compounds of Table 1A can be prepared as illustrated and described in Scheme 1 below.

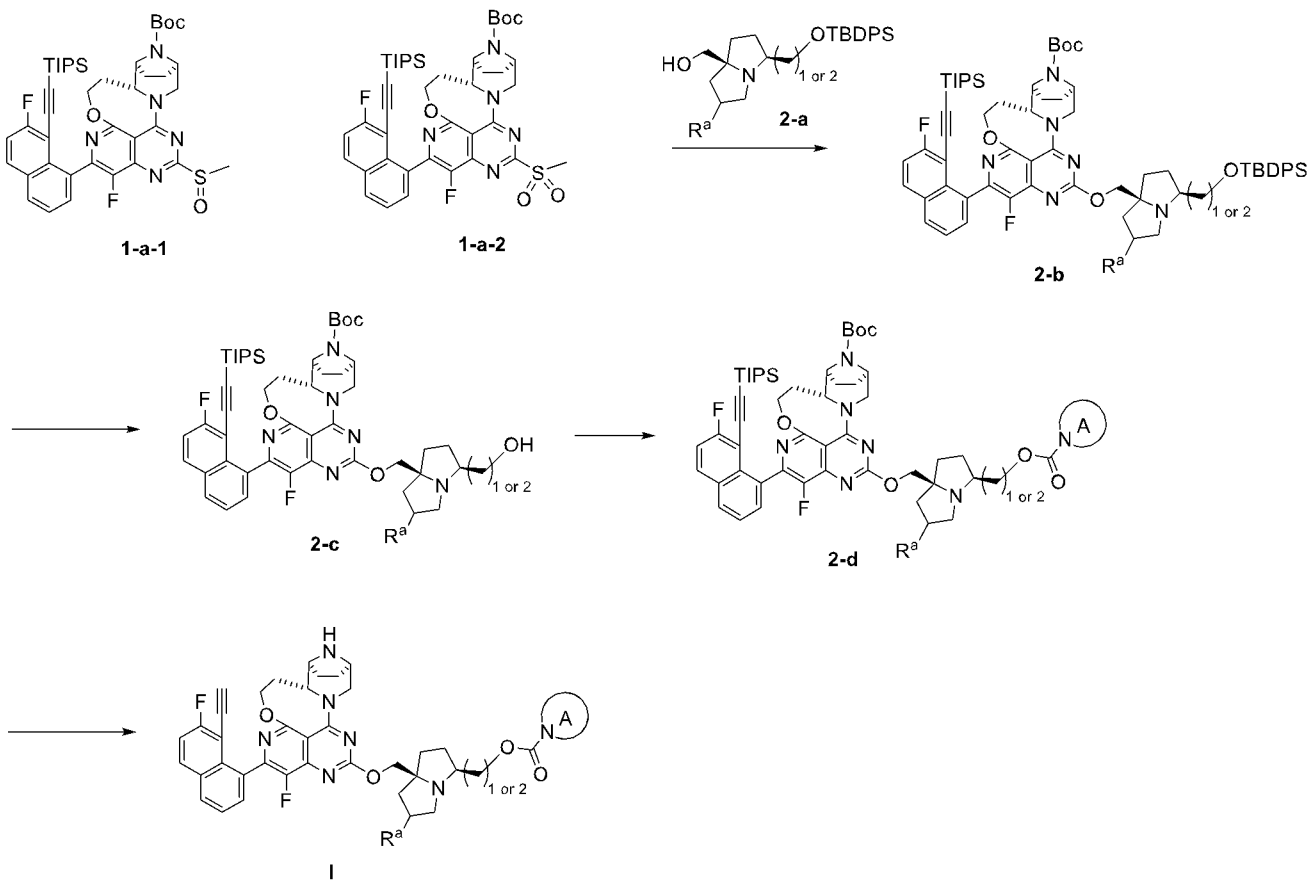
Scheme 1



Reacting compound **1-a-1 and 1-a-2** where PG^2 is an amino protecting group and PG^1 is an alkyne protecting group (synthesized as described in Example 1 below) with an alcohol of formula **1-b** where R^a is hydrogen or methylidenyl (H_2C=) and ring A is a cyclic aminyl R^1 to R^5 in Table 1A can provide a compound of formula **1-c**. Removal of the protecting groups provides compounds of Table 1A.

Alternatively, compounds of Table 1A can be prepared by the method illustrated in Scheme 2.

Scheme 2



Reacting compound **1-a-1 and 1-a-2** (synthesized as described in Example 2 below) with an alcohol of formula **2-a** where R^a is hydrogen or methylidine can provide a compound of formula **2-b**. The TBDPS group can be removed to provide a compound of formula **2-c**. Treatment of a compound of formula **2-c** with a coupling agent such as CDI, (4-nitrophenyl) carbonochloridate and the like, followed by treatment of the resulting intermediate with a suitable amine provides a compound of formula **2-d** which can then be converted to a compound of Table 1A as described above.

Utility

The present disclosure provides treatment of cancer mediated by K-ras, in particular with K-ras G12D mutants. In some embodiments, the cancer is pancreatic cancer, colorectal cancer, lung cancer, gall bladder cancer, thyroid cancer, and bile duct cancer. In certain embodiments the lung cancer is a non- small cell lung carcinoma (NSCLC), for example adenocarcinoma, squamous-cell lung carcinoma or large-cell lung carcinoma. In some embodiments, the lung cancer is a small cell

lung carcinoma. Other lung cancers treatable with the disclosed compounds include, but are not limited to, glandular tumors, carcinoid tumors and undifferentiated carcinomas.

K-ras G12D mutations are observed in hematological malignancies that affect blood, bone marrow, and/or lymph nodes. As such the compounds of Table 1A or a pharmaceutically acceptable salt thereof can be used for the treatment of acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), chronic myelogenous leukemia (CML), acute monocytic leukemia (AMoL) and/ or other leukemias, lymphomas such as all subtypes of Hodgkins lymphoma or non-Hodgkins lymphoma, plasma cell malignancies such as multiple myeloma, mantle cell lymphoma, and Waldenstrom's macroglubunemia.

The compounds of Table 1A, or a pharmaceutically acceptable salt thereof can be used for the treatment of a hyperproliferative disorder or metastasis in human who suffers from a cancer such as acute myeloid leukemia, cancer in adolescents, adrenocortical carcinoma childhood, AIDS related cancers (e.g. Lymphoma and Kaposi's Sarcoma), anal cancer, appendix cancer, astrocytomas, atypical teratoid, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, brain stem glioma, brain tumor, breast cancer, bronchial tumors, Burkitt lymphoma, carcinoid tumor, atypical teratoid, embryonal tumors, germ cell tumor, primary lymphoma, cervical cancer, childhood cancers, chordoma, cardiac tumors, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myleoproliferative disorders, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, extrahepatic ductal carcinoma in situ (DCIS), embryonal tumors, CNS cancer, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, eye cancer, fibrous histiocytoma of bone, gall bladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumors (GIST), germ cell tumor, gestational trophoblastic tumor, hairy cell leukemia, head and neck cancer, heart cancer, liver cancer, Hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors, pancreatic neuroendocrine tumors, kidney cancer, laryngeal cancer, lip and oral cavity cancer, liver cancer, lobular carcinoma in situ (LCIS), lung cancer, lymphoma, metastatic squamous neck cancer with occult primary, midline tract carcinoma, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma/plasma cell neoplasm, mycosis fungoides, myelodysplastic syndromes, myelodysplastic/myeloproliferative neoplasms, multiple myeloma, merkel cell carcinoma, malignant mesothelioma, malignant fibrous histiocytoma of bone and osteosarcoma, nasal cavity and paranasal

sinus cancer, nasopharyngeal cancer, neuroblastoma, non-hodgkin lymphoma, non-small cell lung cancer (NSCLC), oral cancer, lip and oral cavity cancer, oropharyngeal cancer, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pleuropulmonary blastoma, primary central nervous system (CNS) lymphoma, prostate cancer, rectal cancer, transitional cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, skin cancer, stomach (gastric) cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, T-Cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter, trophoblastic tumor, unusual cancers of childhood, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, or viral-induced cancer. The compounds of Table 1A, or a pharmaceutically acceptable salt thereof can also be used for the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e. g., psoriasis), restenosis, or prostate (e. g., benign prostatic hypertrophy (BPH)).

Testing

The K-Ras G12D activity of the compounds of Table 1A, or a pharmaceutically acceptable salt thereof can be tested using the *in vitro* assay described in Biological Examples 1 and 2 below.

Pharmaceutical Compositions

In general, the compounds of Table 1A (unless stated otherwise, reference to compound/compounds of Table 1A herein includes a pharmaceutically acceptable salt thereof) will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. Therapeutically effective amounts of compounds of Table 1A may range from about 0.01 to about 500 mg per kg patient body weight per day, which can be administered in single or multiple doses. A suitable dosage level may be from about 0.1 to about 250 mg/kg per day; about 0.5 to about 100 mg/kg per day. A suitable dosage level may be about 0.01 to about 250 mg/kg per day, about 0.05 to about 100 mg/kg per day, or about 0.1 to about 50 mg/kg per day. Within this range the dosage can be about 0.05 to about 0.5, about 0.5 to about 5 or about 5 to about 50 mg/kg per day. For oral administration, the compositions can be provided in the form of tablets containing about 1.0 to about 1000 milligrams of the active ingredient, particularly about 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, 600, 750, 800, 900, and 1000 milligrams of

the active ingredient. The actual amount of a compound of Table 1A, i.e., the active ingredient, will depend upon numerous factors such as the severity of the disease to be treated, the age and relative health of the patient, the potency of the compound being utilized, the route and form of administration, and other factors.

In general, compounds of Table 1A will be administered as pharmaceutical compositions by any one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository), or parenteral (e.g., intramuscular, intravenous or subcutaneous) administration. The preferred manner of administration is oral using a convenient daily dosage regimen, which can be adjusted according to the degree of affliction. Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate compositions.

The choice of formulation depends on various factors such as the mode of drug administration (e.g., for oral administration, formulations in the form of tablets, pills or capsules, including enteric coated or delayed release tablets, pills or capsules are preferred) and the bioavailability of the drug substance.

The compositions are comprised of in general, a compound of Table 1A in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are generally non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the compounds of Table 1A. Such excipient may be any solid, liquid, semi-solid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk and the like. Liquid and semisolid excipients may be selected from glycerol, propylene glycol, water, ethanol and various oils, including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc. Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose, and glycols.

Compounds of Table 1A may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles,

and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free water, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for parenteral administration include aqueous and non-aqueous (oily) sterile injection solutions of the active compounds which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

In addition to the formulations described previously, the compounds of Table 1A may also be formulated as a depot preparation. Such long -acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, pastilles, or gels formulated in conventional manner. Such compositions may comprise the active ingredient in a flavored basis such as sucrose and acacia or tragacanth.

Compounds of Table 1A may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter, polyethylene glycol, or other glycerides.

Certain compounds of Table 1A may be administered topically, that is by non-systemic administration. This includes the application of a compound of Table 1A externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the

compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as gels, liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient for topical administration may comprise, for example, from 0.001% to 10% w/w (by weight) of the formulation. In certain embodiments, the active ingredient may comprise as much as 10% w/w. In other embodiments, it may comprise less than 5% w/w. In certain embodiments, the active ingredient may comprise from 2% w/w to 5% w/w. In other embodiments, it may comprise from 0.1% to 1% w/w of the formulation.

For administration by inhalation, compounds of Table 1A may be conveniently delivered from an insufflator, nebulizer pressurized packs or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Alternatively, for administration by inhalation or insufflation, the compounds of Table 1A may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form, in for example, capsules, cartridges, gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator. Other suitable pharmaceutical excipients and their formulations are described in Remington's Pharmaceutical Sciences, edited by E. W. Martin (Mack Publishing Company, 20th ed., 2000).

The level of a compound of Table 1A in a formulation can vary within the full range employed by those skilled in the art. Typically, the formulation will contain, on a weight percent (wt. %) basis, from about 0.01-99.99 wt. % of a compound of Table 1A based on the total formulation, with the balance being one or more suitable pharmaceutical excipients. For example, the compound is present at a level of about 1-80 wt. %.

Combinations and Combination Therapies

Compounds of Table 1A or a pharmaceutically acceptable salt thereof may be used in combination with one or more other drugs in the treatment of diseases or conditions for which the

compounds of Table 1A or the other drugs may have utility. Such other drug(s) may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with a compound of Table 1A or a pharmaceutically acceptable salt thereof. When a compound of Table 1A or a pharmaceutically acceptable salt thereof is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of Table 1A or a pharmaceutically acceptable salt thereof can be used. Accordingly, the pharmaceutical compositions of the present disclosure also include those that contain one or more other drugs, in addition to a compound of Table 1A or a pharmaceutically acceptable salt thereof. The combination therapy may also include therapies in which the compound of Table 1A or a pharmaceutically acceptable salt thereof and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of Table 1A and the other active ingredients may be used in lower doses than when each is used singly. The weight ratio of the compound of this disclosure to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used.

Where the subject in need is suffering from or at risk of suffering from cancer, the patient can be treated with a compound of Table 1A or a pharmaceutically acceptable salt thereof in any combination with one or more other anti-cancer agents including but not limited to:

MAP kinase pathway (RAS/RAF/MEK/ERK) inhibitors including but not limited to: Vemurafanib (PLX4032, CAS No. 918504-65-1), Dabrafenib (CAS No. 1195765-45-7), Encorafenib (LGX818 CAS No. 1269440-17-6), TQ-B3233, XL-518 (Cas No. 1029872- 29-4, available from ACC Corp); trametinib (CAS No. 871700-17-3), selumetinib (AZD6244 CAS No. 606143-52-6), TQ-B3234, PD184352 (CAS No. 212631-79-3), PD325901 (CAS No. 391210-10-9), TAK-733 (CAS No. 1035555-63-5), pimasertinib (CAS No. 1236699-92-5), binimetinib (CAS No. 606143-89-9), refametinib (CAS No. 923032-37-5), cobimetinib (GDC- 0973 CAS No. 934660-93-2), AZD8330 (CAS No. 869357-68-6), BVD-523 (CAS No. 869886-67-9), LTT462 (CAS No. 869886-67-9), AMG510 (CAS No. 2296729-00-3), ARS853 (CAS No. 1629268-00-3), and any RAS inhibitors disclosed in patents WO2016049565, W020l6l64675,W020l6l68540, WO2017015562, WO2017058728, WO2017058768, WO2017058792, W02017058805,W02017058807, W02017058902, WO2017058915, W02017070256, WO2017087528, W02017100546, WO2017172979, W02017201161, WO2018064510, WO2018068017, and WO2018119183;

SHP2 inhibitors including but not limited to: SHP099 (CAS No. 2200214-93-1), TNO155 (CAS No. 1801765-04-7), RMC4630, JAB-3312, JAB-3068 and ERAS-601;

SOS1 inhibitors including but not limited to BI1701963 and BAY-293;

CSF1R inhibitors (PLX3397, LY3022855,) and CSF1R antibodies (IMC-054, RG7l55);

TGF beta receptor kinase inhibitor such as LY2157299;

BTK inhibitor such as ibrutinib; BCR-ABL inhibitors: Imatinib (CAS No. 152459-95-5); Inilotinib hydrochloride; Nilotinib (CAS No. 923288-95-3); Dasatinib (BMS-345825 CAS No. 302962-49-8); Bosutinib (SKI-606 CAS No. 380843-75-4); Ponatinib (AP24534 CAS No. 943319-70-8); Bafetinib (INNO406 CAS No. 859212-16-1); Danusertib (PHA-739358 CAS No. 827318-97-8), AT9283 (CAS No. 896466-04-9); Saracatinib (AZD0530 CAS No. 379231-04-6); and PF-03814735 (CAS 942487-16-3);

ALK inhibitors: PF-2341066 (XALKOPJ® ; crizotinib); 5-chloro-N4-(2- (isopropyl-sulfonyl)phenyl)-N2-(2-methoxy-4-(4-(4-methylpiperazin-l-yl)piperidin-l-yl)phenyl)pyrimidine-2,4-diamine; GSK1838705A (CAS No. 1116235-97-2); CH5424802 (CAS No. 1256580-46-7); Ceritinib (ZYKADIA CAS No. 1032900-25-6); TQ-B3139, and TQ-B3101;

PI3K inhibitors: 4-[2-(1H-indazol-4-yl)-6-[[4-(methylsulfonyl)-piperazin-l-yl]methyl]thieno[3,2-d]pyrimidin-4-yl]morpholine (also known as GDC 0941 and described in PCT Publication Nos. WO 09/036082 and WO 09/055730), BEZ235 or NVP-BEZ235 (CAS No. 915019-65-7), disclosed in PCT Publication No. WO 06/122806);

Vascular Endothelial Growth Factor (VEGF) receptor inhibitors: Bevacizumab (sold under the trademark Avastin® by Genentech/Roche), axitinib, (N-methyl-2-[[3-[(E)-2- pyridin-2- ylethenyl]-lH-indazol-6-yl]sulfanyl]benzamide, also known as AG013736, and described in PCT Publication No. WO 01/002369), Brivanib Alaninate ((S)-((R)-l-(4-(4-fluoro-2-methyl-4H-indol- 5-yloxy)-5-methylpyrrolo[2,l-f][l,2,4]triazin-6-yloxy)propan-2-yl)2-aminopropanoate, also known as BMS-582664), motesanib (N-(2,3-dihydro-3,3- dimethyl-1H-indol-6-yl)-2-[(4- pyridinylmethyl)amino]-3-pyridinecarboxamide, and described in PCT Publication No. WO 02/066470), pasireotide (also known as SOM230, and described in PCT Publication No. WO 02/010192), sorafenib (sold under the tradename Nexavar®, CAS No. 284461-73-0); or AL-2846;

MET inhibitor such as foretinib (CAS No. 849217-64-7), cabozantinib (CAS No. 1140909-48-3), capmatinib (CAS No. 1029712-80-8), tepotinib (CAS No. 1100598-32-0), savolitinib (CAS No. 1313725-88-0, or crizotinib (CAS No. 877399-52-5);

FLT3 inhibitors - sunitinib malate (CAS No. 341031-54-7, sold under the tradename Sutent® by Pfizer); PKC412 (CAS No. 120685-11-2, midostaurin); tandutinib (CAS No. 387867-13-2), sorafenib (CAS No. 284461-73-0), lestaurtinib (CAS No. :111358-88-4), KW-2449 (CAS No. 1000669-72-6), quizartinib (AC220, CAS No. 950769-58-1), or crenolanib (CAS No. 670220-88-9);

Epidermal growth factor receptor (EGFR) inhibitors: Gefitnib (sold under the tradename Iressa®), N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(3S)-tetrahydro-3- furanyl]oxy]-6-quinazolinyl]-4(dimethylamino)-2-butenamide, sold under the tradename Tovok® by Boehringer Ingelheim), cetuximab (sold under the tradename Erbitux® by Bristol-Myers Squibb), or panitumumab (sold under the tradename Vectibix® by Amgen);

HER2 receptor inhibitors: Trastuzumab (sold under the trademark Herceptin® by Genentech/Roche), neratinib (also known as HKI-272, (2E)-N-[4-[[3-chloro-4-[(pyridin-2-yl)methoxy]phenyl]amino]-3-cyano-7-ethoxyquinolin-6-yl]-4-(d imethylamino)but-2- enamide, and described PCT Publication No. WO 05/028443), lapatinib (CAS No. 231277-92-2) or lapatinib ditosylate (CAS No: 388082-77-7) (sold under the trademark Tykerb® by GlaxoSmithKline); or Trastuzumab emtansine (in the United States, ado-trastuzumab emtansine, trade name Kadcyla) - an antibody-drug conjugate consisting of the monoclonal antibody trastuzumab (Herceptin) linked to the cytotoxic agent mertansine (DM1);

HER dimerization inhibitors: Pertuzumab (sold under the trademark Omnitarg®, by Genentech);

FGFR inhibitors: Erdafitinib (CAS No. 1346242-81-6), Pemigatinib (CAS No. 1513857-77-6) or Infigratinib (CAS No. 872511-34-7)

Aurora kinase inhibitors: TAS-119 (CAS No. 1453099-83-6), LY3295668 (CAS No. 1919888-06-4), or alisertib (CAS No. 1028486-01-2);

CD20 antibodies: Rituximab (sold under the trademarks Riuxan® and MabThera® by Genentech/Roche), tositumomab (sold under the trademarks Bexxar® by GlaxoSmithKline), or ofatumumab (sold under the trademark Arzerra® by GlaxoSmithKline);

Tyrosine kinase inhibitors: Erlotinib hydrochloride (CAS No. 183319-69-9, sold under the trademark Tarceva® by Genentech/Roche), Linifanib (N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5- methylphenyl)urea, also known as ABT 869, available from Genentech), sunitinib malate (CAS No. 341031-54-7, sold under the tradename Sutent® by Pfizer), bosutinib (4-[(2,4-dichloro-5-methoxyphenyl)amino]-6- methoxy-7-[3-(4-methylpiperazin4-yl)propoxy]quinoline-3-carbonitrile,

also known as SKI-606, and described in US Patent No. 6,780,996), dasatinib (CAS No. 302962-49-8, sold under the tradename Sprycel® by Bristol-Myers Squibb), armala (CAS No. 444731-52-6, also known as pazopanib, sold under the tradename Votrient® by GlaxoSmithKline), imatinib (CAS No. 152459-95-5) and imatinib mesylate (CAS No. 220127-57-1) (sold under the tradenames Gilvec® and Gleevec® by Novartis);

DNA Synthesis inhibitors: Capecitabine (CAS No. 154361-50-9) (sold under the trademark Xeloda® by Roche), gemcitabine hydrochloride (CAS No. 122111-03-9) (sold under the trademark Gemzar® by Eli Lilly and Company), or nelarabine ((2R3S,4R,5R)-2-(2-amino-6-methoxypurin-9-yl)-5-(hydroxymethyl)oxolane-3,4- diol, sold under the tradenames Arranon® and Atriance® by GlaxoSmithKline);

Antineoplastic agents: oxaliplatin (CAS No. 61825-94-3) (sold under the tradename Eloxatin® ay Sanofi- Aventis and described in US Patent No. 4,169,846);

Human Granulocyte colony-stimulating factor (G-CSF) modulators: Filgrastim (sold under the tradename Neupogen® by Amgen);

Immunomodulators: Afutuzumab (available from Roche®), pegfilgrastim (sold under the tradename Neulasta® by Amgen), lenalidomide (CAS No. 191732-72-6, also known as CC-5013, sold under the tradename Revlimid®), or thalidomide (CAS No. 50-35-1, sold under the tradename Thalomid®);

CD40 inhibitors: Dacetuzumab (also known as SGN-40 or huS2C6, available from Seattle Genetics, Inc);

Pro-apoptotic receptor agonists (PARAs): Dulanermin (also known as AMG-951, available from Amgen/Genentech);

Hedgehog antagonists: 2-chloro-N-[4-chloro-3-(2-pyridinyl)phenyl]-4-(methylsulfony 1)-benzamide (also known as GDC-0449, and described in PCT Publication No. WO 06/028958);

Phospholipase A2 inhibitors: Anagrelide (CAS No. 58579-51-4, sold under the tradename Agrylin®);

BCL-2 inhibitors: 4-[4-[[2-(4-chlorophenyl)-5,5-dimethyl-l-cyclohexen-l-yl]met hyl]- 1-piperazinyl]-N-[[4-[[(lR)-3-(4-morpholinyl)-l-[(phenylthio)m ethyl]propyl]amino]-3-[(trifluoromethyl)sulfonyl]phenyl]sulfonyl]benzamide (also known as ABT-263 and described in PCT Publication No. WO 09/155386);

MCL-1 inhibitors: MIK665 (CAS No. 1799631-75-6, S64315), AMG 397, and AZD5991 (CAS No. 2143010-83-5); Aromatase inhibitors: Exemestane (CAS No. 107868-30-4, sold under the trademark Aromasin® by Pfizer), letrozole (CAS No. 112809-51-5, sold under the tradename Femara® by Novartis), or anastrozole (CAS No. 120511-73-1, sold under the tradename Arimidex®);

Topoisomerase I inhibitors: Irinotecan (CAS No. 97682-44-5, sold under the trademark Camptosar® by Pfizer), topotecan hydrochloride (CAS No. 119413-54-6, sold under the tradename Hycamtin® by GlaxoSmithKline);

Topoisomerase II inhibitors: etoposide (CAS No. 33419-42-0, also known as VP-16 and Etoposide phosphate, sold under the tradenames Toposar®, VePesid® and Etopophos®), or teniposide (CAS No. 29767-20-2, also known as VM-26, sold under the tradename Vumon®);

mTOR inhibitors: Temsirolimus (CAS No. 162635-04-3, sold under the tradename Torisel® by Pfizer), ridaforolimus (CAS No. 572924-54-0, formally known as deferolimus, AP23573 and MK8669, and described in PCT Publication No. WO 03/064383), or everolimus (CAS No. 159351-69-6, sold under the tradename Afmitor® by Novartis);

Proteasome inhibitor such as carfilzomib (CAS No. 868540-17-4), MLN9708 (CAS No. 1201902-80-8), delanzomib (CAS No. 847499-27-8), or bortezomib (CAS No. 179324-69-7);

BET inhibitors such as INCB054329 (CAS No. 1628607-64-6), OTX015 (CAS No. 202590-98-5), or CPI-0610 (CAS No. 1380087-89-7);

LSD1 inhibitors such as GSK2979552, or INCB059872;

HIF-2α inhibitors such as PT2977 (1672668-24-4), NKT2152, or PT2385 (CAS No. 1672665-49-4);

Osteoclastic bone resorption inhibitors: 1-hydroxy-2-imidazol-l-yl-phosphonoethyl) phosphonic acid monohydrate (sold under the tradename Zometa® by Novartis);

CD33 Antibody Drug Conjugates: Gemtuzumab ozogamicin (sold under the tradename Mylotarg® by Pfizer/Wyeth);

CD22 Antibody Drug Conjugates: Inotuzumab ozogamicin (also referred to as CMC-544 and WAY-207294, available from Hangzhou Sage Chemical Co., Ltd.);

CD20 Antibody Drug Conjugates: Ibritumomab tiuxetan (sold under the tradename Zevalin®);

Somatostain analogs: octreotide (also known as octreotide acetate, sold under the tradenames Sandostatin® and Sandostatin LAR®);

Synthetic Interleukin- 11 (IL-l 1): oprelvekin (sold under the tradename Neumega® by Pfizer/Wyeth);

Synthetic erythropoietin: Darbepoetin alfa (sold under the tradename Aranesp® by Amgen);

Receptor Activator for Nuclear Factor k B (RANK) inhibitors: Denosumab (sold under the tradename Prolia® by Amgen);

Thrombopoietin mimetic peptibodies: Romiplostim (sold under the tradename Nplate® by Amgen;

Cell growth stimulators: Palifermin (sold under the tradename Kepivance® by Amgen);

Anti-insulin-like Growth Factor-l receptor (IGF-1R) antibodies: Figitumumab (also known as CP-751,871, available from ACC Corp), robatumumab (CAS No. 934235-44-6);

Anti-CSl antibodies: Elotuzumab (HuLuc63, CAS No. 915296-00-3);

CD52 antibodies: Alemtuzumab (sold under the tradename Campath®);

Histone deacetylase inhibitors: Voninostat (sold under the tradename Zolinza® by Merck);

Alkylating agents: Temozolomide (sold under the tradenames Temodar® and Temodal® by Schering-Plough/Merck), dactinomycin (also known as actinomycin-D and sold under the tradename Cosmegen®), melphalan (also known as L-PAM, L-sarcolysin, and phenylalanine mustard, sold under the tradename Alkeran®), altretamine (also known as hexamethylmelamine (HMM), sold under the tradename Hexalen®), carmustine (sold under the tradename BiCNU®), bendamustine (sold under the tradename Treanda®), busulfan (sold under the tradenames Busulfex® and Myleran®), carboplatin (sold under the tradename Paraplatin®), lomustine (also known as CCNU, sold under the tradename CeeNU®), cisplatin (also known as CDDP, sold under the tradenames Platinol® and Platinol®-AQ), chlorambucil (sold under the tradename Leukeran®), cyclophosphamide (sold under the tradenames Cytoxan® and Neosar®), dacarbazine (also known as DTIC, DIC and imidazole carboxamide, sold under the tradename DTIC -Dome®), altretamine (also known as hexamethylmelamine (HMM) sold under the tradename Hexalen®), ifosfamide (sold under the tradename Ifex®), procarbazine (sold under the tradename Matulane®), mechlorethamine (also known as nitrogen mustard, mustine and mechloroethamine hydrochloride, sold under the tradename Mustargen®), streptozocin (sold under the tradename Zanosar®), thiotepa (also known as thiophosphoamide, TESPA and TSPA, sold under the tradename Thioplex®;

Biologic response modifiers: bacillus calmette-guerin (sold under the tradenames theraCys® and TICE® BCG), or Denileukin diftitox (sold under the tradename Ontak®);

Anti-tumor antibiotics: doxorubicin (sold under the tradenames Adriamycin® and Rubex®), bleomycin (sold under the tradename lenoxane®), daunorubicin (also known as dauorubicin hydrochloride, daunomycin, and rubidomycin hydrochloride, sold under the tradename Cerubidine®), daunorubicin liposomal (daunorubicin citrate liposome, sold under the tradename DaunoXome®), mitoxantrone (also known as DHAD, sold under the tradename Novantrone®), epirubicin (sold under the tradename Ellence™), idarubicin (sold under the tradenames Idamycin®, Idamycin PFS®), or mitomycin C (sold under the tradename Mutamycin®);

Anti -microtubule agents: Estramustine (CAS No. 52205-73-9, sold under the tradename Emcyl®);

Cathepsin K inhibitors: Odanacatib (CAS No. 603139-19-1, also know as MK-0822 available from Lanzhou Chon Chemicals, ACC Corp., and ChemieTek, and described in PCT Publication no. WO 03/075836);

Epothilone B analogs: Ixabepilone (CAS No. 219989-84-1, sold under the tradename Lxempra® by Bristol- Myers Squibb);

Heat Shock Protein (HSP) inhibitors: Tanespimycin (17-allylamino-17-demethoxygeldanamycin, also known as KOS-953 and 17-AAG, available from SIGMA, and described in US Patent No. 4,261,989), NVP-HSP990 (CAS No. 934343-74-5), AUY922 (CAS No. 747412-49-3), AT13387 (CAS No. 912999-49-6), STA-9090 (CAS No. 888216-25-9), Debio 0932, KW-2478 (CAS No. 819812-04-9), XL888 (CAS No. 1149705-71-4), CNF2024 (CAS No. 848695-25-0), and TAS-116 (CAS No. 1260533-36-5);

TpoR agonists: Eltrombopag (sold under the tradenames Promacta® and Revolade® by GlaxoSmithKline);

Anti-mitotic agents: Docetaxel (CAS No. 114977-28-5, sold under the tradename Taxotere® by Sanofi- Aventis); Adrenal steroid inhibitors: aminoglutethimide (CAS No. 125-84-8, sold under the tradename Cytadren®);

Anti-androgens: Nilutamide (CAS No. 63612-50-0, sold under the tradenames Nilandron® and Anandron®), bicalutamide (CAS No. 90357-06-5, sold under tradename Casodex®), or flutamide (CAS No. 13311-84-7, sold under the tradename Fulexin™);

Androgens: Fluoxymesterone (CAS No. 76-43-7, sold under the tradename Halotestin®);

CDK (CDK1, CDK2, CDK3, CDK5, CDK7, CDK8, or CDK9) inhibitors including but not limited to: Alvocidib (CAS No. 146426-40-6, pan-CDK inhibitor, also known as flovopirdol or HMR-1275, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-l-methyl -4-piperidinyl]-4-chromenone, and described in US Patent No. 5,621,002);

CDK2 inhibitor PF-07104091;

CDK4/6 inhibitors: pabociclib (CAS No. 827022-33-3), ribociclib (CAS No. 1211441-98-3), abemaciclib (CAS No. 1231929-97-7), PF-06873600 (CAS No. 2185857-97-8), NUV-422 and Trilaciclib (CAS No. 1374743-00-6);

CDK7 inhibitors CT7001 (CAS No. 1805789-54-1) and SY-1365 (CAS No. 1816989-16-8);

CDK9 inhibtiors AZD 4573 (CAS No. 2057509-72-3), P276-00 (CAS No. 920113-03-7), AT7519 (CAS No. 844442-38-2), CYC065 (CAS No. 1070790-89-4) or TP-1287;

Gonadotropin-releasing hormone (GnRH) receptor agonists: Leuprolide or leuprolide acetate (sold under the tradenames Viadure® by Bayer AG, Eligard® by Sanofi-Aventis and Lupron® by Abbott Lab);

Taxane anti-neoplastic agents: Cabazitaxel (l-hydroxy-7,10 -dimethoxy-9-oxo-5,20-epoxytax-11-ene-2a,4,13a-triyl-4-acetate-2-benzoate-13-[(2R,3S)-3-{ [(tert- butoxy)carbonyl]-amino}-2-hydroxy-3-phenylpropanoate), or larotaxel ((2a,3x,4a,5b,7a,10b,13a)- 4,10-bis(acetyloxy)-l3-({ (2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-3- phenylpropanoyl}oxy)-l-hydroxy-9-oxo-5,20-epoxy-7,l9-cyclotax-11-en-2-ylbenzoate);

5HTla receptor agonists: Xaliproden (also known as SR57746, l-[2-(2- naphthyl)ethyl]-4-[3-(trifluoromethyl)phenyl]-l,2,3,6-tetrahydropyridine, and described in US Patent No. 5,266,573);

HPC vaccines: Cervarix® sold by GlaxoSmithKline, Gardasil® sold by Merck;

Iron Chelating agents: Deferasinox (CAS No. 201530-41-8, sold under the tradename Exjade® by Novartis);

Anti-metabolites: Claribine (2-chlorodeoxyadenosine, sold under the tradename leustatin®), 5-fluorouracil (sold under the tradename Adrucil®), 6-thioguanine (sold under the tradename Purinethol®), pemetrexed (sold under the tradename Alimta®), cytarabine (also known as arabinosylcytosine (Ara-C), sold under the tradename Cytosar-U®), cytarabine liposomal (also known as Liposomal Ara-C, sold under the tradename DepoCyt™), decitabine (sold under the tradename Dacogen®), hydroxyurea (sold under the tradenames Hydrea®, Droxia™ and Mylocel™), fludarabine (sold under the tradename Fludara®), floxuridine (sold under the tradename FUDR®),

cladribine (also known as 2-chlorodeoxyadenosine (2-CdA) sold under the tradename Leustatin™), methotrexate (also known as amethopterin, methotrexate sodim (MTX), sold under the tradenames Rheumatrex® and Trexall™), or pentostatin (sold under the tradename Nipent®);

Bisphosphonates: Pamidronate (CAS No. 57248-88-1, sold under the tradename Aredia®), zoledronic acid CAS No. 118072-93-8 (sold under the tradename Zometa®);

Demethylating agents: 5-azacitidine (CAS No. 320-67-2, sold under the tradename Vidaza®), decitabine (CAS No. 2353-33-5, sold under the tradename Dacogen®);

Plant Alkaloids: Paclitaxel protein-bound (sold under the tradename Abraxane®), vinblastine (also known as vinblastine sulfate, vincaleukoblastine and VLB, sold under the tradenames Alkaban-AQ® and Velban®), vincristine (also known as vincristine sulfate, LCR, and VCR, sold under the tradenames Oncovin® and Vincasar Pfs®), vinorelbine (sold under the tradename Navelbine®), or paclitaxel (sold under the tradenames Taxol and Onxal™);

Retinoids: Ali tretinoin (sold under the tradename Panretin®), tretinoin (all-trans retinoic acid, also known as ATRA, sold under the tradename Vesanoid®), Isotretinoin (13- cis-retinoic acid, sold under the tradenames Accutane®, Amnesteem®, Claravis®, Clarus®, Decutan®, Isotane®, Izotech®, Oratane®, Isotret®, and Sotret®), or bexarotene (sold under the tradename Targretin®);

Glucocorticosteroids: Hydrocortisone (also known as cortisone, hydrocortisone sodium succinate, hydrocortisone sodium phosphate, and sold under the tradenames Ala- Cort®, Hydrocortisone Phosphate, Solu-Cortef®, Hydrocort Acetate® and Lanacort®), dexamethazone ((8S,9R,10S,11S,13S,14S,16R,17R)-9-fluoro-11,17-dihydroxy-17-(2- hydroxyacetyl)-10,13,16-trimethyl-6,7,8,9, 10,11,12,13,14,15,16,17-dodecahydro-3H- cyclopenta[a]phenanthren- 3-one), prednisolone (sold under the tradenames Delta-Cortel®, Orapred®, Pediapred® and Prelone®), prednisone (sold under the tradenames Deltasone®, Liquid Red®, Meticorten® and Orasone®), or methylprednisolone (also known as 6-Methylprednisolone, Methylprednisolone Acetate, Methylprednisolone Sodium Succinate, sold under the tradenames Duralone®, Medralone®, Medrol®, M-Prednisol® and Solu- Medrol®);

Cytokines: interleukin-2 (also known as aldesleukin and IL-2, sold under the tradename Proleukin®), interleukin-11 (also known as oprevelkin, sold under the tradename Neumega®), alpha interferon alfa (also known as IFN-alpha, sold under the tradenames Intron® A, and Roferon-A®);

Estrogen receptor downregulators: Fulvestrant (CAS No. 129453-61-8, sold under the tradename Faslodex®);

Anti-estrogens: tamoxifen (CAS No. 10540-29-1, sold under the tradename Novaldex®); or Toremifene (CAS No. 89778-27-8, sold under the tradename Fareston®);

Selective estrogen receptor modulators (SERMs): Raloxifene (CAS No. 84449-90-1, sold under the tradename Evista®);

Leutinizing hormone releasing hormone (LFfRH) agonists: Goserelin (CAS No. 145781-92-6, sold under the tradename Zoladex®); Progesterones: megestrol (also known as megestrol acetate, CAS No. 595-33-5, sold under the tradename Megace®);

Miscellaneous cytotoxic agents: Arsenic trioxide (sold under the tradename Trisenox®), or asparaginase (also known as L-asparaginase, Erwinia L-asparaginase, sold under the tradenames Elspar® and Kidrolase®);

Exemplary immune checkpoint inhibitors include inhibitors (smack molecules or biologies) against immune checkpoint molecules such as CD27, CD28, CD40, CD 122, CD96, CD73, CD39, CD47, 0X40, GITR, CSF1R, JAK, PI3K delta, PI3K gamma, TAM kinase, arginase, CD137 (also known as 4-1BB), ICOS, A2AR, A2BR, HIF-2a, B7-H3, B7- H4, BTLA, CTLA-4, LAG3, TIM3, VISTA, CD96, TIGIT, PD-l, PD-L1 and PD-L2. In some embodiments, the immune checkpoint molecule is a stimulatory checkpoint molecule selected from CD27, CD28, CD40, ICOS, 0X40, GITR, CD137 and STING. In some embodiments, the immune checkpoint molecule is an inhibitory checkpoint molecule selected from B7-H3, B7-H4, BTLA, CTLA-4, IDO, TDO, Arginase, KIR, LAG3, PD-l, TIM3, CD96, TIGIT and VISTA. In some embodiments, the compounds provided herein can be used in combination with one or more agents selected from KIR inhibitors, TIGIT inhibitors, LAIR1 inhibitors, CD 160 inhibitors, 2B4 inhibitors and TGFR beta inhibitors.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PD-l, e.g., an anti-PD-l monoclonal antibody. In some embodiments, the anti-PD-l monoclonal antibody is nivolumab, pembrolizumab (also known as MK-3475), pidilizumab, SHR-1210, PDR001, or AMP - 224. In some embodiments, the anti-PD-l monoclonal antibody is nivolumab, or pembrolizumab or PDR001. In some embodiments, the anti -PD 1 antibody is pembrolizumab.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PD-L1, e.g., an anti-PD-Ll monoclonal antibody. In some embodiments, the anti-PD-Ll monoclonal antibody is BMS-935559, MEDI4736, MPDL3280A (also known as RG7446), or MSB0010718C. In some embodiments, the anti-PD-Ll monoclonal antibody is MPDL3280A (atezolizumab) or

MEDI4736 (durvalumab). In some embodiments, the anti-PD-L1 small molecule inhibitor is INCB86550.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CTLA-4, e.g., an anti-CTLA-4 antibody. In some embodiments, the anti-CTLA-4 antibody is ipilimumab or tremelimumab. In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of LAG3, e.g., an anti-LAG3 antibody. In some embodiments, the anti-LAG3 antibody is BMS-986016 or LAG525. In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of GITR, e.g., an anti-GITR antibody. In some embodiments, the anti-GITR antibody is TRX518 or, MK-4166, INCAGN01876 or MK-1248. In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of 0X40, e.g., an anti-OX40 antibody or OX40L fusion protein. In some embodiments, the anti-OX40 antibody is MED 10562 or, INCAGN01949, GSK2831781, GSK-3174998, MOXR-0916, PF-04518600 or LAG525. In some embodiments, the OX40L fusion protein is MEDI6383.

Compounds of the invention can also be used to increase or enhance an immune response, including increasing the immune response to an antigen; to improve immunization, including increasing vaccine efficacy; and to increase inflammation. In some embodiments, the compounds of the invention can be sued to enhance the immune response to vaccines including, but not limited, Listeria vaccines, oncolytic viral vaccines, and cancer vaccines such as GVAX® (granulocyte-macrophage colony-stimulating factor (GM-CF) gene- transfected tumor cell vaccine). Anti-cancer vaccines include dendritic cells, synthetic peptides, DNA vaccines and recombinant viruses. Other immune-modulatory agents also include those that block immune cell migration such as antagonists to chemokine receptors, including CCR2 and CCR4; Sting agonists and Toll receptor agonists. Other anti-cancer agents also include those that augment the immune system such as adjuvants or adoptive T cell transfer. Compounds of this application may be effective in combination with CAR (Chimeric antigen receptor) T cell treatment as a booster for T cell activation.

A compound of the invention can also be used in combination with the following adjunct therapies: Anti-nausea drugs: NK-l receptor antagonists: Casopitant (sold under the tradenames Rezonic® and Zunrisa® by GlaxoSmithKline); and Cytoprotective agents: Amifostine (sold under the tradename Ethyol®), leucovorin (also known as calcium leucovorin, citrovorum factor and folinic acid). The disclosure of the PCT applications referred to herein above are incorporated herein by reference in their entirety.

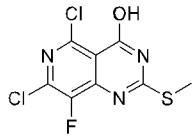
Examples

The following preparations of intermediates and compounds of of the disclosure (Examples) are given to enable those skilled in the art to more clearly understand and to practice the present disclosure. They should not be considered as limiting the scope of the disclosure, but merely as being illustrative and representative thereof.

Synthetic Examples

Intermediate 1

Synthesis of 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4-ol



Step 1: 2,6-dichloro-3-fluoropyridin-4-amine

To a stirred mixture of 2,6-dichloropyridin-4-amine (90 g, 552 mmol, 1.0 equiv) in MeOH (900 mL) and H_2O (180 mL) was added selectfluor (219 g, 618 mmol, 1.1 equiv) in portions at room temperature and the resulting mixture was stirred at 45 °C for 16 h. The reaction mixture was then extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography, eluted with THF/PE (0-20%) to afford the title compound (60 g).

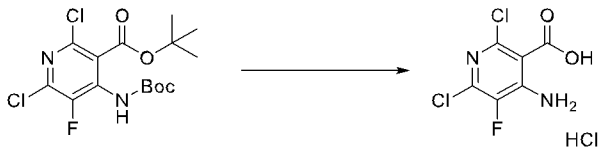
Step 2: di-tert-butyl (2,6-dichloro-3-fluoropyridin-4-yl)carbamate

To a stirred mixture of 2,6-dichloro-3-fluoropyridin-4-amine (59 g, 326 mmol, 1.0 equiv) and DMAP (1.99 g, 17 mmol, 0.05 equiv) in THF (590 mL) was added $(Boc)_2O$ (178 g, 815 mmol, 2.5 equiv) in portions at rt and the resulting mixture was stirred at 60 ℃ for 4 h. After cooling down at rt, the reaction mixture was concentrated under vacuum and to the residue was added MeOH. The precipitate was collected by filtration to obtain the title compound (54 g).

Step 3: tert-butyl 4-((tert-butoxycarbonyl)amino)-2,6-dichloro-5-fluoronicotinate

To a solution of diisopropylamine (40 g, 397 mmol, 2.8 equiv) in THF (200 mL) was added n-BuLi in hexane (2.5 M, 159 mL, 397 mmol, 2.8 equiv) at -78 ℃ under nitrogen atmosphere and the resulting solution was stirred at -78 ℃ for 1 h. To the above mixture was added a solution of di-tert-butyl (2,6-dichloro-3-fluoropyridin-4-yl)carbamate (54 g, 142 mmol, 1.0 equiv) in THF (300 mL) dropwise and the resulting mixture was stirred at -78℃ for additional 1 h. The reaction was quenched by adding AcOH at -78 ℃. After warming to rt, the reaction mixture was diluted with EtOAc and water. The phases were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (0-25%) to afford the title compound (28 g).

Step 4: 4-amino-2,6-dichloro-5-fluoronicotinic acid hydrochloride



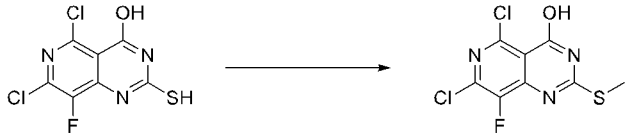
To a stirred mixture of tert-butyl 4-[(tert-butoxycarbonyl)amino]-2,6-dichloro-5-fluoropyridine-3-carboxylate (28 g, 73 mmol, 1.0 equiv) in dioxane (150 mL) was added conc. HCl aq. solution (30 mL) dropwise at room temperature and the resulting mixture was stirred at rt for 16 h. The reaction mixture was concentrated under reduced pressure to provide the title compound (18.6 g).

Step 5: 5,7-dichloro-8-fluoro-2-mercaptopyrido[4,3-d]pyrimidin-4-ol

A solution of 4-amino-2,6-dichloro-5-fluoropyridine-3-carboxylic acid (16 g, 71 mmol, 1.0 equiv) in $SOCl_2$ (285 mL) was stirred at 50 ℃ for 3 h. After cooling to rt, the reaction mixture was concentrated under vacuum. The residue was then dissolved in acetone (285 mL) and the resulting solution was added into a solution of NH_4SCN(16 g, 213 mmol, 3.0 equiv) in acetone (285 mL) dropwise at rt. After stirring at rt for 1 h, the reaction mixture was diluted with water and then

extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated to provide the title compound (8.6 g).

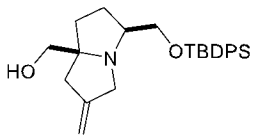
Step 6: 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4-ol



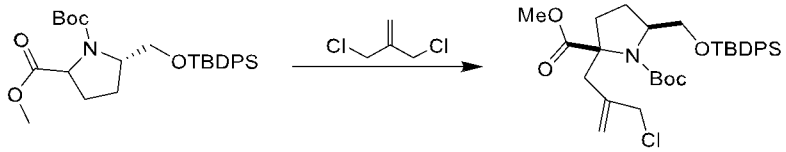
To a stirred solution of 5,7-dichloro-8-fluoro-2-sulfanylpyrido[4,3-d]pyrimidin-4-ol (8.6 g, 32 mmol, 1.0 equiv) in MeOH (323 mL) and 0.1 M NaOH in water (323 mL, 32.3 mmol, 2.0 equiv) was added MeI (9.18 g, 65 mmol, 2.0 equiv.) dropwise at room temperature. The resulting mixture was stirred for 2 h at room temperature. The mixture was acidified to pH 6 with conc. HCl. The precipitated solids were collected by filtration and washed with water. This resulted in the title compound (7.8 g, 86.15%) as a light- yellow solid. MS (ES, m/z): $[M+H]^+ = 280.0$.

Intermediate 2

Synthesis of ((5S,7aS)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol



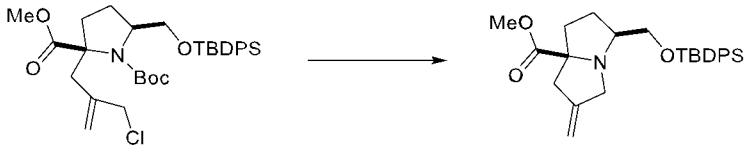
Step 1: 1-(tert-butyl) 2-methyl (2S,5S)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-2-(2-(chloromethyl)allyl)pyrrolidine-1,2-dicarboxylate



To a solution of (5S)-1-tert-butyl 2-methyl 5-(((tert-butyldiphenylsilyl)oxy)methyl)-pyrrolidine-1,2-dicarboxylate (12.0 g, 24.1 mmol, 1 eq) in THF (100 mL) was added LiHMDS (1 M, 48.22 mL, 2 eq) at -70 ℃ and the mixture was stirred at -70 ℃ for 15 min. 3-Chloro-2-(chloromethyl)prop-1-ene (4.52 g, 36.1 mmol, 4.19 mL, 1.5 eq) was added dropwise at -70 °C under nitrogen atmosphere and the resulting mixture was stirred 16 h at 20 ℃. The mixture was quenched with sat. $NaHCO_3$ aq. and extracted with EtOAc. The combined organic layers were washed with

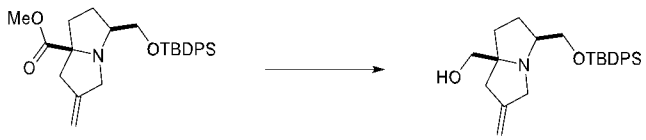
water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography, eluted with EA/PE (0-10%), to afford the title compound (11 g).

Step 2: methyl (5S,7aS)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-2-methylenetetrahydro-1H-pyrrolizine-7a(5H)-carboxylate



To a solution of 1-(tert-butyl) 2-methyl (2S,5S)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-2-(2-(chloromethyl)allyl)pyrrolidine-1,2-dicarboxylate (10.7 g, 18.2 mmol, 1 eq) in DCM (90 mL) was added TFA (45 mL) at 0 ℃ and the resulting mixture was stirred at 20 ℃ for 2 h. The reaction was quenched by adding sat. aq. $NaHCO_3$ solution at 0 ℃ and extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4 filtered and concentrated. The residue was purified by column chromatography eluted with EA/PE (0-10%), to afford the title compound (3.2 g, crude).

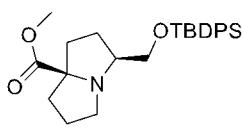
Step 3: ((5S,7aS)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol



To a solution of $LiAlH_4$ (540 mg, 14.2 mmol, 2 eq) in THF (20 mL) was added dropwise methyl (5S,7aS)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-2-methylenetetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (3.2 g, 7.12 mmol, 1 eq) in THF (10 mL) at -40 ℃ and the resulting mixture was stirred at -40 ℃ for 1 h. After cooling the mixture to 0 °C, the mixture was quenched by adding $Na_2SO_4.10H_2O$. The mixture was then filtered and concentrated under reduced pressure to give the title compound (2.83 g, crude). MS (ESI) m/z = 422.6 $[M+1]^+$

Intermediate 3

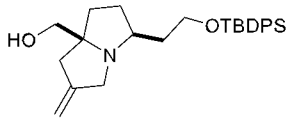
Synthesis of methyl (3S,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)tetrahydro-1H-pyrrolizine-7a(5H)-carboxylate



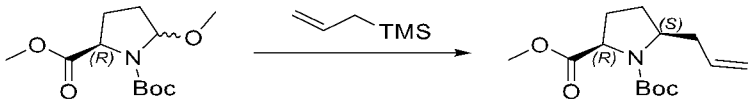
The title compound was prepared by proceeding analogously as described in Intermediate 2, Step 1-2 using 1-chloro-3-iodopropane instead of 3-Chloro-2-(chloromethyl)prop-1-ene in Step 1.

Intermediate 4

Synthesis of ((5S,7aS)-5-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol

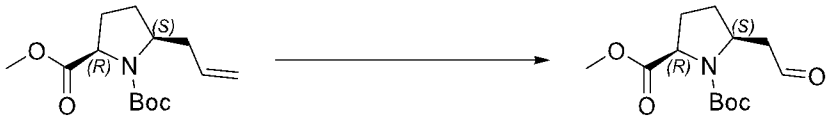


Step 1: 1-(tert-butyl) 2-methyl (2R,5S)-5-allylpyrrolidine-1,2-dicarboxylate



To a stirred solution of 1-(tert-butyl) 2-methyl (2R)-5-methoxypyrrolidine-1,2-dicarboxylate (*J. Org. Chem.* **2008**, *73*, 1661) (25 g, 96 mmol, 1 equiv) and allyltrimethylsilane (49.60 g, 434 mmol, 4.5 equiv) in DCM (250 mL) was added $TiCl_4$ (18.29 g, 96 mmol, 1 equiv) dropwise at -78 ℃ and the resulting mixture was stirred for 1 h at -78 ℃. The reaction mixture was basified to pH=7 with saturated $NaHCO_3$ aq. solution. The mixture was filtered and the filtrate was extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-10%) to afford the title compound (10 g).

Step 2: 1-(tert-butyl) 2-methyl (2R,5S)-5-(2-oxoethyl)pyrrolidine-1,2-dicarboxylate



To a solution of 1-tert-butyl 2-methyl (2R,5S)-5-(prop-2-en-1-yl)pyrrolidine-1,2-dicarboxylate (10 g, 37 mmol, 1 equiv) in THF (120 mL) and H_2O (40 mL) were added $K_2OsO_4.2H_2O$ (1.36 g, 3.7mmol, 0.1 equiv) and $NaIO_4$ (23.80 g, 111 mmol, 3.0 equiv) at 0 °C. The resulting mixture was stirred for 16 h at room temperature under air atmosphere. The mixture was then filtered and the filter cake was washed with EtOAc. The filtrate was extracted with EtOAc. The combined organic layers were washed with $NaHSO_3$ aq. solution and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-50%) to afford the title compound (7 g).

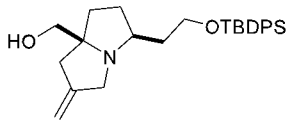
Step 3: 1-(tert-butyl) 2-methyl (2R,5S)-5-(2-hydroxyethyl)pyrrolidine-1,2-dicarboxylate

To a stirred solution of 1-(tert-butyl) 2-methyl (2R,5S)-5-(2-oxoethyl)pyrrolidine-1,2-dicarboxylate (7 g, 25 mmol, 1 equiv) in MeOH (15 mL) was added $NaBH_4$ (1.95 g, 51 mmol, 2 equiv) in portions at 0 ℃ and the resulting mixture was stirred for 30 min. at 0 ℃. The mixture was acidified to pH=6 with 2.0 M HCl aq. solution and then concentrated under reduced pressure. The mixture was then extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-50%) to afford the title compound (7 g).

Step 4: 1-(tert-butyl) 2-methyl (2R,5S)-5-(2-((tert-butyldiphenylsilyl)oxy)ethyl)pyrrolidine-1,2-dicarboxylate

To a stirred solution of 1-(tert-butyl) 2-methyl (2R,5S)-5-(2-hydroxyethyl)pyrrolidine-1,2-dicarboxylate (7 g, 25 mmol, 1 equiv) and TBDPSCl (8.45 g, 30 mmol, 1.2 equiv) in DCM (150 mL) was added imidazole (2.62 g, 38 mmol, 1.5 equiv) in portions at room temperature and the resulting mixture was stirred for 2 h at room temperature. The mixture was diluted with water and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography, eluted with THF/PE (0-10%) to afford the title compound (7.0 g).

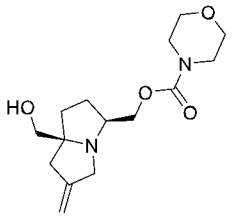
Step 5: ((5S,7aS)-5-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol



The title compound was prepared by proceeding analogously as described in Intermediate 2, Steps 1-3, using 1-(tert-butyl) 2-methyl (2R,5S)-5-(2-((tert-butyldiphenylsilyl)oxy)-ethyl)pyrrolidine-1,2-dicarboxylate instead of (5S)-1-tert-butyl 2-methyl 5-(((tert-butyldiphenylsilyl)oxy)-methyl)pyrrolidine-1,2-dicarboxylate in Step 1.

Intermediate 5

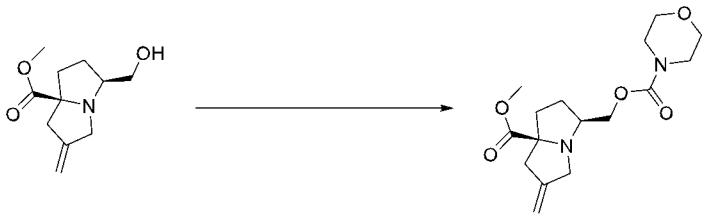
Synthesis of ((3S,7aS)-7a-(hydroxymethyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl morpholine-4-carboxylate



Step 1: methyl (5S,7aR)-5-(hydroxymethyl)-2-methylenetetrahydro-1H-pyrrolizine-7a(5H)-carboxylate

To a stirred solution of methyl (5S,7aS)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-2-methylenetetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (5 g, 11.11 mmol, 1.0 equiv) in THF (50 mL) was added 1M TBAF in THF (16.6 mL, 16.6 mmol, 1.5 equiv) dropwise at room temperature. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with THF/PE (0-50%) to afford the title compound (2.1 g, 89.36%) as a colorless oil.

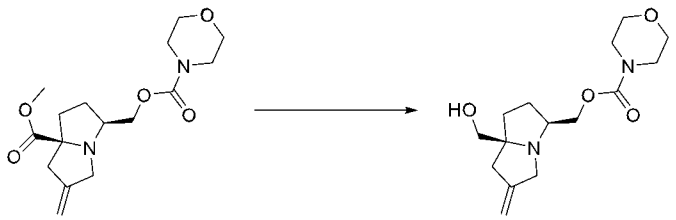
Step 2: ((3S,7aS)-7a-(methoxycarbonyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl morpholine-4-carboxylate



To a stirred solution of methyl (5S,7aR)-5-(hydroxymethyl)-2-methylenetetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (2.1 g, 9.95 mmol, 1.0 equiv) and TEA (6.0 g, 59.7 mmol, 6.0 equiv) in THF (100 mL) was added 4-nitrophenyl carbonochloridate (10.0 g, 49.75 mmol, 5.0 equiv) in portions at 0-5 ℃. The resulting mixture was stirred 2 h at room temperature. To the above mixture was added morpholine (4.33 g, 49.75 mmol, 5.0 equiv) dropwise at 0-5 ℃. The resulting mixture was stirred for additional 16 h at room temperature. The resulting mixture was diluted with water. The resulting mixture was extracted with EA. The combined organic layers were washed with water and

brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-100%) to afford the title compound (2.25 g, 69.8 %) as yellow oil.

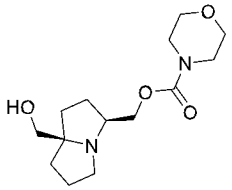
Step 3: ((3S,7aS)-7a-(hydroxymethyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl morpholine-4-carboxylate



To a stirred solution of ((3S,7aS)-7a-(methoxycarbonyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl morpholine-4-carboxylate (2.25 g, 7.58 mmol, 1.0 equiv) and $CaCl_2$ (2.1 g, 18.9 mmol, 2.5 equiv) in EtOH (24 mL) and H_2O (6 mL) was added $NaBH_4$ (1.54 g, 40.9 mmol, 5.4 equiv) in portions at 0 ℃. The resulting mixture was stirred for 1 h at 0 - 5℃. The reaction was quenched with water at 0 ℃. The resulting mixture was extracted with EA. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in the title compound (1.7 g, 82.5%) as a yellow oil. MS (ES, *m/z*): $[M+H]^+$=297.1.

Intermediate 6

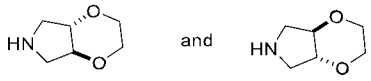
Synthesis of ((3S,7aR)-7a-(hydroxymethyl)hexahydro-1H-pyrrolizin-3-yl)methyl morpholine-4-carboxylate



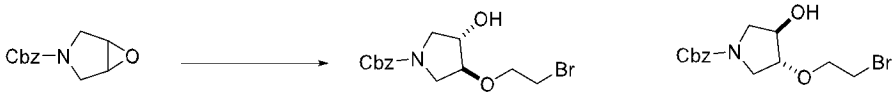
The title compound was prepared by proceeding analogously as described in Intermediate 5, Steps 1-3, using methyl (3S,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)tetrahydro-1H-pyrrolizine-7a(5H)-carboxylate instead of methyl (5S,7aR)-5-(hydroxymethyl)-2-methylenetetrahydro-1H-pyrrolizine-7a(5H)-carboxylate in Step 1.

Intermediate 7

Synthesis of (4aS,7aS)-hexahydro-5H-[1,4]dioxino[2,3-c]pyrrole and (4aR,7aR)-hexahydro-5H-[1,4]dioxino[2,3-c]pyrrole

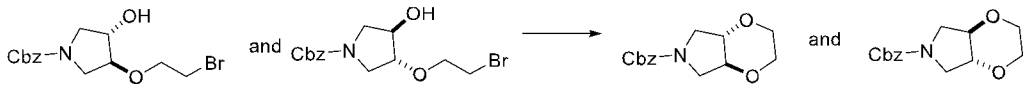


Step 1: a mixture of benzyl (3S,4S)-3-(2-bromoethoxy)-4-hydroxypyrrolidine-1-carboxylate and benzyl (3R,4R)-3-(2-bromoethoxy)-4-hydroxypyrrolidine-1-carboxylate



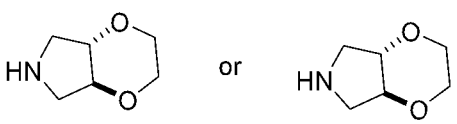
To a stirred solution of benzyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (3.00 g, 13.7 mmol, 1.00 eq), 2-bromoethanol (1.88 g, 15.1 mmol, 1.10 eq) in DCM (30 mL) was added dropwise $BF_3 \cdot Et_2O$ (194 mg, 1.37 mmol, 0.10 eq) at 20 ℃. After stirring at 20℃ for 12 h, the reaction mixture was washed with brine, dried over Na_2SO_4, filtered and then concentrated. The residue was purified by silica gel column chromatography, eluted with EA/PE (25-50%), to provide a mixture of the title compounds (1.1 g).

Step 2: benzyl (4aS,7aS)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate and benzyl (4aR,7aS)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate



To a stirred solution of benzyl (3S,4S)-3-(2-bromoethoxy)-4-hydroxypyrrolidine-1-carboxylate and benzyl (3R,4R)-3-(2-bromoethoxy)-4-hydroxypyrrolidine-1-carboxylate (800 mg, 2.32 mmol, 1.00 eq) in EtOH (8.0 mL) was added dropwise KOH (143 mg, 2.56 mmol, 1.10 eq). The resulting mixture was stirred at 80 ℃ for 6 h, cooled and then filtered. The filtrate was concentrated. The residue was purified by silica gel column chromatography eluted with EA/PE (20-25%). The product was further purified by SFC (column: DAICEL CHIRALPAK AD (250mm*30mm,10um); mobile phase: [CO_2-EtOH(0.1%NH_3H_2O)]; B%: 25%, isocratic elution mode) to give each of the title compounds.

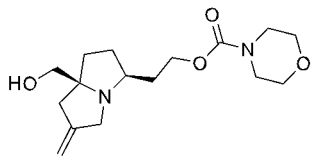
Step 4: (4aS,7aS)-hexahydro-5H-[1,4]dioxino[2,3-c]pyrrole and (4aR,7aR)-hexahydro-5H-[1,4]dioxino[2,3-c]pyrrole



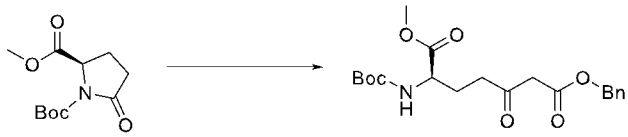
To a stirred solution of benzyl(4aS,7aS)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate or benzyl(4aR,7aR)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate (140 mg, 531.74 μmol, 1.00 eq) in THF (5 mL) was added Pd/C (10%, 0.05 g) under N_2. The reaction mixture was degassed and purged with H_2 for 3 times. The reaction mixture was stirred under H_2 (15 Psi) at 20℃ for 12 h and then filtered, and then concentrated to give (4aS,7aS)-hexahydro-5H-[1,4]dioxino[2,3-c]pyrrole or (4aR,7aR)-hexahydro-5H-[1,4]dioxino[2,3-c]pyrrole, respectively.

Intermediate 8

Synthesis of 2-((3S,7aS)-7a-(hydroxymethyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl morpholine-4-carboxylate

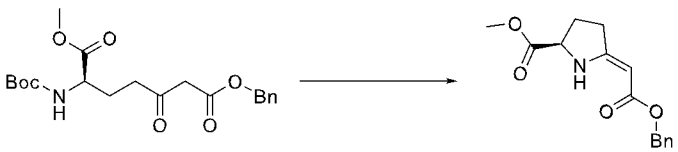


Step 1: 7-benzyl 1-methyl (R)-2-((tert-butoxycarbonyl)amino)-5-oxoheptanedioate



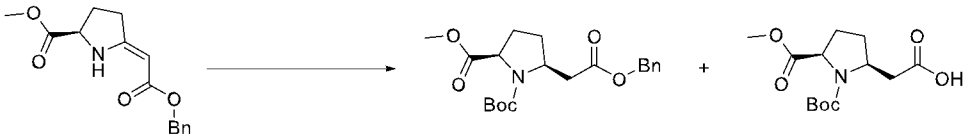
To a solution of LDA (2.0 M in THF/hexane, 205 mL, 410 mmol, 1.0 eq) in THF (1.0 L) was added benzyl acetate (61.5 g, 410 mmol, 1.0 eq) dropwise at -78 ℃ and the resulting mixture was stirred for 30 min. To the above mixture was added a solution of 1-(tert-butyl) 2-methyl (R)-5-oxopyrrolidine-1,2-dicarboxylate (100 g, 411 mmol, 1.0 eq) in THF (150 mL) dropwise at -78 °C and the resulting mixture was stirred for an additional 1 h. After warming to RT, the reaction mixture was quenched with sat. NH_4Cl aq. solution and then extracted with EtOAc. The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-50%), to afford the title compound (120 g).

Step 2: methyl (R)-5-(2-(benzyloxy)-2-oxoethylidene)pyrrolidine-2-carboxylate



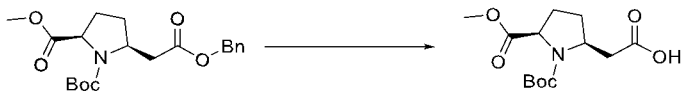
To a stirred solution 7-benzyl 1-methyl (R)-2-((tert-butoxycarbonyl)amino)-5-oxoheptanedioate (120 g, 305 mmol, 1.0 eq) in DCM (600 mL) was added CF_3COOH (34.8 g, 305 mmol, 1.0 eq) dropwise at RT and the resulting mixture was stirred at RT for 2 h. The reaction mixture was concentrated, and the residue was diluted with water and then extracted with EtOAc. The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and then concentrated. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-10%), to afford the title compound (75 g).

Step 3: 1-(tert-butyl) 2-methyl (2R,5S)-5-(2-(benzyloxy)-2-oxoethyl)pyrrolidine-1,2-dicarboxylate and 2-((2S,5R)-1-(tert-butoxycarbonyl)-5-(methoxycarbonyl)pyrrolidin-2-yl)acetic acid



To a stirred solution of methyl (R)-5-(2-(benzyloxy)-2-oxoethylidene)pyrrolidine-2-carboxylate (75 g, 272.4 mmol, 1.0 eq) and Boc_2O (59.5 g, 272 mmol, 1.0 eq) in MeOH (750 mL) was added PtO_2 (6.19 g, 27.24 mmol, 0.1 eq) at RT. The resulting mixture was stirred at RT for 4 h under 1 atm hydrogen atmosphere. The reaction mixture was filtered through a celite pad, and the filtrate was concentrated. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-100%), to afford 1-(tert-butyl) 2-methyl (2R,5S)-5-(2-(benzyloxy)-2-oxoethyl)pyrrolidine-1,2-dicarboxylate (17.7 g) and 2-((2S,5R)-1-(tert-butoxycarbonyl)-5-(methoxycarbonyl)pyrrolidin-2-yl)acetic acid (37.5 g).

Step 4: 2-((2S,5R)-1-(tert-butoxycarbonyl)-5-(methoxycarbonyl)pyrrolidin-2-yl)acetic acid



To a stirred solution of 1-(tert-butyl) 2-methyl (2R,5S)-5-(2-(benzyloxy)-2-oxoethyl)-pyrrolidine-1,2-dicarboxylate (17.2 g, 45.57 mmol, 1.00 eq) in MeOH(180 mL) was added 10% Pd/C (1.72 g). The reaction mixture was stirred at RT for 2 h under 1 atm hydrogen atmosphere, filtered through celite and then concentrated to afford the title compound (9.7 g).

Step 5: 1-(tert-butyl) 2-methyl (2R,5S)-5-(2-hydroxyethyl)pyrrolidine-1,2-dicarboxylate

To a solution of 2-((2S,5R)-1-(tert-butoxycarbonyl)-5-(methoxycarbonyl)pyrrolidin-2-yl)acetic acid (41 g, 142.7 mmol, 1 equiv) in THF (410 mL) at 5℃ was added BH_3-Me_2S (54.2 g, 713.5 mmol, 5.0 equiv) dropwise and the resulting mixture was stirred for 16 h at rt. The resulting mixture was quenched by adding MeOH and then concentrated under vacuum. The remaining material was diluted with DCM and washed with brine, dried over anhydrous Na_2SO_4 to afford the title compound (30.4 g).

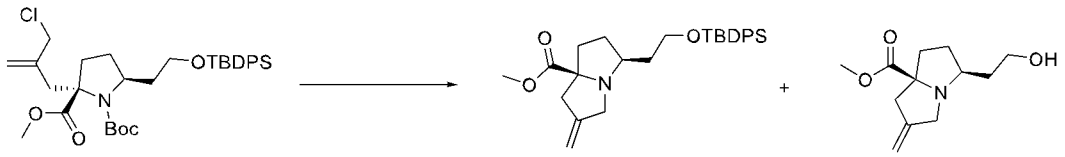
Step 6: 1-(tert-butyl) 2-methyl (2R,5S)-5-(2-((tert-butyldiphenylsilyl)oxy)ethyl)pyrrolidine-1,2-dicarboxylate

To a solution of 1-tert-butyl 2-methyl (2R,5S)-5-(2-hydroxyethyl)pyrrolidine-1,2-dicarboxylate (30 g, 109.75 mmol, 1 equiv) and imidazole (14.94 g, 219.5 mmol, 2 equiv) in DCM (300 mL) at rt was added TBDPSCl (45.25 g, 164.63 mmol, 1.5 equiv) dropwise and the resulting mixture was stirred for 2 h. The reaction mixture was then extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-20%) to afford the title compound (40 g).

Step 7: 1-(tert-butyl) 2-methyl (2S,5S)-5-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-2-(2-(chloromethyl)-allyl)pyrrolidine-1,2-dicarboxylate

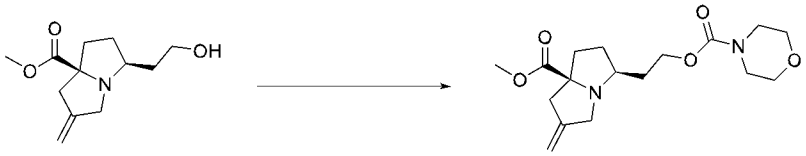
To a solution of 1-(tert-butyl) 2-methyl (2R,5S)-5-(2-((tert-butyldiphenylsilyl)oxy)-ethyl)pyrrolidine-1,2-dicarboxylate (40 g, 78 mmol, 1 equiv) in THF (400 mL) was added LiHMDS (1.0 M in THF, 166 mL, 166 mmol, 2 equiv) dropwise at -78 °C and the mixture was stirred for 30 min at -78 °C. 3-Chloro-2-(chloromethyl)prop-1-ene (29.31 g, 234 mmol, 3 equiv) was added and the resulting mixture was warmed to rt over 1 h. After re-cooling the mixture tot -78 °C, the reaction mixture was quenched with sat. NH_4Cl aq. solution and then extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-20%) to afford the title compound (35 g).

Step 8: methyl (5S,7aS)-5-(2-hydroxyethyl)-2-methylenetetrahydro-1H-pyrrolizine-7a(5H)-carboxylate



To solution of 1-(tert-butyl) 2-methyl (2S,5S)-5-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-2-(2-(chloromethyl)allyl)pyrrolidine-1,2-dicarboxylate (35 g, 56 mmol, 1 equiv) in DCM (270 mL) was added TFA (90 mL) and the resulting mixture was stirred for 1 h at rt. The solvent was removed under vacuum and remaining material was dissolved in MeOH (200 mL). To the above mixture was added K_2CO_3 (38.5 g, 2810 mmol, 5 equiv) in portions at rt and the resulting mixture was stirred at rt for 6 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-100%) to afford methyl (5S,7aS)-5-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-2-methylenetetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (5.4 g) and methyl (5S,7aS)-5-(2-hydroxyethyl)-2-methylenetetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (5.5 g).

Step 9: 2-((3S,7aS)-7a-(methoxycarbonyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl morpholine-4-carboxylate



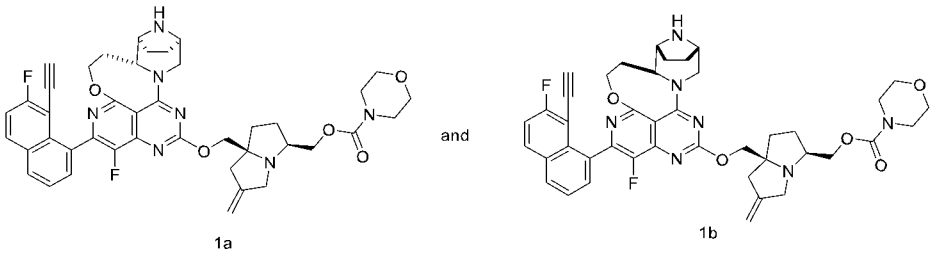
To a solution of methyl (5S,7aS)-5-(2-hydroxyethyl)-2-methylidene-tetrahydro-1H-pyrrolizine-7a-carboxylate (1.1 g, 4.88 mmol, 1 equiv) and TEA (0.99 g, 9.76 mmol, 2 equiv) in THF (11 mL) at rt was added 4-nitrophenyl carbonochloridate (1.48 g, 7.32 mmol, 1.5 equiv) and the resulting mixture was stirred for 2 h at rt. To the above mixture was added morpholine (1.06 g, 12.2 mmol, 2.5 equiv) and the resulting mixture was stirred for 2 h at rt. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-50%) to afford the title compound (850 mg). MS (ES, m/z): [M+H]+ =339.2.

Step 10: 2-((3S,7aS)-7a-(hydroxymethyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl morpholine-4-carboxylate

To a solution of 2-((3S,7aS)-7a-(methoxycarbonyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl morpholine-4-carboxylate (850 mg, 1.25 mmol, 1 equiv) and $CaCl_2$ (348 mg, 3.14 mmol, 2.5 equiv) in EtOH (8.5 mL) and THF (8.5 mL) was added $NaBH_4$ (237 mg, 6.28 mmol, 5 equiv) at 0 ℃ and the resulting mixture was stirred for 1 h at this temperature. The reaction mixture was then extracted with DCM. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated to provide the title compound (800 mg). MS (ES, m/z): [M+H]+ =311.2.

Example 1

Synthesis of ((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl morpholine-4-carboxylate (1a) and ((3S,7aS)-7a-((((6aS,7R,10S)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl morpholine-4-carboxylate (1b)



Step 1: tert-butyl (1R,5S)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

To a stirred solution of tert-butyl (1R,5S)-8-benzyl-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (50 g, 165 mmol, 1.0 equiv) and TMEDA (25 g, 215 mmol, 1.3 equiv) in Et_2O (500 mL) was added s-BuLi (1.3 M in hexane,165 mL, 215 mmol, 1.3 equiv) dropwise at -78 °C under nitrogen atmosphere and the resulting mixture was stirred at -78°C for 1.5 h. Allyl bromide (30 g, 248 mmol, 1.5 equiv) was then added dropwise into the mixture at -78°C, and then the resulting mixture was stirred for additional 2 h at -78 °C. The reaction mixture was poured into NH_4Cl aq. solution and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography and eluted with EtOAc/PE (0-15%), to afford the title compound (30 g).

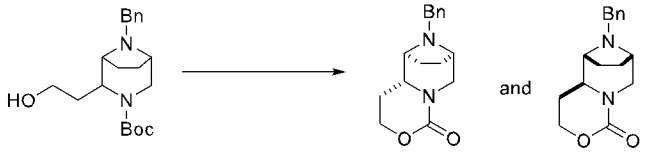
Step 2: tert-butyl (1R,5S)-8-benzyl-2-(2-oxoethyl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

To a stirred mixture of tert-butyl (1R,5S)-2-allyl-8-benzyl-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (25 g, 73 mmol, 1.0 equiv) and $NaIO_4$ (46.8 g, 219 mmol, 3.0 equiv) in THF (750 mL) and H_2O (250 mL) was added K_2OsO_4 (2.43 g, 7.3 mmol, 0.1 equiv) in portions at 0 °C and the resulting mixture was stirred for 2 h at room temperature. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (0-30%), to afford the title compound (7.5 g).

Step 3: tert-butyl (1R,5S)-8-benzyl-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

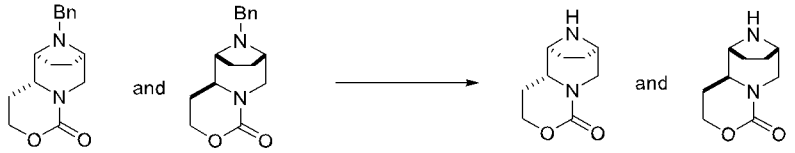
To a stirred solution of tert-butyl (1R,5S)-8-benzyl-2-(2-oxoethyl)-3,8-diazabicyclo-[3.2.1]octane-3-carboxylate (16 g, 46.4 mmol, 1.0 equiv) in MeOH (160 mL) was added $NaBH_4$ (3.51 g, 92.9 mmol, 2.0 equiv) at room temperature and the resulting mixture was stirred for 1.0 h at room temperature. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and then concentrated to provide the title compound (7 g).

Step 4: a mixture of (4aR,5S,8R)-11-benzyloctahydro-1H-5,8-epimino[1,3]oxazino[3,4-a]azepin-1-one and (4aS,5R,8S)-11-benzyloctahydro-1H-5,8-epimino[1,3]oxazino[3,4-a]azepin-1-one



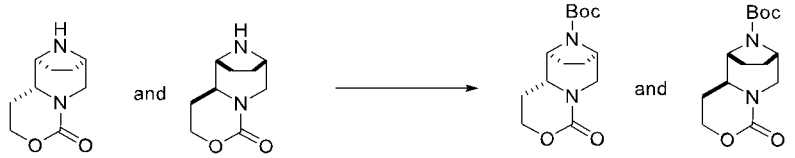
To a stirred solution of tert-butyl (1R,5S)-8-benzyl-2-(2-hydroxyethyl)-3,8-diazabicyclo-[3.2.1]octane-3-carboxylate (7 g, 20.2 mmol, 1.0 equiv) in THF (70 mL) was added NaH (2.4 g, 60.6 mmol, 3.0 equiv, 60%) in portions at 0 °C under nitrogen atmosphere and the resulting mixture was stirred for 3 h at room temperature under nitrogen atmosphere. To the reaction mixture was quenched by adding MeOH at 0 °C and the resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with THF/PE (0-50%), to afford a mixture of the title compounds (3.5 g).

Step 5: a mixture of (4aR,5S,8R)-octahydro-1H-5,8-epimino[1,3]oxazino[3,4-a]azepin-1-one and (4aS,5R,8S)-octahydro-1H-5,8-epimino[1,3]oxazino[3,4-a]azepin-1-one



To a stirred solution of a mixture of (4aR,5S,8R)-11-benzyloctahydro-1H-5,8-epimino[1,3]oxazino[3,4-a]azepin-1-one and (4aS,5R,8S)-11-benzyloctahydro-1H-5,8-epimino[1,3]oxazino[3,4-a]azepin-1-one (3.5 g, 12.8 mmol, 1.0 equiv) in MeOH (120 mL) was added Pd/C (10%, 350 mg). The mixture was stirred at room temperature under 30 psi of hydrogen for 3 h. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to provide a mixture of the title compounds (2.0 g).

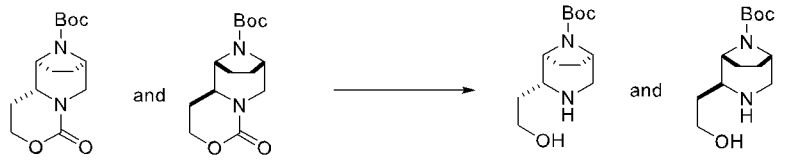
Step 6: a mixture of tert-butyl (4aR,5S,8R)-1-oxooctahydro-1H-5,8-epimino[1,3]oxazino[3,4-a]azepine-11-carboxylate and tert-butyl (4aS,5R,8S)-1-oxooctahydro-1H-5,8-epimino[1,3]oxazino[3,4-a]azepine-11-carboxylate



To a stirred solution of a mixture (4aR,5S,8R)-octahydro-1H-5,8-epimino[1,3]oxazino[3,4-a]azepin-1-one and (4aS,5R,8S)-octahydro-1H-5,8-epimino[1,3]oxazino[3,4-a]azepin-1-one (1.9 g,

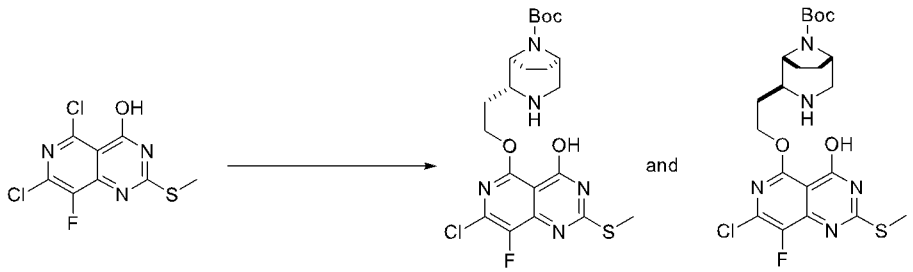
10.4 mmol, 1.0 equiv) and DIEA (2 g, 15.6 mmol, 1.5 equiv) in DCM (20 mL) was added Boc_2O (3.4 g, 15.6 mmol, 1.5 equiv) at room temperature under nitrogen atmosphere and the resulting mixture was stirred for 3 h at room temperature. The reaction mixture was concentrated under vacuum and the residue was purified by silica gel column chromatography, eluted with THF/PE (0-50%), to afford a mixture of the title compounds (2.4 g).

Step 7: a mixture of tert-butyl (1S,2R,5R)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and tert-butyl (1R,2S,5S)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a stirred solution of a mixture of tert-butyl (4aR,5S,8R)-1-oxooctahydro-1H-5,8-epimino[1,3]oxazino[3,4-a]azepine-11-carboxylate and tert-butyl (4aS,5R,8S)-1-oxooctahydro-1H-5,8-epimino[1,3]oxazino[3,4-a]azepine-11-carboxylate (2.3 g, 8.1 mmol, 1.0 equiv) in EtOH (20 mL) and water (7 mL) was added NaOH (0.98 g, 24.4 mmol, 3.0 equiv) at room temperature and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was neutralized to pH = 6 by adding 2.0 M HCl aq. solution. The resulting mixture was extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated to provide a mixture of the title compounds (2.1 g).

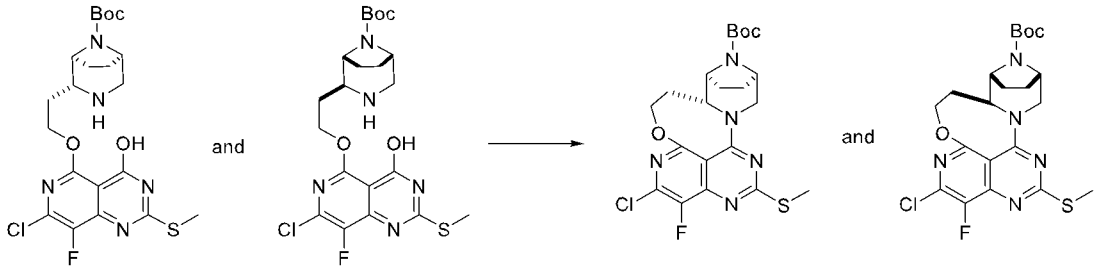
Step 8: a mixture of tert-butyl (1S,2R,5R)-2-(2-((7-chloro-8-fluoro-4-hydroxy-2-(methylthio)-pyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and tert-butyl (1R,2S,5S)-2-(2-((7-chloro-8-fluoro-4-hydroxy-2-(methylthio)pyrido[4,3-d]pyrimidin-5-yl)oxy)-ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



To a stirred solution of a mixture of 5,7-dichloro-8-fluoro-2-(methylsulfanyl)pyrido[4,3-d]pyrimidin-4-ol (1 g, 3.57 mmol, 1.0 equiv) and tert-butyl (1S,2R,5R)-2-(2-hydroxyethyl)-3,8-

diazabicyclo[3.2.1]octane-8-carboxylate and tert-butyl (1R,2S,5S)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (915 mg, 3.57 mmol, 1.0 equiv) in THF (10 mL) was added NaH (428 mg, 10.7 mmol, 3.0 equiv, 60%) in portions at 0-5 ℃. The resulting mixture was stirred at rt for 2 h, diluted with water and then extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was used in the next step directly without further purification.

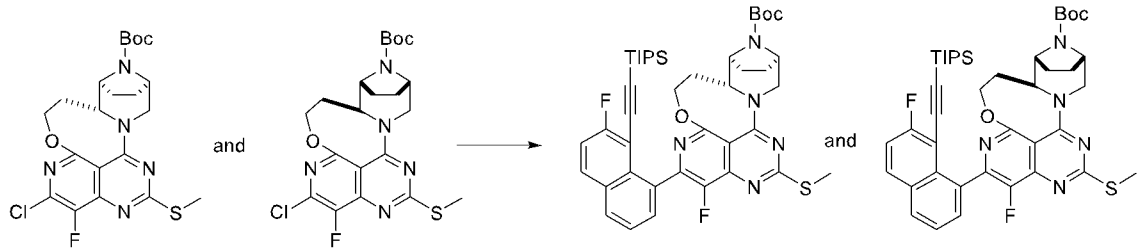
Step 9: a mixture of tert-butyl (6aR,7S,10R)-2-chloro-1-fluoro-13-(methylthio)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta-[1,2,3-de]naphthalene-15-carboxylate and tert-butyl (6aS,7R,10S)-2-chloro-1-fluoro-13-(methylthio)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta-[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



A solution of a mixture of tert-butyl (1S,2R,5R)-2-(2-((7-chloro-8-fluoro-4-hydroxy-2-(methylthio)-pyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and tert-butyl (1R,2S,5S)-2-(2-((7-chloro-8-fluoro-4-hydroxy-2-(methylthio)pyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (crude from step 8, 3.57 mmol, 1.0 equiv), was added bis(2-oxo-1,3-oxazolidin-3-yl)phosphinoyl chloride (3.18 g, 12.5 mmol, 3.5 equiv) and DIEA (6 g, 46.4 mmol, 13.0 equiv) in DCM (100 mL) and the resulting mixture was stirred at rt for 40 h. The reaction mixture was diluted with water and then extracted with DCM. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and then concentrated. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-70%), to afford a mixture of the title compounds (700 mg).

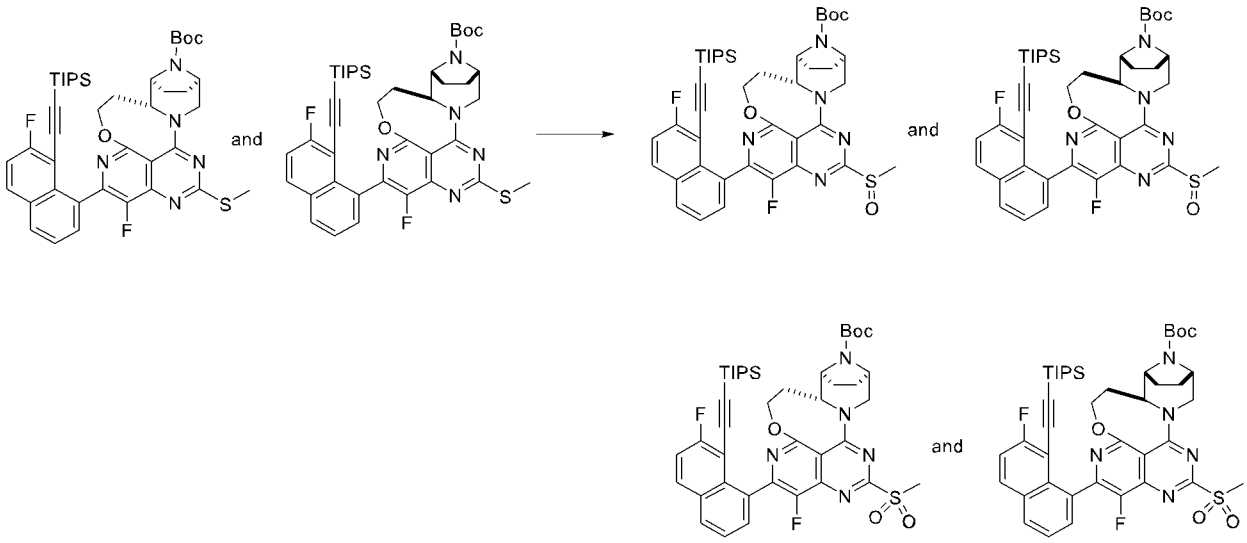
Step 10: a mixture of tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)-ethynyl)-naphthalen-1-yl)-13-(methylthio)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate and tert-butyl (6aS,7R,10S)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(methylthio)-

5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta-[1,2,3-de]naphthalene-15-carboxylate



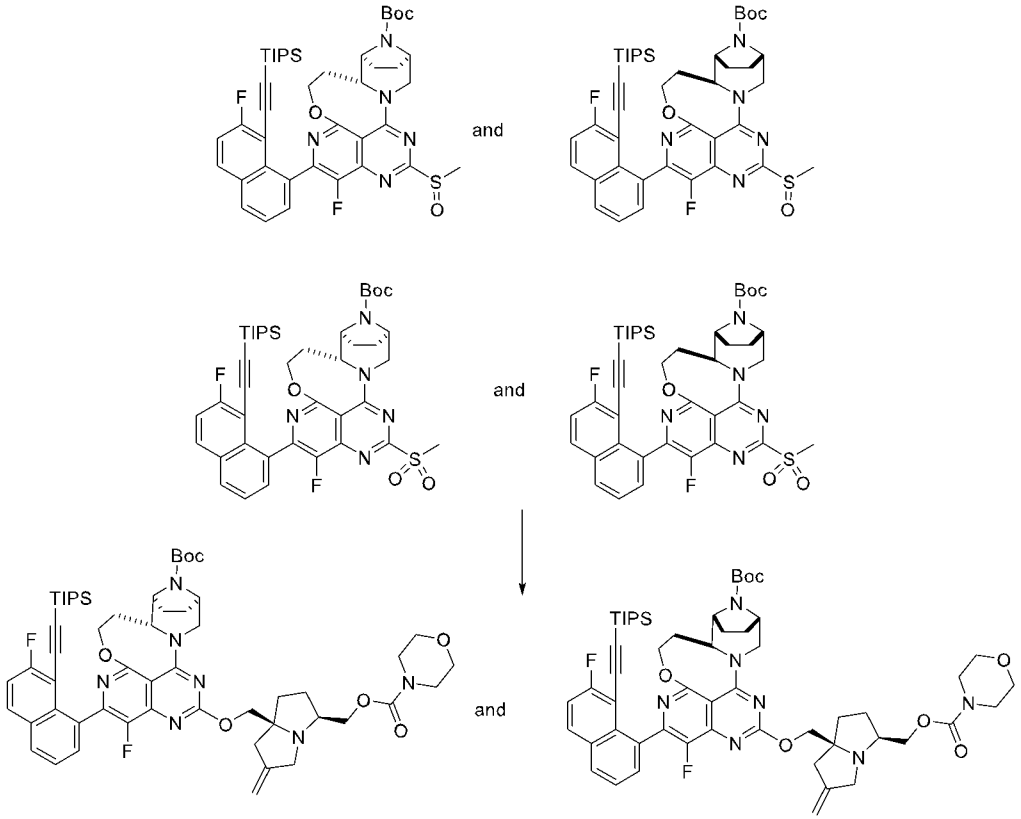
To a stirred solution of tert-butyl (6aR,7S,10R)-2-chloro-1-fluoro-13-(methylthio)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]-cycloocta[1,2,3-de]naphthalene-15-carboxylate and tert-butyl (6aS,7R,10S)-2-chloro-1-fluoro-13-(methylthio)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate (650 mg, 1.35 mmol, 1.0 equiv) and ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (915 mg, 2.0 mmol, 1.5 equiv) in DME (13 mL) and H_2O (2.0 mL) were added cataCXium A Pd G3 (98 mg, 0.135 mmol, 0.1 equiv) and K_2CO_3 (559 mg, 4.0 mmol, 3.0 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 85℃ for 2 h, cooled to rt and then extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and then concentrated. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (0 - 50%), to afford a mixture of the title compounds (640 mg).

Step 11: a mixture of tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)-naphthalen-1-yl)-13-(methylsulfinyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate and tert-butyl (6aS,7R,10S)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(methylsulfinyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]-cycloocta[1,2,3-de]naphthalene-15-carboxylate and tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)-naphthalen-1-yl)-13-(methylsulfonyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate and tert-butyl (6aS,7R,10S)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(methylsulfonyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methano-cyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



To a stirred solution of tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)-ethynyl)naphthalen-1-yl)-13-(methylthio)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate and tert-butyl (6aS,7R,10S)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(methylthio)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]-cycloocta[1,2,3-de]naphthalene-15-carboxylate (640 mg, 0.83 mmol, 1.0 equiv) in DCM (6.4 mL) was added m-CPBA (335 mg, 1.66 mmol, 2.0 equiv, 85%) in portions at rt and the resulting mixture was stirred at rt for 2 h. The reaction was quenched by adding $NaHSO_3$ aq. solution at 5℃ and then extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and then concentrated. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (0 - 50%), to afford a mixture of the title compounds.

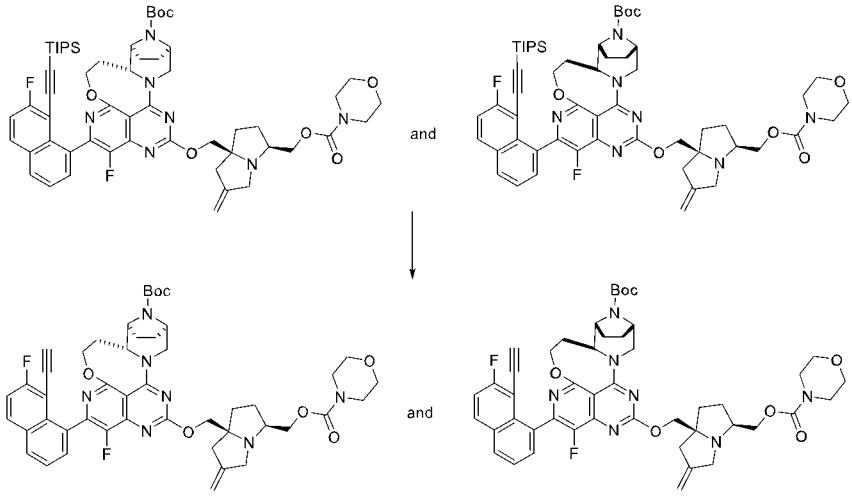
Step 12: a mixture of tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)-naphthalen-1-yl)-13-(((5S,7aS)-2-methylene-5-(((morpholine-4-carbonyl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate and tert-butyl (6aS,7R,10S)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)-naphthalen-1-yl)-13-(((5S,7aS)-2-methylene-5-(((morpholine-4-carbonyl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]-cycloocta[1,2,3-de]naphthalene-15-carboxylate



To a stirred solution of a mixture of a mixture of tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(methylsulfinyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate and tert-butyl (6aS,7R,10S)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)-naphthalen-1-yl)-13-(methylsulfinyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate and tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)-naphthalen-1-yl)-13-(methyl-sulfonyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methano-cyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate and tert-butyl (6aS,7R,10S)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(methylsulfonyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methano-cyclohepta[4,5]cycloocta[1,2,3-de]-naphthalene-15-carboxylate (760 mg, 0.945 mmol, 1.0 equiv) and [(3S,7aS)-7a-(hydroxymethyl)-6-methylidene-tetrahydro-1H-pyrrolizin-3-yl]methyl morpholine-4-carboxylate (560 mg, 1.89 mmol, 2.0 equiv) in dioxane (7.6 mL) was added t-BuONa (180 mg, 1.88 mmol, 2.0 equiv) in portions at 0-5℃. The resulting mixture was stirred at rt for 2 h, diluted with water and then extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and

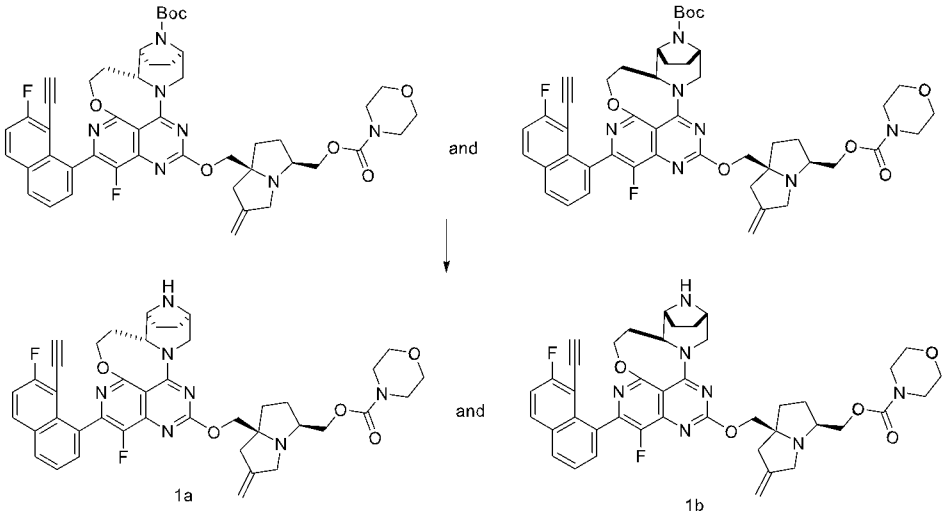
then concentrated. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (0 - 100%), to afford a mixture of the title compounds (580 mg).

Step 13: a mixture of tert-butyl (6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((5S,7aS)-2-methylene-5-(((morpholine-4-carbonyl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate and tert-butyl (6aS,7R,10S)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((5S,7aS)-2-methylene-5-(((morpholine-4-carbonyl)oxy)methyl)-tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



To a stirred solution of a mixture of tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(((5S,7aS)-2-methylene-5-(((morpholine-4-carbonyl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate and tert-butyl (6aS,7R,10S)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)-naphthalen-1-yl)-13-(((5S,7aS)-2-methylene-5-(((morpholine-4-carbonyl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methano-cyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate (580 mg, 0.57 mmol, 1.0 equiv) in DMF (5.8 mL) at rt was added CsF (604 mg, 3.98 mmol, 7.0 equiv) in portions and the resulting mixture was stirred at rt for 1 h. The reaction mixture was diluted with water and then extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and then concentrated to provide the mixture of the title compounds (370 mg).

Step 14: a mixture of ((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta-[4,5]cyclo-octa[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl morpholine-4-carboxylate and ((3S,7aS)-7a-((((6aS,7R,10S)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclo-hepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl morpholine-4-carboxylate



To a stirred solution of a mixture of tert-butyl (6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((5S,7aS)-2-methylene-5-(((morpholine-4-carbonyl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate and tert-butyl (6aS,7R,10S)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((5S,7aS)-2-methylene-5-(((morpholine-4-carbonyl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate (370 mg, 0.428 mmol, 1.0 equiv) in DCM (3.7 mL) was added HCl solution in 1,4-dioxane (4.0 M, 0.35 mL) and DCM (1.75 mL) under nitrogen atmosphere. The resulting mixture was stirred at 0℃ for 1 h, basified to pH = 8 by adding a solution of NH_3 in MeOH (1.0 M) and then concentrated under reduced pressure. The residue was purified by Prep-HPLC to afford the title compound (120 mg). MS (ES, *m/z*): $[M+H]^+$=764.4.

The two isomers were separated by Prep-Chiral HPLC with the following conditions to provide isomer **1a** and **1b**.

Column: CHIRAL ART Cellulose-SC, 3*25 cm, 5 μm;

Mobile Phase A: HEX: DCM=3: 1, Mobile Phase B: EtOH (0.1% IPA);

Flow rate: 35 mL/min; Gradient: isocratic 30;

Sample Solvent: EtOH; Sample concentration: 13 mg/mL; Injection Volume: 1.5 mL

One of compound **1a** and **1b** had: retention time 4.38 min, MS (ES, *m/z*): $[M+H]^+$=764.4.;

The other of **1a** and **1b** had: retention time 5.21 min, MS (ES, *m/z*): $[M+H]^+$=764.4.

Chiral HPLC column condition:

Shimadzu LC-20AD

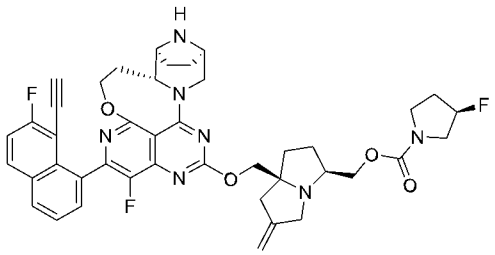
Mobile Phase: A: n-Hexane/DCM=3/1 B: Ethanol(0.1% IPA); A/B = 7/3

Column: YMC Cellulose-SC, 100*4.6mm, 3um 108YB10067

Flow rate: 1.0 mL/min

Example 2

Synthesis of ((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methano-cyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl (R)-3-fluoropyrrolidine-1-carboxylate



Step 1. tert-butyl (1S,2R,5R)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

A mixture of tert-butyl (1S,2R,5R)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and tert-butyl (1R,2S,5S)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (26 g) was separated by chiral SFC to provide tert-butyl (1R,2S,5S)-2-(2-hydroxyethyl)-

3,8-diazabicyclo[3.2.1]octane-8-carboxylate (11 g) and tert-butyl (1S,2R,5R)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (10.5 g).

Separation conditions:

Column: XA Lux Cellulose-4, 5*25 cm, 10 μm;

Mobile Phase A: CO_2, Mobile Phase B: IPA(0.1% 2M NH_3-MEOH)

Flow rate: 150 mL/min;

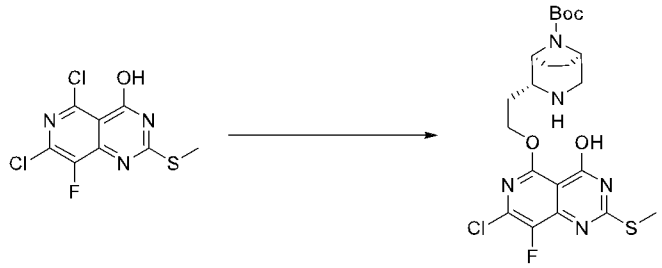
Gradient: isocratic 50% B; Column Temperature(°C): 35;

Back Pressure(bar): 100; Wavelength: 220 nm;

tert-butyl (1R,2S,5SR)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate retention time: 3.29 min; MS (ES, m/z): $[M+H]^+$=257.4.

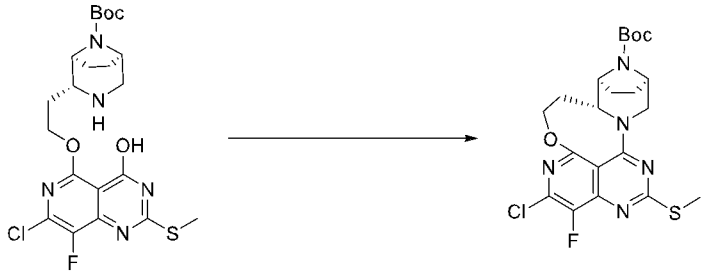
tert-butyl (1S,2R,5R)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate retention time: 4.29 min; MS (ES, m/z): $[M+H]^+$=257.4.

Step 2: tert-butyl (1S,2R,5R)-2-(2-((7-chloro-8-fluoro-4-hydroxy-2-(methylthio)pyrido[4,3-d]-pyrimidin-5-yl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



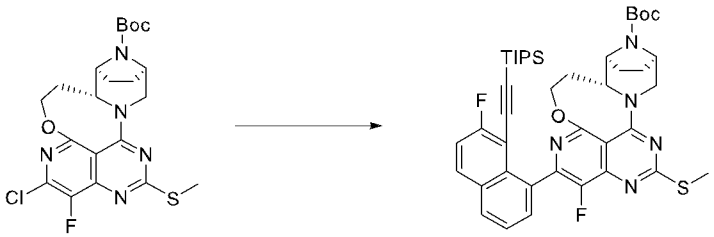
To a solution of 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4-ol (12 g, 42.8 mmol, 1 equiv) and tert-butyl (1S,2R,5R)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (10.9 g, 42.8 mmol, 1 equiv) in THF (120 mL) at 0 ℃ was added NaH (5.14 g, 128.5 mmol, 3 equiv, 60%) in portions and the resulting mixture was stirred for 2 h at room temperature. The reaction mixture was cooled at 0 ℃ and quenched with sat. NH_4Cl aq. solution. The mixture was extracted with DCM, and the combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated to afford the title compound (25 g, crude).

Step 3: tert-butyl (6aR,7S,10R)-2-chloro-1-fluoro-13-(methylthio)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



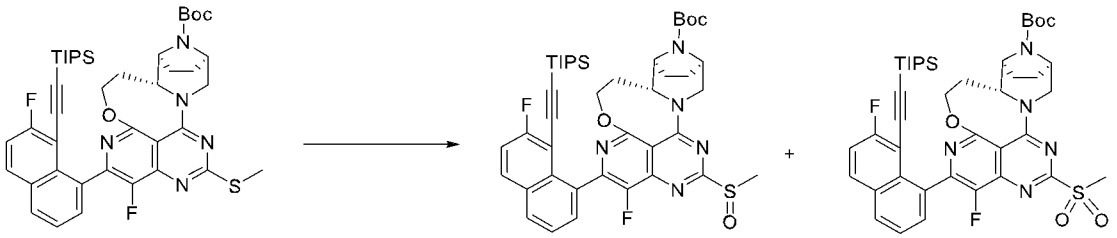
To a solution of tert-butyl (1S,2R,5R)-2-(2-((7-chloro-8-fluoro-4-hydroxy-2-(methylthio)-pyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (25 g, 50.0 mmol, 1 equiv) and DIEA (32.31 g, 250.0 mmol, 5 equiv) in CH_3CN (375 mL) at rt was added bis(2-oxo-1,3-oxazolidin-3-yl)phosphinoyl chloride (15.27 g, 60.0 mmol, 1.2 equiv) and the resulting mixture was stirred for 1 h at 60 ℃. After cooling at rt, the mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-40%) to afford the title compound (9.8 g).

Step 4: tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(methylthio)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta [4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



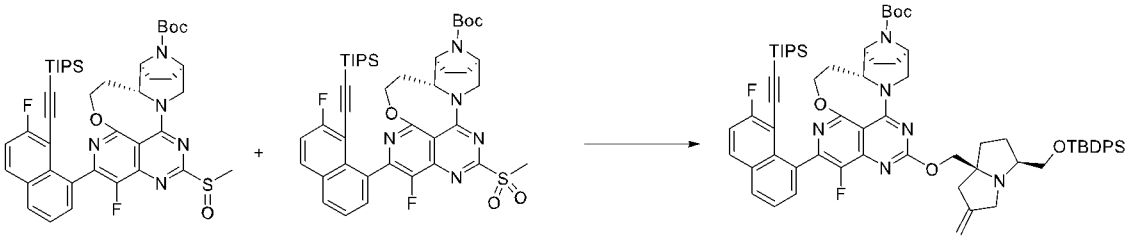
A flask was charged with tert-butyl (6aR,7S,10R)-2-chloro-1-fluoro-13-(methylthio)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta-[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate (8.8 g, 18.3 mmol, 1 equiv), ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (10.74 g, 23.7 mmol, 1.3 equiv), cataCXium-A-Pd-G3(2.66 g, 3.7 mmol, 0.20 equiv), K_3PO_4 (11.63 g, 54.8 mmol, 3.00 equiv), and dioxane (90 mL) and H_2O (9 mL). The mixture was stirred for 2 h at 90 ℃ under nitrogen atmosphere. After cooling at rt, the reaction mixture was diluted with water and extracted with DCM. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography, eluted with EA / PE (0-40%) to afford the title compound (9.2 g).

Step 5: tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl) ethynyl) naphthalen-1-yl)-13-(methylsulfinyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate and tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(methylsulfonyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



To a stirred solution of tert-butyl (6aR,7R,10S)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)-ethynyl)naphthalen-1-yl)-13-(methylthio)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate (1.7 g, 2.2 mmol) in ethyl acetate (17.0 mL) was added 3-chloroperoxybenzoic acid (894.1 mg, 4.4 mmol) at 0 ℃ and the mixture was stirred for 6 h under argon atmosphere. The reaction mixture was diluted with EtOAc, washed with sat. sodium thiosulfate aq. solution, sat. sodium bicarbonate aq. solution and brine. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the title compound (1.7 g).

Step 6: tert-butyl (6aR,7S,10R)-13-(((5S,7aS)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-2-methylene-tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)-naphthalen-1-yl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methano-cyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



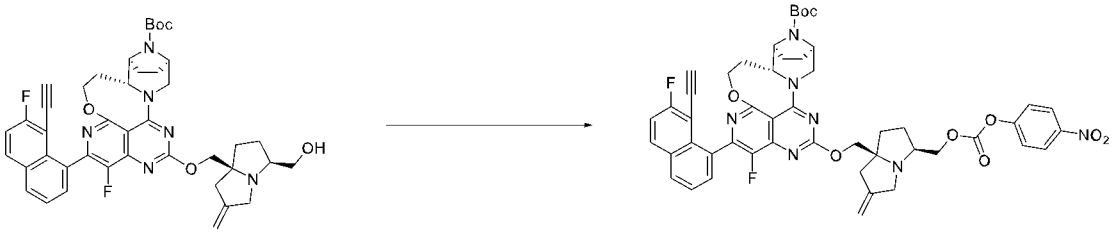
To a stirred solution of tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl) ethynyl)naphthalen-1-yl)-13-(methylsulfinyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclo-hepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate and tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(methyl-

sulfonyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclo-hepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate (1.7g, 2.11 mmol) and ((5S,7aS)-5-(((tert-butyldiphenylsilyl)-oxy)methyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (980.68 mg, 2.33 mmol) in anhydrous toluene (17.0 mL) was added sodium tert-butoxide (406.37 mg, 4.23 mmol) at 0 ℃ under argon atmosphere and the resulting mixture was stirred at 0 ℃ for 0.5 h. The reaction mixture was quenched with sat. ammonium chloride aq. solution and then extracted with EtOAc. The combined organic layers were washed with water, brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was purified by flash chromatography, eluted with ethyl acetate/dichloromethane (0~10%) to afford the title compound (1.1 g).

Step 7: tert-butyl (6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((5S,7aS)-5-(hydroxymethyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl) methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]-naphthalene-15-carboxylate

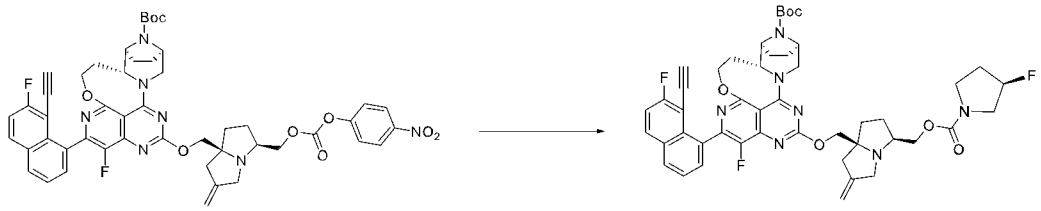
To a stirred solution of tert-butyl (6aR,7S,10R)-13-(((5S,7aS)-5-(((tert-butyldiphenylsilyl)-oxy)methyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta [4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate (1.1 g, 0.96 mmol) in anhydrous tetrahydrofuran (5.0 mL) was added TBAF (9.6 mL, 9.6 mmol, 1.0 M in THF) at 20 ℃, and the reaction mixture was stirred for 2 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulphate and concentrated. The residue was purified by flash chromatography, eluted with methanol/dichloromethane (0~5%) to afford the title compound (580 mg).

Step 8: tert-butyl (6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((5S,7aS)-2-methylene-5-((((4-nitrophenoxy)carbonyl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]-cycloocta[1,2,3-de]naphthalene-15-carboxylate



To a stirred solution of tert-butyl (6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((5S,7aS)-5-(hydroxymethyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]-cycloocta[1,2,3-de]naphthalene-15-carboxylate (100 mg, 0.13 mmol) and triethylamine (134.77 mg, 1.33 mmol) in anhydrous tetrahydrofuran (0.5 mL) was added 4-nitrophenyl carbonochloridate (134.22 mg, 0.67 mmol) at 20 ℃ and the resulting mixture was stirred at 20 ℃ for 16 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with water, brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the title compound (120 mg), which was used to next step directly without further purification.

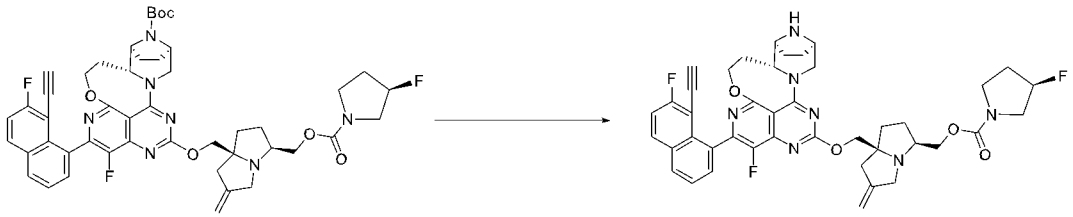
Step 9: tert-butyl (6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((5S,7aS)-5-((((R)-3-fluoropyrrolidine-1-carbonyl)oxy)methyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta [1,2,3-de]naphthalene-15-carboxylate



To a stirred solution of tert-butyl (6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((5S,7aS)-2-methylene-5-((((4-nitrophenoxy)carbonyl)oxy)methyl) tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methano-cyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate (20 mg, 0.02 mmol) and triethylamine (22.1 mg, 0.22 mmol) in THF (0.5 mL) was added (R)-3-fluoropyrrolidine (9.73 mg, 0.11 mmol) at 20 ℃ and the resulting mixture was stirred at 20 ℃ for 1 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was

purified by flash chromatography, eluted with methanol/dichloromethane (0~4%) to afford the title compound (8.0 mg).

Step 10: ((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]-cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl (R)-3-fluoropyrrolidine-1-carboxylate



To a stirred solution of tert-butyl (6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((5S,7aS)-5-((((R)-3-fluoropyrrolidine-1-carbonyl)oxy)methyl)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta [1,2,3-de]naphthalene-15-carboxylate (8.0 mg, 0.0092 mmol) in DCM (1.0 mL) was added HCl solution in dioxane (0.5 mL, 4.0 M) at 20 ℃ and the resulting solution was stirred at rt for 1 h. The solvent was removed under reduced pressure. The residue was purified by reverse flash chromatography, eluted with (5%~50% acetonitrile in water with 0.05% ammonium bicarbonate) to afford the title compound (2.50 mg). MS (ES, m/z): $[M+H]^+$ = 766.4.

The compounds in Table 6 were prepared by proceeding analogously as described in Example 2, Steps 9-11, using the amines in the table below instead of (R)-3-fluoropyrrolidine in Step 8. Table 1.

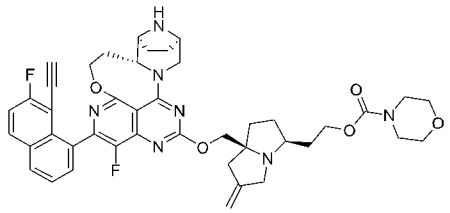
Table 1

Compound # (Cpd Table IA)	MS (ES, m/z): $[M+H]^+$
1.50	748.4
1.51	766.4
1.55	778.4
1.56	778.4
1.61	784.4
1.62	818.4
1.64	790.4
1.69	776.4
1.66	760.4

1.72	808.4
1.73	792.5
1.75	776.4
1.80	804.5
1.81	791.4
1.82	778.4
1.84	806.4
1.85	806.4
1.87	790.4
1.89	818.5
1.90	818.5

Example 3

Synthesis of 2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl morpholine-4-carboxylate

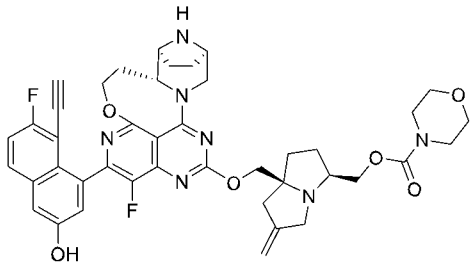


The title compound was prepared by proceeding analogously as described in Example 1, Steps 12-14, using a mixture of tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl) ethynyl) naphthalen-1-yl)-13-(methylsulfinyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclo-hepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate and tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(methylsulfonyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate and 2-[(3S,7aS)-7a-(hydroxymethyl)-6-methylidene-tetrahydro-1H-pyrrolizin-3-yl]ethyl morpholine-4-carboxylate instead of a mixture of tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)-naphthalen-1-yl)-13-(methylsulfinyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta-[1,2,3-de]naphthalene-15-carboxylate and tert-butyl (6aS,7R,10S)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(methylsulfinyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]-

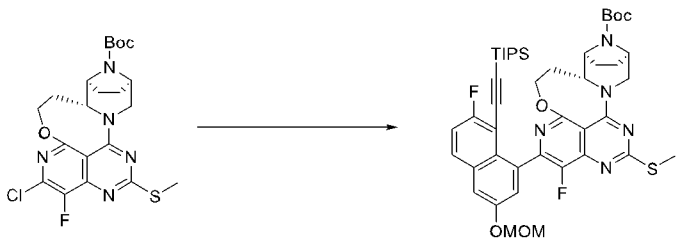
cycloocta[1,2,3-de]naphthalene-15-carboxylate and tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)-naphthalen-1-yl)-13-(methylsulfonyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methano-cyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate and tert-butyl (6aS,7R,10S)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)-naphthalen-1-yl)-13-(methylsulfonyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methano-cyclohepta[4,5]cycloocta-[1,2,3-de]naphthalene-15-carboxylate and [(3S,7aS)-7a-(hydroxymethyl)-6-methylidene-tetrahydro-1H-pyrrolizin-3-yl]methyl morpholine-4-carboxylate in Step 12. MS (ES, m/z): $[M+H]^+$ = 778.4.

Example 4

Synthesis of ((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl morpholine-4-carboxylate



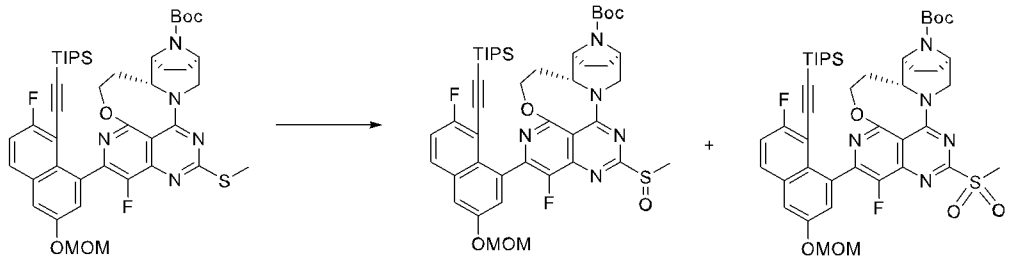
Step 1: tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)-ethynyl)naphthalen-1-yl)-13-(methylthio)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



A mixture of tert-butyl (6aR,7S,10R)-2-chloro-1-fluoro-13-(methylthio)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]-naphthalene-15-carboxylate (414 mg, 0.86 mmol), ((2-fluoro-6-(methoxy-methoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (658 mg, 1.28 mmol),

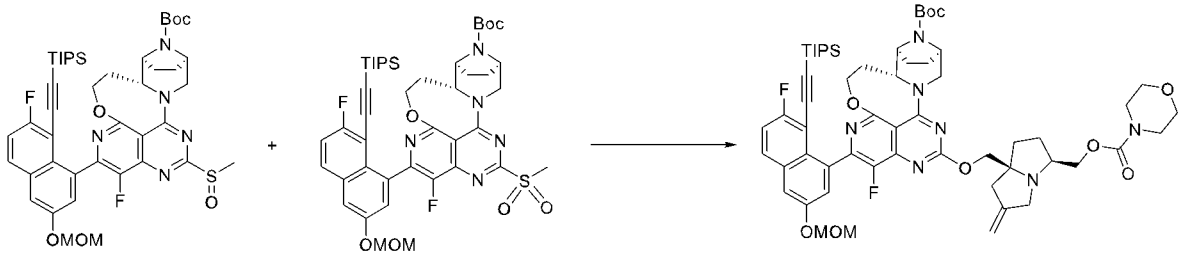
K_2CO_3 (354 mg, 2.58 mmol) and cataCXiumA Pd G3 (192 mg, 0.26 mmol) in DME (4 mL) and H_2O (1 mL) was stirred for 6 h at 85 ℃ under nitrogen atmosphere. After coolig to rt, the reaction mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (0-100%) to afford the title compound (350 mg).

Step 2: a mixture of tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(methylsulfinyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate and tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)-ethynyl)naphthalen-1-yl)-13-(methylsulfonyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



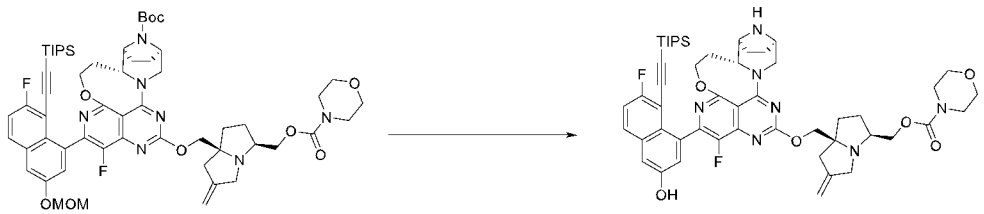
To a stirred solution of tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(methylthio)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate (230 mg, 0.34 mmol) in DCM (2 mL) was added m-CPBA (138 mg, 0.68 mmol) in portions at rt and the resulting mixture was stirred for 2 h at rt. The reaction mixture was quenched by adding sat. $Na_2S_2O_3$ aq. solution at 5 ℃ and then extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to afford the title compounds.

Step 3: tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)-ethynyl)naphthalen-1-yl)-13-(((5S,7aS)-2-methylene-5-(((morpholine-4-carbonyl)oxy)methyl)-tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



To a solution of a mixture of tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(methylsulfinyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]-cycloocta[1,2,3-de]naphthalene-15-carboxylate and tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(methylsulfonyl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]-cycloocta[1,2,3-de]naphthalene-15-carboxylate (60 mg) in DCM (2 mL) was added ((3S,7aS)-7a-(hydroxymethyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl morpholine-4-carboxylate (39. mg, 0.13 mmol), the reaction was cooled to 0 °C. t-BuONa (12. mg, 0.13 mmol) was added in portions and the resulting mixture was stirred at 0 °C for 2 h. The reaction was quenched by water, extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatograph, eluted with MeOH/DCM = 0-3% to ptovide the title compound.

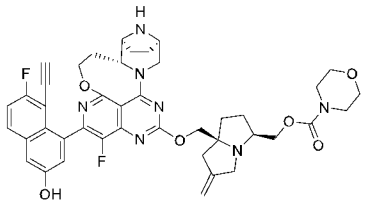
Step 4: ((3S,7aS)-7a-((((6aR,7S,10R)-1-fluoro-2-(7-fluoro-3-hydroxy-8-((triisopropylsilyl)-ethynyl)naphthalen-1-yl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl morpholine-4-carboxylate



To a solution of tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(((5S,7aS)-2-methylene-5-(((morpholine-4-carbonyl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate (40 mg, 0.037 mmol) in EtOAc (1mL) was added HCl solution in EtOAc (4.0 M, 1.0 mL) and the resulting mixture was stirred at 0 °C for 2 hrs. The reaction was quenched by adding sat.

Na_2CO_3 aq. solution and then extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4 and concentrated to provide the title compound.

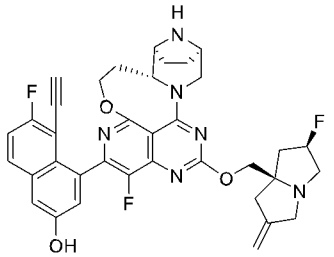
Step 5: ((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]-cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl morpholine-4-carboxylate



To a solution of ((3S,7aS)-7a-((((6aR,7S,10R)-1-fluoro-2-(7-fluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl morpholine-4-carboxylate (38 mg, crude) in DMF (1mL) was added CsF (26 mg, 0.18 mmol) and the resulting mixture was stirred at 50 °C for 4 h. The reaction mixture was filtered and the filtrate was purified by reverse flash, eluted with CH_3CN/ Water (0.05% NH_4HCO_3) = 0 - 60%, to afford the title compound (11.5 mg). LCMS (ESI, m/z) $[M+H]^+$ = 780.5.

Example 5

Synthesis of 5-ethynyl-6-fluoro-4-((6aR,7S,10R)-1-fluoro-13-(((2R,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-2-yl)-naphthalen-2-ol

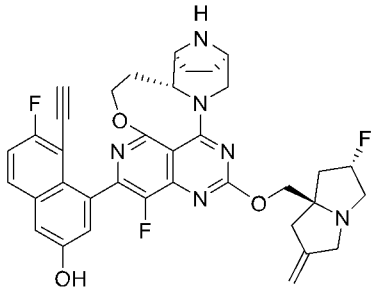


The tile compound was prepared by proceeding analogously as described in Example 4, Steps 3-5, using ((2R,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol instead of

((3S,7aS)-7a-(hydr oxy methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl morpholine-4-carboxylate in Step 3. LCMS (ESI, m/z) $[M+H]^+ = 655.4$.

Example 6

Synthesis of 5-ethynyl-6-fluoro-4-((6aR,7S,10R)-1-fluoro-13-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-2-yl)-naphthalen-2-ol



The title compound wase prepared by proceeding analogously as described in Example 4, Steps 3-5, using ((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol instead of ((3S,7aS)-7a-(hydr oxy methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl morpholine-4-carboxylate in Step 3. LCMS (ESI, m/z) $[M+H]^+ = 655.4$.

Biological Examples

Example 1

AspC-1 3D Spheroid Cell Proliferation Assays

AspC-1 cells were seeded into 96-well round black/clear bottom, ultra-low attachment surface plate in 100 µl cell culture medium (RPMI1640 with 10% FBS). After 3 days incubation at 37 °C and 5% CO_2, compounds solubilized in DMSO were added by Tecan D300e dispenser (0.5% DMSO final). The cells were incubated for 4 days at 37 °C and 5% CO_2. Cell proliferation was quantitated by addition of 50 µl/well of CellTiter-Glo® 3D reagent (Promega). The solutions were well mixed by shaking the plate for 10 minutes using an orbital plate shaker and then incubated at room temperature for a total of 30 minutes. After incubation, luminescence was then measured on an EnVision multimode plate reader (PerkinElmer). The results were normalized to percentage inhibition with

DMSO control as 0% inhibition. The normalized luminescence results were plotted against compound concentration, and the data fit to 4-Parameter Logistic Model to calculate the EC_{50} by *XLfit* 5.5.0 The EC_{50} of compounds tested in this assay are provided in Table 2 below.

Table 2

Compound # (Cpd Table 1A)	AsPC-1 3D CTG EC_{50} (nM)
1.50	2.3
1.51	16.3
1.55	6.2
1.56	10
1.61	7.8
1.62	2.5
1.64	7.4
2.19	10
1.69	11
1.66	27.8
21.72	9.0
1.73	5.2
1.75	26
1.80	8
1.81	4.3
1.82	6.2
1.84 and 1.85	one of 1.84 and 1.85 is 2.8 and the other is 3.7
1.87	9.8
1.89	4.4
1.90	16.7
2.51	7.1
2.82	6.9
2.96	6.3
2.97	2.8
2.98	3.5

Example 2

p-ERK Cellular 1-plate Assay

The ability of the compound of Table 1A or a pharmaceutically acceptable salt thereof (test compound) to inhibit K-Ras G12D activity can be tested using AGS (Cobioer, CBP60476) cell lines which harbor KRAS G12D mutation as described below.

AGS (Cobioer, CBP60476) is seeded in 384-well plates and cultured overnight (5,000 cells per well, 40 μl total volume). The following morning, cells are treated with test compound, with starting concentration at 10 μM and 3- fold dilution down to 0.5 nM for 3 h at 37 °C. DMSO treatment served as control. p-ERK is then measured using AlphaLISA SureFire Ultra p-ERK1/2 (Thr202/Tyr204) Assay Kit (Perkin Elmer, cat# ALSU-PERK) following the manufacturer's instruction as follows.

Briefly, the culture medium is removed and 10 μl 1× lysis buffer is added to each well, followed by 10 minutes incubation on a plate shaker at room temperature. Acceptor mixture is prepared according to manufacturer's instruction. 5 μl acceptor mixture is added to the cell lysate and the plate is wrapped with foil, spun at 500 rpm for 10s and incubated at RT for 60 min. Donor mixture is prepared under subdued light. 5 μl donor mixture is added to the cell lysate and the plate is spun at 500 rpm for 10s and incubated at RT for another 60 min. in the dark. Signal is then measured on a EnVision 2105 multimode plate reader. Percentage inhibition is calculated with DMSO treatment as 100% of signal, and EC_{50} was calculated by XL*fit* 5.5.x.

Formulation

Examples

The following are representative pharmaceutical formulations containing a compound of the present disclosure.

Tablet Formulation

The following ingredients are mixed intimately and pressed into single scored tablets.

Ingredient	Quantity per tablet (mg)
compound of Table 1A	400
cornstarch	50
croscarmellose sodium	25

lactose	120
magnesium stearate	5

Capsule Formulation

The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

Ingredient	Quantity per capsule (mg)
compound of Table 1A	200
lactose spray dried	148
magnesium stearate	2

Injectable Formulation

Compound of the disclosure (e.g., compound 1) in 2% HPMC, 1% Tween 80 in DI water, pH 2.2 with MSA, q.s. to at least 20 mg/mL

Inhalation Composition

To prepare a pharmaceutical composition for inhalation delivery, 20 mg of a compound disclosed herein is mixed with 50 mg of anhydrous citric acid and 100 mL of 0.9% sodium chloride solution. The mixture is incorporated into an inhalation delivery unit, such as a nebulizer, which is suitable for inhalation administration.

Topical Gel Composition

To prepare a pharmaceutical topical gel composition, 100 mg of a compound disclosed herein is mixed with 1.75 g of hydroxypropyl cellulose, 10 mL of propylene glycol, 10 mL of isopropyl myristate and 100 mL of purified alcohol USP. The resulting gel mixture is then ncorporated into containers, such as tubes, which are suitable for topical administration.

Ophthalmic Solution Composition

To prepare a pharmaceutical ophthalmic solution composition, 100 mg of a compound disclosed herein is mixed with 0.9 g of NaCl in 100 mL of purified water and filtered using a 0.2 micron filter. The resulting isotonic solution is then incorporated into ophthalmic delivery units, such as eye drop containers, which are suitable for ophthalmic administration.

Nasal spray solution

To prepare a pharmaceutical nasal spray solution, 10 g of a compound disclosed herein is mixed with 30 mL of a 0.05M phosphate buffer solution (pH 4.4). The solution is placed in a nasal administrator designed to deliver 100 ul of spray for each application.

CLAIMS

What is Claimed:

1. A compound selected from:

Cpd #	Name
1.1	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl pyrrolidine-1-carboxylate
1.2	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methano-cyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl (S)-3-fluoropyrrolidine-1-carboxylate
1.3	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methano-cyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 3-methylpyrrolidine-1-carboxylate
1.4	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl (R)-3-methylpyrrolidine-1-carboxylate
1.5	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 3-fluoro-3-methylpyrrolidine-1-carboxylate
1.6	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl (S)-3-methoxypyrrolidine-1-carboxylate
1.7	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-

Cpd #	Name
	methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl (R)-3-methoxypyrrolidine-1-carboxylate
1.8	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 3-(difluoromethoxy)pyrrolidine-1-carboxylate
1.9	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl (3S,4R)-3,4-dimethoxypyrrolidine-1-carboxylate
1.10	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl (3R,4R)-3,4-dimethoxypyrrolidine-1-carboxylate
1.11	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 3,3-dimethylpyrrolidine-1-carboxylate
1.12	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 3,3-difluoropyrrolidine-1-carboxylate
1.13	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 8-oxa-2-azaspiro[4.5]decane-2-carboxylate
1.14	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-

Cpd #	Name
	methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 1-oxa-6-azaspiro[3.4]octane-6-carboxylate
1.15	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-7-azaspiro[4.4]nonane-7-carboxylate
1.16	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-6-azaspiro[3.4]octane-6-carboxylate
1.17	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 6,9-dioxa-2-azaspiro[4.5]decane-2-carboxylate
1.18	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 3-methylmorpholine-4-carboxylate
1.19	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate
1.20	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-5-azabicyclo[4.1.0]heptane-5-carboxylate
1.21	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-

Cpd #	Name
	1H-pyrrolizin-3-yl)methyl 2,2-dimethyltetrahydro-5H-[1,3]dioxolo[4,5-c]pyrrole-5-carboxylate
1.22	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl (3aR,6aS)-tetrahydro-1H-furo[3,4-c]pyrrole-5(3H)-carboxylate
1.23	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 3-azabicyclo[3.1.0]hexane-3-carboxylate
1.24	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 3,3-difluoropiperidine-1-carboxylate
1.25	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 2-(methoxymethyl)morpholine-4-carboxylate
1.26	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 2,6-dimethylmorpholine-4-carboxylate
1.27	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 2,2-difluoromorpholine-4-carboxylate
1.28	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-

Cpd #	Name
	methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 6-oxa-3-azabicyclo[3.1.1]heptane-3-carboxylate
1.29	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 3,5-dimethylmorpholine-4-carboxylate
1.30	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 2,2-dimethylmorpholine-4-carboxylate
1.31	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 4-(difluoromethoxy)piperidine-1-carboxylate
1.32	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 1-oxa-7-azaspiro[3.5]nonane-7-carboxylate
1.33	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-7-azaspiro[3.5]nonane-7-carboxylate
1.34	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 4-oxa-7-azaspiro[2.5]octane-7-carboxylate
1.35	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-

Cpd #	Name
	methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 4-methoxypiperidine-1-carboxylate
1.36	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 1,4-oxazepane-4-carboxylate
1.37	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl piperidine-1-carboxylate
1.38	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl (4aR,7aR)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate
1.39	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl (4aS,7aS)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate
1.40	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl (4aR,7aS)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate
1.41	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl hexahydro-5H-furo[2,3-c]pyrrole-5-carboxylate

Cpd #	Name
1.42	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate
1.43	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 3-(methoxymethyl)morpholine-4-carboxylate
1.44	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-8-azaspiro[4.5]decane-8-carboxylate
1.45	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 1-oxa-8-azaspiro[4.5]decane-8-carboxylate
1.46	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-6-azaspiro[3.5]nonane-6-carboxylate
1.47	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 1-oxa-6-azaspiro[3.5]nonane-6-carboxylate
1.48	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 7,7-difluoro-2-oxa-5-azabicyclo[4.1.0]heptane-5-carboxylate

Cpd #	Name
1.49	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl 4-(1H-pyrazol-1-yl)piperidine-1-carboxylate
1.50	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl pyrrolidine-1-carboxylate
1.51	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl (S)-3-fluoropyrrolidine-1-carboxylate
1.52	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 3-methylpyrrolidine-1-carboxylate
1.53	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl (R)-3-methylpyrrolidine-1-carboxylate
1.54	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 3-fluoro-3-methylpyrrolidine-1-carboxylate
1.55	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-

Cpd #	Name
	methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl (S)-3-methoxypyrrolidine-1-carboxylate
1.56	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl (R)-3-methoxypyrrolidine-1-carboxylate
1.57	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 3-(difluoromethoxy)pyrrolidine-1-carboxylate
1.58	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl (3S,4R)-3,4-dimethoxypyrrolidine-1-carboxylate
1.59	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl (3R,4R)-3,4-dimethoxypyrrolidine-1-carboxylate
1.60	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 3,3-dimethylpyrrolidine-1-carboxylate

Cpd #	Name
1.61	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 3,3-difluoropyrrolidine-1-carboxylate
1.62	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 8-oxa-2-azaspiro[4.5]decane-2-carboxylate
1.63	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 1-oxa-6-azaspiro[3.4]octane-6-carboxylate
1.64	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-6-azaspiro[3.4]octane-6-carboxylate
1.65	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 6,9-dioxa-2-azaspiro[4.5]decane-2-carboxylate
1.66	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 3-azabicyclo[3.1.0]hexane-3-carboxylate

Cpd #	Name
1.67	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 3-methylmorpholine-4-carboxylate
1.68	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate
1.69	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-5-azabicyclo[4.1.0]heptane-5-carboxylate
1.70	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 2,2-dimethyltetrahydro-5H-[1,3]dioxolo[4,5-c]pyrrole-5-carboxylate
1.71	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 3,3-difluoropiperidine-1-carboxylate
1.72	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 2-(methoxymethyl)morpholine-4-carboxylate

Cpd #	Name
1.73	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 2,6-dimethylmorpholine-4-carboxylate
1.74	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 2,2-difluoromorpholine-4-carboxylate
1.75	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 6-oxa-3-azabicyclo[3.1.1]heptane-3-carboxylate
1.77	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 3,5-dimethylmorpholine-4-carboxylate
1.77	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 2,2-dimethylmorpholine-4-carboxylate
1.78	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 4-(difluoromethoxy)piperidine-1-carboxylate

Cpd #	Name
1.79	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 1-oxa-7-azaspiro[3.5]nonane-7-carboxylate
1.80	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-7-azaspiro[3.5]nonane-7-carboxylate
1.81	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 4-oxa-7-azaspiro[2.5]octane-7-carboxylate
1.82	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 1,4-oxazepane-4-carboxylate
1.83	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl piperidine-1-carboxylate
1.84	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl (4aR,7aR)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate

Cpd #	Name
1.85	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl (4aS,7aS)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate
1.86	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl hexahydro-5H-furo[2,3-c]pyrrole-5-carboxylate
1.87	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate
1.88	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 3-(methoxymethyl)morpholine-4-carboxylate
1.89	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-8-azaspiro[4.5]decane-8-carboxylate
1.90	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 1-oxa-8-azaspiro[4.5]decane-8-carboxylate

Cpd #	Name
1.91	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 2-oxa-6-azaspiro[3.5]nonane-6-carboxylate
1.92	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 1-oxa-6-azaspiro[3.5]nonane-6-carboxylate
1.93	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 7,7-difluoro-2-oxa-5-azabicyclo[4.1.0]heptane-5-carboxylate
1.94	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl 4-(1H-pyrazol-1-yl)piperidine-1-carboxylate
1.95	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl pyrrolidine-1-carboxylate
1.96	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl (S)-3-fluoropyrrolidine-1-carboxylate

Cpd #	Name
1.97	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 3-methylpyrrolidine-1-carboxylate
1.98	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl (R)-3-methylpyrrolidine-1-carboxylate
1.99	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 3-fluoro-3-methylpyrrolidine-1-carboxylate
2.1	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl (S)-3-methoxypyrrolidine-1-carboxylate
2.2	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl (R)-3-methoxypyrrolidine-1-carboxylate
2.3	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 3-(difluoromethoxy)pyrrolidine-1-carboxylate
2.4	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl (3S,4R)-3,4-dimethoxypyrrolidine-1-carboxylate

Cpd #	Name
2.5	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl (3R,4R)-3,4-dimethoxypyrrolidine-1-carboxylate
2.6	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 3,3-dimethylpyrrolidine-1-carboxylate
2.7	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 3,3-difluoropyrrolidine-1-carboxylate
2.8	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 8-oxa-2-azaspiro[4.5]decane-2-carboxylate
2.9	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 1-oxa-6-azaspiro[3.4]octane-6-carboxylate
2.10	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-7-azaspiro[4.4]nonane-7-carboxylate
2.11	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-6-azaspiro[3.4]octane-6-carboxylate

Cpd #	Name
2.12	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 6,9-dioxa-2-azaspiro[4.5]decane-2-carboxylate
2.13	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 3-methylmorpholine-4-carboxylate
2.14	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate
2.15	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-5-azabicyclo[4.1.0]heptane-5-carboxylate
2.16	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 2,2-dimethyltetrahydro-5H-[1,3]dioxolo[4,5-c]pyrrole-5-carboxylate
2.17	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl (3aR,6aS)-tetrahydro-1H-furo[3,4-c]pyrrole-5(3H)-carboxylate
2.18	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-

Cpd #	Name
	methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 3-azabicyclo[3.1.0]hexane-3-carboxylate
2.19	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 3,3-difluoropiperidine-1-carboxylate
2.20	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 2-(methoxymethyl)morpholine-4-carboxylate
2.21	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 2,6-dimethylmorpholine-4-carboxylate
2.22	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 2,2-difluoromorpholine-4-carboxylate
2.23	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 6-oxa-3-azabicyclo[3.1.1]heptane-3-carboxylate
2.24	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 3,5-dimethylmorpholine-4-carboxylate
2.25	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-

Cpd #	Name
	methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 2,2-dimethylmorpholine-4-carboxylate
2.26	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 4-(difluoromethoxy)piperidine-1-carboxylate
2.27	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 1-oxa-7-azaspiro[3.5]nonane-7-carboxylate
2.28	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-7-azaspiro[3.5]nonane-7-carboxylate
2.29	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 4-oxa-7-azaspiro[2.5]octane-7-carboxylate
2.30	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 4-methoxypiperidine-1-carboxylate
2.31	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 1,4-oxazepane-4-carboxylate
2.32	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-

Cpd #	Name
	methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl morpholine-4-carboxylate
2.33	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl piperidine-1-carboxylate
2.34	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl (4aR,7aR)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate
2.35	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl (4aS,7aS)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate
2.36	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl (4aR,7aS)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate
2.37	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl hexahydro-5H-furo[2,3-c]pyrrole-5-carboxylate
2.38	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate

Cpd #	Name
2.39	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 3-(methoxymethyl)morpholine-4-carboxylate
2.40	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-8-azaspiro[4.5]decane-8-carboxylate
2.41	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 1-oxa-8-azaspiro[4.5]decane-8-carboxylate
2.42	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-6-azaspiro[3.5]nonane-6-carboxylate
2.43	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 1-oxa-6-azaspiro[3.5]nonane-6-carboxylate
2.44	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 7,7-difluoro-2-oxa-5-azabicyclo[4.1.0]heptane-5-carboxylate
2.45	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl 4-(1H-pyrazol-1-yl)piperidine-1-carboxylate

Cpd #	Name
2.46	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl pyrrolidine-1-carboxylate
2.47	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl (S)-3-fluoropyrrolidine-1-carboxylate
2.48	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 3-methylpyrrolidine-1-carboxylate
2.49	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl (R)-3-methylpyrrolidine-1-carboxylate
2.50	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 3-fluoro-3-methylpyrrolidine-1-carboxylate
2.51	2((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl (S)-3-methoxypyrrolidine-1-carboxylate

Cpd #	Name
2.52	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl (R)-3-methoxypyrrolidine-1-carboxylate
2.53	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 3-(difluoromethoxy)pyrrolidine-1-carboxylate
2.54	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl (3S,4R)-3,4-dimethoxypyrrolidine-1-carboxylate
2.55	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl (3R,4R)-3,4-dimethoxypyrrolidine-1-carboxylate
2.56	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 3,3-dimethylpyrrolidine-1-carboxylate
2.57	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 3,3-difluoropyrrolidine-1-carboxylate

Cpd #	Name
2.58	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 8-oxa-2-azaspiro[4.5]decane-2-carboxylate
2.59	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 1-oxa-6-azaspiro[3.4]octane-6-carboxylate
2.60	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-7-azaspiro[4.4]nonane-7-carboxylate
2.61	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-6-azaspiro[3.4]octane-6-carboxylate
2.62	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 6,9-dioxa-2-azaspiro[4.5]decane-2-carboxylate
2.63	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 3-methylmorpholine-4-carboxylate

Cpd #	Name
2.64	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate
2.65	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-5-azabicyclo[4.1.0]heptane-5-carboxylate
2.66	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 2,2-dimethyltetrahydro-5H-[1,3]dioxolo[4,5-c]pyrrole-5-carboxylate
2.67	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl (3aR,6aS)-tetrahydro-1H-furo[3,4-c]pyrrole-5(3H)-carboxylate
2.68	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 3-azabicyclo[3.1.0]hexane-3-carboxylate
2.69	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 3,3-difluoropiperidine-1-carboxylate

Cpd #	Name
2.70	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 2-(methoxymethyl)morpholine-4-carboxylate
2.71	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 2,6-dimethylmorpholine-4-carboxylate
2.72	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 2,2-difluoromorpholine-4-carboxylate
2.73	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 6-oxa-3-azabicyclo[3.1.1]heptane-3-carboxylate
2.74	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 3,5-dimethylmorpholine-4-carboxylate
2.75	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 2,2-dimethylmorpholine-4-carboxylate
2.76	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-

Cpd #	Name
	methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 4-(difluoromethoxy)piperidine-1-carboxylate
2.77	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 1-oxa-7-azaspiro[3.5]nonane-7-carboxylate
2.78	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-7-azaspiro[3.5]nonane-7-carboxylate
2.79	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 4-oxa-7-azaspiro[2.5]octane-7-carboxylate
2.80	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 4-methoxypiperidine-1-carboxylate
2.81	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 1,4-oxazepane-4-carboxylate
2.82	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl morpholine-4-carboxylate

Cpd #	Name
2.83	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl piperidine-1-carboxylate
2.84	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl (4aR,7aR)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate
2.85	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl (4aS,7aS)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate
2.86	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl (4aR,7aS)-hexahydro-6H-[1,4]dioxino[2,3-c]pyrrole-6-carboxylate
2.87	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl hexahydro-5H-furo[2,3-c]pyrrole-5-carboxylate
2.88	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate

Cpd #	Name
2.89	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 3-(methoxymethyl)morpholine-4-carboxylate
2.90	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-8-azaspiro[4.5]decane-8-carboxylate
2.91	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 1-oxa-8-azaspiro[4.5]decane-8-carboxylate
2.92	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 2-oxa-6-azaspiro[3.5]nonane-6-carboxylate
2.93	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 1-oxa-6-azaspiro[3.5]nonane-6-carboxylate
2.94	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 7,7-difluoro-2-oxa-5-azabicyclo[4.1.0]heptane-5-carboxylate

Cpd #	Name
2.95	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl 4-(1H-pyrazol-1-yl)piperidine-1-carboxylate
2.96	5-ethynyl-6-fluoro-4-((6aR,7S,10R)-1-fluoro-13-(((2S,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-2-yl)naphthalen-2-ol
2.97	5-ethynyl-6-fluoro-4-((6aR,7S,10R)-1-fluoro-13-(((2R,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-2-yl)naphthalen-2-ol
2.98	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl morpholine-4-carboxylate
2.99	((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl morpholine-4-carboxylate
3.1	((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)methyl pyrrolidine-1-carboxylate
3.2	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl morpholine-4-carboxylate

Cpd #	Name
3.3	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl morpholine-4-carboxylate
3.4	2-((3S,7aS)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)-6-methylenehexahydro-1H-pyrrolizin-3-yl)ethyl pyrrolidine-1-carboxylate or
3.5	2-((3S,7aR)-7a-((((6aR,7S,10R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-13-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)ethyl pyrrolidine-1-carboxylate;

or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

3. A method of treating cancer in a patient comprising administering to the patient, a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof; or a pharmaceutical composition of claim 2.

4. The method of claim 3, wherein the cancer is non-small cell lung cancer, colorectal cancer, or pancreatic cancer.

5. The method of claim 3 or 4, wherein the compound of claim 1, or a pharmaceutically acceptable salt thereof; or the pharmaceutical composition of claim 2 is administered in combination with at least one additional anticancer agent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2024/074923

A. CLASSIFICATION OF SUBJECT MATTER

C07D498/22(2006.01)i; C07D519/00(2006.01)i; A61K31/553(2006.01)i; A61P35/00(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC:C07D,A61K,A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNTXT,CNKI,ENTXT,WPABS,STN(CAPLUS,REGISTRY):KRAS,inhibitor,tetracyclic,cancer,tumor,structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2023001141 A1 (SHANGHAI ZION PHARMA CO. LTD.) 26 January 2023 (2023-01-26) Claims 1, 75, 86-97; page 99, line 5, left compound; page 171, compound 7; pages 192-195, compounds 41, 46-47 and 49	1-5
X	WO 2023030385 A1 (GENFLEET THERAPEUTICS (SHANGHAI) INC. et al.) 09 March 2023 (2023-03-09) Claims 1-22; pages 101-111, examples 19-21, 23-25; pages 177-178, example 61; examples 1-2	1-5
X	WO 2022188729 A1 (JACOBIO PHARMACEUTICALS CO. LTD.) 15 September 2022 (2022-09-15) Tables 1,2 and 10 in description, lines 11-17 on page 1 and lines 1-26 on page 40 in description,lines 1-5 on page 13,pages 15-20 in description	1-5
X	WO 2022194245 A1 (GENFLEET THERAPEUTICS (SHANGHAI) INC. et al.) 22 September 2022 (2022-09-22) Table (I) on page 20 in description, line 1 on page 20 - line 16 on page 22 in description	1-5

☑ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 April 2024	**11 April 2024**

Name and mailing address of the ISA/CN	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2024/074923

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2023001123 A1 (SHANGHAI ALLIST PHARMACEUTICALS CO. LTD.) 26 January 2023 (2023-01-26) page 6 in description, lines 5-29 on page 51 in description	1-5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2024/074923

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **3-5**
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 3-5 are directed to methods for the treatment of the human body by therapy, and thus relate to the subject matter for which an international search is not required. The search has been established and based on the subject matter of use in the manufacture of medicament for treating the corresponding diseases.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2024/074923

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
WO	2023001141	A1	26 January 2023	CA	3226720	A1	26 January 2023
				AU	2022314009	A1	25 January 2024
WO	2023030385	A1	09 March 2023	TW	202315626	A	16 April 2023
WO	2022188729	A1	15 September 2022	None			
WO	2022194245	A1	22 September 2022	EP	4310091	A1	24 January 2024
				JP	2024510022	A	05 March 2024
				AU	2022235948	A1	02 November 2023
				BR	112023018785	A2	12 December 2023
				KR	20230157463	A	16 November 2023
				CA	3211725	A1	22 September 2022
WO	2023001123	A1	26 January 2023	None			