



(51) International Patent Classification:

A61K 31/343 (2006.01) A61K 31/55 (2006.01)

A61K 31/37 (2006.01) A61P 25/28 (2006.01)

A61K 31/473 (2006.01)

(21) International Application Number:

PCT/IB2024/000400

(22) International Filing Date:

17 May 2024 (17.05.2024)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

63/467,507 18 May 2023 (18.05.2023) US

(71) Applicant: VANDRIA SA [CH/CH]; EPFL Innovation Park, Bâtiment E, 1015 Lausanne (CH).

(72) Inventors: ANDREUX, Penelope; Gondoux-dessus 12, 1312 Eclepens (CH). DUGI, Klaus, Andreas; Avenue Eugene-Rambert 30, 1005 Lausanne (CH).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: USE OF UROLITHIN DERIVATIVES IN THE TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS

(57) Abstract: Disclosed are methods of treating amyotrophic lateral sclerosis (ALS). Also disclosed are methods of treating C9orf72 amyotrophic lateral sclerosis (C9-ALS).



WO 2024/236367 A2

**USE OF UROLITHIN DERIVATIVES IN THE TREATMENT
OF AMYOTROPHIC LATERAL SCLEROSIS**

RELATED APPLICATION

This application claims the benefit of priority to U.S. Provisional Patent Application No. 63/467,507, filed May 18, 2023.

BACKGROUND

Urolithins have potent effects on the improvement of a number of health conditions, and they have been shown to be highly biologically active *in vitro* and *in vivo*. Urolithins have been proposed as treatments of a variety of conditions including conditions related to inadequate mitochondrial activity, including obesity, memory decline, reduced metabolic rate, metabolic syndrome, diabetes mellitus, cardiovascular disease, hyperlipidemia, neurodegenerative diseases, cognitive disorder, mood disorder, stress, anxiety disorder, fatty liver disease and for improving liver function and weight management. In particular, urolithins have been shown to have beneficial effects in the enhancement of muscle function.

Amyotrophic lateral sclerosis (ALS) is a progressive, generally fatal motor neuron disorder. ALS is encountered in both sporadic (SALS) and familial (FALS) forms. A GGGGCC hexanucleotide repeat expansion in the first intron of C9orf72 causes the most common forms of familial amyotrophic lateral sclerosis (ALS). An FDA-approved therapy for ALS is riluzole, a compound that prolongs survival by about 10%. Accordingly, additional and improved treatments are needed.

SUMMARY

One aspect of the invention provides methods useful for treating amyotrophic lateral sclerosis (ALS), *e.g.* C9orf72 amyotrophic lateral sclerosis (C9-ALS).

Accordingly, provided herein is a method of treating amyotrophic lateral sclerosis (ALS), *e.g.* C9orf72 amyotrophic lateral sclerosis (C9-ALS), in a subject in need thereof, comprising administering to the subject an effective amount of a compound of Formula (Ia), Formula (Ic), Formula (Id), Formula (Ie), Formula (If), Formula (Ih), Formula (IIa), or Formula (IIb).

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Other features, objects, and advantages of the invention will be apparent from the detailed description, and from the claims.

DETAILED DESCRIPTION

Definitions

For convenience, before further description of the present invention, certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and understood as by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

In order for the present invention to be more readily understood, certain terms and phrases are defined below and throughout the specification.

The articles “a” and “an” are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

The phrase “and/or,” as used herein in the specification and in the claims, should be understood to mean “either or both” of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Multiple elements listed with “and/or” should be construed in the same fashion, i.e., “one or more” of the elements so conjoined. Other elements may optionally be present other than the elements specifically identified by the “and/or” clause, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, a reference to “A and/or B”, when used in conjunction with open-ended language such as “comprising” can refer, in one embodiment, to A

only (optionally including elements other than B); in another embodiment, to B only (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

As used herein in the specification and in the claims, “or” should be understood to have the same meaning as “and/or” as defined above. For example, when separating items in a list, “or” or “and/or” shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as “only one of” or “exactly one of,” or, when used in the claims, “consisting of,” will refer to the inclusion of exactly one element of a number or list of elements. In general, the term “or” as used herein shall only be interpreted as indicating exclusive alternatives (i.e., “one or the other but not both”) when preceded by terms of exclusivity, such as “either,” “one of,” “only one of,” or “exactly one of.” “Consisting essentially of,” when used in the claims, shall have its ordinary meaning as used in the field of patent law.

As used herein in the specification and in the claims, the phrase “at least one,” in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase “at least one” refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, “at least one of A and B” (or, equivalently, “at least one of A or B,” or, equivalently “at least one of A and/or B”) can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

It should also be understood that, unless clearly indicated to the contrary, in any methods claimed herein that include more than one step or act, the order of the steps or acts of the method is not necessarily limited to the order in which the steps or acts of the method are recited.

In the claims, as well as in the specification above, all transitional phrases such as “comprising,” “including,” “carrying,” “having,” “containing,” “involving,” “holding,” “composed of,” and the like are to be understood to be open-ended, i.e., to mean including but not limited to. Only the transitional phrases “consisting of” and “consisting essentially of” shall be closed or semi-closed transitional phrases, respectively, as set forth in the United States Patent Office Manual of Patent Examining Procedures, Section 2111.03.

Certain compounds contained in compositions of the present invention may exist in particular geometric or stereoisomeric forms. In addition, polymers of the present invention may also be optically active. The present invention contemplates all such compounds, including cis- and trans-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

“Geometric isomer” means isomers that differ in the orientation of substituent atoms in relationship to a carbon-carbon double bond, to a cycloalkyl ring, or to a bridged bicyclic system. Atoms (other than H) on each side of a carbon-carbon double bond may be in an E (substituents are on opposite sides of the carbon-carbon double bond) or Z (substituents are oriented on the same side) configuration. “R,” “S,” “S*,” “R*,” “E,” “Z,” “cis,” and “trans,” indicate configurations relative to the core molecule. Certain of the disclosed compounds may exist in “atropisomeric” forms or as “atropisomers.” Atropisomers are stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers. The compounds of the invention may be prepared as individual isomers by either isomer-specific synthesis or resolved from a mixture of isomers. Conventional resolution techniques include forming the salt of a free base of each isomer of an isomeric pair using an optically active acid (followed by fractional crystallization and regeneration of the free base), forming the salt of the acid form of each isomer of an isomeric pair using an optically active amine (followed by fractional crystallization and regeneration of the free acid), forming an ester or amide of each of the isomers of an isomeric pair using an optically pure acid, amine or alcohol (followed by chromatographic separation and removal of the chiral auxiliary), or resolving an isomeric mixture of either a starting material or a final product using various well known chromatographic methods.

If, for instance, a particular enantiomer of compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

Percent purity by mole fraction is the ratio of the moles of the enantiomer (or diastereomer) or over the moles of the enantiomer (or diastereomer) plus the moles of its optical isomer. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least about 60%, about 70%, about 80%, about 90%, about 99% or about 99.9% by mole fraction pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least about 60%, about 70%, about 80%, about 90%, about 99% or about 99.9% by mole fraction pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least about 60%, about 70%, about 80%, about 90%, about 99% or about 99.9% by mole fraction pure.

When a disclosed compound is named or depicted by structure without indicating the stereochemistry, and the compound has at least one chiral center, it is to be understood that the name or structure encompasses either enantiomer of the compound free from the corresponding optical isomer, a racemic mixture of the compound or mixtures enriched in one enantiomer relative to its corresponding optical isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry and has two or more chiral centers, it is to be understood that the name or structure encompasses a diastereomer free of other diastereomers, a number of diastereomers free from other diastereomeric pairs, mixtures of diastereomers, mixtures of diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s) or mixtures of diastereomers in which one or more diastereomer is enriched relative to the other diastereomers. The invention embraces all of these forms.

Structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds produced by the

replacement of a hydrogen with deuterium or tritium, or of a carbon with a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention.

The term “prodrug” as used herein encompasses compounds that, under physiological conditions, are converted into therapeutically active agents. A common method for making a prodrug is to include selected moieties that are hydrolyzed under physiological conditions to reveal the desired molecule. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal.

The phrase “pharmaceutically acceptable excipient” or “pharmaceutically acceptable carrier” as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject chemical from one organ or portion of the body, to another organ or portion of the body. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation, not injurious to the patient, and substantially non-pyrogenic. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose, and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil, and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol, and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer’s solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations. In certain embodiments, pharmaceutical compositions of the present invention are non-pyrogenic, i.e., do not induce significant temperature elevations when administered to a patient.

The term “pharmaceutically acceptable salts” refers to the relatively non-toxic, inorganic and organic acid addition salts of the compound(s). These salts can be prepared in situ during the final isolation and purification of the compound(s), or by separately reacting a purified compound(s) in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate,

phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts, and the like. (See, for example, Berge et al. (1977) “Pharmaceutical Salts”, *J. Pharm. Sci.* 66:1-19.)

In other cases, the compounds useful in the methods of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. The term “pharmaceutically acceptable salts” in these instances refers to the relatively non-toxic inorganic and organic base addition salts of a compound(s). These salts can likewise be prepared in situ during the final isolation and purification of the compound(s), or by separately reacting the purified compound(s) in its free acid form with a suitable base, such as the hydroxide, carbonate, or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts, and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, and the like (see, for example, Berge et al., *supra*).

The term “pharmaceutically acceptable cocrystals” refers to solid coformers that do not form formal ionic interactions with the small molecule.

A “therapeutically effective amount” (or “effective amount”) of a compound with respect to use in treatment, refers to an amount of the compound in a preparation which, when administered as part of a desired dosage regimen (to a mammal, preferably a human) alleviates a symptom, ameliorates a condition, or slows the onset of disease conditions according to clinically acceptable standards for the disorder or condition to be treated or the cosmetic purpose, e.g., at a reasonable benefit/risk ratio applicable to any medical treatment.

The term “prophylactic or therapeutic” treatment is art-recognized and includes administration to the host of one or more of the subject compositions. If it is administered prior to clinical manifestation of the unwanted condition (e.g., disease or other unwanted state of the host animal) then the treatment is prophylactic, (i.e., it protects the host against developing the unwanted condition), whereas if it is administered after manifestation of the unwanted condition,

the treatment is therapeutic, (i.e., it is intended to diminish, ameliorate, or stabilize the existing unwanted condition or side effects thereof).

The term “patient” or “subject” refers to a mammal in need of a particular treatment. In certain embodiments, a patient is a primate, canine, feline, or equine. In certain embodiments, a patient is a human.

An aliphatic chain comprises the classes of alkyl, alkenyl and alkynyl defined below. A straight aliphatic chain is limited to unbranched carbon chain moieties. As used herein, the term “aliphatic group” refers to a straight chain, branched-chain, or cyclic aliphatic hydrocarbon group and includes saturated and unsaturated aliphatic groups, such as an alkyl group, an alkenyl group, or an alkynyl group.

“Alkyl” refers to a fully saturated cyclic or acyclic, branched or unbranched carbon chain moiety having the number of carbon atoms specified, or up to 30 carbon atoms if no specification is made. For example, alkyl of 1 to 8 carbon atoms refers to moieties such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, and octyl, and those moieties which are positional isomers of these moieties. Alkyl of 10 to 30 carbon atoms includes decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, eicosyl, heneicosyl, docosyl, tricosyl and tetracosyl. In certain embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C₁-C₃₀ for straight chains, C₃-C₃₀ for branched chains), and more preferably 20 or fewer. Alkyl groups may be substituted or unsubstituted.

As used herein, the term “heteroalkyl” refers to an alkyl moiety as hereinbefore defined which contain one or more oxygen, sulfur, nitrogen, phosphorus, or silicon atoms in place of carbon atoms.

As used herein, the term “haloalkyl” refers to an alkyl group as hereinbefore defined substituted with at least one halogen.

As used herein, the term “hydroxyalkyl” refers to an alkyl group as hereinbefore defined substituted with at least one hydroxyl.

As used herein, the term “alkylene” refers to an alkyl group having the specified number of carbons, for example from 2 to 12 carbon atoms, which contains two points of attachment to the rest of the compound on its longest carbon chain. Non-limiting examples of alkylene groups include methylene -(CH₂)-, ethylene -(CH₂CH₂)-, n-propylene -(CH₂CH₂CH₂)-, isopropylene -

(CH₂CH(CH₃))-, and the like. Alkylene groups can be cyclic or acyclic, branched or unbranched carbon chain moiety, and may be optionally substituted with one or more substituents.

"Cycloalkyl" means mono- or bicyclic or bridged or spirocyclic, or polycyclic saturated carbocyclic rings, each having from 3 to 12 carbon atoms. Preferred cycloalkyls have from 3-10 carbon atoms in their ring structure, and more preferably have 3-6 carbons in the ring structure. Cycloalkyl groups may be substituted or unsubstituted.

As used herein, the term "halocycloalkyl" refers to a cycloalkyl group as hereinbefore defined substituted with at least one halogen.

"Cycloheteroalkyl" or "heterocycloalkyl" refers to an cycloalkyl moiety as hereinbefore defined which contain one or more oxygen, sulfur, nitrogen, phosphorus, or silicon atoms in place of carbon atoms. Preferred cycloheteroalkyls have from 4-8 carbon atoms and heteroatoms in their ring structure, and more preferably have 4-6 carbons and heteroatoms in the ring structure. Cycloheteroalkyl or heterocycloalkyl groups may be substituted or unsubstituted.

Unless the number of carbons is otherwise specified, "lower alkyl," as used herein, means an alkyl group, as defined above, but having from one to ten carbons, more preferably from one to six carbon atoms in its backbone structure such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, and tert-butyl. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths. Throughout the application, preferred alkyl groups are lower alkyls. In certain embodiments, a substituent designated herein as alkyl is a lower alkyl.

"Alkenyl" refers to any cyclic or acyclic, branched or unbranched unsaturated carbon chain moiety having the number of carbon atoms specified, or up to 26 carbon atoms if no limitation on the number of carbon atoms is specified; and having one or more double bonds in the moiety. Alkenyl of 6 to 26 carbon atoms is exemplified by hexenyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, dodenyl, tridecenyl, tetradecenyl, pentadecenyl, hexadecenyl, heptadecenyl, octadecenyl, nonadecenyl, eicosenyl, heneicosoenyl, docosenyl, tricosenyl, and tetracosenyl, in their various isomeric forms, where the unsaturated bond(s) can be located anywhere in the moiety and can have either the (Z) or the (E) configuration about the double bond(s).

"Alkynyl" refers to hydrocarbyl moieties of the scope of alkenyl, but having one or more triple bonds in the moiety.

The term “aryl” as used herein includes 3- to 12-membered substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon (i.e., carbocyclic aryl) or where one or more atoms are heteroatoms (i.e., heteroaryl). Preferably, aryl groups include 5- to 12-membered rings, more preferably 6- to 10-membered rings. The term “aryl” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryl, and/or heterocyclyls. Carbocyclic aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline, and the like. Heteroaryl groups include substituted or unsubstituted aromatic 3- to 12-membered ring structures, more preferably 5- to 12-membered rings, more preferably 5- to 10-membered rings, whose ring structures include one to four heteroatoms. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Aryl and heteroaryl can be monocyclic, bicyclic, or polycyclic.

The term “halo”, “halide”, or “halogen” as used herein means halogen and includes, for example, and without being limited thereto, fluoro, chloro, bromo, iodo and the like, in both radioactive and non-radioactive forms. In a preferred embodiment, halo is selected from the group consisting of fluoro, chloro and bromo.

The terms “heterocyclyl” or “heterocyclic group” refer to 3- to 12-membered ring structures, more preferably 5- to 12-membered rings, more preferably 5- to 10-membered rings, whose ring structures include one to four heteroatoms. Heterocycles can be monocyclic, bicyclic, spirocyclic, or polycyclic. Heterocyclyl groups include, for example, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxathiin, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. The heterocyclic ring can be substituted at one or more positions with such substituents as described above, as for example, halogen, alkyl, arylalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino,

amido, phosphate, phosphonate, phosphinate, carbonyl, carboxyl, silyl, sulfamoyl, sulfinyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, -CF₃, -CN, and the like.

As used herein, the terms “arylalkyl” and “aralkyl” refer to an alkyl group as hereinbefore defined substituted with at least one aryl.

As used herein, the terms “heteroarylalkyl” and “heteroaralkyl” refer to an alkyl group as hereinbefore defined substituted with at least one heteroaryl. The term “substituted” refers to moieties having substituents replacing a hydrogen on one or more carbons of the backbone. It will be understood that “substitution” or “substituted with” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term “substituted” is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxy, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an arylalkyl, or an aromatic or heteroaromatic moiety. In preferred embodiments, the substituents on substituted alkyls are selected from C₁₋₆ alkyl, C₃₋₆ cycloalkyl, halogen, carbonyl, cyano, or hydroxyl. In more preferred embodiments, the substituents on substituted alkyls are selected from fluoro, carbonyl, cyano, or hydroxyl. It will be understood by those skilled in the art that substituents can themselves be substituted, if appropriate. Unless specifically stated as “unsubstituted,” references to chemical moieties herein are understood to include substituted

variants. For example, reference to an “aryl” group or moiety implicitly includes both substituted and unsubstituted variants.

As used herein, the definition of each expression, e.g., alkyl, m, n, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

As used herein, “small molecules” refers to small organic or inorganic molecules of molecular weight below about 3,000 Daltons. In general, small molecules useful for the invention have a molecular weight of less than 3,000 Daltons (Da). The small molecules can be, e.g., from at least about 100 Da to about 3,000 Da (e.g., between about 100 to about 3,000 Da, about 100 to about 2500 Da, about 100 to about 2,000 Da, about 100 to about 1,750 Da, about 100 to about 1,500 Da, about 100 to about 1,250 Da, about 100 to about 1,000 Da, about 100 to about 750 Da, about 100 to about 500 Da, about 200 to about 1500, about 500 to about 1000, about 300 to about 1000 Da, or about 100 to about 250 Da).

In some embodiments, a “small molecule” refers to an organic, inorganic, or organometallic compound typically having a molecular weight of less than about 1000. In some embodiments, a small molecule is an organic compound, with a size on the order of 1 nm. In some embodiments, small molecule drugs of the invention encompass oligopeptides and other biomolecules having a molecular weight of less than about 1000.

An “effective amount” is an amount sufficient to effect beneficial or desired results. For example, a therapeutic amount is one that achieves the desired therapeutic effect. This amount can be the same or different from a prophylactically effective amount, which is an amount necessary to prevent onset of disease or disease symptoms. An effective amount can be administered in one or more administrations, applications or dosages. A therapeutically effective amount of a composition depends on the composition selected. The compositions can be administered from one or more times per day to one or more times per week; including once every other day. The skilled artisan will appreciate that certain factors may influence the dosage and timing required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of the compositions described herein can include a single treatment or a series of treatments.

The terms “decrease,” “reduce,” “reduced,” “reduction,” “decrease,” and “inhibit” are all used herein generally to mean a decrease by a statistically significant amount relative to a reference. However, for avoidance of doubt, “reduce,” “reduction” or “decrease” or “inhibit” typically means a decrease by at least 10% as compared to a reference level and can include, for example, a decrease by at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, up to and including, for example, the complete absence of the given entity or parameter as compared to the reference level, or any decrease between 10-99% as compared to the absence of a given treatment.

The terms “increased,” “increase” or “enhance” or “activate” are all used herein to generally mean an increase by a statically significant amount; for the avoidance of any doubt, the terms “increased,” “increase” or “enhance” or “activate” means an increase of at least 10% as compared to a reference level, for example an increase of at least about 20%, or at least about 30%, or at least about 40%, or at least about 50%, or at least about 60%, or at least about 70%, or at least about 80%, or at least about 90% or up to and including a 100% increase or any increase between 10-100% as compared to a reference level, or at least about a 2-fold, or at least about a 3-fold, or at least about a 4-fold, or at least about a 5-fold or at least about a 10-fold increase, or any increase between 2-fold and 10-fold or greater as compared to a reference level.

As used herein, the term “modulate” includes up-regulation and down-regulation, e.g., enhancing or inhibiting a response.

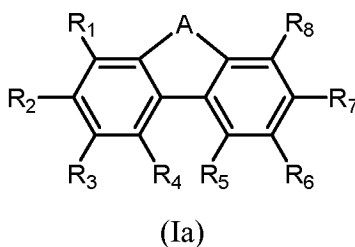
A “radiopharmaceutical agent,” as defined herein, refers to a pharmaceutical agent which contains at least one radiation-emitting radioisotope. Radiopharmaceutical agents are routinely used in nuclear medicine for the diagnosis and/or therapy of various diseases. The radiolabelled pharmaceutical agent, for example, a radiolabelled antibody, contains a radioisotope (RI) which serves as the radiation source. As contemplated herein, the term “radioisotope” includes metallic and non-metallic radioisotopes. The radioisotope is chosen based on the medical application of the radiolabeled pharmaceutical agents. When the radioisotope is a metallic radioisotope, a chelator is typically employed to bind the metallic radioisotope to the rest of the molecule. When

the radioisotope is a non-metallic radioisotope, the non-metallic radioisotope is typically linked directly, or via a linker, to the rest of the molecule.

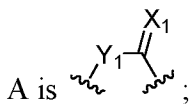
For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover.

Methods of Treatment

One aspect of the invention relates to a method of treating amyotrophic lateral sclerosis (ALS), comprising administering to a subject in need thereof an effective amount of a compound of Formula (Ia),



wherein



X₁ is selected from O and S;

Y₁ is O;

R₁, R₄, R₅ and R₈ are independently selected from H and halogen;

R₃ and R₆ are independently selected from H, CN, OH, CF₃, halogen, and alkyl;

one of R₂ and R₇ is H, OH, or OAc and the other of R₂ and R₇ is halogen, CN, CF₃, CO₂H, NO₂, NHAc, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkylamino, alkyl-R₉, alkenyl-R₉, alkynyl-R₉, OR₁₀, NHR₁₀, NR₁₁C(O)R₁₂, C(O)NR₁₁R₁₂, and NR₁₁SO₂R₁₂;

each occurrence of R₉ is independently selected from OH, NH₂, O-alkyl, O-alkyl-O-alkyl, alkylamino, NHC(O)-alkyl, N(CH₃)C(O)-alkyl, NHSO₂-alkyl, N(CH₃)SO₂-alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

R₁₀ is selected from C₂-C₁₂ alkyl, C(O)-alkyl, hydroxyalkyl, aminoalkyl, alkyl-O-alkyl, alkyl-O-alkyl-OH, alkyl-O-alkyl-O-alkyl, alkenyl, alkynyl, arylalkyl, heteroarylalkyl,

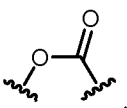
alkyl-cycloalkyl, alkyl-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, SO₃H, SO₂-alkyl, and SO₂-haloalkyl;

each occurrence of R₁₁ is selected from H and alkyl; and

each occurrence of R₁₂ is selected from alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, O-alkyl, aminoalkyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, and alkyl-heterocycloalkyl;

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound provided that if X₁ and Y₁ are each O, R₂ is OH, and R₁, R₃, R₄, R₅, R₆ and R₈ are each H, then R₇ is not OBn, and if X₁ and Y₁ are each O, R₇ is OH, and R₁, R₃, R₄, R₅, R₆ and R₈ are each H, then R₂ is not OCH₂C(O)NH₂.

In some embodiments, A is .

In some embodiments, R₂ is H. In other embodiments, R₂ is OH. In other embodiments, R₂ is OAc.

In some embodiments, the compound wherein R₂ is selected from haloalkyl, substituted cycloalkyl, alkynyl-R₉, OR₁₀, and C(O)NR₁₁R₁₂; R₉ is selected from OH, substituted cycloalkyl and heterocycloalkyl; R₁₀ is selected from alkyl, substituted cycloalkyl, heterocycloalkyl and alkyl-heterocycloalkyl; and R₁₁ is H and R₁₂ is alkyl-heterocycloalkyl.

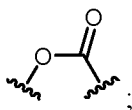
In some embodiments, R₇ is H. In other embodiments, R₇ is OH. In other embodiments, R₇ is OAc.

In some embodiments, the compound wherein R₇ is selected from haloalkyl, substituted cycloalkyl, alkynyl-R₉, OR₁₀, and C(O)NR₁₁R₁₂; R₉ is selected from OH, substituted cycloalkyl and heterocycloalkyl; R₁₀ is selected from alkyl, substituted cycloalkyl, heterocycloalkyl and alkyl-heterocycloalkyl; and R₁₁ is H and R₁₂ is alkyl-heterocycloalkyl.

In some embodiments, each occurrence of substituted cycloalkyl is independently substituted with OH, halogen, or hydroxyalkyl.

In some embodiments, R₁, R₃, R₄, R₅, R₆, and R₈ are each H. In other embodiments, one of R₁, R₃, R₄, R₅, R₆, and R₈ is not H. In other embodiments, two of R₁, R₃, R₄, R₅, R₆, and R₈ are not H.

In some embodiments, one of R₁, R₃, R₄, R₅, R₆, and R₈ is alkyl or halogen. In other embodiments, two of R₁, R₃, R₄, R₅, R₆, and R₈ are independently alkyl or halogen.



In some embodiments, A is

R_1 , R_4 , R_5 and R_8 are independently selected from H and halogen;

R_3 and R_6 are independently selected from H, CN, OH, CF_3 , halogen, and alkyl;

R_2 is OH and R_7 is haloalkyl, cycloalkyl, alkyl- R_9 , alkynyl- R_9 , OR_{10} , and $NR_{11}SO_2R_{12}$; each occurrence of R_9 is independently selected from OH, NH_2 , O-alkyl, O-alkyl-O-alkyl, alkylamino, $NHC(O)$ -alkyl, $N(CH_3)C(O)$ -alkyl, $NHSO_2$ -alkyl, $N(CH_3)SO_2$ -alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

R_{10} is selected from C_2 - C_{12} alkyl, $C(O)$ -alkyl, hydroxyalkyl, aminoalkyl, alkyl-O-alkyl, alkyl-O-alkyl-OH, alkyl-O-alkyl-O-alkyl, alkenyl, alkynyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, alkyl-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, SO_3H , SO_2 -alkyl, and SO_2 -haloalkyl;

R_{11} is selected from H and alkyl;

R_{12} is alkyl,

or a pharmaceutically acceptable salt thereof.

In some embodiments, R_9 is independently selected from OH, NH_2 , O-alkyl, O-alkyl-O-alkyl, alkylamino, $NHC(O)$ -alkyl, $N(CH_3)C(O)$ -alkyl, $NHSO_2$ -alkyl, $N(CH_3)SO_2$ -alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl.

In some embodiments, R_9 is independently selected from OH, NH_2 , alkylamino, and heterocycloalkyl.

In some embodiments, R_9 is independently selected from OH, O-alkyl, $NHC(O)$ -alkyl, $N(CH_3)C(O)$ -alkyl, $NHSO_2$ -alkyl, $N(CH_3)SO_2$ -alkyl, cycloalkyl (OH), and heterocycloalkyl.

In some embodiments, the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with halo, alkyl, hydroxy, hydroxyalkyl, alkoxy, or alkoxyalkyl.

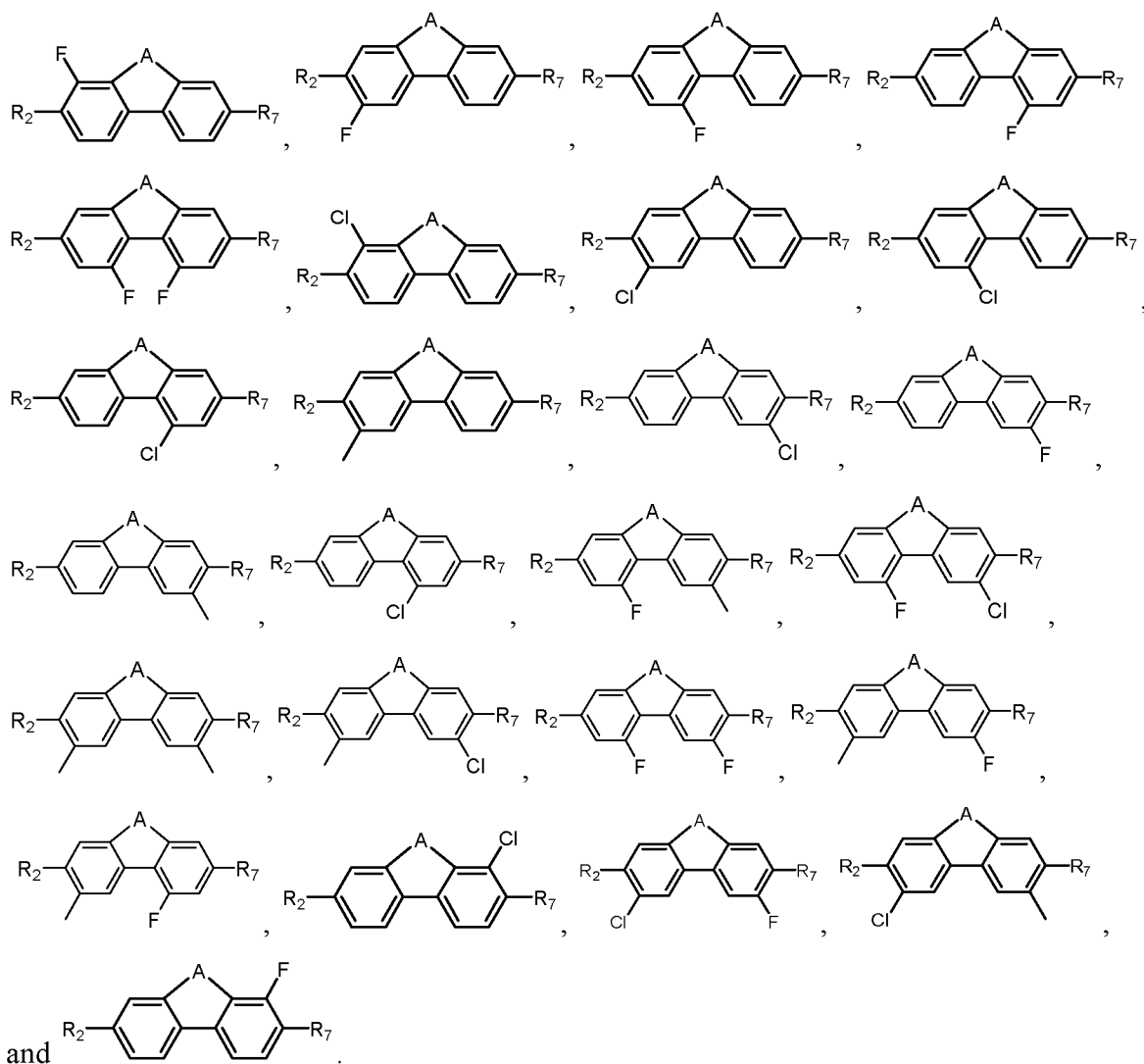
In some embodiments, the compound of Formula (Ia), wherein R_{12} is selected from alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, alkyl-heterocycloalkyl, and alkyl-alkylamino.

In some embodiments, R_7 is selected from CN, CF_3 , alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkylamino, alkyl- R_9 , alkenyl- R_9 , alkynyl- R_9 , OR_{10} , NHR_{10} , $NR_{11}C(O)R_{12}$, $C(O)NR_{11}R_{12}$, and $NR_{11}SO_2R_{12}$.

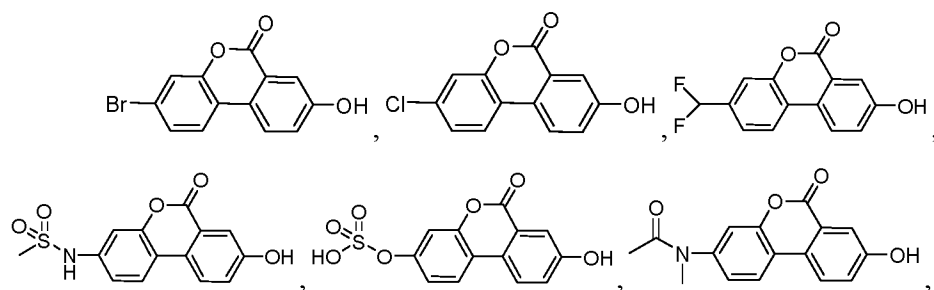
In some embodiments, R_7 is selected from haloalkyl, cycloalkyl, alkyl- R_9 , alkynyl- R_9 , OR_{10} , and $NR_{11}SO_2R_{12}$.

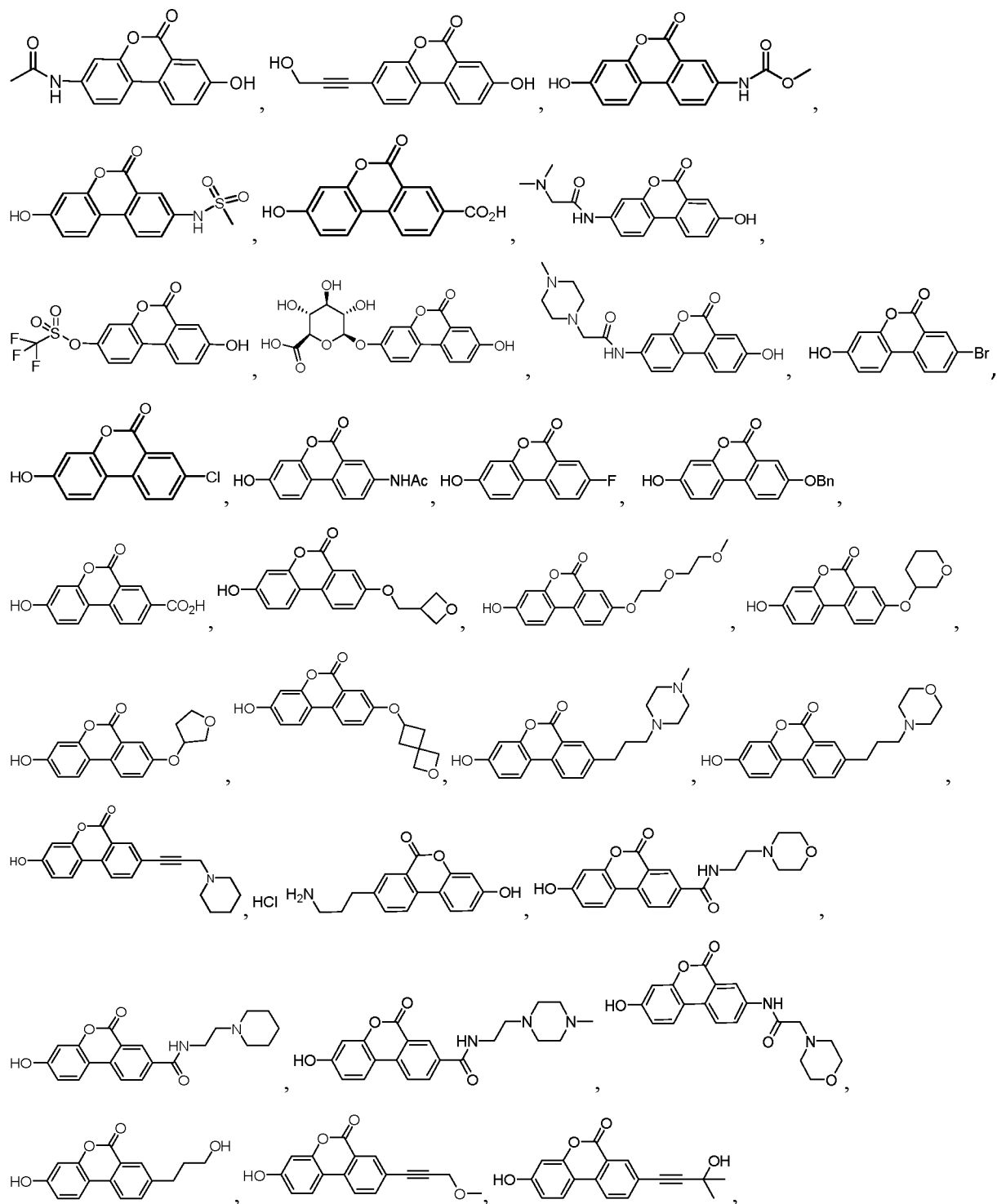
In some embodiments, provided that if X_1 is O, and R_1 , R_3 , R_4 , R_5 , R_6 and R_8 are each H, then R_7 is not -OBn.

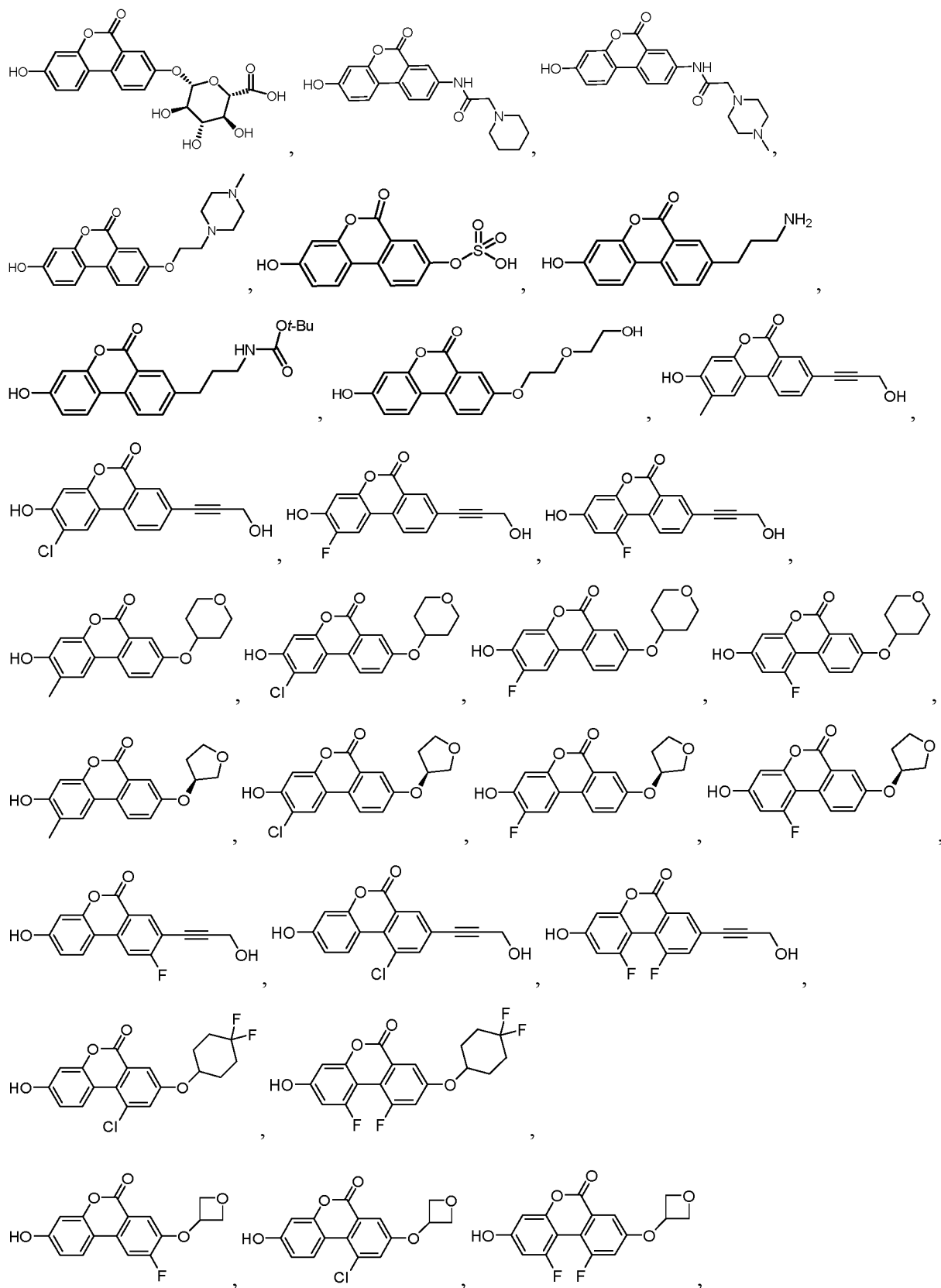
In some embodiments, the compound of Formula (Ia) is selected from:

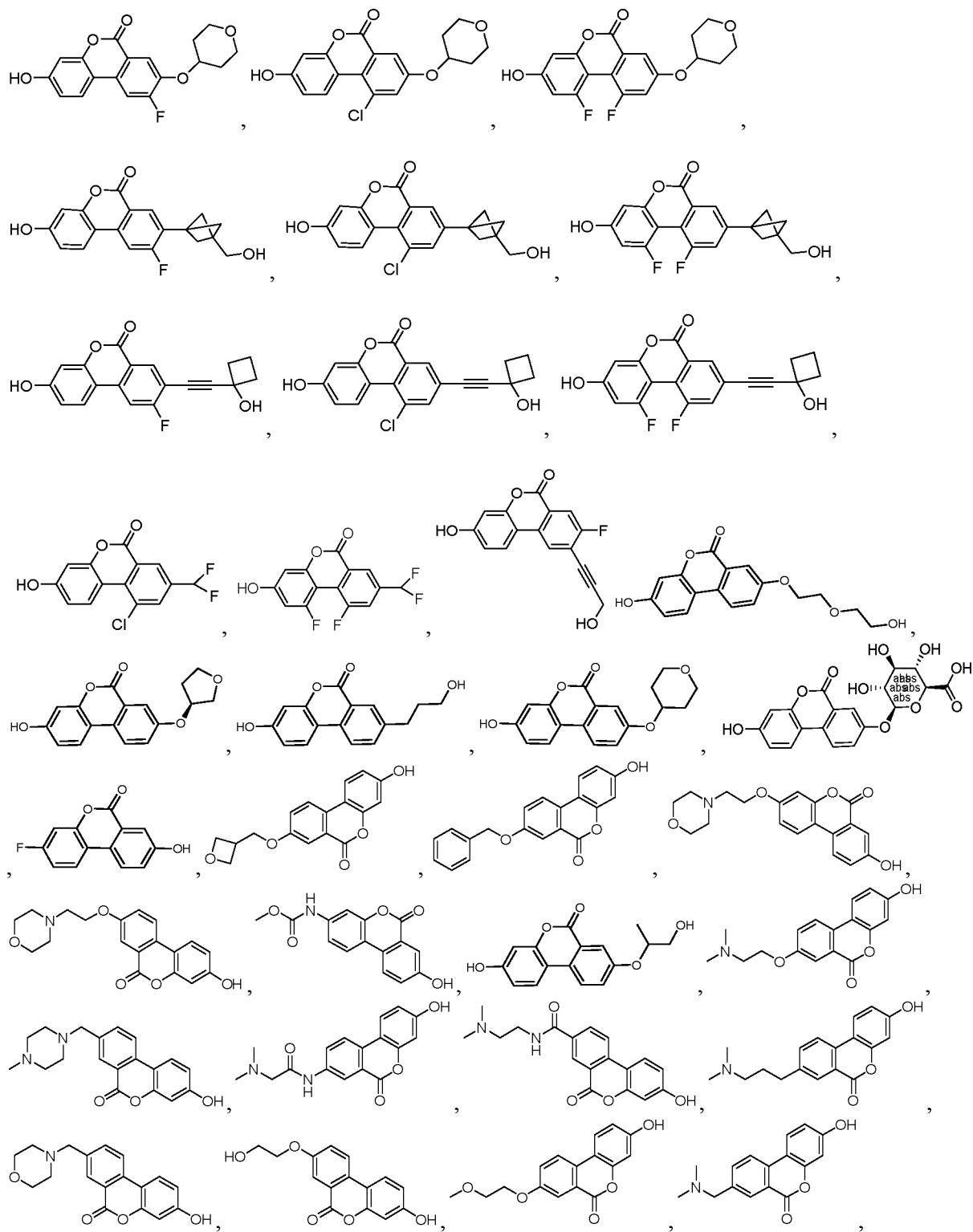


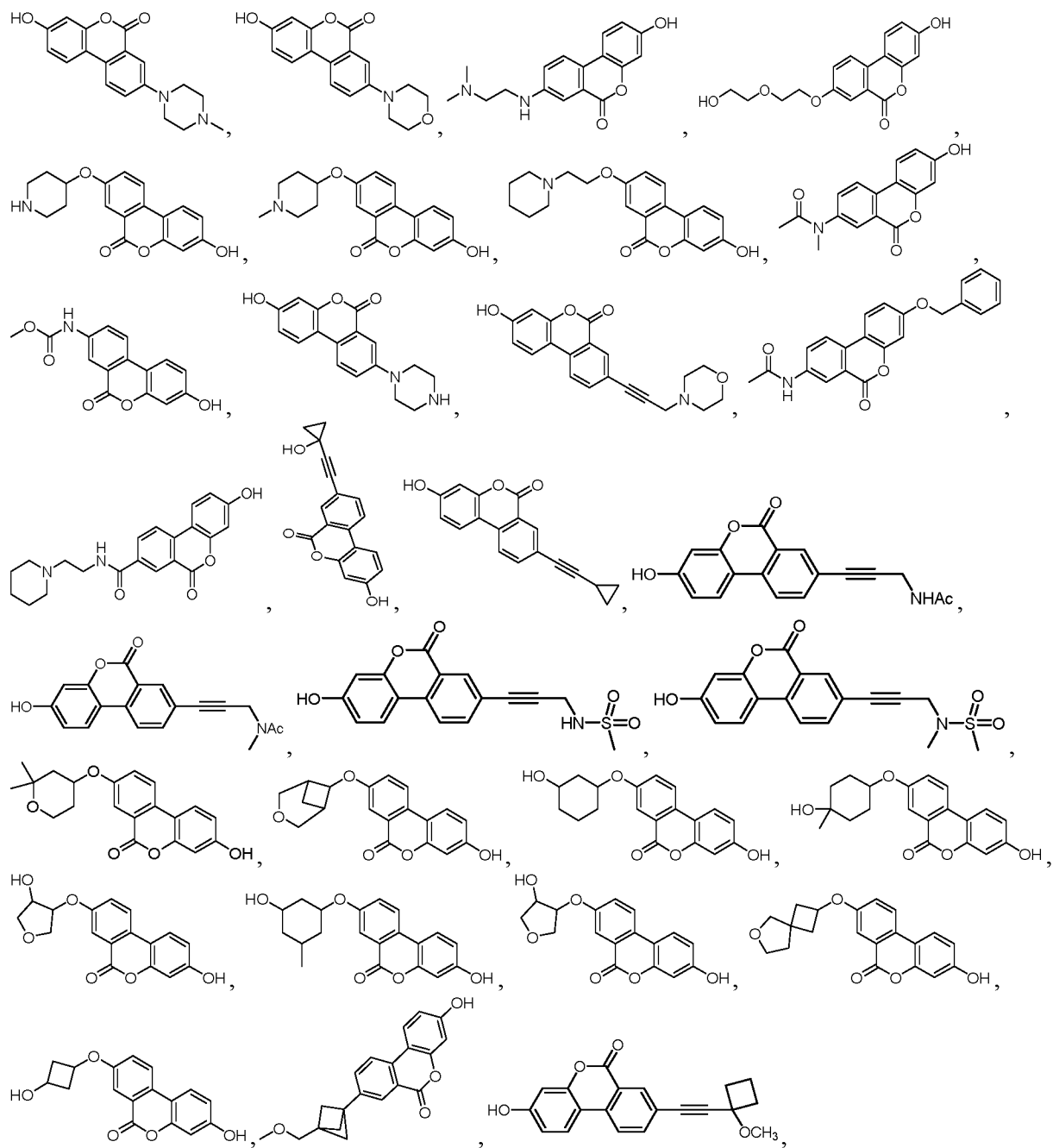
In some embodiments, the compound of Formula (Ia) is selected from:

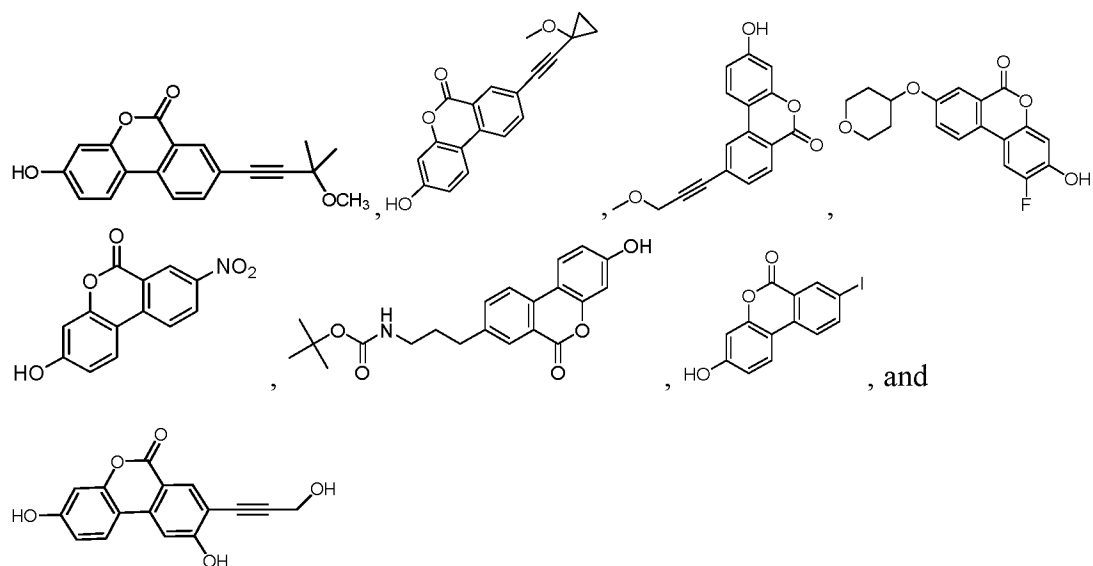




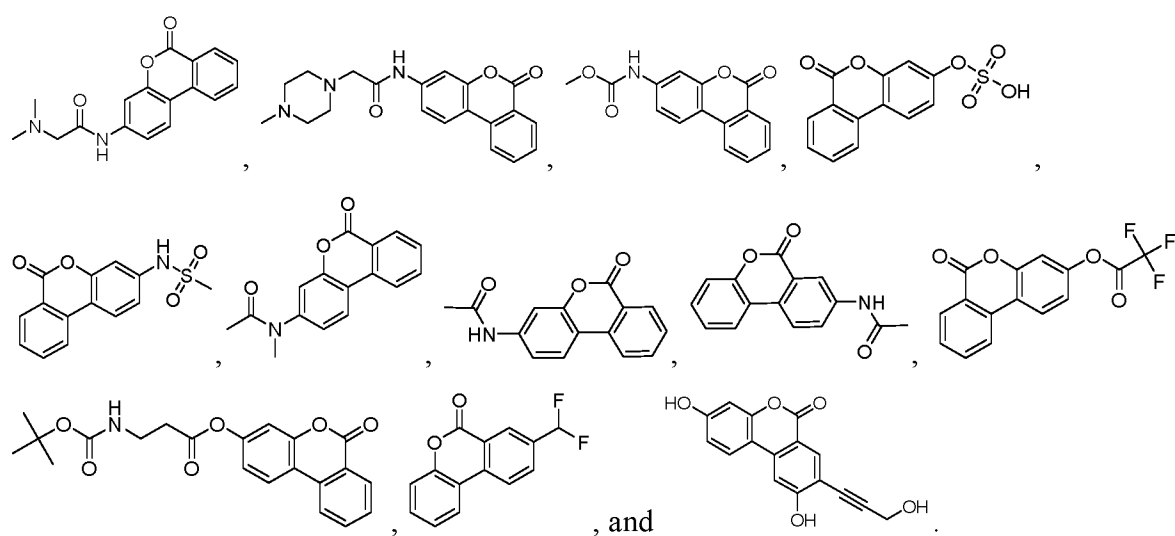




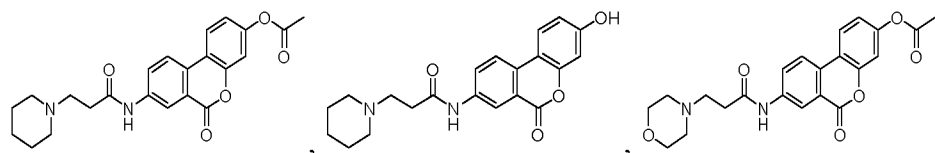


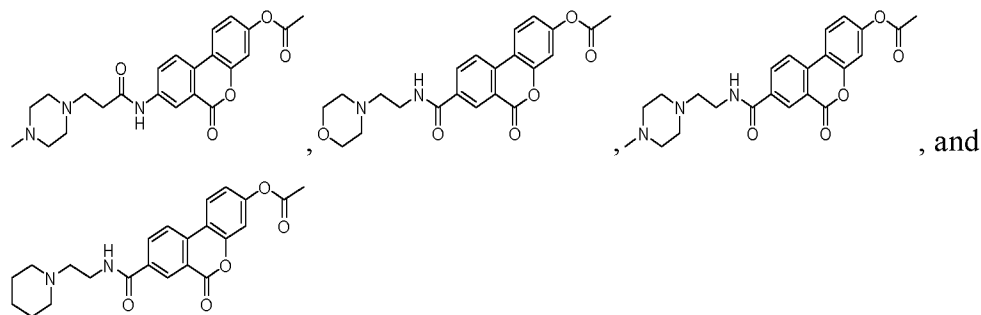


In some embodiments, the compound of Formula (Ia) is selected from:

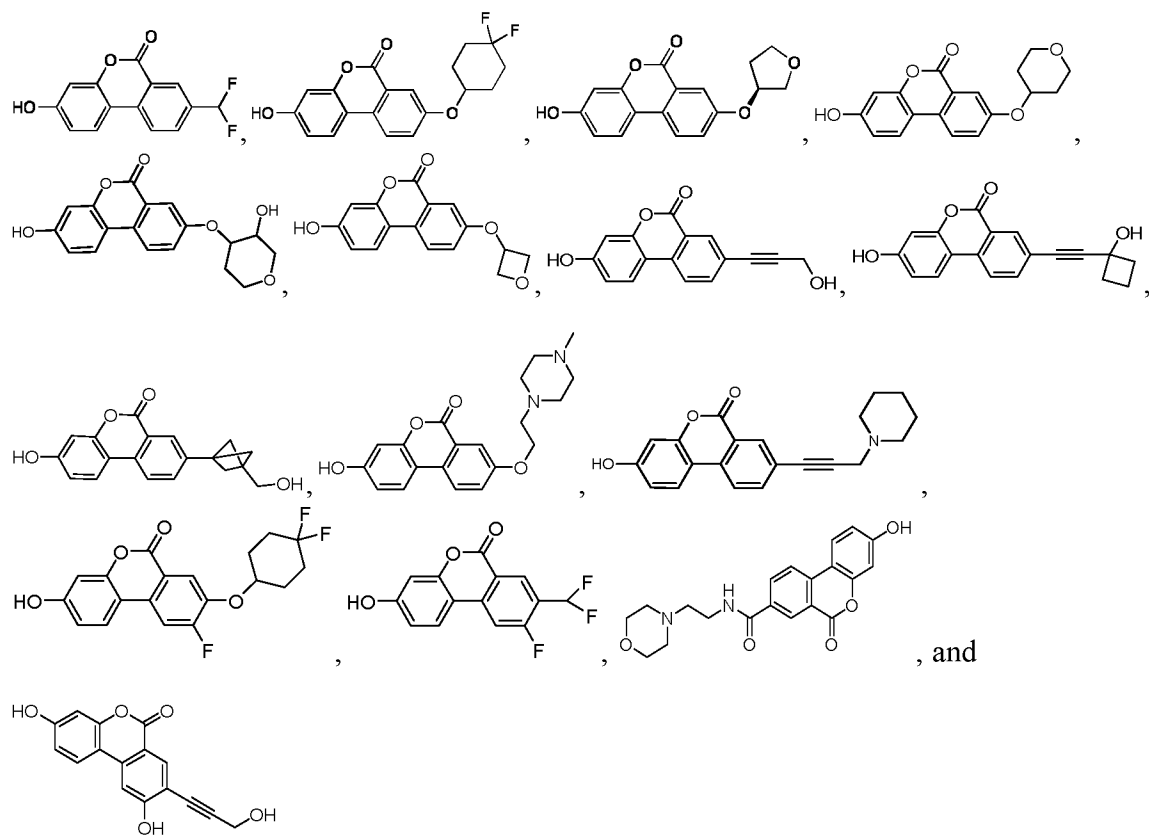


In some embodiments, the compound of Formula (Ia) is selected from:

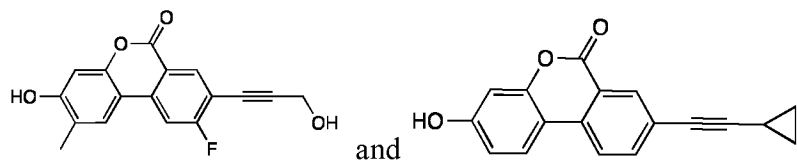




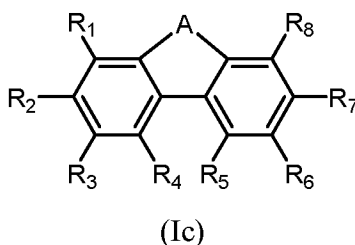
In some embodiments, the compound of Formula (Ia) is selected from:



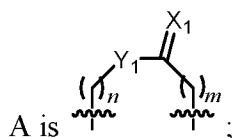
In some embodiments, the compound of Formula (Ia) is selected from:



Another aspect of the invention relates to a method of treating amyotrophic lateral sclerosis (ALS), comprising administering to a subject in need thereof an effective amount of a compound of Formula (Ic),



wherein



one of n and m is 0; and the other of n and m is 1;

X_1 and Y_1 are each O;

R_1 , R_2 , R_3 , R_6 , R_7 , and R_8 are independently selected from H, OH, OCH₃, OAc, NH₂, halogen, CN, CF₃, CO₂H, NO₂, NHAc, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkylamino, alkyl-R₉, alkenyl-R₉, alkynyl-R₉, OR₁₀, NHR₁₀, NR₁₁C(O)R₁₂, C(O)NR₁₁R₁₂, and NR₁₁SO₂R₁₂;

R_4 and R_5 are independently selected from H, halogen and alkyl;

each occurrence of R₉ is independently selected from OH, NH₂, O-alkyl, O-alkyl-O-alkyl, alkylamino, NHC(O)-alkyl, N(CH₃)C(O)-alkyl, NHSO₂-alkyl, N(CH₃)SO₂-alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

R₁₀ is selected from C₂-C₁₂ alkyl, hydroxyalkyl, aminoalkyl, alkyl-O-alkyl, alkyl-O-alkyl-OH, alkyl-O-alkyl-O-alkyl, alkenyl, alkynyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, alkyl-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, SO₃H, SO₂-alkyl, and SO₂-haloalkyl;

each occurrence of R₁₁ is selected from H and alkyl; and

each occurrence of R₁₂ is selected from alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, O-alkyl, aminoalkyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, and alkyl-heterocycloalkyl;

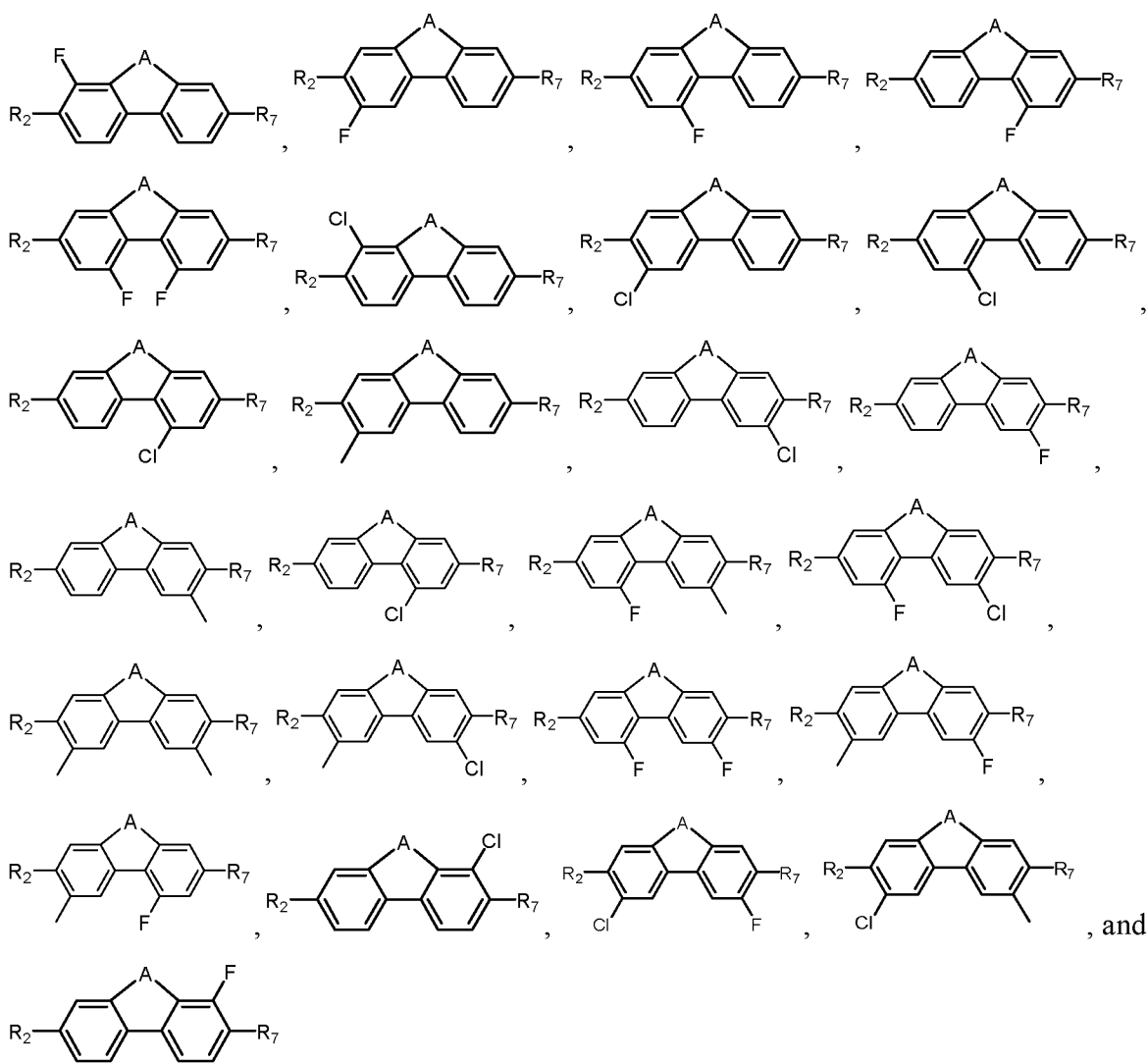
or a pharmaceutically acceptable salt thereof.



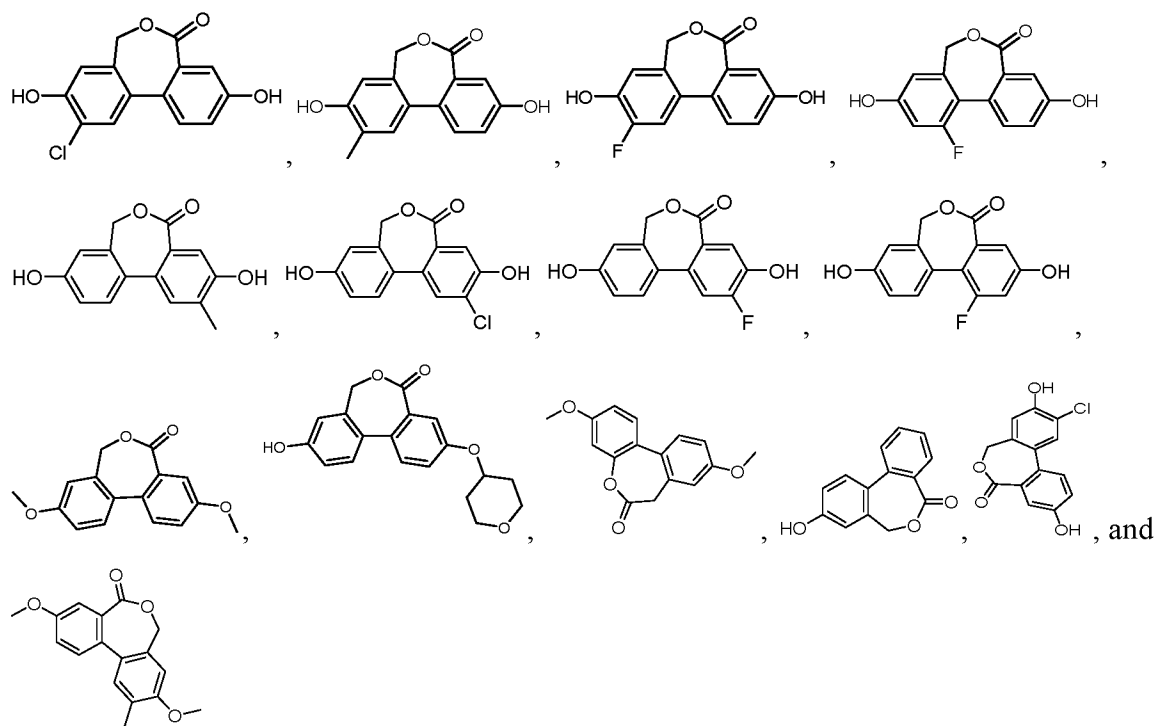
In some embodiments, R_2 and R_7 are each OH. In other embodiments, R_2 and R_7 are each O-alkyl. In other embodiments, R_2 is OH; and R_7 is H or O-alkyl. In other embodiments, R_2 is H or O-alkyl; and R_7 is OH.

In some embodiments, wherein R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 are each H. In other embodiments, one of R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 is not H. In other embodiments, two of R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 are not H. In other embodiments, one of R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 is alkyl or halogen. In other embodiments, two of R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 are alkyl or halogen.

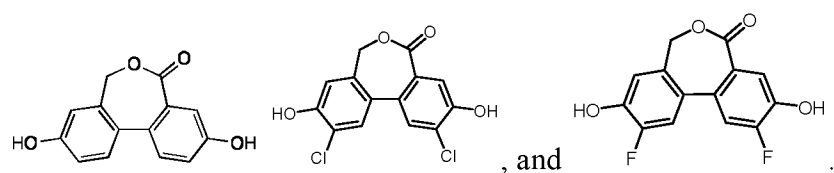
In some embodiments, the compound Formula (Ic) is selected from:



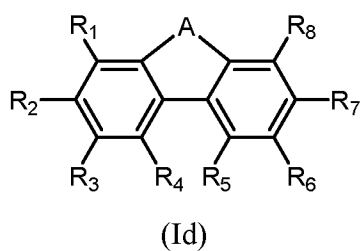
In some embodiments, the compound of Formula (Ic) is selected from:



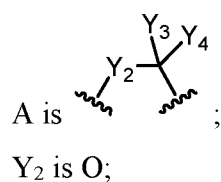
In some embodiments, the compound Formula (Ic) is selected from:



Another aspect of the invention relates to a method of treating amyotrophic lateral sclerosis (ALS), comprising administering to a subject in need thereof an effective amount of a compound of Formula (Id),



wherein



Y_3 and Y_4 are independently selected from H, halogen and alkyl; or together with the carbon to which they are bonded combine to form a cycloalkyl or heterocycloalkyl;

R_1 , R_4 , R_5 , and R_8 are independently selected from H and halogen;

R_2 , R_3 , R_6 , and R_7 are independently selected from H, OH, OCH₃, OAc, NH₂, halogen, CN, CF₃, CO₂H, NO₂, NHAc, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkylamino, alkyl- R_9 , alkenyl- R_9 , alkynyl- R_9 , OR₁₀, NHR₁₀, NR₁₁C(O)R₁₂, C(O)NR₁₁R₁₂, and NR₁₁SO₂R₁₂;

each occurrence of R_9 is independently selected from OH, NH₂, O-alkyl, O-alkyl-O-alkyl, alkylamino, NHC(O)-alkyl, N(CH₃)C(O)-alkyl, NHSO₂-alkyl, N(CH₃)SO₂-alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

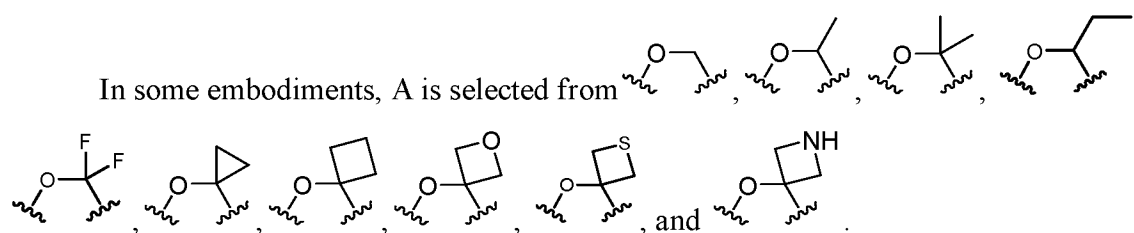
R_{10} is selected from C₂-C₁₂ alkyl, hydroxyalkyl, aminoalkyl, alkyl-O-alkyl, alkyl-O-alkyl-OH, alkyl-O-alkyl-O-alkyl, alkenyl, alkynyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, alkyl-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, SO₃H, SO₂-alkyl, and SO₂-haloalkyl;

each occurrence of R_{11} is selected from H and alkyl; and

each occurrence of R_{12} is selected from alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, O-alkyl, aminoalkyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, and alkyl-heterocycloalkyl;

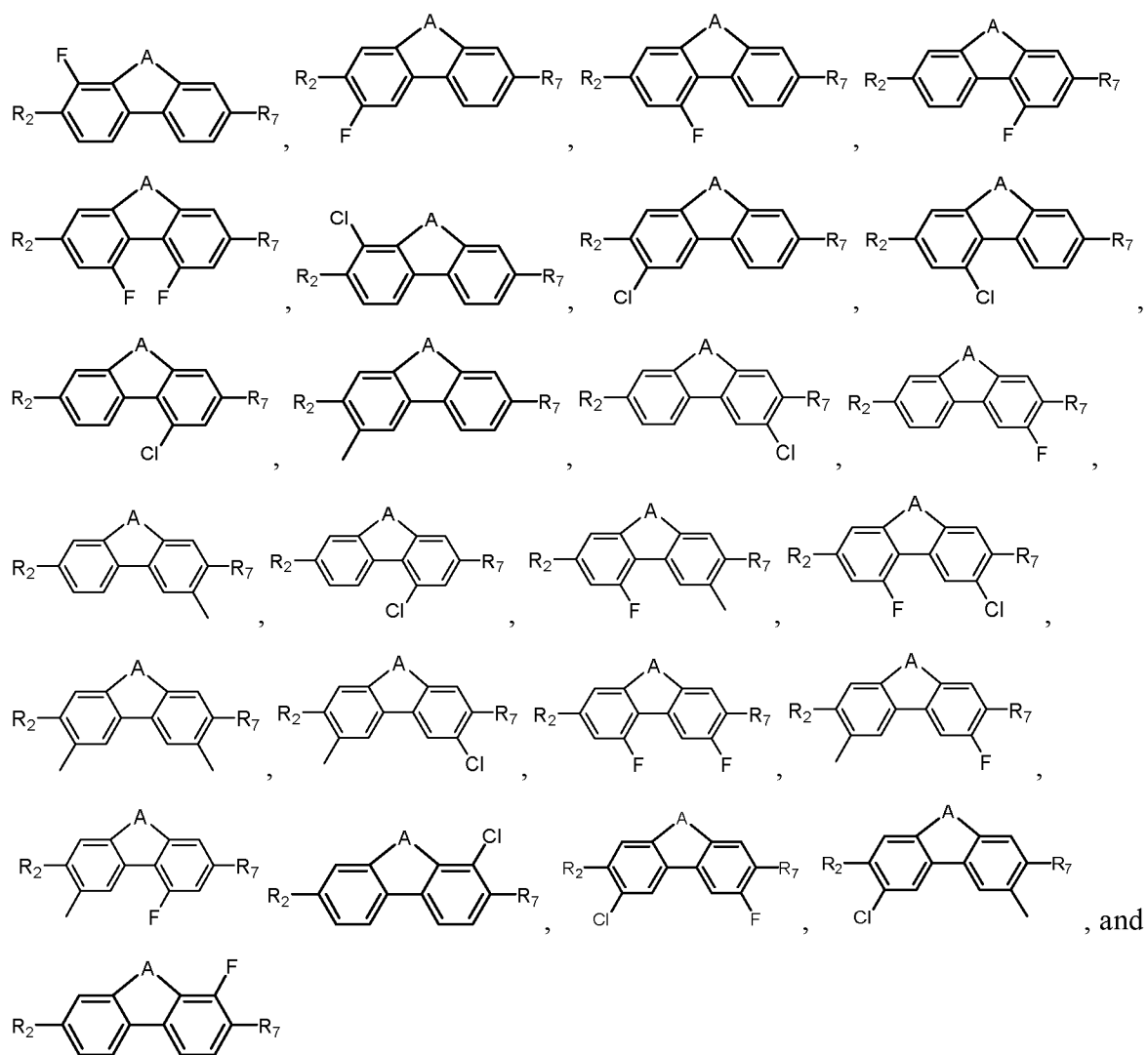
or a pharmaceutically acceptable salt thereof.

In some embodiments the compound provided that when Y_2 is O, R_2 and R_7 are each OH, and R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 are each H, then Y_3 and Y_4 are not both halogen.

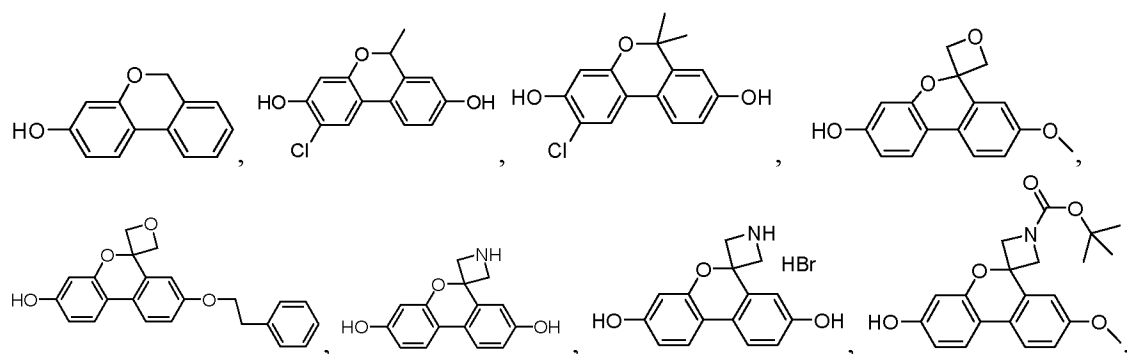


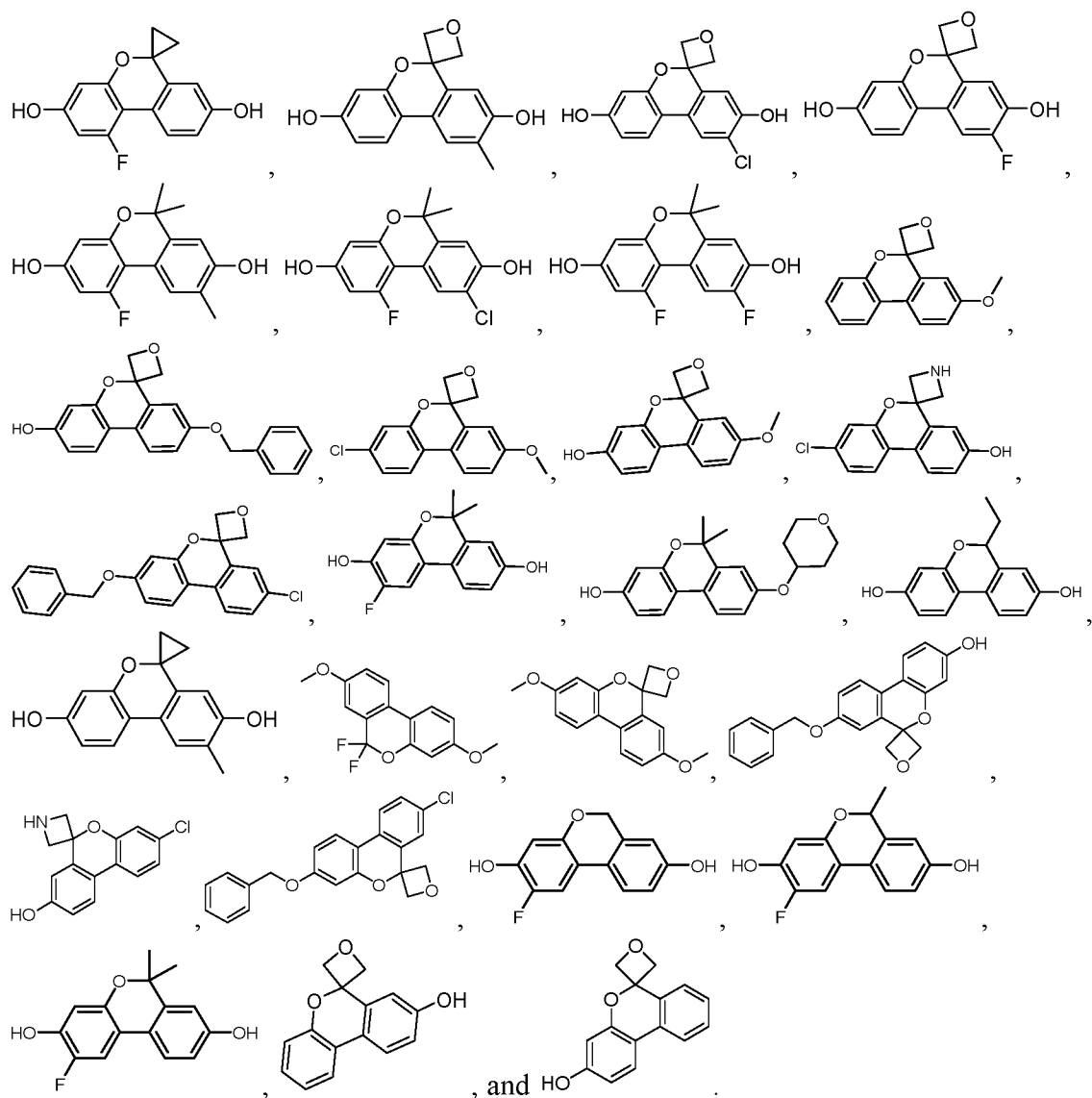
In some embodiments, R_2 and R_7 are each OH. In other embodiments, one of R_2 and R_7 is OH and the other of R_2 and R_7 is O-alkyl. In other embodiments, one of R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 is alkyl or halogen. In other embodiments, two of R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 are alkyl or halogen

In some embodiments, the compound Formula (Id) is selected from:

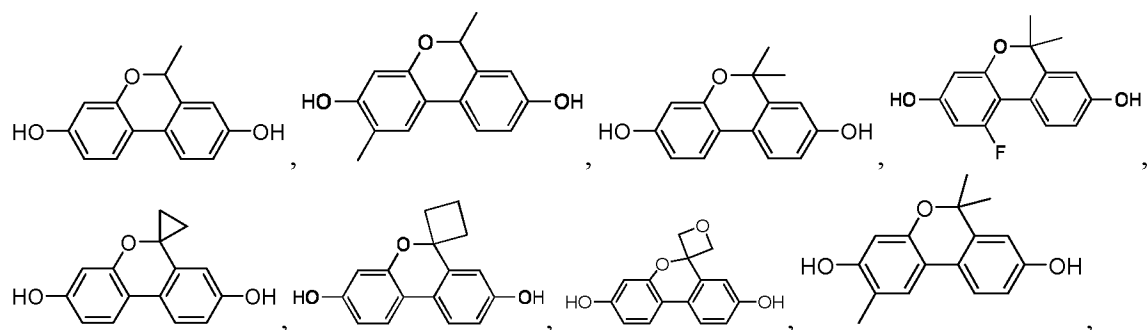


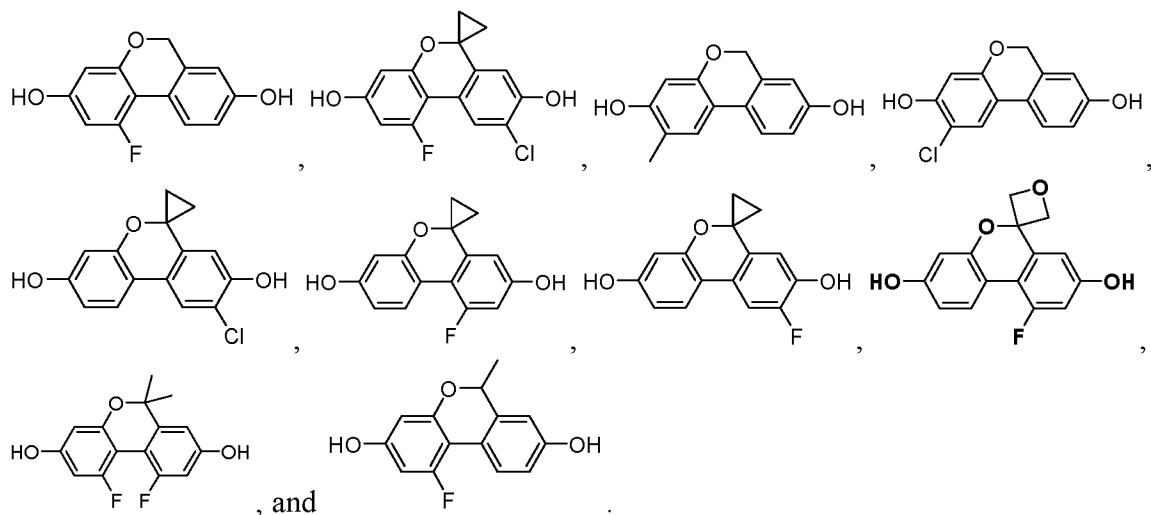
In some embodiments, the compound Formula (Id) is selected from:



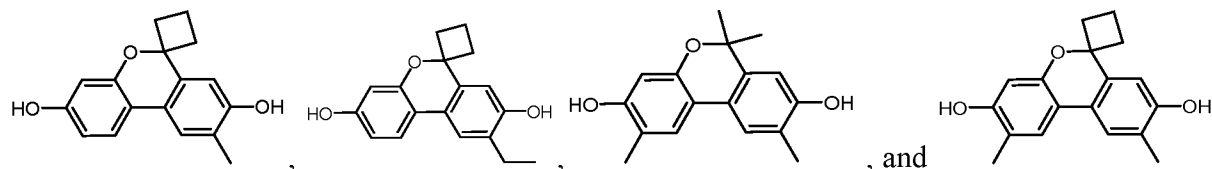


In some embodiments, the compound Formula (Id) is selected from:

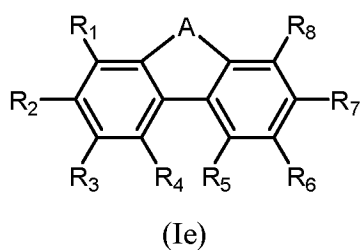




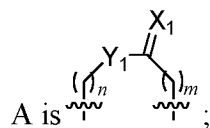
In some embodiments, the compound of Formula (Id) is selected from:



Another aspect of the invention relates to a method of treating amyotrophic lateral sclerosis (ALS), comprising administering to a subject in need thereof an effective amount of a compound of Formula (Ie),



wherein



n and m are both 0; or one of n and m is 0, and the other of n and m is 1;

X_1 is O;

Y_1 is selected from NH, N-CH₃, N-*t*-Bu, N-cycloalkyl, and N-heterocycloalkyl;

R_1 , R_2 , R_3 , R_6 , R_7 , and R_8 are independently selected from H, OH, OCH₃, OAc, NH₂, halogen, CN, CF₃, CO₂H, NO₂, NHAc, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkylamino, alkyl- R_9 , alkenyl- R_9 , alkynyl- R_9 , OR₁₀, NHR₁₀, NR₁₁C(O)R₁₂, C(O)NR₁₁R₁₂, and NR₁₁SO₂R₁₂;

R_4 and R_5 are independently selected from H, alkyl, and halogen;

each occurrence of R_9 is independently selected from OH, NH₂, O-alkyl, O-alkyl-O-alkyl, alkylamino, NHC(O)-alkyl, N(CH₃)C(O)-alkyl, NHSO₂-alkyl, N(CH₃)SO₂-alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

R_{10} is selected from C₂-C₁₂ alkyl, hydroxyalkyl, aminoalkyl, alkyl-O-alkyl, alkyl-O-alkyl-OH, alkyl-O-alkyl-O-alkyl, alkenyl, alkynyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, alkyl-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, SO₃H, SO₂-alkyl, and SO₂-haloalkyl;

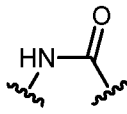
each occurrence of R_{11} is selected from H and alkyl; and

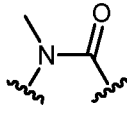
each occurrence of R_{12} is selected from alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, O-alkyl, aminoalkyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, and alkyl-heterocycloalkyl;

or a pharmaceutically acceptable salt thereof.

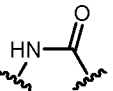
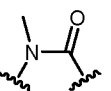
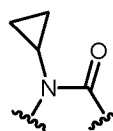
In some embodiments, R_2 and R_7 are each -OH, or each -O-alkyl, or one R_2 and R_7 is -OH and the other of R_2 and R_7 is not -OH.

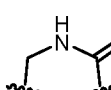
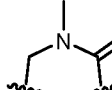
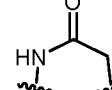
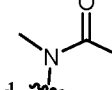
In some embodiments, the compound provided that no more than two of R_1 , R_2 , R_3 , R_6 , R_7 , and R_8 are OH or OCH₃,

if A is , and R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 are each H, then R_2 and R_7 are not both OH, both OCH₃ or both OR₁₀, and

if A is , and R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 are each H, then R_2 and R_7 are not both OR₁₀.

In some embodiments, wherein n and m are both 0. In other embodiments, one of n and m is 0, and the other of n and m is 1.

In some embodiments, A is selected from , , and . In other

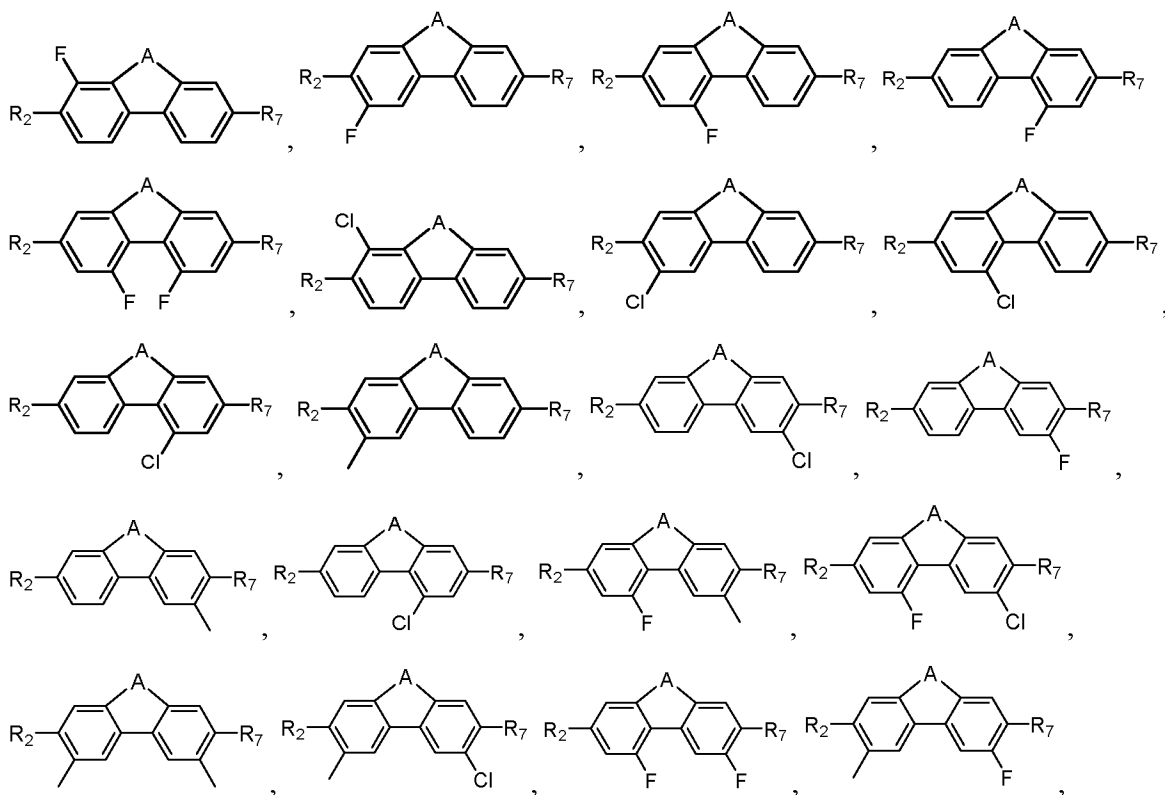
embodiments, A is selected from , , , and .

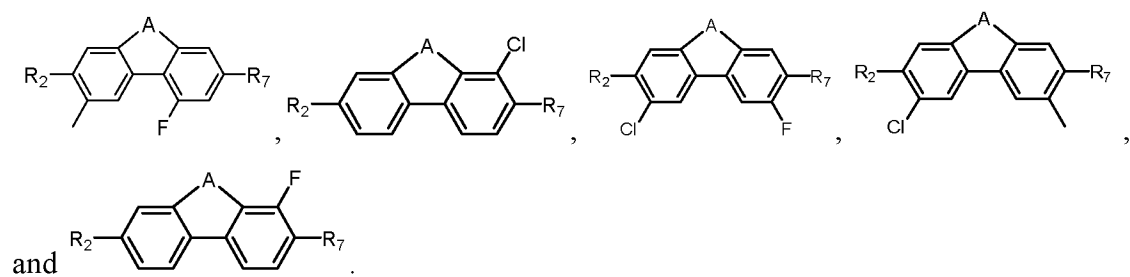
In some embodiments, wherein R_2 and R_7 are each OH.

In some embodiments, wherein one of R_2 and R_7 is OH and the other of R_2 and R_7 is OH is not OH. In other embodiments, R_2 and R_7 are each O-alkyl. In other embodiments, R_2 is OH and R_7 is O-alkyl; or R_2 is O-alkyl and R_7 is OH.

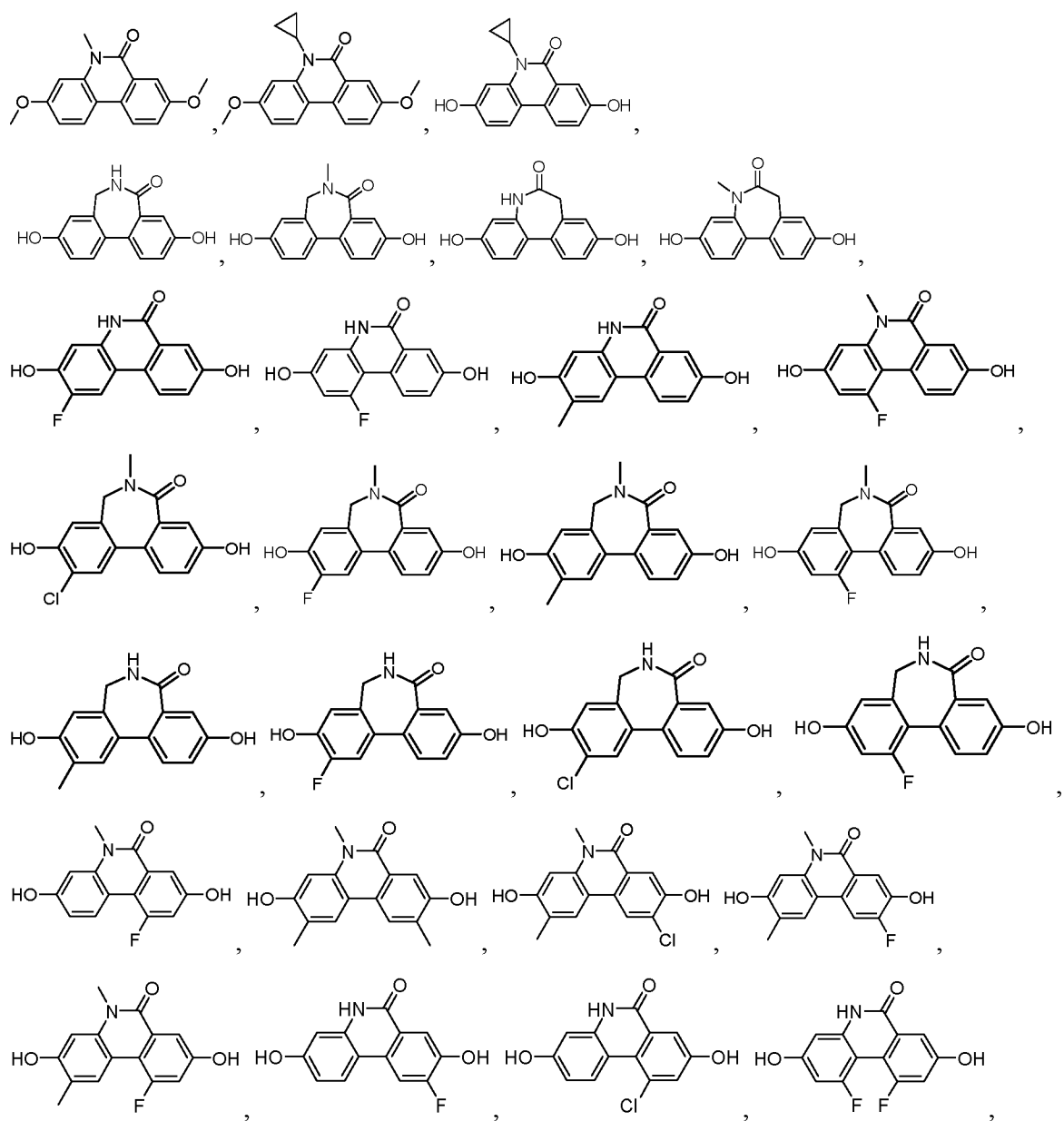
In some embodiments, wherein R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 are each H. In other embodiments, one of R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 is not H. In other embodiments, a compound two of R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 are not H. In other embodiments, one of R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 is alkyl or halogen. In other embodiments, two of R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 are alkyl or halogen.

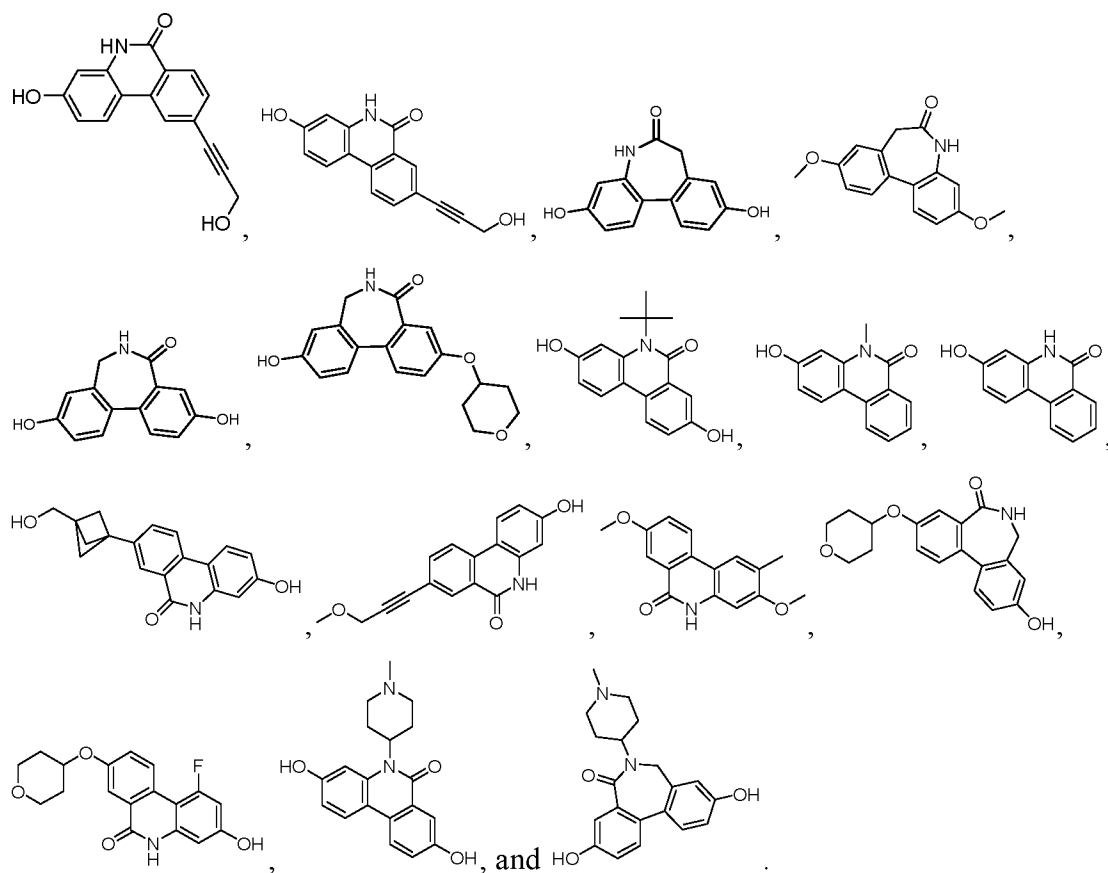
In some embodiments, the compound of Formula (Ie) is selected from:



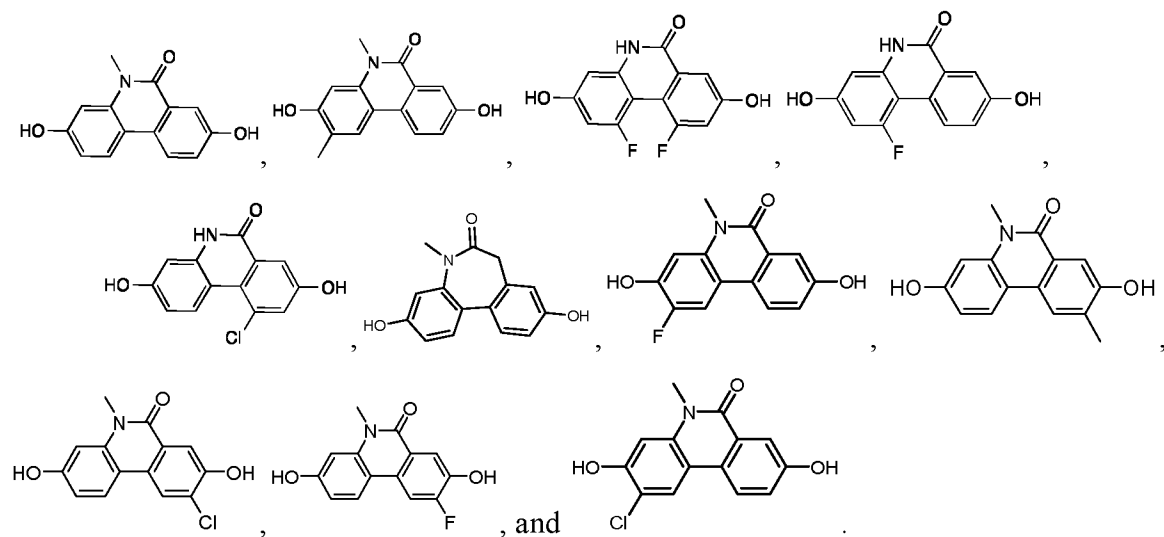


In some embodiments, the compound of Formula (Ie) is selected from:

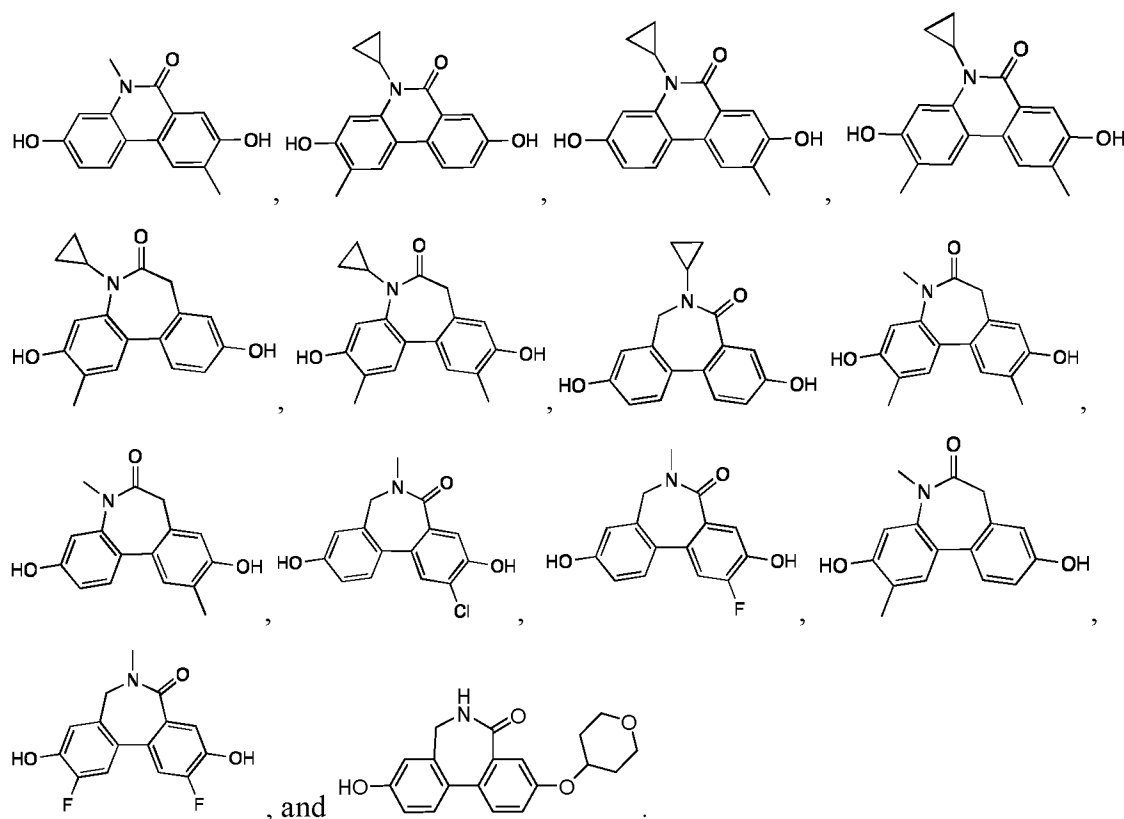




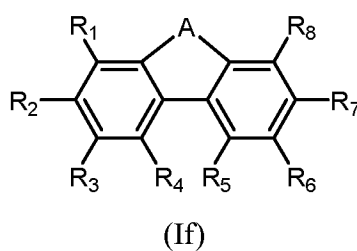
In some embodiments, the compound of Formula (Ie) is selected from:



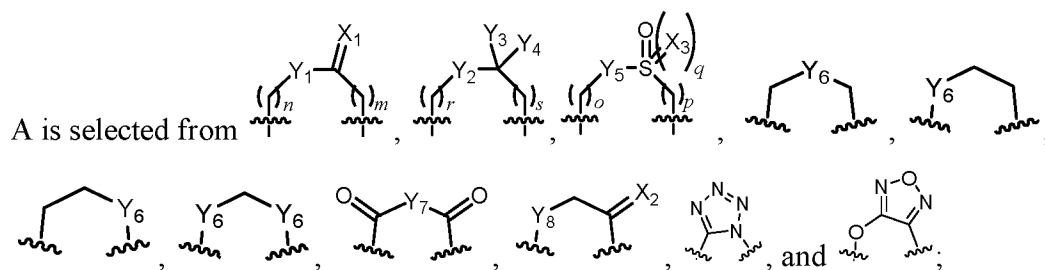
In one embodiment, the compound of Formula (Ie) is selected from:



Another aspect of the invention relates to a method of treating amyotrophic lateral sclerosis (ALS), comprising administering to a subject in need thereof an effective amount of a compound of Formula (If),



wherein



n and m are both 0; or one of n and m is 0 and the other of n and m is 1;

o and p are both 0; or one of o and p is 0 and the other of o and p is 1;

q is 0 or 1;

r and s are both 0; or one of r and s is 0 and the other of r and s is 1;

X_1 and X_2 are each O;

X_3 is O or N(alkyl);

Y_1 is S;

Y_2 is selected from O, CH₂, NH, N-alkyl, S, S(O), and SO₂;

Y_3 and Y_4 are independently selected from H, halogen, OH, and alkyl, or together with the carbon to which they are bonded combine to form a cycloalkyl or cycloheteroalkyl;

Y_5 is selected from CH₂, NH, N-alkyl, N-arylalkyl, N-cycloalkyl, and N-heterocycloalkyl;

Each occurrence of Y_6 is independently selected from O, S, S(O), SO₂, NH, N-alkyl, N-alkylaryl, and N-cycloalkyl;

Y_7 is selected from O, NH and N-alkyl;

Y_8 is selected from O and S;

R_1 , R_2 , R_3 , R_6 , R_7 , and R_8 are independently selected from H, OH, OCH₃, OAc, NH₂, halogen, CN, CF₃, CO₂H, NO₂, NHAc, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkylamino, alkyl-R₉, alkenyl-R₉, alkynyl-R₉, OR₁₀, NHR₁₀, NR₁₁C(O)R₁₂, C(O)NR₁₁R₁₂, and NR₁₁SO₂R₁₂,

R_4 and R_5 are independently selected from H, alkyl, and halogen;

each occurrence of R_9 is independently selected from OH, NH₂, O-alkyl, O-alkyl-O-alkyl, alkylamino, NHC(O)-alkyl, N(CH₃)C(O)-alkyl, NHSO₂-alkyl, N(CH₃)SO₂-alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

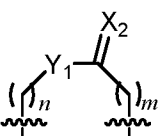
R_{10} is selected from C₂-C₁₂ alkyl, hydroxyalkyl, aminoalkyl, alkyl-O-alkyl, alkyl-O-alkyl-OH, alkyl-O-alkyl-O-alkyl, alkenyl, alkynyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, alkyl-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, SO₃H, SO₂-alkyl, and SO₂-haloalkyl;

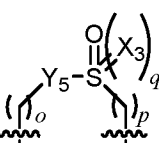
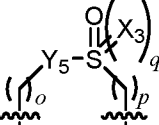
each occurrence of R_{11} is selected from H and alkyl; and

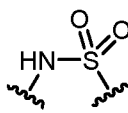
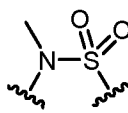
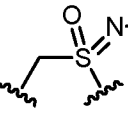
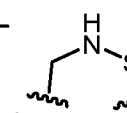
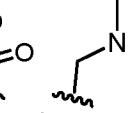
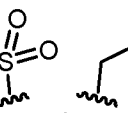
each occurrence of R_{12} is selected from alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, O-alkyl, aminoalkyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, and alkyl-heterocycloalkyl;

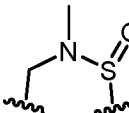
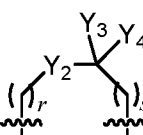
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound provided that if Y_2 is CH_2 , one of Y_3 or Y_4 is not H, or Y_3 or Y_4 together with the carbon to which they are bonded combine to form a cycloalkyl or heterocycloalkyl, and if Y_2 is O, then one of r and s is 0 and the other of r and s is 1.

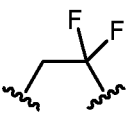
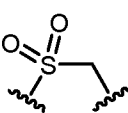
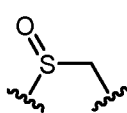
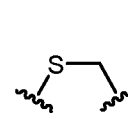
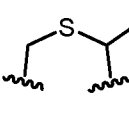
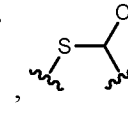
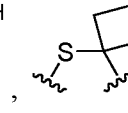
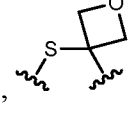
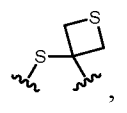
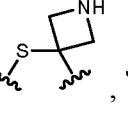
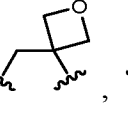
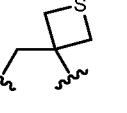
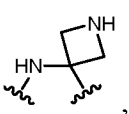
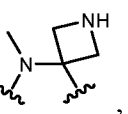
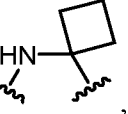
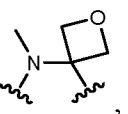
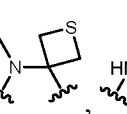
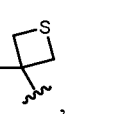
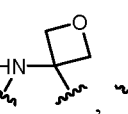
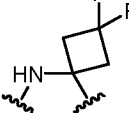
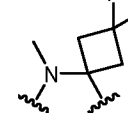
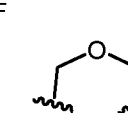
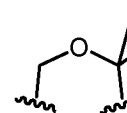
In some embodiments, A is ; and n and m are both 0. In other embodiments,

A is . In some embodiments, A is . In other embodiments, A is selected

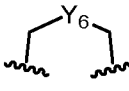
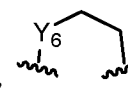
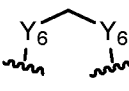
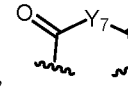
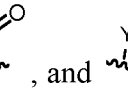
from , , , , , , and

. In some embodiments, A is .

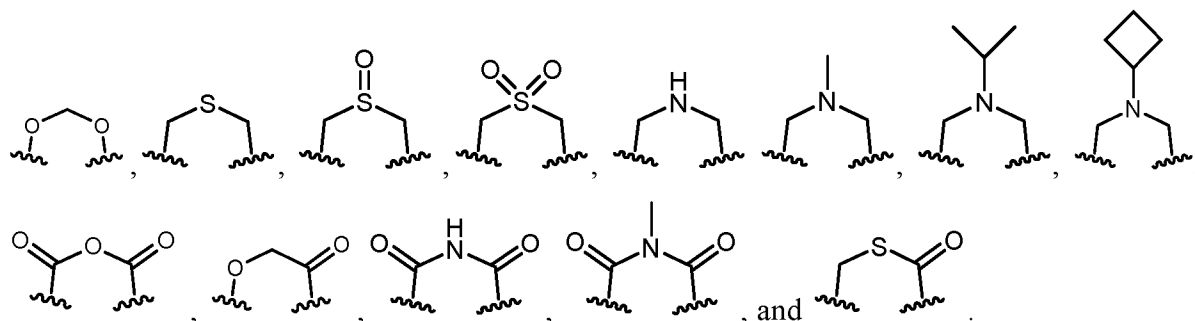
In other embodiments, A is selected from

, , , , , , , , , , , , , , , , , , , , , , , and .

In some embodiments, A is selected from

, , , , , and .

In other embodiments, A is selected from ,

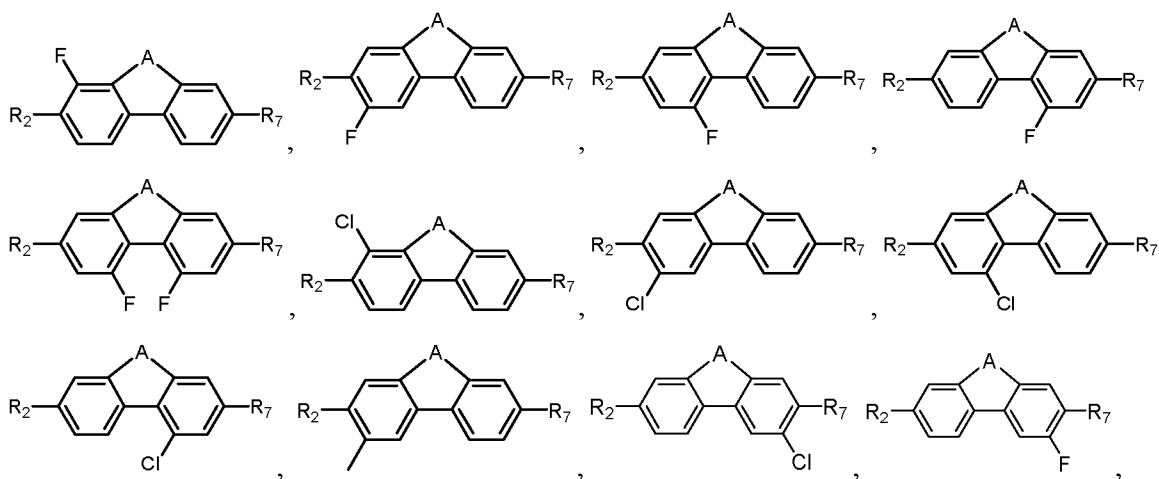


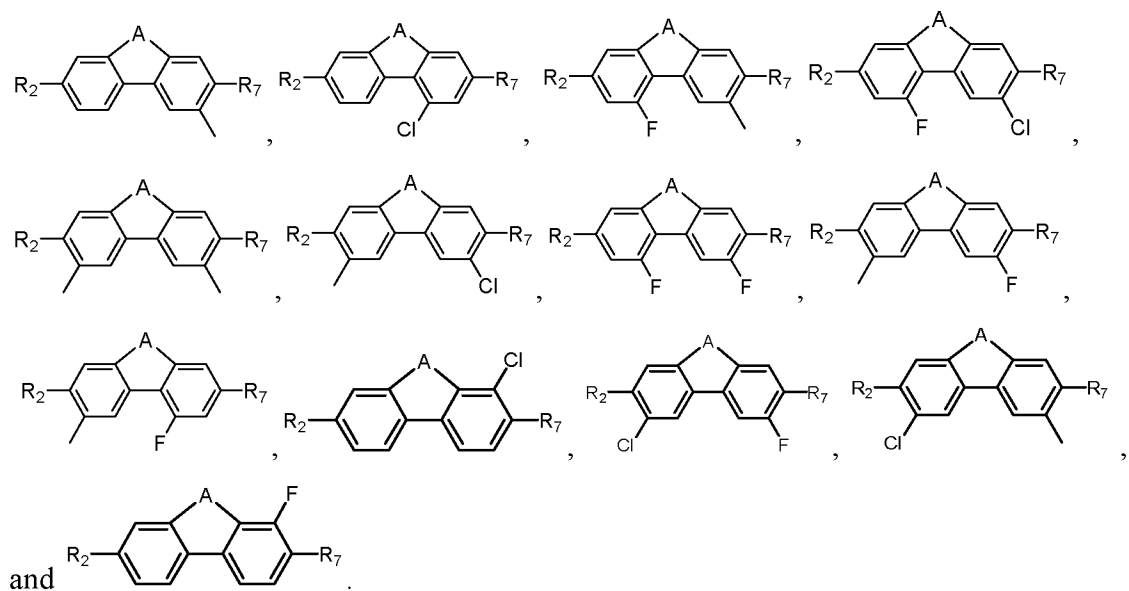
In some embodiments, Y₂ is selected from CH₂, NH, N-alkyl, S, S(O), and SO₂.

In some embodiments, R₂ and R₇ are each OH. In other embodiments, one of R₂ and R₇ is OH and the other of R₂ and R₇ is not OH. In other embodiments, R₂ and R₇ are each O-alkyl. In other embodiments, R₂ is OH and R₇ is O-alkyl; or R₂ is O-alkyl and R₇ is OH.

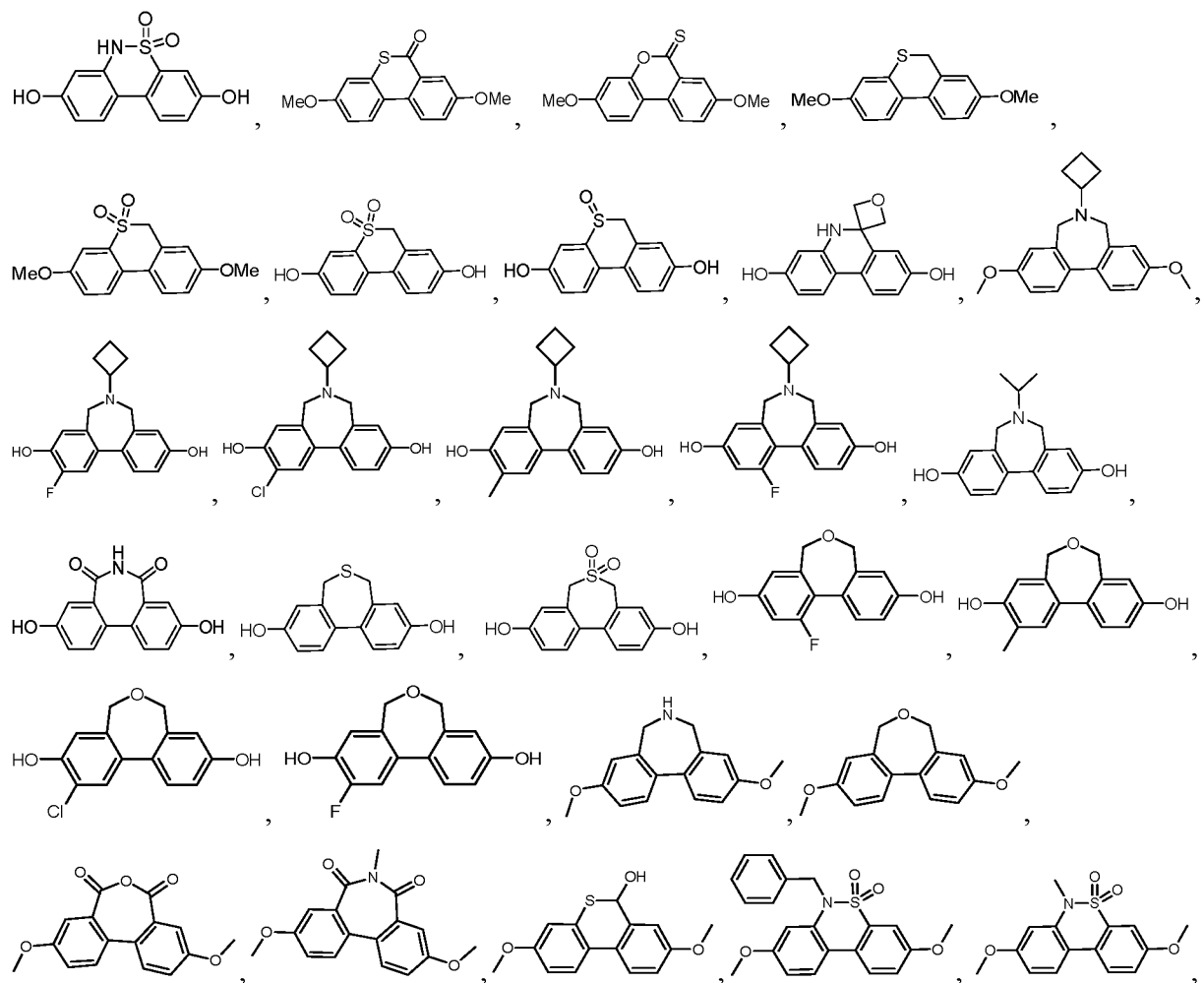
In some embodiments, R₁, R₃, R₄, R₅, R₆, and R₈ are each H. In other embodiments, one of R₁, R₃, R₄, R₅, R₆, and R₈ is not H. In other embodiments, two of R₁, R₃, R₄, R₅, R₆, and R₈ are not H. In other embodiments, one of R₁, R₃, R₄, R₅, R₆, and R₈ is alkyl or halogen. In other embodiments, two of R₁, R₃, R₄, R₅, R₆, and R₈ are alkyl or halogen.

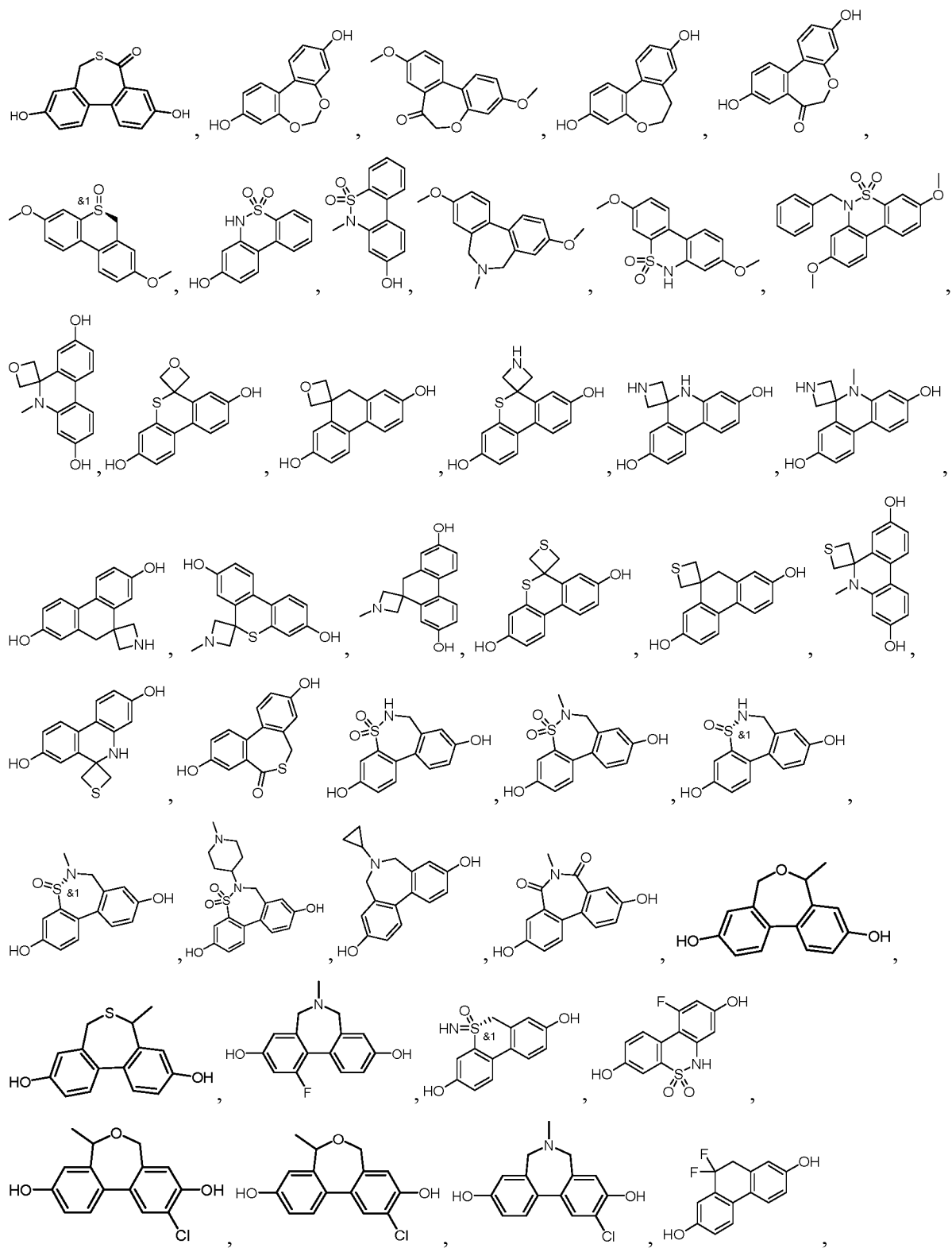
In some embodiments, the compound of Formula (If) is selected from:

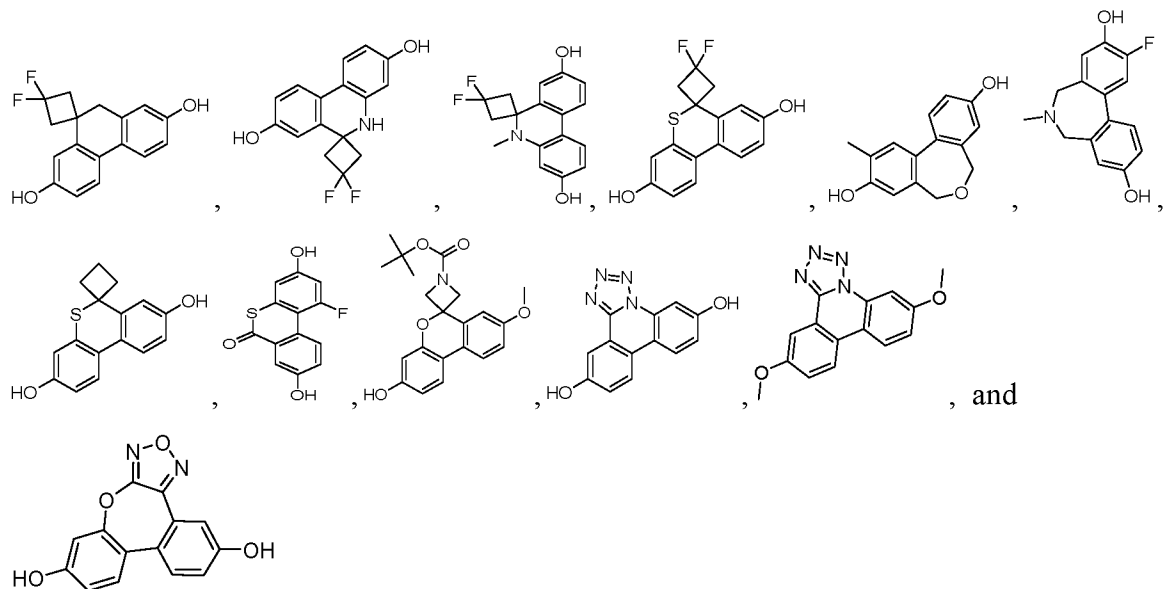




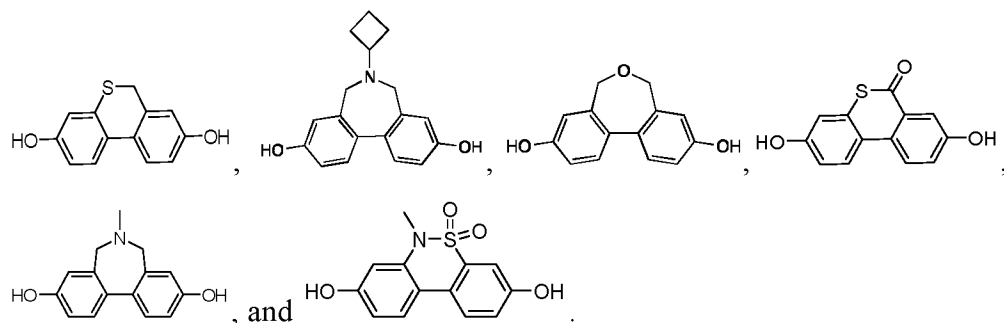
In some embodiments, the compound of Formula (If) is selected from:



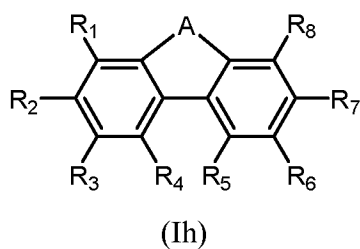




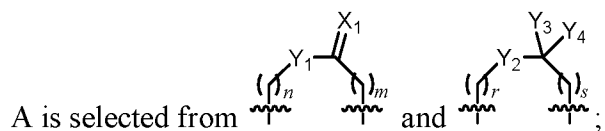
In some embodiments, the compound of Formula (If) is selected from:



Another aspect of the invention relates to a method of treating amyotrophic lateral sclerosis (ALS), comprising administering to a subject in need thereof an effective amount of a compound of Formula (Ih),



wherein



n and m are both 0; or one of n and m is 0 and the other of n and m is 1;

r and s are both 0; or one of r and s is 0 and the other of r and s is 1;

X_1 is O;

Y_1 is selected from O, NH, N-alkyl, and N-cycloalkyl;

Y_2 is O;

Y_3 and Y_4 are independently selected from H, halogen, and alkyl, or together with the carbon to which they are bonded combine to form a cycloalkyl or cycloheteroalkyl;

R_1 , R_4 , R_5 and R_8 are independently selected from H and halogen;

R_3 and R_6 are independently selected from H, CN, OH, CF_3 , halogen, and alkyl;

one of R_2 and R_7 is NH_2 , $NHCH_3$, and $N(CH_3)_2$ and the other of R_2 and R_7 is H, halogen, OCH_3 , CN, CF_3 , CO_2H , NO_2 , $NHAc$, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkylamino, alkyl- R_9 , alkenyl- R_9 , alkynyl- R_9 , OR_{10} , NHR_{10} , $NR_{11}C(O)R_{12}$, $C(O)NR_{11}R_{12}$, and $NR_{11}SO_2R_{12}$;

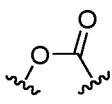
each occurrence of R_9 is independently selected from OH, NH_2 , O-alkyl, O-alkyl-O-alkyl, alkylamino, $NHC(O)$ -alkyl, $N(CH_3)C(O)$ -alkyl, $NHSO_2$ -alkyl, $N(CH_3)SO_2$ -alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

R_{10} is selected from C_2 - C_{12} alkyl, hydroxyalkyl, aminoalkyl, alkyl-O-alkyl, alkyl-O-alkyl-OH, alkyl-O-alkyl-O-alkyl, alkenyl, alkynyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, alkyl-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, SO_3H , SO_2 -alkyl, and SO_2 -haloalkyl;

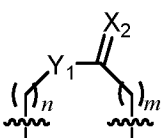
each occurrence of R_{11} is selected from H and alkyl; and

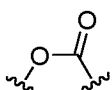
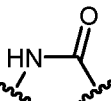
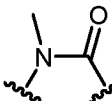
each occurrence of R_{12} is selected from alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, O-alkyl, aminoalkyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, and alkyl-heterocycloalkyl;

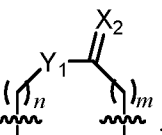
or a pharmaceutically acceptable salt thereof

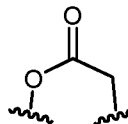
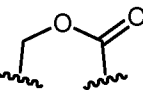
In some embodiments, the compound provided that if A is , R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 are each H, and R_7 is NH_2 , then R_2 is not OH.

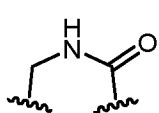
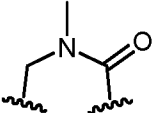
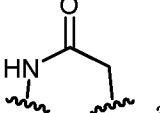
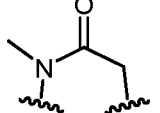
In some embodiments, Y_1 is selected from O, NH, and N-alkyl.

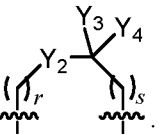
In some embodiments, A is ; and n and m are both 0. In other embodiments,

A is . In other embodiments, A is , or .

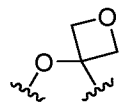
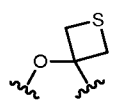
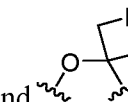
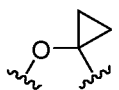
In some embodiments, A is ; and one of n or m is 0 and the other of n or m is

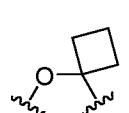
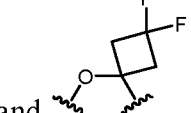
1. In other embodiments, A is  or . In other embodiments, A is selected

from , , , and .

In some embodiments, A is ; and r and s are both 0. In other embodiments, A

is selected from, , , , , , , , , .

, , and . In other embodiments, A is selected from ,

, and .

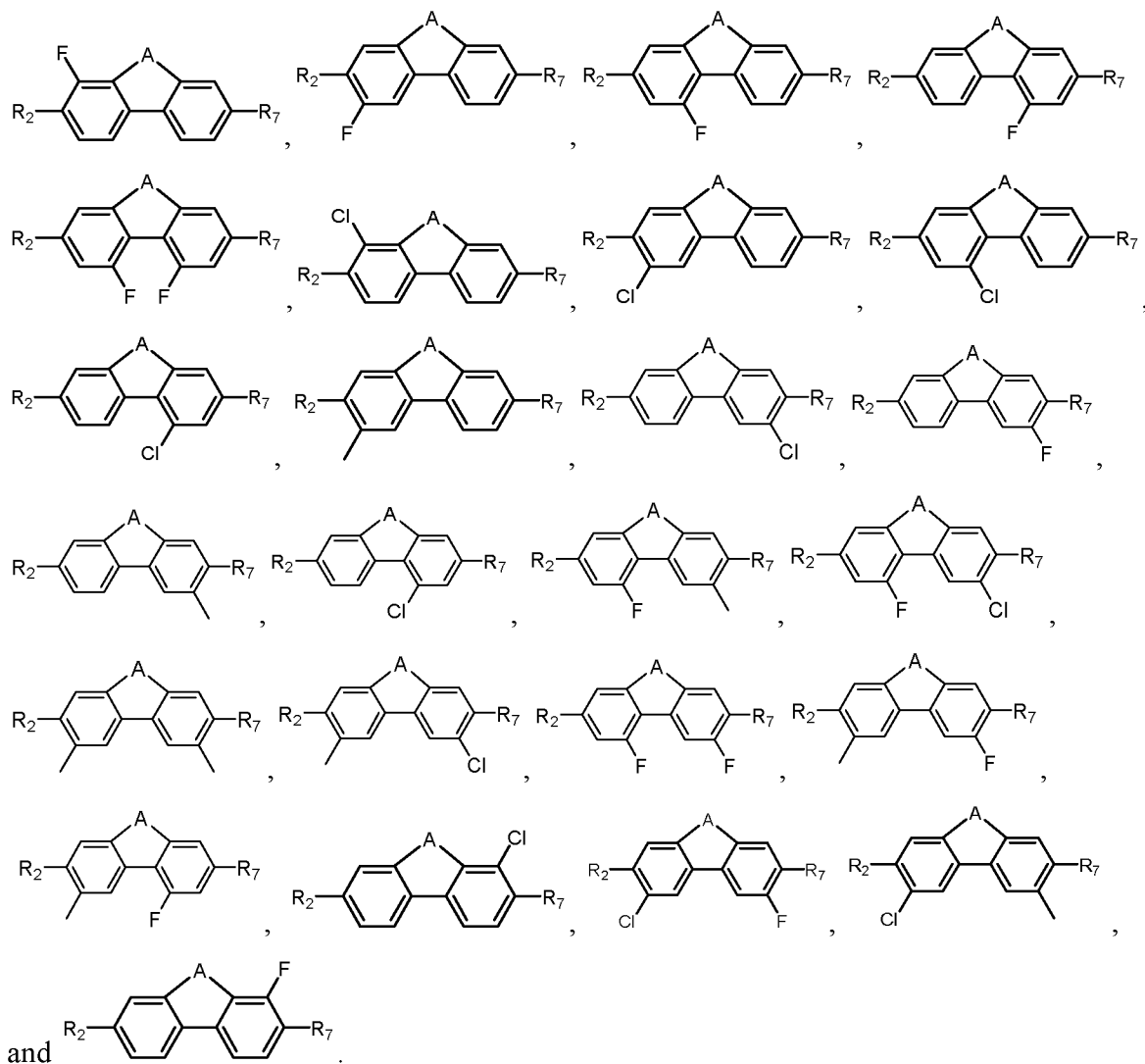
In some embodiments, wherein R_2 is selected from NH_2 , $NHCH_3$, and $N(CH_3)_2$.

In some embodiments, R_7 is selected from H, OH, halogen, O-alkyl, and haloalkyl.

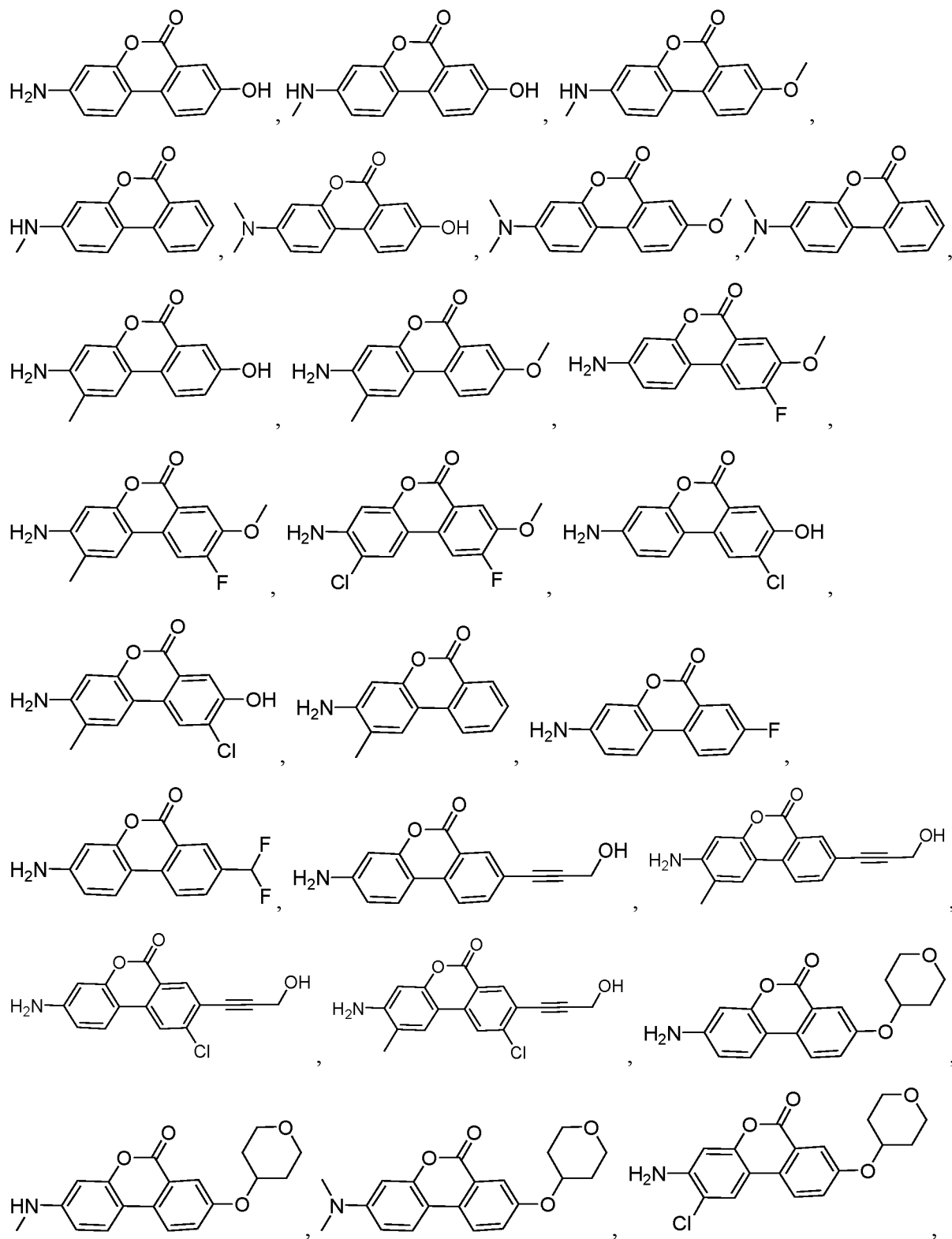
In some embodiments, R_7 is selected from alkynyl- R_9 and OR_{10} ; R_9 is OH; and R_{10} is alkyl-heterocycloalkyl.

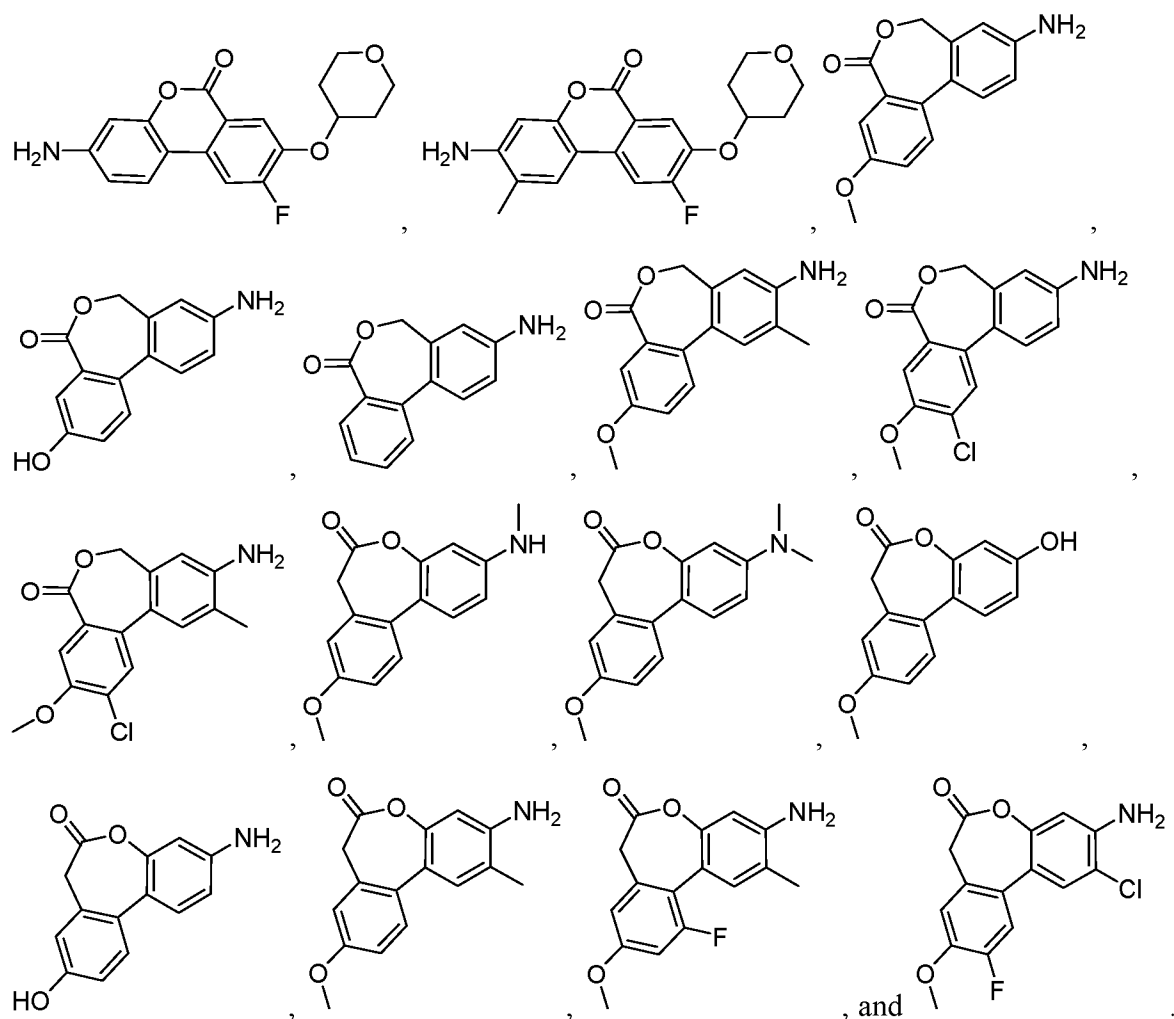
In some embodiments, wherein R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 are each H. In other embodiments, one of R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 is not H. In other embodiments, two of R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 are not H. In other embodiments, one of R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 is alkyl or halogen. In other embodiments, two of R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 are independently alkyl or halogen.

In some embodiments, the compound of Formula (Ih) is selected from:

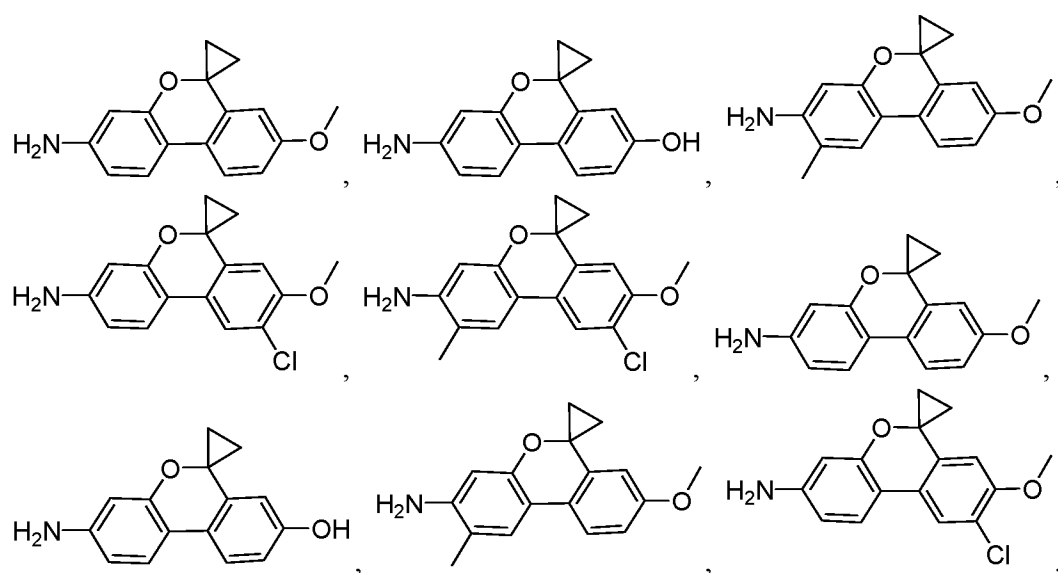


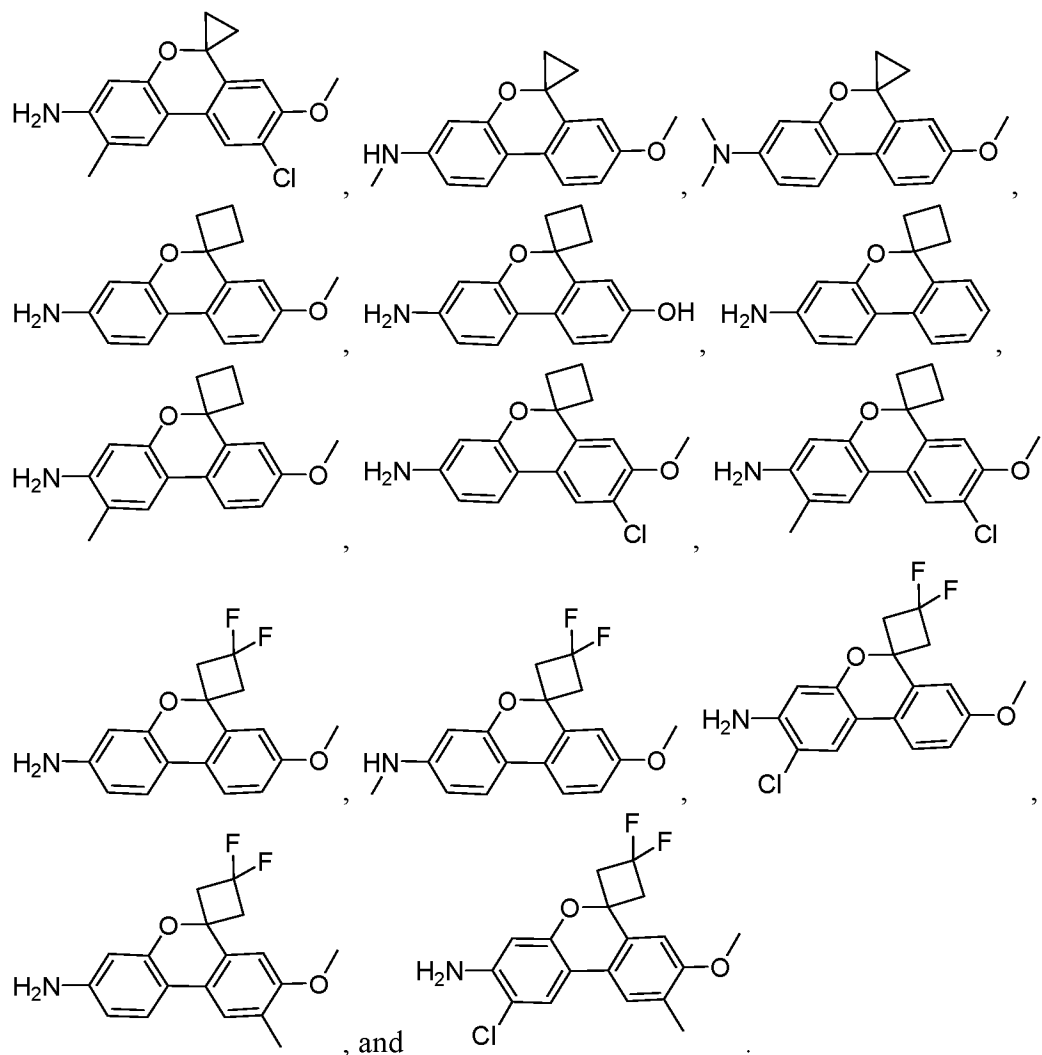
In some embodiments, the compound of Formula (Ih) is selected from:



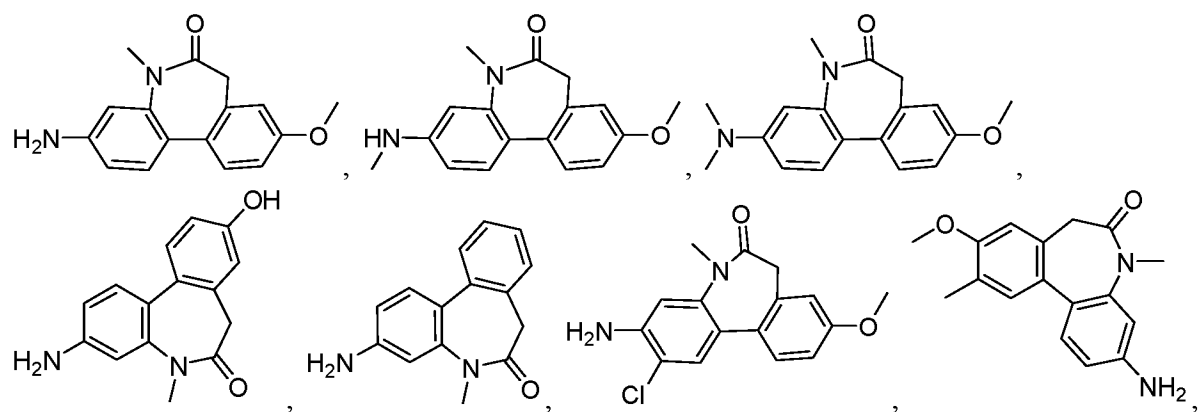


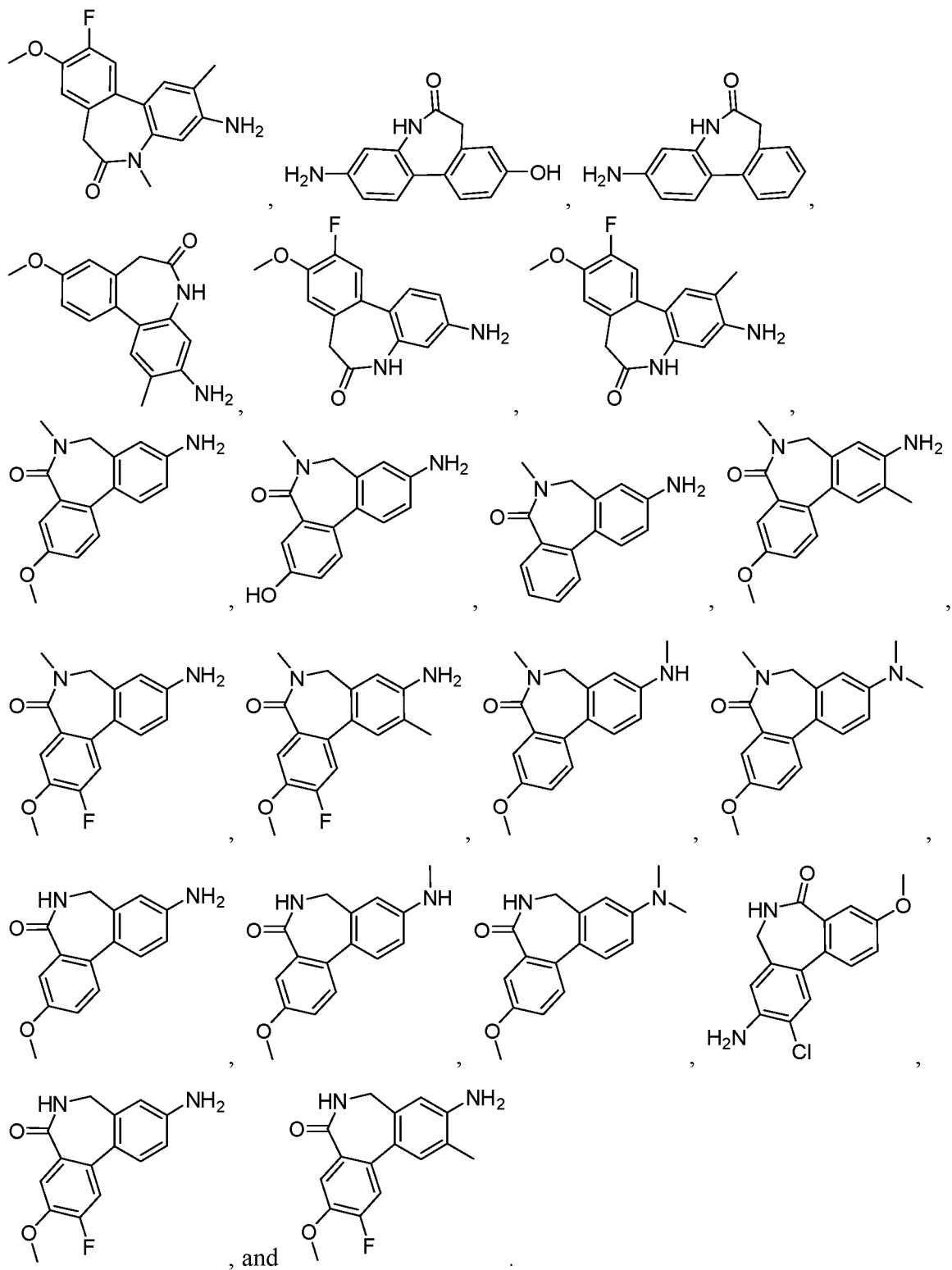
In some embodiments, the compound of Formula (Ih) is selected from:



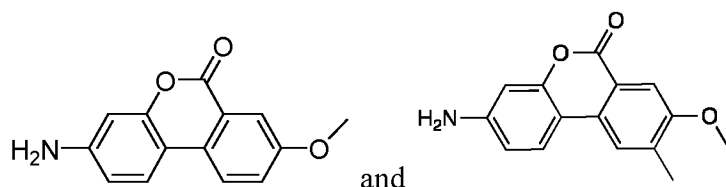


In some embodiments, the compound of Formula (Ih) is selected from:

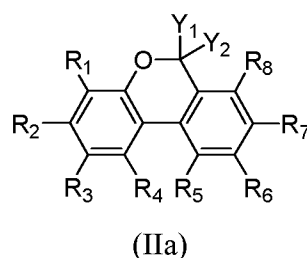




In some embodiments, the compound Formula (Ih) is selected from:



Another aspect of the invention relates to a method of treating amyotrophic lateral sclerosis (ALS), comprising administering to a subject in need thereof an effective amount of a compound of Formula (IIa),



wherein

Y_1 and Y_2 are each alkyl; or taken together with the carbon to which they are bonded combine to form an unsubstituted or substituted spiro cycloalkyl;

R_1 , R_4 , R_5 , and R_8 are independently selected from $-H$ and halogen;

R_2 and R_7 are independently selected from $-H$, $-OH$, $-OAc$, $-NH_2$, halogen, $-CN$, $-CF_3$, $-CO_2H$, $-NO_2$, $-NHAc$, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkylamino, alkyl- R_9 , alkenyl- R_9 , alkynyl- R_9 , $-OR_{10}$, $-NHR_{10}$, $-NR_{11}C(O)R_{12}$, $-C(O)NR_{11}R_{12}$, and $-NR_{11}SO_2R_{12}$;

R_3 and R_6 are alkyl;

each occurrence of R_9 is independently selected from OH , NH_2 , O -alkyl, O -alkyl- O -alkyl, alkylamino, $NHC(O)$ -alkyl, $N(CH_3)C(O)$ -alkyl, $NHSO_2$ -alkyl, $N(CH_3)SO_2$ -alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

R_{10} is selected from alkyl, hydroxyalkyl, aminoalkyl, alkyl- O -alkyl, alkyl- O -alkyl- OH , alkyl- O -alkyl- O -alkyl, alkenyl, alkynyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, alkyl-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, SO_3H , SO_2 -alkyl, and SO_2 -haloalkyl;

each occurrence of R_{11} is selected from H and alkyl; and

each occurrence of R_{12} is selected from alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, O-alkyl, aminoalkyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, and alkyl-heterocycloalkyl;

provided that when R_1 , R_4 , R_5 , and R_8 are each $-H$, R_2 and R_7 are each $-OH$, and R_3 and R_6 are each CH_3 , then Y_1 and Y_2 are not each $-Me$ or are not taken together with the carbon to which they are bonded to form an unsubstituted spiro cyclobutyl;

or a pharmaceutically acceptable salt thereof.

In some embodiments, Y_1 and Y_2 are each independently C_1 - C_4 alkyl. In some embodiments, Y_1 and Y_2 are each $-CH_3$.

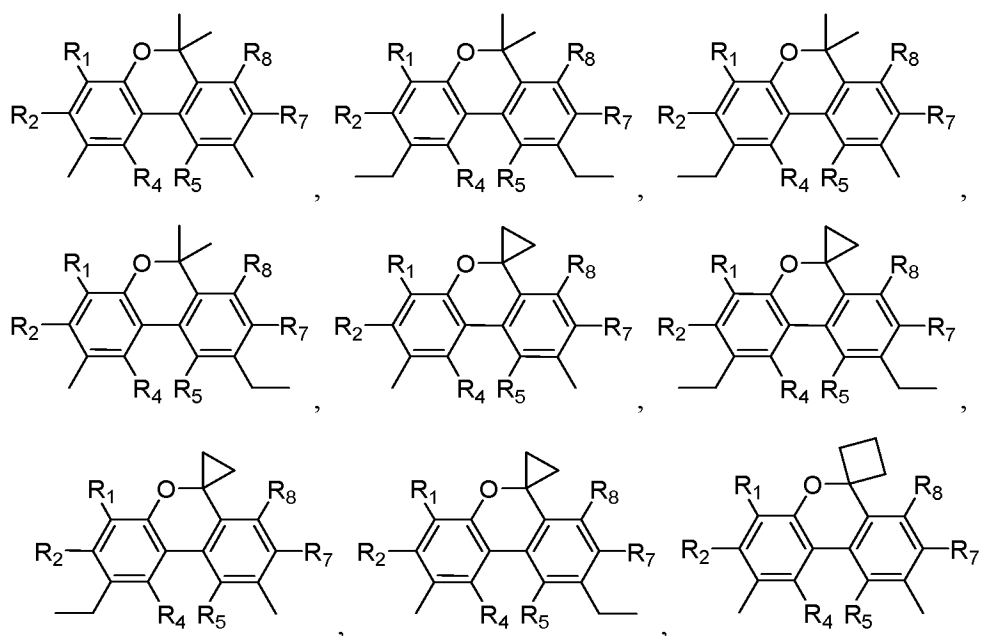
In some embodiments, Y_1 and Y_2 taken together with the carbon to which they are bonded combine to form an unsubstituted spiro cycloalkyl. In other embodiments, Y_1 and Y_2 taken together with the carbon to which they are bonded combine to form an unsubstituted spiro cyclopropyl, cyclobutyl, or cyclopentyl.

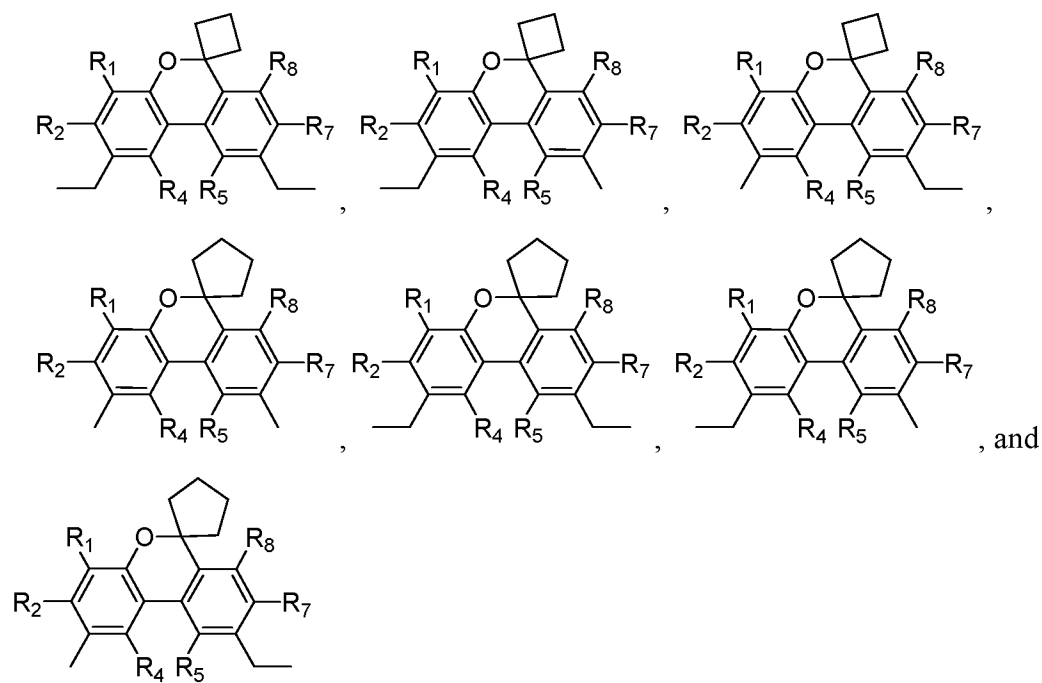
In some embodiments, R_3 and R_6 are each independently C_1 - C_4 alkyl.

In some embodiments, R_3 and R_6 are each independently selected from $-CH_3$ and $-CH_2CH_3$. In other embodiments, R_3 and R_6 are each $-CH_3$. In other embodiments, R_3 and R_6 are each $-CH_2CH_3$.

In some embodiments, one of R_3 and R_6 is $-CH_3$ and the other of R_3 and R_6 is $-CH_2CH_3$.

In some embodiments, the compound having the structure selected from:





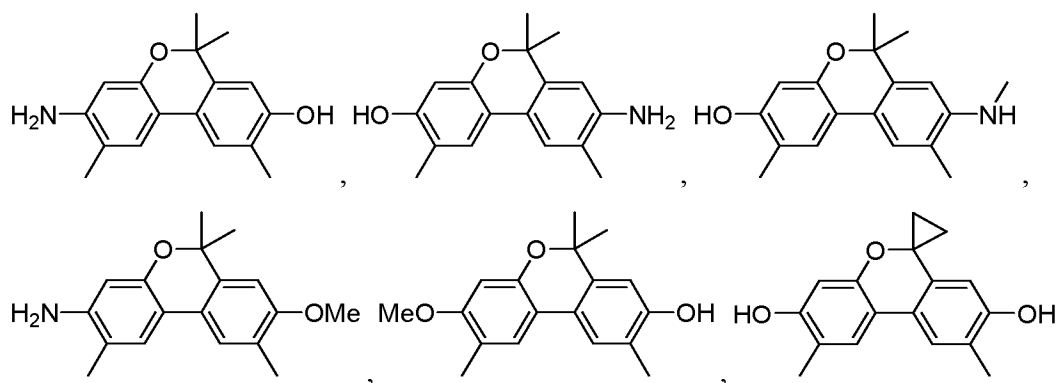
In some embodiments, R₂ and R₇ are independently selected from -OH, -NH₂, alkylamino, and -OR₁₀.

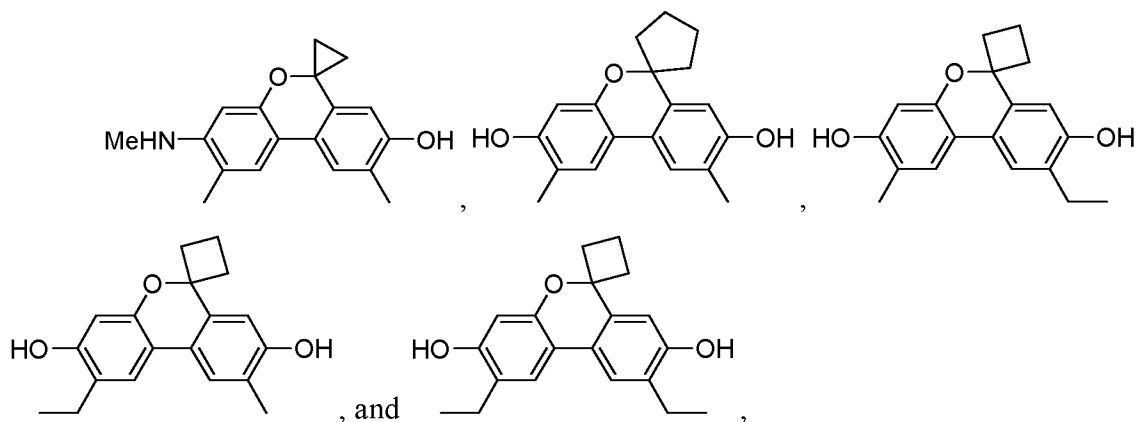
In some embodiments, R₂ and R₇ are each OH. In other embodiments, R₂ is -OH; and R₇ is -OCH₃. In other embodiments, R₇ is -OH; and R₂ is -OCH₃.

In some embodiments, R₂ is selected from -NH₂, -NHCH₃, and -NH(CH₃)₂; and R₇ is OH. In other embodiments, R₇ is selected from -NH₂, -NHCH₃, and -NH(CH₃)₂; and R₂ is OH.

In some embodiments, R₁, R₄, R₅, and R₈ are each -H.

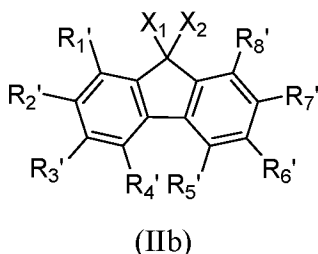
In some embodiments, the compound is selected from:





or a pharmaceutically acceptable salt thereof.

Another aspect of the invention relates to a method of treating amyotrophic lateral sclerosis (ALS), comprising administering to a subject in need thereof an effective amount of a compound of Formula (IIb),



wherein

X_1 and X_2 are each alkyl; or taken together with the carbon to which they are bonded combine to form an unsubstituted or substituted spiro cycloalkyl;

R_1' , R_4' , R_5' , and R_8' are independently selected from $-H$, $-OH$, $-NH_2$, alkyl, and halogen;

R_2' , R_3' , R_6' , and R_7' are independently selected from $-H$, $-OH$, $-OAc$, $-NH_2$, halogen, $-CN$, $-CF_3$, $-CO_2H$, $-NO_2$, $-NHAc$, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkylamino, and $-OR_8'$; and

R_8' is selected from alkyl, hydroxyalkyl, aminoalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

or a pharmaceutically acceptable salt thereof.

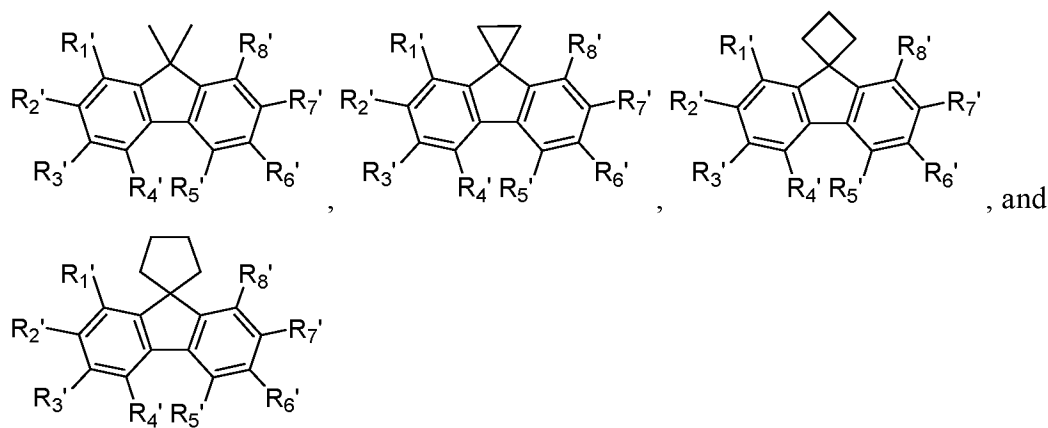
In some embodiments, X_1 and X_2 are each independently C_1 - C_4 alkyl.

In some embodiments, X_1 and X_2 are each $-CH_3$.

In some embodiments, X_1 and X_2 taken together with the carbon to which they are bonded combine to form an unsubstituted spiro cycloalkyl. In other embodiments, X_1 and X_2

taken together with the carbon to which they are bonded combine to form an unsubstituted spiro cyclopropyl, cyclobutyl, or cyclopentyl.

In some embodiments, the compound having the structure selected from:



In some embodiments, R_2' and R_7' are independently selected from $-OH$, $-NH_2$, alkylamino, and $-OR_{10}$.

In some embodiments, wherein R_2' and R_7' are each OH . In other embodiments, R_2' is $-OH$; and R_7' is $-OCH_3$. In other embodiments, R_7' is $-OH$; and R_2' is $-OCH_3$.

In some embodiments, R_2' is selected from $-NH_2$, $-NHCH_3$, and $-NH(CH_3)_2$; and R_7' is OH .

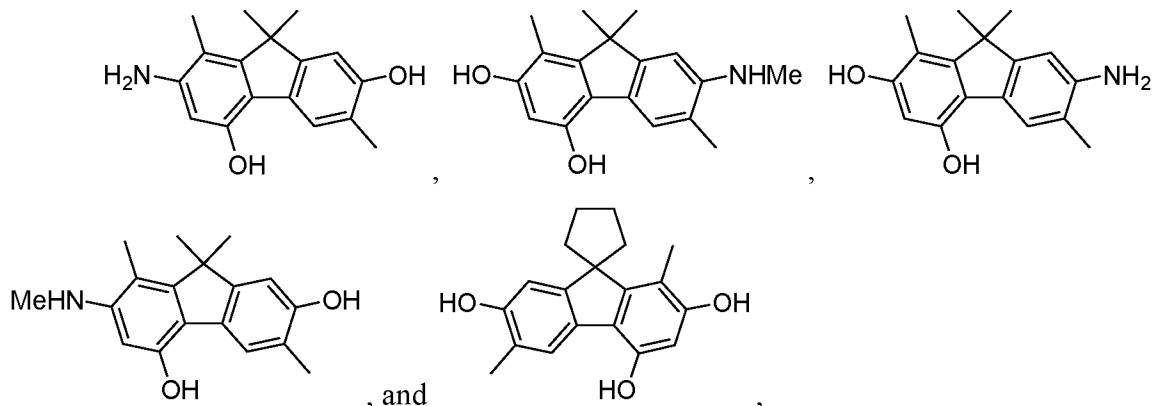
In some embodiments, R_7' is selected from $-NH_2$, $-NHCH_3$, and $-NH(CH_3)_2$; and R_2' is OH .

In some embodiments, R_3' and R_6' are each independently $-H$ or C_1-C_4 alkyl. In other embodiments, R_3' and R_6' are each independently $-H$ or $-CH_3$.

In some embodiments, R_1' and R_8' are each independently $-H$ or C_1-C_4 alkyl. In other embodiments, R_1' and R_8' are each independently $-H$ or $-CH_3$.

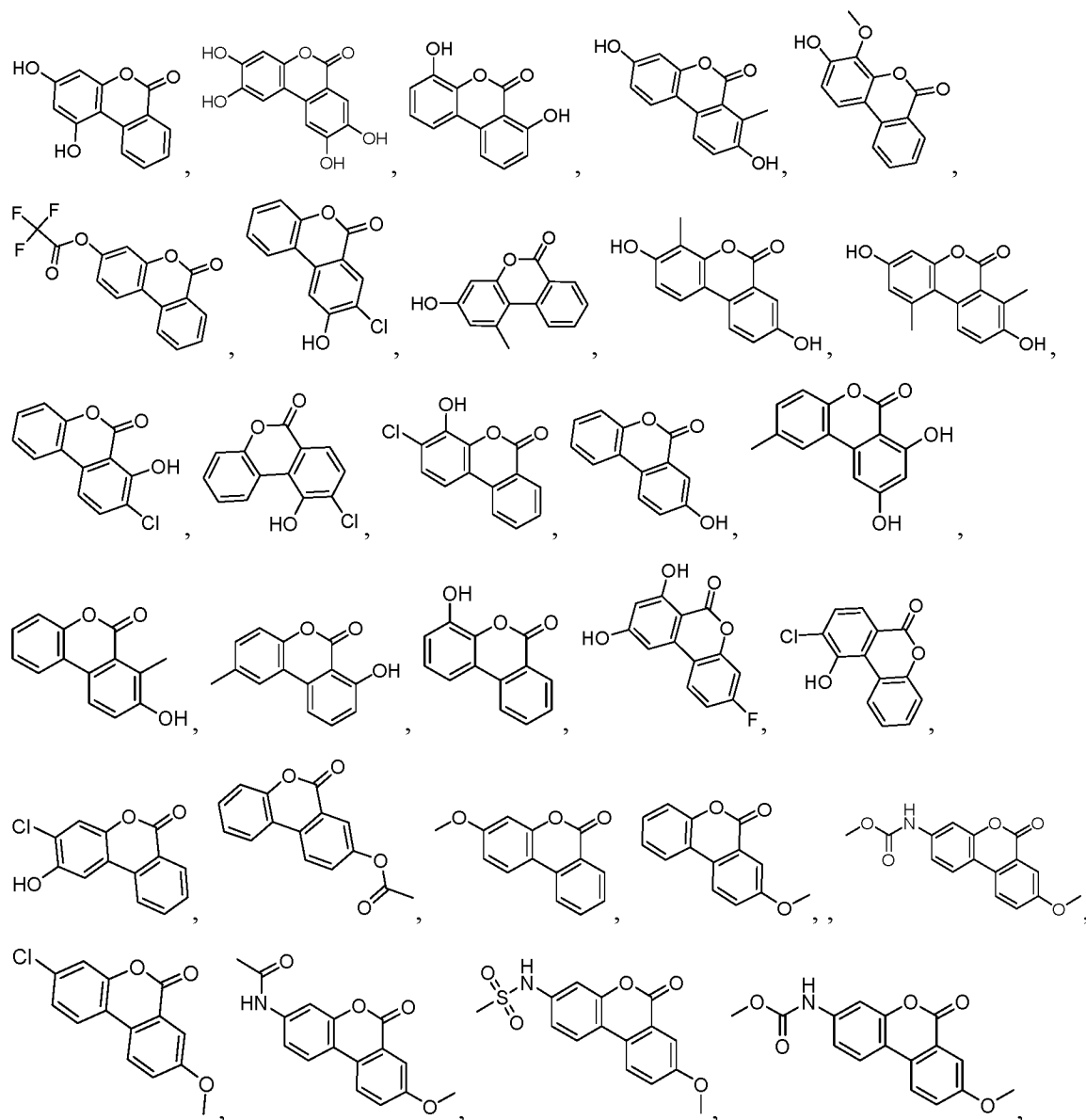
In some embodiments, wherein R_4' and R_5' are each independently $-H$ or $-OH$.

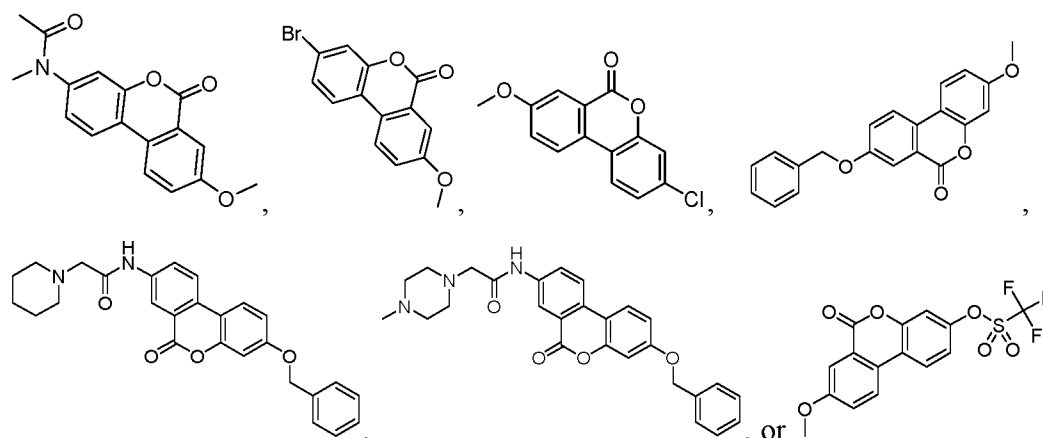
In some embodiments, the compound is selected from:



or a pharmaceutically acceptable salt thereof.

Another aspect of the invention relates to a method of treating amyotrophic lateral sclerosis (ALS), comprising administering to a subject in need thereof an effective amount of a compound having the structure:

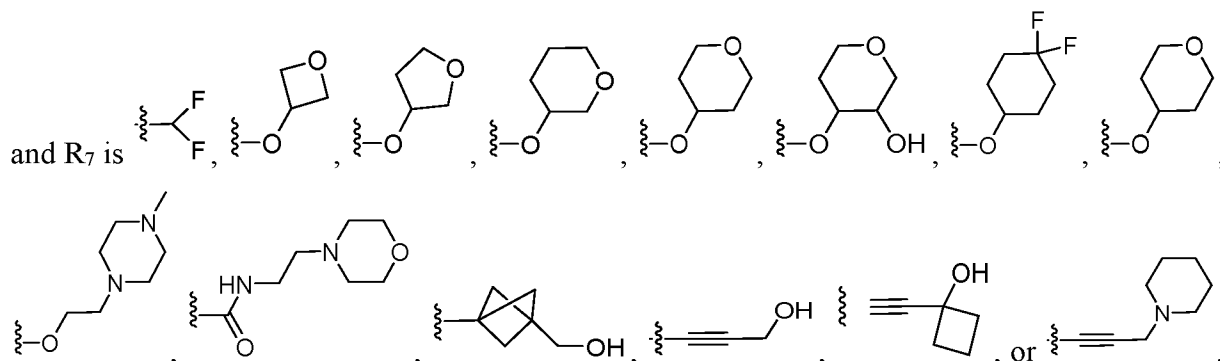




In some embodiments of any of the disclosed methods, the compound wherein R_2 and R_7 are each OH. In other embodiments, R_2 is OH and R_7 is not OH. In other embodiments, R_2 is OH and R_7 is not OCH_3 . In other embodiments, R_2 is OH and R_7 is not H.

In some embodiments of any of the disclosed compounds, R_2 is OH and R_7 is OCH_3 . In other embodiments, R_2 is OH and R_7 is H. In other embodiments, R_2 is OH and R_7 is alkynyl- R_9 . In other embodiments, R_2 is OH and R_7 is OR_{10} . In other embodiments, R_2 is OH and R_7 is OR_{10} .

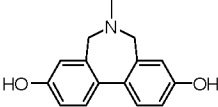
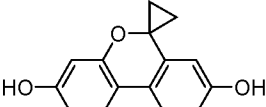
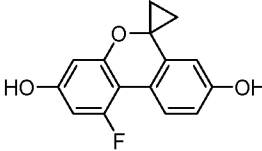
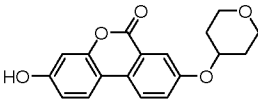
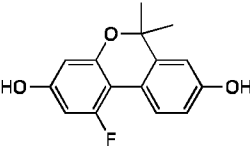
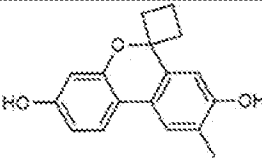
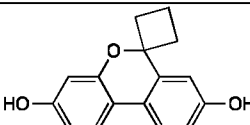
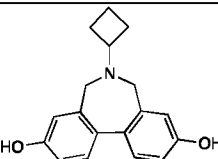
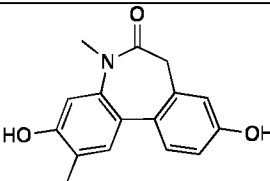
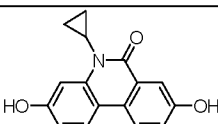
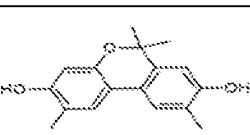
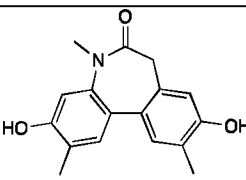
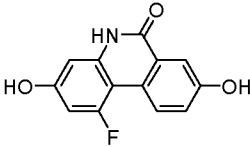
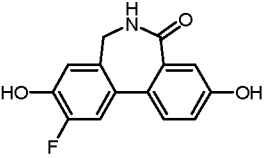
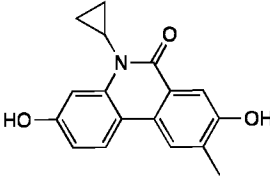
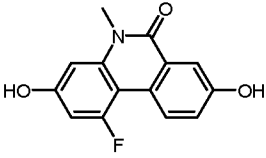
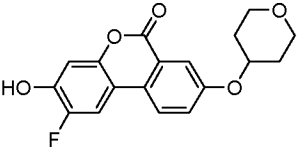
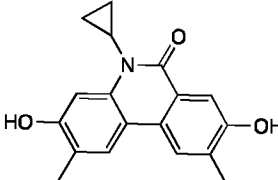
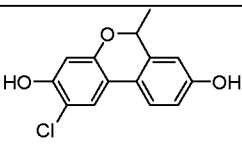
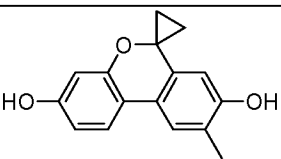
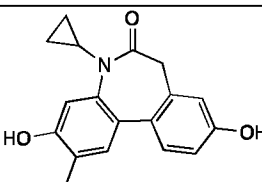
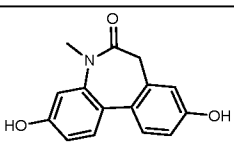
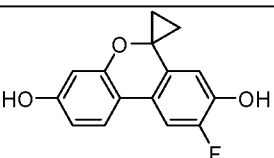
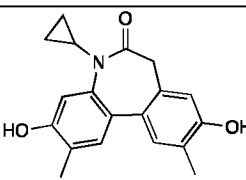
In some embodiments of any of the disclosed methods, the compound wherein R_2 is OH

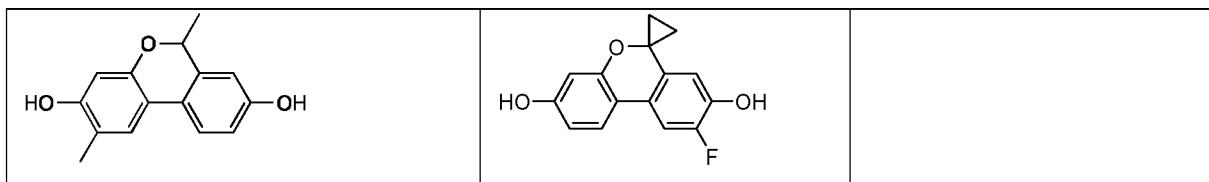


In some embodiments of any of the disclosed methods, the compound administered is selected from Table 1.

Table 1.

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In some embodiments of any of the disclosed methods, the compounds are atropisomers. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds produced by the replacement of a hydrogen with deuterium or tritium, or of a carbon with a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention. For example, in the case of variable R^1 , the $(\text{C}_1\text{-C}_4)\text{alkyl}$ or the $-\text{O}-(\text{C}_1\text{-C}_4)\text{alkyl}$ can be suitably deuterated (*e.g.*, $-\text{CD}_3$, $-\text{OCD}_3$).

Any compound of the invention can also be radiolabeled for the preparation of a radiopharmaceutical agent.

In some embodiments, the amyotrophic lateral sclerosis (ALS) is C9orf72 amyotrophic lateral sclerosis (C9-ALS).

Pharmaceutical Compositions, Routes of Administration, and Dosing

In certain embodiments, the invention is directed to a method of treating amyotrophic lateral sclerosis (ALS), comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition comprising a compound of Formula (Ia), Formula (Ic), Formula (Id), Formula (Ie), Formula (If), or Formula (Ih) and a pharmaceutically acceptable carrier.

In some embodiments, the amyotrophic lateral sclerosis (ALS) is C9orf72 amyotrophic lateral sclerosis (C9-ALS).

In certain embodiments, the pharmaceutical composition comprises a plurality of compounds of the invention and a pharmaceutically acceptable carrier.

In certain embodiments, a pharmaceutical composition of the invention further comprises at least one additional pharmaceutically active agent other than a compound of the invention. The at least one additional pharmaceutically active agent can be an agent useful in the treatment of ischemia-reperfusion injury.

Pharmaceutical compositions of the invention can be prepared by combining one or more compounds of the invention with a pharmaceutically acceptable carrier and, optionally, one or more additional pharmaceutically active agents.

As stated above, an “effective amount” refers to any amount that is sufficient to achieve a desired biological effect. Combined with the teachings provided herein, by choosing among the various active compounds and weighing factors such as potency, relative bioavailability, patient body weight, severity of adverse side-effects and mode of administration, an effective prophylactic or therapeutic treatment regimen can be planned which does not cause substantial unwanted toxicity and yet is effective to treat the particular subject. The effective amount for any particular application can vary depending on such factors as the disease or condition being treated, the particular compound of the invention being administered, the size of the subject, or the severity of the disease or condition. One of ordinary skill in the art can empirically determine the effective amount of a particular compound of the invention and/or other therapeutic agent without necessitating undue experimentation. A maximum dose may be used, that is, the highest safe dose according to some medical judgment. Multiple doses per day may be contemplated to achieve appropriate systemic levels of compounds. Appropriate systemic levels can be determined by, for example, measurement of the patient’s peak or sustained plasma level of the drug. “Dose” and “dosage” are used interchangeably herein.

The formulations of the invention can be administered in pharmaceutically acceptable solutions, which may routinely contain pharmaceutically acceptable concentrations of salt, buffering agents, preservatives, compatible carriers, adjuvants, and optionally other therapeutic ingredients.

Pharmaceutical compositions of the invention contain an effective amount of a compound as described herein and optionally therapeutic agents included in a pharmaceutically acceptable carrier. The term “pharmaceutically acceptable carrier” means one or more compatible solid or liquid filler, diluents or encapsulating substances which are suitable for administration to a human or other vertebrate animal. The term “carrier” denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The components of the pharmaceutical compositions also are capable of being commingled with the compounds of the present invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficiency.

It will be understood by one of ordinary skill in the relevant arts that other suitable modifications and adaptations to the compositions and methods described herein are readily apparent from the description of the invention contained herein in view of information known to the ordinarily skilled artisan, and may be made without departing from the scope of the invention or any embodiment thereof. Having now described the present invention in detail, the same will be more clearly understood by reference to the following examples, which are included herewith for purposes of illustration only and are not intended to be limiting of the invention.

EXAMPLES

The invention is further described in the following examples, which do not limit the scope of the invention described in the claims.

Example 1: Synthesis of representative compounds employed in the method of the invention

All reactions were performed with oven-dried glassware and under an inert atmosphere (nitrogen) unless otherwise stated. All solvents were used as purchased unless otherwise stated. Commercial reagents were used as purchased without further purification. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.

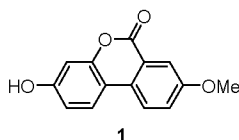
Thin-layer chromatography was carried out using Merck Kieselgel 60 F254 (230–400 mesh) fluorescent treated silica and were visualized under UV light (254 and 366 nm) and/or by staining with aqueous potassium permanganate solution. ¹H NMR spectra were recorded in deuterated solvents on Bruker spectrometer at 400 MHz or Nanalysis NMReady-60PRO spectrometer at 60 MHz, with residual protic solvent as the internal standard. ¹³C NMR spectra were recorded in deuterated solvents on Bruker spectrometer at 100 MHz, with the central peak of the deuterated solvent as the internal standard. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) are given in Hertz (Hz) rounded to the nearest 0.1 Hz. The ¹H NMR spectra are reported as δ /ppm downfield from tetramethylsilane (multiplicity, number of protons, coupling constant J/Hz). The ¹³C NMR spectra are reported as δ /ppm. TLC-MS data was obtained on Advion Expression CMS coupled with Plate Express TLC-plate Reader. Medium pressure liquid chromatography (MPLC) was performed on a Biotage Isolera Four with built-in UV-detector and fraction collector with Interchim silica gel columns.

1. Synthesis of 6-membered Urolithin A analogues

A) Ester “A” group analogues via the Hurtley reaction

General Procedure 1A (GP1a)

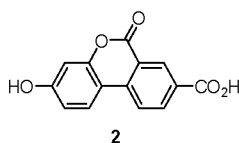
General procedure for cyclisation using NaOH and CuSO₄ (GP1a) using the synthesis of 3-hydroxy-8-methoxy-6H-benzo[c]chromen-6-one (**1**) as a generic example.



A mixture of 2-bromo-5-methoxybenzoic acid (0.500 g, 2.16mmol, 1.0 eq), resorcinol (0.477g, 4.33mmol, 2.0 eq) and sodium hydroxide (0.2g, 4.98mmol, 2.4eq) in water (10 mL) was heated under reflux for 30 minutes. After the addition of copper sulphate (5% aqueous solution, 2.5 mL), the mixture was refluxed again o/n, a precipitate was formed which was filtered off and washed with 1M HCl, then dried under vacuum to afford 3-hydroxy-8-methoxy-6H-benzo[c]chromen-6-one (300mg, 1.24mmol 57%). ¹H NMR (400 MHz, DMSO) δ 8.27 (d, J = 8.9 Hz, 1H), 8.14 (d, J = 8.8 Hz, 1H), 7.67 (d, J = 2.8 Hz, 1H), 7.56 (dd, J = 8.8, 2.9 Hz, 1H), 6.88 (dd, J = 8.7, 2.4 Hz, 1H), 6.80 (d, J = 2.4 Hz, 1H), 3.95 (s, 3H).

General Procedure 1B (GP1b)

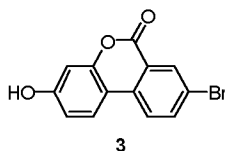
General procedure for cyclisation using Na₂CO₃ and CuI (GP1b) using the synthesis of 3-hydroxy-6-oxo-6H-benzo[c]chromen-8-carboxylic acid (**2**) as a generic example.



Resorcinol (8.9g, 81.6mmol, 2.0 eq) was dissolved in water and sodium carbonate (8.60 g, 81.6mmol, 2.0 eq) was added and the mixture heated to 50 °C until everything had dissolved. Then, the acid (10.00 g, 40.8mmol, 1.0 eq) was added and stirring at 50 °C was continued for 1h. Afterwards, CuI (0.77g, 4.08mmol) was added in one portion and the reaction was stirred o.n. A precipitate was formed which was filtered and washed with 1M HCl twice to get 3-hydroxy-6-oxo-6H-benzo[c]chromene-8-carboxylic acid (4.45g, 17.4mmol, 43%) as a beige solid. ¹H NMR

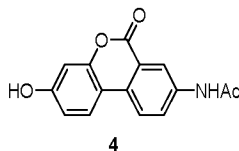
(400 MHz, DMSO) δ 13.31 (s, 1H), 10.52 (s, 1H), 8.65 (s, 1H), 8.35 (d, $J = 5.9$ Hz, 1H), 8.29 (s, 1H), 8.18 (d, $J = 8.7$ Hz, 1H), 6.85 (dd, $J = 8.7, 2.3$ Hz, 1H), 6.75 (d, $J = 2.2$ Hz, 1H).

Synthesis of 8-bromo-3-hydroxy-6H-benzo[c]chromen-6-one (3)



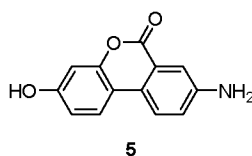
The compound was prepared according to GP1a starting from resorcinol (3.93g, 35.7mmol) and 2,5-dibromobenzoic acid (5.00 g, 17.9mmol) to afford of 8-bromo-3-hydroxy-6H-benzo[c]chromen-6-one (2.14g, 42%) as a brownish solid. ^1H NMR (400 MHz, DMSO) δ 10.44 (s, 1H), 8.21 (d, $J = 2.2$ Hz, 1H), 8.18 (d, $J = 8.8$ Hz, 1H), 8.12 (d, $J = 8.8$ Hz, 1H), 8.01 (dd, $J = 8.7, 2.2$ Hz, 1H), 6.84 (dd, $J = 8.7, 2.4$ Hz, 1H), 6.74 (d, $J = 2.4$ Hz, 1H).

Synthesis of N-(3-hydroxy-6-oxo-6H-benzo[c]chromen-8-yl)acetamide (4)

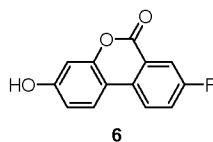


The compound was prepared according to GP1b starting from resorcinol (1.40, 12.8mmol) and 5-acetamido-2-bromobenzoic acid (1.00 g, 3.87mmol) to afford N-(3-hydroxy-6-oxo-6H-benzo[c]chromen-8-yl)acetamide (620 mg, 29%) as a beige solid. ^1H NMR (400 MHz, DMSO) δ 10.32 (s, 1H), 10.27 (s, 1H), 8.50 (d, $J = 2.2$ Hz, 1H), 8.20 (d, $J = 8.8$ Hz, 1H), 8.07 (d, $J = 8.7$ Hz, 1H), 7.99 (dd, $J = 8.8, 2.3$ Hz, 1H), 6.83 (dd, $J = 8.7, 2.4$ Hz, 1H), 6.74 (d, $J = 2.3$ Hz, 1H), 2.10 (s, 3H).

Deprotection of 4 afforded 8-amino-3-hydroxy-6H-benzo[c]chromen-6-one (5)



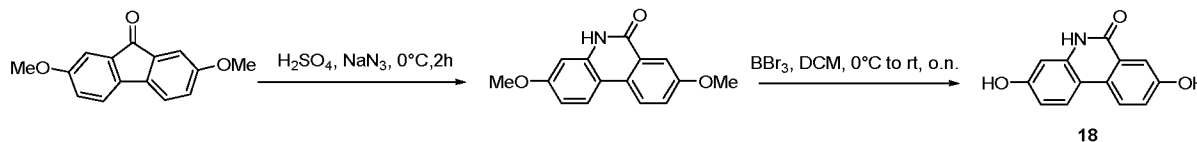
Synthesis of 8-fluoro-3-hydroxy-6H-benzo[c]chromen-6-one (6)



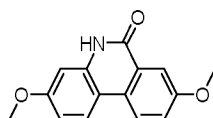
The compound was prepared according to GP1a starting from resorcinol (2.01 g, 18.3 mmol) and 2-bromo-5-fluorobenzoic acid (2.00 g, 9.13 mmol) to afford of 8-fluoro-3-hydroxy-6H-benzo[c]chromen-6-one (1.00 g, 48%) as a brownish solid. ^1H NMR (400 MHz, DMSO) δ 10.54 (s, 1H), 8.31 (d, J = 2.2 Hz, 1H), 8.28 (d, J = 8.8 Hz, 1H), 8.32 (d, J = 8.8 Hz, 1H), 8.21 (dd, J = 8.7, 2.2 Hz, 1H), 7.04 (dd, J = 8.7, 2.4 Hz, 1H), 6.94 (d, J = 2.4 Hz, 1H).

B) Amide “A” group analogues

Synthesis of 3,8-dihydroxyphenanthridin-6(5H)-one (**18**)

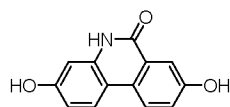


Step 1: Synthesis of 3,8-dimethoxyphenanthridin-6(5H)-one



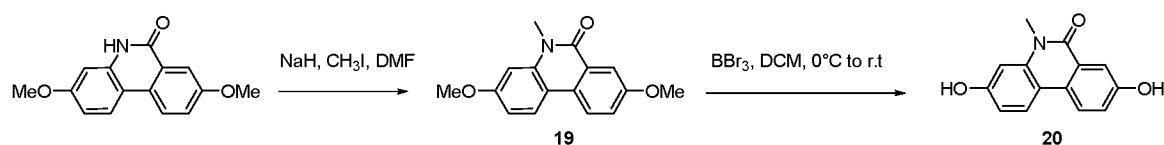
To cold sulfuric acid (10 mL) was added at 0 °C 2,7-dimethoxy-9H-fluoren-9-one (1.10 g, 4.57 mmol), and then carefully sodium azide (387 mg, 5.95 mmol). The reaction mixture was stirred at 0 °C for 3 h. EtOAc (10 mL) was added and the mixture was poured into ice water and stirred for 1 h. The brownish precipitate was filtered and the aqueous phase was extracted with EtOAc 3 times. The organic phase was dried over sodium sulfate and evaporated under vacuum. The crude was purified by MPLC (SiO_2 , EtOAc/cyclohexane from 0% to 80%) to afford 3,8-dimethoxyphenanthridin-6(5H)-one (150 mg, 13%) as a brown solid. R_f = 0.4 (EtOAc /hexane 50%). ^1H NMR (400 MHz, DMSO) δ 11.60 (s, 1H), 8.32 (d, J = 8.9 Hz, 1H), 8.20 (d, J = 8.7 Hz, 1H), 7.70 (d, J = 2.8 Hz, 1H), 7.40 (dd, J = 8.9, 2.9 Hz, 1H), 6.91 – 6.81 (m, 2H), 3.89 (s, 3H), 3.81 (s, 3H).

Step 2: Synthesis of 3,8-dihydroxyphenanthridin-6(5H)-one

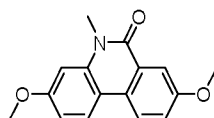


18 was prepared according to GP2 from 3,8-dimethoxyphenanthridin-6(5H)-one (90mg, 0.35mmol) and BBr_3 (1M in THF, 2.10ml, 2.10 mmol) to afford after purification by MPLC (SiO_2 , MeOH/DCM 0% to 10%) 3,8-dihydroxyphenanthridin-6(5H)-one (70mg, 87%) as a brownish solid. $R_f = 0.2$ (MeOH in DCM 10%). ^1H NMR (400 MHz, DMSO) δ 11.91 – 11.20 (m, 1H), 10.34 – 9.57 (m, 2H), 8.08 (d, $J = 49.2$ Hz, 2H), 7.82 – 7.48 (m, 1H), 7.23 (s, 1H), 6.70 (d, $J = 27.5$ Hz, 2H).

Synthesis of 3,8-dihydroxy-5-methylphenanthridin-6(5H)-one (**20**)

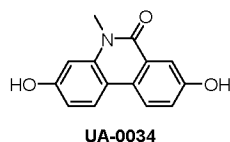


Step 1: Synthesis of 3,8-dimethoxy-5-methylphenanthridin-6(5H)-one (**19**)



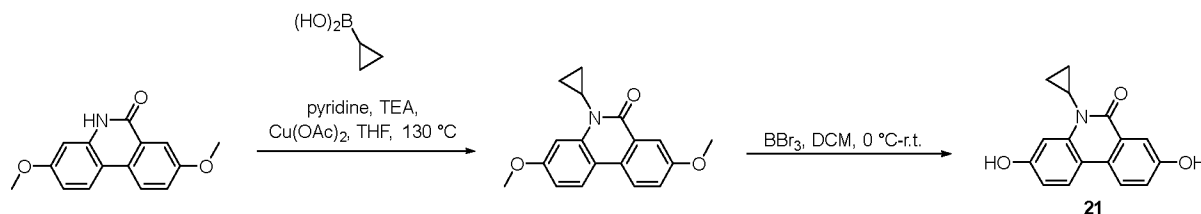
NaH (60 % mineral oil dispersion, 59mg, 1.5mmol) was added to a solution of 3,8-dimethoxyphenanthridin-6(5H)-one (250mg, 0.98mmol) in DMF (10 mL) at 0°C and the mixture was stirred for 30 min at 0°C . Then, MeI (0.122ml, 1.96mmol) was added and stirring continued at rt for 2h. The reaction mixture was poured into a sat. aq. Solution of NH_4Cl and extracted with EtOAc 3 times. The combined organic phases were dried over sodium sulfate and concentrated under vacuum. The crude product was purified by MPLC (SiO_2 , EtOAc/cyclohexane 0% to 40%) to afford 3,8-dimethoxy-5-methylphenanthridin-6(5H)-one (176mg, 67%). $R_f = 0.3$ eluent (EtOAc/hexane 50%). ^1H NMR (400 MHz, CDCl_3) δ 8.10 (dd, $J = 9.2, 8.0$ Hz, 2H), 7.93 (d, $J = 2.8$ Hz, 1H), 7.32 (dd, $J = 8.9, 2.9$ Hz, 1H), 6.93 – 6.86 (m, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 3.80 (s, 3H).

Step 2: Synthesis of 3,8-dihydroxy-5-methylphenanthridin-6(5H)-one (**20**)

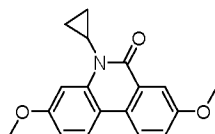


20 was prepared according to GP2 starting from 3,8-dimethoxy-5-methylphenanthridin-6(5H)-one (150mg, 0.550mmol) to afford after purification by MPLC (SiO₂, MeOH/DCM 0% to 10%) 3,8-dihydroxy-5-methylphenanthridin-6(5H)-one (120mg, 89%) as a beige solid. R_f = 0.8 (MeOH/DCM 10/90). ¹H NMR (400 MHz, DMSO) δ 9.92 (s, 2H), 8.18 (d, J = 8.9 Hz, 1H), 8.13 (d, J = 8.8 Hz, 1H), 7.64 (d, J = 2.7 Hz, 1H), 7.22 (dd, J = 8.8, 2.7 Hz, 1H), 6.85 (d, J = 2.3 Hz, 1H), 6.77 (dd, J = 8.7, 2.3 Hz, 1H), 3.63 (s, 3H).

Synthesis of 5-cyclopropyl-3,8-dihydroxyphenanthridin-6(5H)-one (**21**)

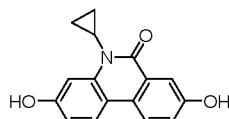


Step 1: Synthesis of 5-cyclopropyl-3,8-dimethoxyphenanthridin-6(5H)-one

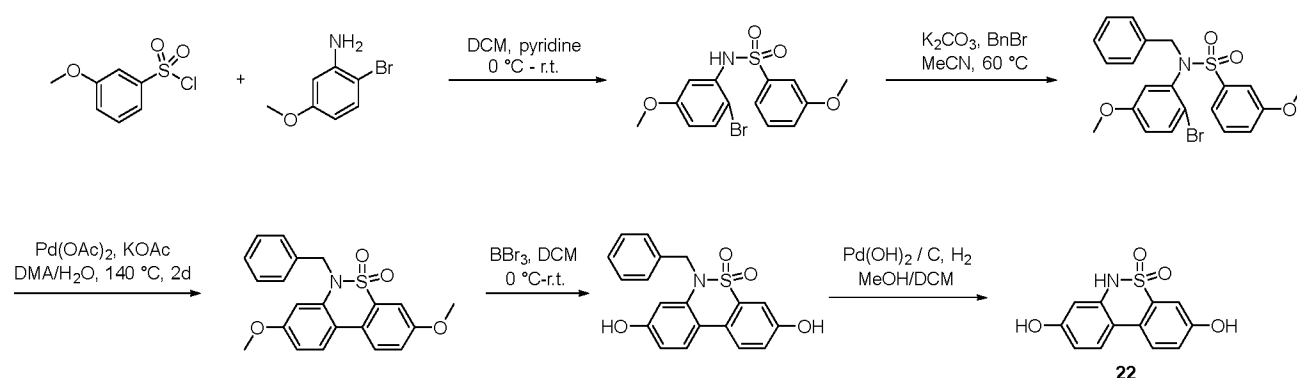


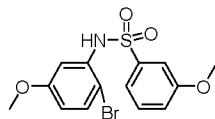
A microwave vial was charged with 3,8-dimethoxyphenanthridin-6(5H)-one (120mg, 0.470 mmol, 1.0 eq.), cyclopropylboronic acid (121mg, 1.41mmol, 3.0 eq.), pyridine (355mg, 4.23mmol, 9.0 eq.), triethylamine (285mg, 2.82mmol, 6.0 eq.) and THF (2.0 mL) and the resulting mixture was degassed with a N₂ balloon for 10min at r.t.. Then, Cu(OAc)₂ (171mg, 0.940 mmol, 2.0 eq.) was added in one portion and the vial was closed and put into a preheated 130 °C oil-bath for 2h. Upon complete consumption of the starting material the reaction was allowed to cool to r.t., and subsequently quenched with water, extracted with EtOAc, dried over Na₂SO₄, and concentrated under vacuum. The crude product was purified by MPLC (SiO₂, 25g, EtOAc in Hex 0-50 %) to afford 5-cyclopropyl-3,8-dimethoxyphenanthridin-6(5H)-one (50mg, 36%) as a brown solid.

¹H NMR (400 MHz, CDCl₃) δ 8.02 (dd, J = 8.9, 2.1 Hz, 2H), 7.87 (d, J = 2.8 Hz, 1H), 7.39 (d, J = 2.5 Hz, 1H), 7.29 (dd, J = 8.9, 2.8 Hz, 1H), 6.87 (dd, J = 8.8, 2.5 Hz, 1H), 3.93 (d, J = 3.2 Hz, 6H), 3.05 – 2.99 (m, 1H), 1.45 – 1.36 (m, 2H), 0.97 – 0.90 (m, 2H).

Step 2: Synthesis of 5-cyclopropyl-3,8-dihydroxyphenanthridin-6(5H)-one

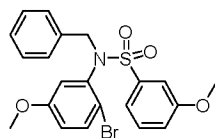
5-cyclopropyl-3,8-dimethoxyphenanthridin-6(5H)-one (20mg, 0.070 mmol, 1.0eq.) was dissolved in DCM (1mL) and cooled down to 0 °C in an ice-bath and stirring was continued for 5min. Then, BBr₃ (0.20ml, 1M in DCM, 0.020 mmol, 3.0 eq.) was added dropwise to the reaction mixture. Upon complete addition the mixture was left in the ice bath and was allowed to warm to r.t. over the course of 2h. When no more starting material could be observed (TLC), the reaction mixture was dropwise added into 0 °C cold methanol (10 mL) and stirred for an additional 10min. Then, the mixture was concentrated and loaded on silica to be purified by MPLC (SiO₂, 12 g, MeOH in DCM 0-5%) to afford 5-cyclopropyl-3,8-dihydroxyphenanthridin-6(5H)-one (13mg, 0.050 mmol, 71%) as white solid. MS (ESI⁺): m/z = 268. ¹H NMR (400 MHz, DMSO) δ 9.86 (d, J = 9.3 Hz, 2H), 8.12 (d, J = 8.9 Hz, 1H), 8.06 (d, J = 8.8 Hz, 1H), 7.57 (d, J = 2.7 Hz, 1H), 7.27 (d, J = 2.3 Hz, 1H), 7.18 (dd, J = 8.7, 2.8 Hz, 1H), 6.73 (dd, J = 8.7, 2.3 Hz, 1H), 2.94 (dt, J = 7.0, 3.1 Hz, 1H), 1.35 – 1.18 (m, 2H), 0.74 (p, J = 5.4, 5.0 Hz, 2H).

C) Sulfonamide “A” group analogues**Synthesis of 3,8-dihydroxy-6H-dibenzo[c,e][1,2]thiazine 5,5-dioxide (22)****Step 1:** Synthesis of *N*-(2-bromo-5-methoxyphenyl)-3-methoxybenzenesulfonamide



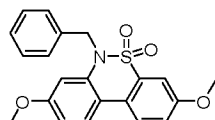
3-methoxybenzenesulfonyl chloride (2.00 g, 9.68 mmol, 1.3 eq.) was slowly added to a solution of 2-bromo-5-methoxyaniline (1.79 g, 8.81 mmol, 1.0 eq.) and pyridine (2.79 g, 35.2 mmol, 4.0 eq.) in DCM (20 mL) at 0 °C. Upon warming up to r.t. no more starting material could be observed by TLC, and the reaction mixture was concentrated under vacuum. The reaction mixture was diluted with EtOAc and washed with 1N aqueous HCl. The organic phase was dried over Na₂SO₄ and concentrated in vacuum to afford *N*-(2-bromo-5-methoxyphenyl)-3-methoxybenzenesulfonamide (3.28g, 99%) as a brown oil. ¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.21 (m, 4H), 7.07 (ddd, *J* = 7.7, 2.5, 1.5 Hz, 1H), 6.94 (s, 1H), 6.55 (dd, *J* = 8.9, 3.0 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H).

Step 2: Synthesis of *N*-benzyl-*N*-(2-bromo-5-methoxyphenyl)-3-methoxybenzenesulfonamide



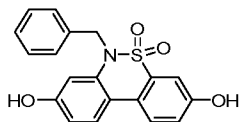
N-(2-bromo-5-methoxyphenyl)-3-methoxybenzenesulfonamide (5.90 g, 18.9 mmol, 1.0 eq.) was dissolved in MeCN (53mL) and K₂CO₃ (6.57g, 47.6mmol, 3.0 eq.) was added in one portion. At r.t. benzyl bromide (2.98g, 17.4mmol, 1.1 eq.) was added dropwise and upon complete addition the reaction mixture was heated to 60 °C in an oil bath for 3h. After complete consumption of the starting material (as indicated by TLC) the reaction mixture was allowed to cool down to r.t. and filtered. The filtrate was concentrated under vacuum and loaded on silica to be purified by MPLC (SiO₂, 240 g, EtOAc in Hex 0 -10%) to afford *N*-benzyl-*N*-(2-bromo-5-methoxyphenyl)-3-methoxybenzenesulfonamide (6.83g, 93%) as a light brown solid. ¹H NMR (400 MHz, CDCl₃) δ 7.42 – 7.34 (m, 3H), 7.28 – 7.18 (m, 6H), 7.15 – 7.10 (m, 1H), 6.69 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.48 (d, *J* = 3.0 Hz, 1H), 4.89 (d, *J* = 14.4 Hz, 1H), 4.66 (d, *J* = 14.3 Hz, 1H), 3.79 (s, 3H), 3.59 (s, 3H).

Step 3: Synthesis of 6-benzyl-3,8-dimethoxy-6H-dibenzo[*c,e*][1,2]thiazine 5,5-dioxide



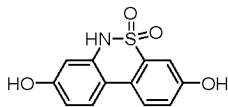
N-benzyl-*N*-(2-bromo-5-methoxyphenyl)-3-methoxybenzenesulfonamide (2.00 g, 4.33 mmol, 1.0 eq.) was dissolved in a mixture of DMA (20 mL) and water (5mL) and thereupon were added Pd(OAc)₂ (291 mg, 1.30 mmol, 0.3 eq.) and KOAc (1.69g, 17.3mmol, 4.0 eq.). Upon complete dissolution of the reagents, the flask was put into a 140 °C oil bath and stirring was continued over a period of 48h. Afterwards the reaction mixture was concentrated to complete dryness using a rotary evaporator at 90 °C. The reaction mixture was loaded on silica and purified by MPLC (SiO₂, 80 g, EtOAc in Hex 0-15%) to afford 6-benzyl-3,8-dimethoxy-6H-dibenzo[*c,e*][1,2]thiazine 5,5-dioxide (560mg, 34%) as a white solid. ¹H NMR (400 MHz, DMSO) δ 8.00 (t, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 2.7 Hz, 1H), 7.34 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.25 – 7.09 (m, 5H), 6.95 (d, *J* = 2.5 Hz, 1H), 6.91 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.16 (s, 2H), 3.91 (s, 3H), 3.75 (s, 3H).

Step 4: Synthesis of 6-benzyl-3,8-dihydroxy-6H-dibenzo[*c,e*][1,2]thiazine 5,5-dioxide



6-benzyl-3,8-dimethoxy-6H-dibenzo[*c,e*][1,2]thiazine 5,5-dioxide (180mg, 0.470 mmol, 1.0 eq.) was dissolved in DCM (2mL) and cooled down to 0 °C in an ice-bath and stirring was continued for 5min. Then, BBr₃ (1.89ml, 1M in DCM, 1.88mmol, 4.0 eq.) was added dropwise to the reaction mixture. Upon complete addition the mixture was left in the ice bath and was allowed to warm to r.t. over the course of 2h. When no more starting material could be observed (TLC), the reaction mixture was dropwise added into 0 °C cold methanol (20 mL) and stirred for an additional 10min. Then, the mixture was concentrated, loaded on silica, and purified by MPLC (SiO₂, 20 g, MeOH in DCM 0-3%) to afford 6-benzyl-3,8-dihydroxy-6H-dibenzo[*c,e*][1,2]thiazine 5,5-dioxide (100mg, 60%) as a light yellow solid. ¹H NMR (400 MHz, DMSO) δ 10.33 (s, 1H), 9.94 (s, 1H), 7.90 – 7.80 (m, 2H), 7.39 – 7.09 (m, 7H), 6.83 – 6.62 (m, 2H), 5.04 (s, 2H).

Step 5: Synthesis of 3,8-dihydroxy-6H-dibenzo[*c,e*][1,2]thiazine 5,5-dioxide

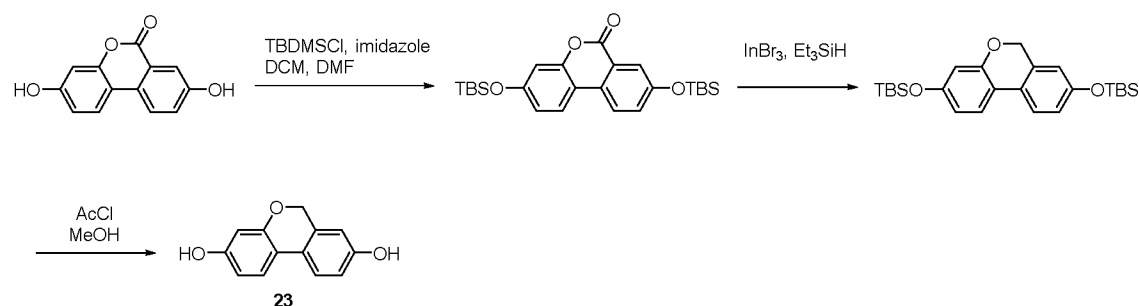


6-benzyl-3,8-dihydroxy-6H-dibenzo[*c,e*][1,2]thiazine 5,5-dioxide (100mg, 0.370 mmol, 1.0 eq.) was dissolved in MeOH (10 mL) and Pd(OH)₂/C (26mg) was added in one portion. Then, the

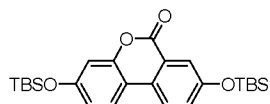
reaction mixture was evacuated and backfilled with N₂ three times before putting it under hydrogen atmosphere (balloon). The reaction mixture was stirred for 4h and upon complete consumption of starting material (as indicated by TLC) filtered over silica and concentrated under vacuum. The crude product was loaded on silica, and purified by MPLC (SiO₂, 12g, EtOAc in Hex 0-50 %) to give 3,8-dihydroxy-6H-dibenzo[c,e][1,2]thiazine 5,5-dioxide (65mg, 67%) as a white solid. ¹H NMR (400 MHz, DMSO) δ 10.24 (s, 1H), 9.87 (s, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.83 (d, J = 8.5 Hz, 1H), 7.17 (d, J = 2.6 Hz, 1H), 7.11 (dd, J = 8.7, 2.6 Hz, 1H), 6.64 (dd, J = 8.7, 2.5 Hz, 1H), 6.55 (d, J = 2.5 Hz, 1H).

D) Ether “A” group analogues

Synthesis of 6H-benzo[c]chromene-3,8-diol (**23**)

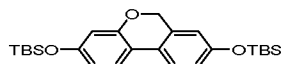


Step 1: Synthesis of 3,8-bis((*tert*-butyldimethylsilyl)oxy)-6H-benzo[c]chromen-6-one



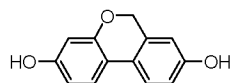
Urolithin A (12g 53 mmol) was added to a solution of imidazole (9.0 g, 0.13mol) in DCM (100 mL) and stirred for 1 h. No reaction took place, therefore DMF (20 mL) was added and stirring continued overnight. DCM was removed in vacuum. Water was added and the mixture was extracted with Et₂O (3*), the organic layers were washed successively with water twice and brine, dried with Na₂SO₄, filtered over silica and concentrated. The crude product was purified by MPLC (SiO₂, EtOAc/Cyclohexane 0 to 20%) to afford 3,8-bis((*tert*-butyldimethylsilyl)oxy)-6H-benzo[c]chromen-6-one (20 g, 96%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.89 (d, J = 8.8 Hz, 1H), 7.85 – 7.80 (m, 1H), 7.76 (d, J = 2.6 Hz, 1H), 7.29 (dd, J = 8.7, 2.7 Hz, 1H), 6.86 – 6.80 (m, 2H), 1.02 (s, 9H), 0.98 (s, 9H), 0.26 (s, 6H), 0.24 (s, 6H).

Step 2: Synthesis of ((6H-benzo[c]chromene-3,8-diyl)bis(oxy))bis(*tert*-butyldimethylsilane)



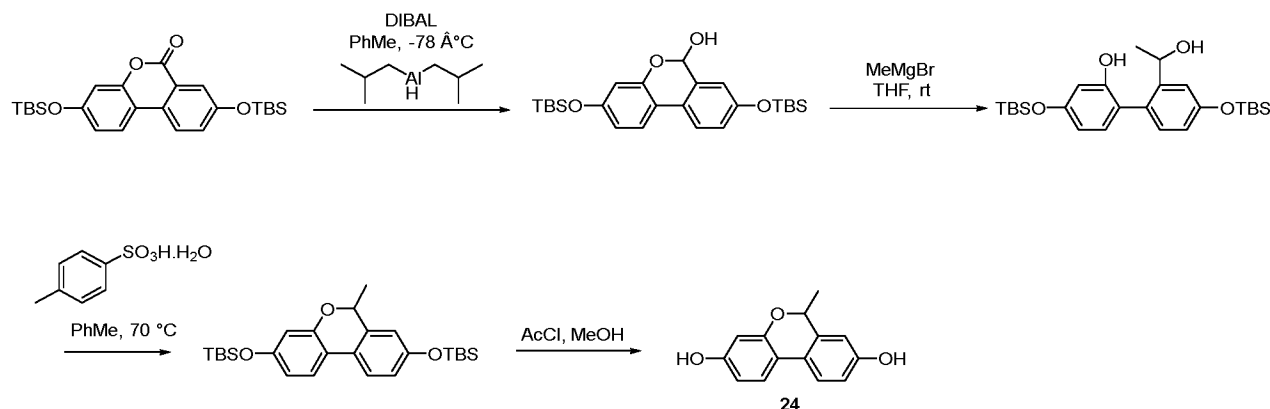
InBr₃ (142mg, 0.400 mmol) was added to a solution of 3,8-bis((*tert*-butyldimethylsilyl)oxy)-6H-benzo[c]chromen-6-one (1.8g, 4.0 mmol) in toluene (20 mL) and the reaction mixture was heated at 70 °C for 1 hour. The reaction mixture was cooled down to room temperature and filtered. The solvent was evaporated under vacuum and the crude was purified by MPLC (SiO₂, cyclohexane/dichloromethane from 0% to 10%) to afford ((6H-benzo[c]chromene-3,8-diyl)bis(oxy))bis(*tert*-butyldimethylsilane), 81mg, 88%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.48 (t, *J* = 8.5 Hz, 2H), 6.81 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.60 (d, *J* = 2.4 Hz, 1H), 6.53 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.47 (d, *J* = 2.4 Hz, 1H), 5.02 (s, 2H), 1.00 (s, 9H), 0.98 (s, 9H), 0.22 (s, 6H), 0.20 (s, 6H).

Step 3: Synthesis of 6H-benzo[c]chromene-3,8-diol

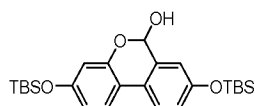


Acetyl chloride (0.105ml, 1.40mmol) was added to a solution of ((6H-benzo[c]chromene-3,8-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) (421mg, 0.950mmol) in methanol (10 mL) at room temperature and stirred overnight. The reaction mixture was concentrated under vacuum and purified by MPLC (SiO₂, EtOAc in Hex 0-100%) to afford 6H-benzo[c]chromene-3,8-diol (203mg, 0.950 mmol, 99%) as a white solid. ¹H NMR (400 MHz, DMSO) δ 9.50 (s, 1H), 9.48 (s, 1H), 7.49 (dd, *J* = 12.5, 8.4 Hz, 2H), 6.74 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.60 (d, *J* = 2.5 Hz, 1H), 6.45 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.32 (d, *J* = 2.4 Hz, 1H), 4.96 (s, 2H).

Synthesis of 6-methyl-6H-benzo[c]chromene-3,8-diol (24)

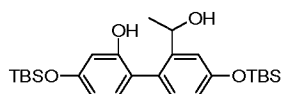


Step 1: Synthesis of 3,8-bis((tert-butyldimethylsilyl)oxy)-6H-benzo[c]chromen-6-ol



DIBAL-H (2.10 mL, 2.10 mmol) was added slowly along the side of the flask to a solution of 3,8-bis((*tert*-butyldimethylsilyl)oxy)-6H-benzo[c]chromen-6-one (912mg, 2.00mmol) in toluene (20 mL) under nitrogen at -78 °C. The reaction was monitored by TLC eluent (Cyclohexane/DCM 1:1). The reaction was complete within 1 hour stirring. After a Fieser work-up the product was used in the step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.60 (dd, *J* = 8.9, 6.9 Hz, 2H), 6.93 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.83 (d, *J* = 2.6 Hz, 1H), 6.62 – 6.58 (m, 2H), 6.26 (s, 1H), 1.00 (s, 9H), 0.98 (s, 9H), 0.25 – 0.18 (m, 12H).

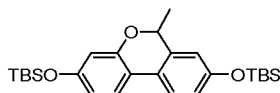
Step 2: Synthesis of 4,4'-bis((tert-butyldimethylsilyl)oxy)-2'-(1-hydroxyethyl)-[1,1'-biphenyl]-2-ol



To a solution of 3,8-bis((*tert*-butyldimethylsilyl)oxy)-6H-benzo[c]chromen-6-ol (456mg, 1.00 mmol, 1.0 eq.) in anhydrous THF (10 mL) was slowly added at 0 °C MeMgBr (3M in Et₂O, 1.0 mL, 3.0 mmol, 3.0 eq.) under a nitrogen atmosphere. The reaction was complete within 1 hour. The reaction mixture was diluted with ether, filtered over a pad of silica, with ether washings, and concentrated to afford the title product as a thick colourless oily 60:40 mixture of rota/diastereomers (474 mg, quant.), which was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.15 (d, *J* = 2.6 Hz, 0.4H), 7.12 (d, *J* = 2.6 Hz, 0.6H), 7.07 (s, 0.4H), 7.04 (s, 0.6H), 6.96

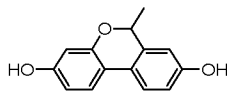
(d, $J = 8.1$ Hz, 0.4H), 6.90 (d, $J = 8.5$ Hz, 0.6H), 6.86 – 6.78 (m, 1H), 6.52 – 6.43 (m, 2H), 4.79 (q, $J = 6.4$ Hz, 0.4H), 4.73 (q, $J = 6.5$ Hz, 0.6H), 1.36 (d, $J = 6.4$ Hz, 1.2H), 1.30 (d, $J = 6.4$ Hz, 1.8H), 1.01 (s, 7.2H), 1.00 (s, 10.8H), 0.25 (s, 4.8H), 0.24 (s, 7.2H).

Step 3: ((6-methyl-6H-benzo[c]chromene-3,8-diyl)bis(oxy))bis(*tert*-butyldimethylsilane)



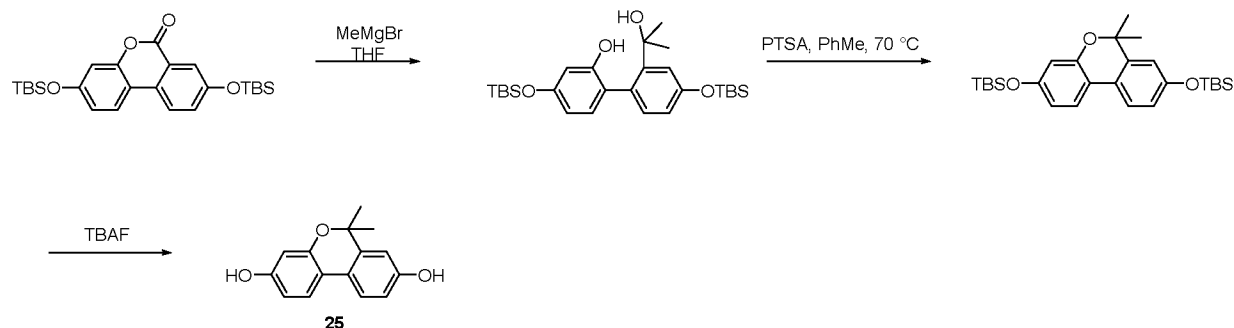
A solution of 4-methylbenzenesulfonic acid hydrate (19mg, 0.19mmol) and 4,4'-bis((*tert*-butyldimethylsilyl)oxy)-2'-(1-hydroxyethyl)-[1,1'-biphenyl]-2-ol (474mg, 1.00mmol) in toluene (10 mL) was heated at 80 °C overnight. TLC (Cyclohexane/dichlorometahne 9:1) showed no more starting material. The reaction mixture was concentrated under vacuum and purified by column (SiO₂, CyH/DCM) to afford ((6-methyl-6H-benzo[c]chromene-3,8-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) (411mg, 90%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.48 (dd, $J = 8.5, 4.1$ Hz, 2H), 6.80 (dd, $J = 8.4, 2.5$ Hz, 1H), 6.61 (dd, $J = 2.4, 0.8$ Hz, 1H), 6.52 (dd, $J = 8.4, 2.4$ Hz, 1H), 6.47 (d, $J = 2.4$ Hz, 1H), 5.17 (q, $J = 6.5$ Hz, 1H), 1.00 (s, 9H), 0.98 (s, 9H) 0.92 – 0.84 (m, 3H), 0.21 (s, 6H), 0.20 (s, 6H).

Step 4: 6-methyl-6H-benzo[c]chromene-3,8-diol

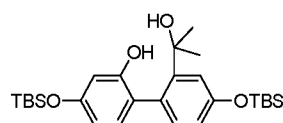


Acetylchloride (0.100ml, 1.40mmol) was added to a solution of ((6H-benzo[c]chromene-3,8-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) (411mg, 0.900mmol) in methanol (10 mL) at room temperature and stirred overnight. The reaction mixture was concentrated under vacuum and purified by MPLC (SiO₂, EtOAc in Hex 0-100%) to afford the 6-methyl-6H-benzo[c]chromene-3,8-diol (202mg, 98%) as a white solid. ¹H NMR (400 MHz, DMSO) δ 9.47 (s, 1H), 9.45 (s, 1H), 7.49 (t, $J = 8.7$ Hz, 2H), 6.73 (dd, $J = 8.4, 2.5$ Hz, 1H), 6.60 (d, $J = 2.4$ Hz, 1H), 6.43 (dd, $J = 8.4, 2.4$ Hz, 1H), 6.30 (d, $J = 2.4$ Hz, 1H), 5.14 (q, $J = 6.5$ Hz, 1H), 1.44 (d, $J = 6.5$ Hz, 3H).

Synthesis of 6,6-dimethyl-6H-benzo[c]chromene-3,8-diol (25)

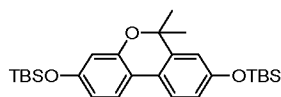


Step 1: Synthesis of 4,4'-bis((*tert*-butyldimethylsilyl)oxy)-2'-(2-hydroxypropan-2-yl)-[1,1'-biphenyl]-2-ol



To a solution of 3,8-bis((*tert*-butyldimethylsilyl)oxy)-6H-benzo[c]chromen-6-one (456mg, 1.00 mmol, 1.0 eq.) in anhydrous THF (10 mL) was slowly added at 0 °C MeMgBr (3M in Et₂O, 1.00 mL, 3.00 mmol, 3.0 eq.) under a nitrogen atmosphere. The reaction was complete within 1 hour. The reaction mixture was diluted with ether, filtered over a pad of silica, with ether washings, and concentrated to afford the synthesis of 4,4'-bis((*tert*-butyldimethylsilyl)oxy)-2'-(2-hydroxypropan-2-yl)-[1,1'-biphenyl]-2-ol as a thick colourless oil (489 mg, quant.), which was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.13 (d, *J* = 2.5 Hz, 1H), 6.96 (d, *J* = 1.0 Hz, 1H), 6.94 (d, *J* = 1.1 Hz, 1H), 6.76 (dd, *J* = 8.2, 2.6 Hz, 1H), 6.49 (d, *J* = 2.4 Hz, 1H), 6.45 (dd, *J* = 8.2, 2.4 Hz, 1H), 1.52 (s, 3H), 1.40 (s, 3H), 1.01 (s, 9H), 1.00 (s, 9H), 0.25 (s, 6H), 0.23 (s, 6H).

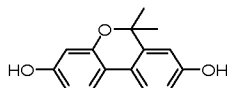
Step 2: Synthesis of ((6,6-dimethyl-6H-benzo[c]chromene-3,8-diyl)bis(oxy))bis(*tert*-butyldimethylsilane)



A solution of 4-methylbenzenesulfonic acid hydrate (19mg, 0.19mmol) and 4,4'-bis((*tert*-butyldimethylsilyl)oxy)-2'-(1-hydroxyethyl)-[1,1'-biphenyl]-2-ol (489mg, 1.00mmol) in toluene (10 mL) was heated at 80 °C overnight. TLC (Cyclohexane/dichloromethane 9:1) showed no more starting material. The reaction mixture was concentrated under vacuum and purified by MPLC

(SiO₂, CyH/DCM) to afford ((6-methyl-6H-benzo[c]chromene-3,8-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) (446mg, 95%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.49 (dd, J = 8.5, 3.4 Hz, 2H), 6.79 (dd, J = 8.4, 2.4 Hz, 1H), 6.69 (d, J = 2.4 Hz, 1H), 6.50 (dd, J = 8.4, 2.4 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H), 1.58 (s, 6H), 1.00 (s, 9H), 0.99 (s, 9H), 0.22 (s, 6H), 0.21 (s, 6H).

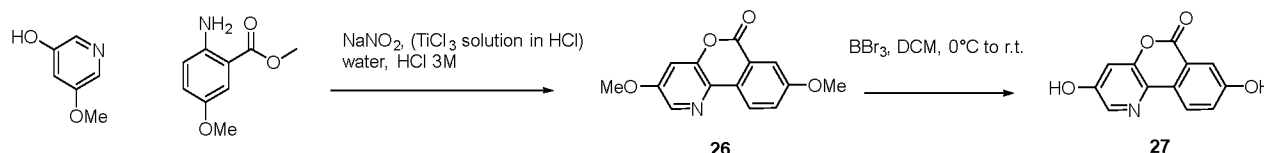
Step 3: Synthesis 6,6-dimethyl-6H-benzo[c]chromene-3,8-diol



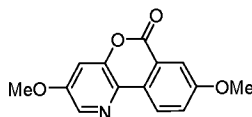
Acetyl chloride (0.100 mL, 1.40mmol) was added to a solution of 4,4'-bis((*tert*-butyldimethylsilyl)oxy)-2'-(2-hydroxypropan-2-yl)-[1,1'-biphenyl]-2-ol (446mg, 0.900mmol) in methanol (10 mL) at room temperature and the solution was stirred overnight. The reaction mixture was concentrated under vacuum and the residue purified by MPLC (SiO₂, EtOAc in Hex 0-100%) to afford the 6,6-dimethyl-6H-benzo[c]chromene-3,8-diol (228 mg, 98%) as a white solid. MS (ESI+): m/z = 243. ¹H NMR (400 MHz, DMSO) δ 9.44 (s, 1H), 9.42 (s, 1H), 7.49 (dd, J = 8.5, 4.2 Hz, 2H), 6.72 (dd, J = 8.4, 2.5 Hz, 1H), 6.67 (d, J = 2.4 Hz, 1H), 6.40 (dd, J = 8.4, 2.4 Hz, 1H), 6.26 (d, J = 2.4 Hz, 1H), 1.49 (s, 6H).

E) Ester "A" group analogues with pyridine ring

Synthesis of 3,8-dihydroxy-6H-isochromeno[4,3-b]pyridin-6-one (27)



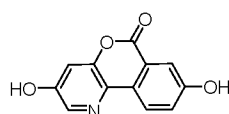
Step 1: Synthesis of 3,8-dimethoxy-6H-isochromeno[4,3-b]pyridin-6-one (26)



Sodium nitrite (130mg, 1.88mmol) was added to a solution of methyl 2-amino-5-methoxybenzoate (341mg, 1.88mmol) in water (1 mL) and HCl (3N, 1 mL) at 0°C. The reaction mixture was stirred 15 min at 0 °C, and this solution was added dropwise to a solution of 5-methoxypyridin-3-ol (1.18g, 9.42mmol) in water (1 mL) and HCl (3N, 1 mL) and TiCl₃ (0.25ml, 1.88mmol) at 0°C, and stirring continued o.n. at rt. A saturated solution of Na₂CO₃ was added. After extraction with

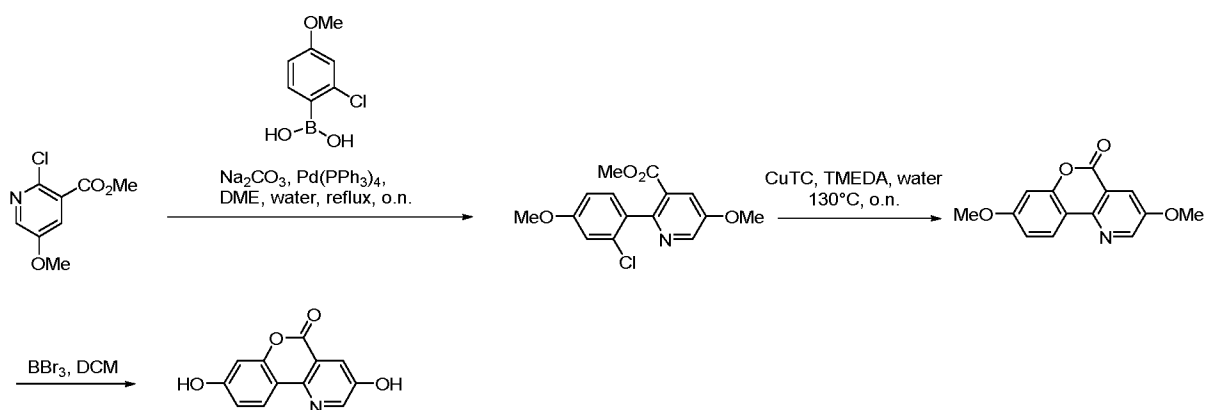
EtOAc 3 times the combined organic phases were dried over sodium sulfate and concentrated under vacuum. The crude product was purified by MPLC (SiO₂, EtOAc/cyclohexane 0% to 30%) to afford 3,8-dimethoxy-6H-isochromeno[4,3-b]pyridin-6-one (85mg, 18%) as a white solid. R_f = 0.25 (EtOAc/hexane 20%). ¹H NMR (400 MHz, CDCl₃) δ 8.47 (d, J = 8.8 Hz, 1H), 8.33 (d, J = 2.6 Hz, 1H), 7.74 (d, J = 2.7 Hz, 1H), 7.45 (dd, J = 8.8, 2.7 Hz, 1H), 7.14 (d, J = 2.6 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H).

Step2: Synthesis of 3,8-dihydroxy-6H-isochromeno[4,3-b]pyridin-6-one (**27**)

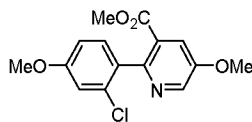


27 was prepared according to GP2 starting from 3,8-dimethoxy-6H-isochromeno[4,3-b]pyridin-6-one **26** (120mg, 0.460mmol) to afford after purification by MPLC (SiO₂, EtOAc/cyclohexane 5% to 90%) 3,8-dihydroxy-6H-isochromeno[4,3-b]pyridin-6-one (20mg, 19%) as a white solid. R_f = 0.1 (EtOAc/hexane 80%). ¹H NMR (400 MHz, DMSO) δ 10.60 (s, 1H), 10.39 (s, 1H), 8.30 (d, J = 8.7 Hz, 1H), 8.19 (d, J = 2.4 Hz, 1H), 7.50 (d, J = 2.6 Hz, 1H), 7.38 (dd, J = 8.7, 2.6 Hz, 1H), 7.15 (d, J = 2.4 Hz, 1H).

Synthesis of 3,8-dihydroxy-5H-chromeno[4,3-b]pyridin-5-one (**28**)

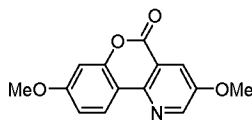


Step 1: Synthesis of methyl 2-(2-chloro-4-methoxyphenyl)-5-methoxynicotinate



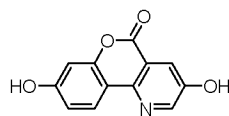
Water (1ml) was added to a mixture of (2-hydroxy-4-methoxyphenyl)boronic acid (144mg, 0.774mmol), methyl 2-chloro-5-methoxynicotinate (120 mg, 0.595 mmol), cesium carbonate (170mg, 1.61mmol) and palladium tetrakis(triphenylphosphine)palladium (35mg, 0.029 mmol) in DME (5mL) and the mixture was refluxed for 3 h. TLC showed complete conversion of the starting material. A saturated solution of NH_4Cl was added and the aqueous phase was extracted with EtOAc 3 times. The combined organic phases were dried over sodium sulfate and concentrated under vacuum. The crude product was purified by MPLC (SiO_2 , EtOAc/hexane 0% to 60%) to afford methyl 2-(2-chloro-4-methoxyphenyl)-5-methoxynicotinate (160mg, 87%) as a colorless oil. $R_f = 0.3$ (EtOAc/hexane 50%). ^1H NMR (400 MHz, CDCl_3) δ 8.49 (d, $J = 3.0$ Hz, 1H), 7.77 (d, $J = 3.0$ Hz, 1H), 7.33 (d, $J = 8.5$ Hz, 1H), 6.96 (d, $J = 2.5$ Hz, 1H), 6.90 (dd, $J = 8.5, 2.5$ Hz, 1H), 3.95 (s, 3H), 3.84 (s, 3H), 3.74 (s, 3H).

Step 2: Synthesis of 3,8-dimethoxy-5H-chromeno[4,3-b]pyridin-5-one



In a microwave vessel, to a mixture of methyl 2-(2-chloro-4-methoxyphenyl)-5-methoxynicotinate (900mg, 2.92mmol, 1.0 eq.), Copper(I) thiophene-2-carboxylate (278mg, 1.46mmol, 0.5 eq.), Cs_2CO_3 (476mg, 1.46mmol, 0.5 eq.) in deionized water (10 mL) was added TMEDA (339mg, 2.92mmol, 1.0 eq.) via micro-syringe. The mixture was allowed to stir at room temperature for 15 min and then refluxed at 130°C overnight. The reaction mixture was cooled down to r.t. and extracted with EtOAc and with a saturated solution of NH_4Cl . The organic phases were dried over sodium sulfate and concentrated under vacuum. The crude product was purified by MPLC (SiO_2 , EtOAc/cyclohexane 0% to 30%) to afford 3,8-dimethoxy-5H-chromeno[4,3-b]pyridin-5-one (120mg, 16%) as a white solid. $R_f = 0.4$ (EtOAc/hexane 80%). ^1H NMR (400 MHz, CDCl_3) δ 8.69 (d, $J = 3.1$ Hz, 1H), 8.37 (d, $J = 8.8$ Hz, 1H), 7.93 (d, $J = 3.1$ Hz, 1H), 6.96 (dd, $J = 8.8, 2.5$ Hz, 1H), 6.87 (d, $J = 2.4$ Hz, 1H), 3.96 (s, 3H), 3.89 (s, 3H).

Step 3: Synthesis of 3,8-dihydroxy-5H-chromeno[4,3-b]pyridin-5-one

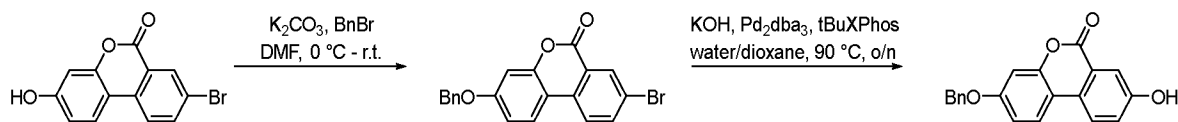


28 was prepared according to GP2 starting from 3,8-dimethoxy-5H-chromeno[4,3-b]pyridin-5-one (120mg, 0.460mmol) to afford after purification by MPLC (SiO₂, MeOH/DCM 0% to 10%) 3,8-dihydroxy-5H-chromeno[4,3-b]pyridin-5-one (26mg, 56%) as a white solid. R_f = 0.1 (EtOAc/hexane 80%). ¹H NMR (400 MHz, DMSO) δ 10.55 (s, 1H), 10.50 (s, 1H), 8.62 (d, J = 2.9 Hz, 1H), 8.19 (dd, J = 8.6, 1.5 Hz, 1H), 7.74 (d, J = 2.9 Hz, 1H), 6.86 (dd, J = 8.7, 2.3 Hz, 1H), 6.76 (d, J = 2.3 Hz, 1H).

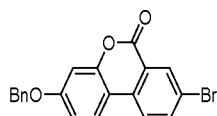
F) Ester “A” ring analogues with ether substitution prepared by Mitsunobu reaction

The Mitsunobu targets were achieved starting from two common intermediates (CI1 and CI2) which are described below.

Synthesis of CI1



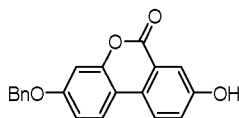
Step 1: Synthesis of 3-(benzyloxy)-8-bromo-6H-benzo[c]chromen-6-one



To a suspension of **3** (synthesis vide supra) (500 mg, 1.72mmol, 1.0 eq.) in DMF (5mL) was added in one portion K₂CO₃ (522mg, 3.78mmol, 2.2 eq.). Following the suspension was cooled to 0 °C in an ice-bath and stirred for 5min. Benzyl bromide (323mg, 1.89mmol, 1.2 eq.) was added dropwise over a period of 1min and upon complete addition the reaction mixture was stirred at 0 °C for 10min before being allowed to warm up to room temperature overnight. After the complete consumption of starting material (as indicated by TLC) the reaction mixture was quenched with half-saturated aqueous sodium bicarbonate solution. The precipitate was filtered over a Buchner funnel, washed with hexanes and dried to obtain 3-(benzyloxy)-8-bromo-6H-benzo[c]chromen-6-one (400mg, 61%) as a light brown solid. ¹H NMR (400 MHz, CDCl₃) δ 10.27 (s, 1H), 8.18 (d,

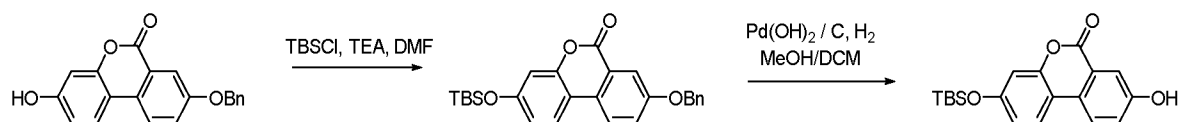
$J = 8.8$ Hz, 1H), 8.14 (d, $J = 8.9$ Hz, 1H), 7.53 (d, $J = 2.7$ Hz, 1H), 7.51 – 7.47 (m, 2H), 7.44 – 7.39 (m, 2H), 7.37 – 7.32 (m, 1H), 7.07 (d, $J = 2.5$ Hz, 1H), 7.04 (dd, $J = 8.7, 2.5$ Hz, 1H), 5.21 (s, 2H).

Step 2: Synthesis of 3-(benzyloxy)-8-hydroxy-6H-benzo[c]chromen-6-one CI1

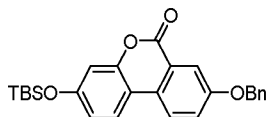


3-(benzyloxy)-8-bromo-6H-benzo[c]chromen-6-one (700mg, 1.84mmol, 1.0 eq.) was suspended in 1,4-dioxane (7mL) in a 20 mL Biotage MW vial. To this suspension was added Pd_2dba_3 (43mg, 0.18mmol, 0.1 eq.) followed by *t*BuXPhos (175mg, 0.370 mmol, 0.2 eq.). Subsequently the MW vial was sealed and degased with nitrogen for 10min. Then, a solution of KOH (412mg, 7.34mmol, 4.4 eq.) in H_2O (3mL) was added slowly to the reaction mixture, which was then stirred in a pre-heated oil bath at 90 °C for 3h. Upon complete consumption of starting material (as indicated by TLC) the reaction mixture was cooled to 0 °C and the pH was adjusted to 1 with 6M aqueous HCl. The mixture was extracted with ethyl acetate (3x10 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude material was purified by MPLC (SiO_2 , 40 g, EtOAc in Hexanes 0-30%) to afford 3-(benzyloxy)-8-hydroxy-6H-benzo[c]chromen-6-one (390mg, 67%) as a light yellow solid. ^1H NMR (400 MHz, DMSO) δ 10.27 (s, 1H), 8.18 (d, $J = 8.8$ Hz, 1H), 8.14 (d, $J = 8.9$ Hz, 1H), 7.53 (d, $J = 2.7$ Hz, 1H), 7.51 – 7.47 (m, 2H), 7.44 – 7.39 (m, 2H), 7.37 – 7.32 (m, 2H), 7.07 (d, $J = 2.5$ Hz, 1H), 7.04 (dd, $J = 8.7, 2.5$ Hz, 1H), 5.21 (s, 2H).

Synthesis of CI2

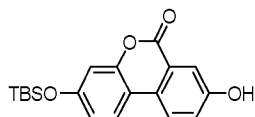


Step 1: Synthesis of 8-(benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)-6H-benzo[c]chromen-6-one



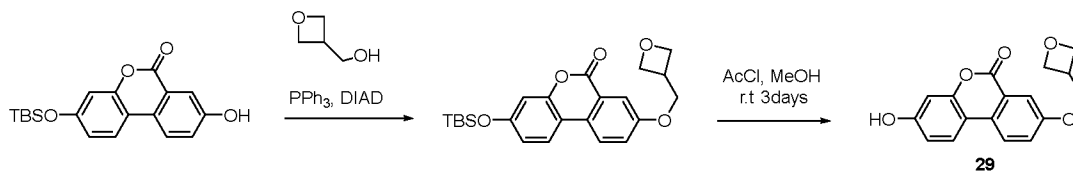
8-(benzyloxy)-3-hydroxy-6H-benzo[c]chromen-6-one (1.46g, 4.59mmol) was dissolved in dry THF 12ml. Triethylamine (1.92ml, 13.8mmol) was added dropwise at room temperature and stirred for 15 minutes then *tert*-butylchlorodimethylsilane (832mg, 5.51mmol) was added and stirring continued for 3 hours at room temperature. TLC showed no more starting material. The reaction mixture was extracted with EtOAc and HCl (1M) twice. The organic phases were washed successively with water and brine then dried over sodium sulfate to afford 8-(benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)-6H-benzo[c]chromen-6-one (1.83 g, 92%) as a brownish solid. ¹H NMR (400 MHz, CDCl₃) δ 7.94 (d, J = 8.9 Hz, 1H), 7.88 (d, J = 2.8 Hz, 1H), 7.86 – 7.81 (m, 1H), 7.50 – 7.34 (m, 6H), 6.86 – 6.80 (m, 2H), 5.18 (s, 2H), 1.00 (s, 9H), 0.25 (s, 6H).

Step 2: Synthesis of 3-((*tert*-butyldimethylsilyl)oxy)-8-hydroxy-6H-benzo[c]chromen-6-one C2

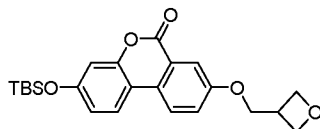


8-(benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)-6H-benzo[c]chromen-6-one (1.83g, 4.23mmol, 1.0 eq) was dissolved in Methanol (20 mL) and dichloromethane (10 mL), Pd(OH)₂/C (368mg, 0.5mmol, 0.12 eq) was added and the reaction mixture was hydrogenated under atmospheric pressure. The mixture was filtered over a pad of celite and the solvent evaporated under vacuum to afford 3-((*tert*-butyldimethylsilyl)oxy)-8-hydroxy-6H-benzo[c]chromen-6-one (1.3g, 3.8mmol, 90%) as a beige solid. ¹H NMR (400 MHz, CDCl₃) δ 7.95 (d, J = 8.8 Hz, 1H), 7.91 (d, J = 2.7 Hz, 1H), 7.89 – 7.83 (m, 1H), 7.39 (dd, J = 8.7, 2.8 Hz, 1H), 6.92 – 6.83 (m, 2H), 6.21 (s, 1H), 1.03 (s, 9H), 0.28 (s, 6H).

Synthesis of 3-hydroxy-8-(oxetan-3-ylmethoxy)-6H-benzo[c]chromen-6-one (29)

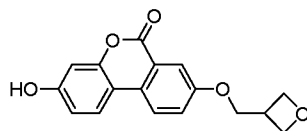


Step 1: Synthesis of 3-((*tert*-butyldimethylsilyl)oxy)-8-(oxetan-3-ylmethoxy)-6H-benzo[c]chromen-6-one



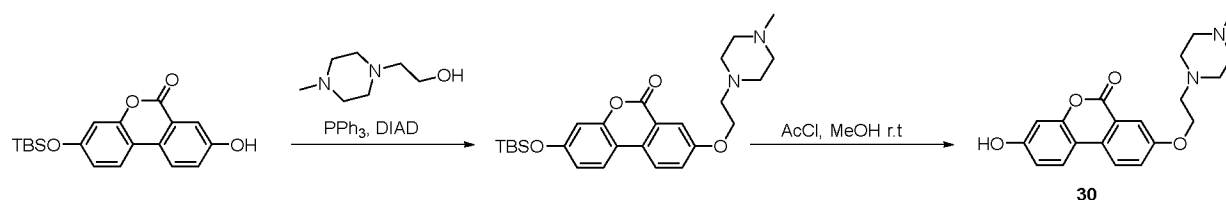
In a sealed tube, DIAD (0.187ml, 0.960mmol) was added to a solution of a solution of 3-((*tert*-butyldimethylsilyl)oxy)-8-hydroxy-6H-benzo[c]chromen-6-one (150mg, 0.430mmol) and oxetan-3-ylmethanol (58mg, 0.65mmol) in THF (2 mL) at 0°C and stirring continued overnight at room temperature. TLC indicated complete conversion of the starting material. The reaction mixture was loaded on silica gel and purified by MPLC (SiO₂, EtOAc/cyclohexane 0% to 30%) to afford 280 mg of a mixture of 3-((*tert*-butyldimethylsilyl)oxy)-8-(oxetan-3-ylmethoxy)-6H-benzo[c]chromen-6-one and reduced DIAD. *R_f* = 0.3 (EtOAc/hexane 20/80). After purification there was a significant amount of reduced DIAD present in the NMR therefore it is not further described since it was used crude in the next step.

Step 2: Synthesis of 3-hydroxy-8-(oxetan-3-ylmethoxy)-6H-benzo[c]chromen-6-one

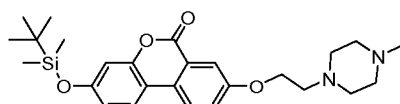


KHF₂ (108mg, 1.38mmol) was added in one portion at r.t. to a solution of 3-((*tert*-butyldimethylsilyl)oxy)-8-(oxetan-3-ylmethoxy)-6H-benzo[c]chromen-6-one (285 mg, 0.690 mmol) (crude mixture of PPh₃O and reduced DIAD) in MeOH (5ml) and was stirred for 4h. The formed white precipitate was filtered and dried under vacuum to afford 3-hydroxy-8-(oxetan-3-ylmethoxy)-6H-benzo[c]chromen-6-one (65 mg, 32%) as a white solid. ¹H NMR (400 MHz, DMSO) δ 10.27 (s, 1H), 8.26 – 8.06 (m, 2H), 7.64 – 7.52 (m, 1H), 7.52 – 7.27 (m, 1H), 7.08 – 6.96 (m, 1H), 6.85 – 6.71 (m, 1H), 4.73 (ddd, *J* = 7.6, 6.0, 1.4 Hz, 2H), 4.46 (dt, *J* = 11.9, 6.1 Hz, 2H), 4.33 (dd, *J* = 18.2, 6.7 Hz, 2H), 3.43 (tt, *J* = 6.8, 6.8 Hz, 1H).

Synthesis of 3-hydroxy-8-(2-(4-methylpiperazin-1-yl)ethoxy)-6H-benzo[c]chromen-6-one (30)

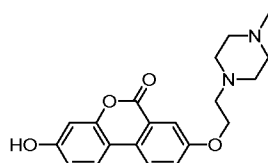


Step 1: Synthesis of 3-((*tert*-butyldimethylsilyl)oxy)-8-(2-(4-methylpiperazin-1-yl)ethoxy)-6H-benzo[c]chromen-6-one



3-((*tert*-butyldimethylsilyl)oxy)-8-(2-(4-methylpiperazin-1-yl)ethoxy)-6H-benzo[c]chromen-6-one was prepared from 3-((*tert*-butyldimethylsilyl)oxy)-8-hydroxy-6H-benzo[c]chromen-6-one (80mg, 0.23 mmol) and 2-(4-Methyl-piperazin-1-yl)-ethanol (34mg, 0.23mmol) (according to the synthesis of **29**) to afford after MPLC purification (SiO₂, MeOH/DCM 0% to 20%) 3-((*tert*-butyldimethylsilyl)oxy)-8-(2-(4-methylpiperazin-1-yl)ethoxy)-6H-benzo[c]chromen-6-one (60mg, 55%) as yellowish oil. The NMR still showed significant amounts of reduced DIAD, but the impure/ crude material was carried forward to the next step. $R_f = 0.4$ (20% MeOH/DCM).

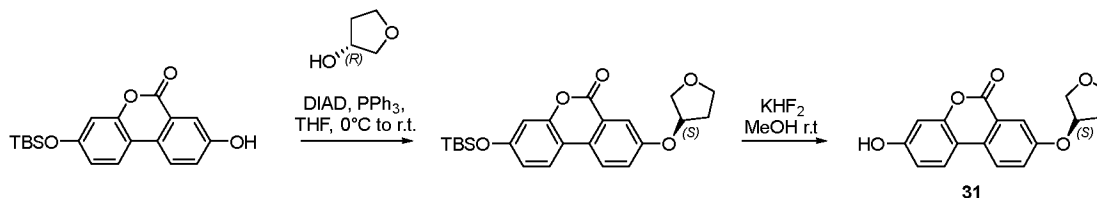
Step 2: Synthesis of 3-hydroxy-8-(2-(4-methylpiperazin-1-yl)ethoxy)-6H-benzo[c]chromen-6-one



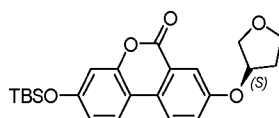
Acetyl chloride (0.046ml, 0.64mmol, 5.0 eq) was added to a solution of 3-((*tert*-butyldimethylsilyl)oxy)-8-(2-(4-methylpiperazin-1-yl)ethoxy)-6H-benzo[c]chromen-6-one (60 mg, 0.13 mmol, 1.0 eq) in MeOH (2 ml) at r.t. and the reaction mixture was stirred overnight. Methanol was evaporated under vacuum, the crude product was diluted with EtOAc and washed with a saturated solution of sodium carbonate. The aqueous layer was extracted with EtOAc, and the combined organic phases were dried over sodium sulfate. The crude product was purified by MPLC (SiO₂, MeOH/DCM 0% to 30%) to afford 3-hydroxy-8-(2-(4-methylpiperazin-1-yl)ethoxy)-6H-benzo[c]chromen-6-one (17mg, 0.048mmol, 37%). ¹H NMR (400 MHz, DMSO) δ 10.23 (br, 1H), 8.25 – 8.06 (m, 2H), 7.53 (d, $J = 2.7$ Hz, 1H), 7.50 (dd, $J = 8.8, 2.9$ Hz, 1H), 7.02

– 6.94 (m, 1H), 6.86 – 6.71 (m, 1H), 4.18 (dt, $J = 18.4, 5.7$ Hz, 3H), 2.76 – 2.65 (m, 6H), 2.34–2.32 (m, 3H), 2.14 (s, 3H).

Synthesis of (S)-3-hydroxy-8-((tetrahydrofuran-3-yl)oxy)-6H-benzo[c]chromen-6-one (**31**)

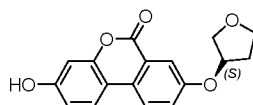


Step1: Synthesis of (S)-3-((tert-butyldimethylsilyl)oxy)-8-((tetrahydrofuran-3-yl)oxy)-6H-benzo[c]chromen-6-one



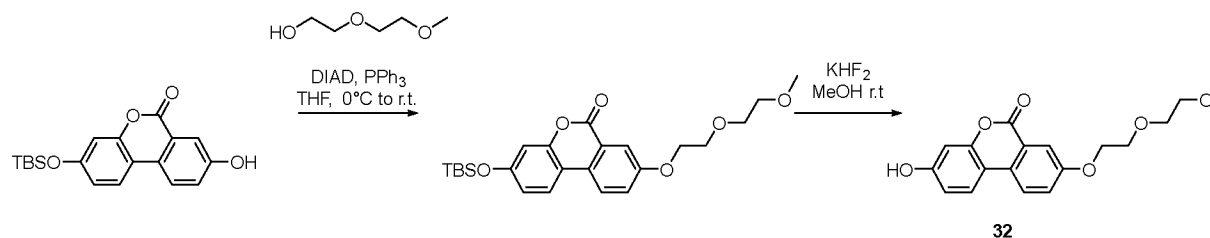
(S)-3-((tert-butyldimethylsilyl)oxy)-8-((tetrahydrofuran-3-yl)oxy)-6H-benzo[c]chromen-6-one was prepared (according to synthesis of **29**) starting from C2 (80mg, 0.23mmol) and (R)-tetrahydrofuran-3-ol (31mg, 0.35mmol) to afford (S)-3-((tert-butyldimethylsilyl)oxy)-8-((tetrahydrofuran-3-yl)oxy)-6H-benzo[c]chromen-6-one (45mg, 47%) as yellowish oil. $R_f = 0.6$ (EtOAc/hexane 1/1). ^1H NMR (400 MHz, CDCl_3) δ 8.00 – 7.80 (m, 2H), 7.74 (dd, $J = 23.0, 2.7$ Hz, 1H), 7.33 (ddd, $J = 26.5, 8.8, 2.7$ Hz, 1H), 6.90 – 6.80 (m, 2H), 5.09 – 4.95 (m, 1H), 4.13 – 3.88 (m, 4H), 2.43 – 2.07 (m, 2H), 1.02 (s, $J = 3.8$ Hz, 9H), 0.27 (s, 3H), 0.25 (s, 3H).

Step 2: Synthesis of (S)-3-hydroxy-8-((tetrahydrofuran-3-yl)oxy)-6H-benzo[c]chromen-6-one

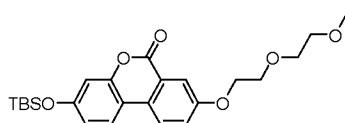


31 was prepared according to synthesis of **29** starting from (S)-3-((tert-butyldimethylsilyl)oxy)-8-((tetrahydrofuran-3-yl)oxy)-6H-benzo[c]chromen-6-one (40mg, 0.097mmol) and KHF_2 (27mg, 0.34mmol) to give (S)-3-hydroxy-8-((tetrahydrofuran-3-yl)oxy)-6H-benzo[c]chromen-6-one (22mg, 76%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.92 – 7.76 (m, 2H), 7.69 (s, 1H), 7.29 (ddd, $J = 11.3, 8.8, 2.8$ Hz, 1H), 6.88 – 6.70 (m, 2H), 5.41–5.35 (m, 1H), 4.01 – 3.82 (m, 4H), 2.36 – 2.04 (m, 2H).

Synthesis of 3-hydroxy-8-(2-(2-methoxyethoxy)ethoxy)-6H-benzo[c]chromen-6-one (**32**)

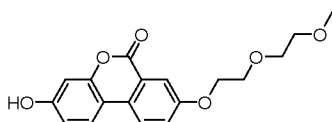


Step 1: Synthesis of 3-((*tert*-butyldimethylsilyl)oxy)-8-(2-(2-methoxyethoxy)ethoxy)-6H-benzo[c]chromen-6-one



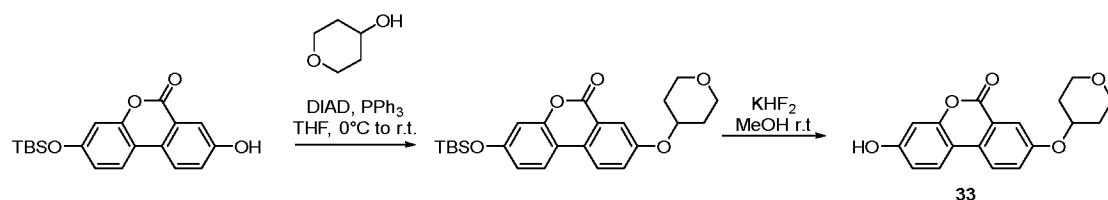
3-((*tert*-butyldimethylsilyl)oxy)-8-(2-(2-methoxyethoxy)ethoxy)-6H-benzo[c]chromen-6-one was prepared (according to synthesis of **29**) starting from C2 (100 mg, 0.29mmol) and 2-(2-methoxyethoxy)ethan-1-ol (42mg, 0.35mmol) to afford 3-((*tert*-butyldimethylsilyl)oxy)-8-(2-(2-methoxyethoxy)ethoxy)-6H-benzo[c]chromen-6-one (125mg, 47%), which is contaminated with reduced DIAD as yellowish oil. $R_f = 0.5$ (EtOAc/hexane 1/1). ^1H NMR (400 MHz, CDCl_3) δ 7.91 - 7.66 (m, 3H), 7.32-7.24 (m, 1H), 6.88 - 6.74 (m, 2H), 4.22 - 4.11 (m, 2H), 3.87 - 3.81 (m, 2H), 3.74 - 3.63 (m, 2H), 3.59 - 3.49 (m, 2H), 3.33 (s, 3H), 0.95-0.93 (m, 9H), 0.20 (s, 3H).

Step 2: Synthesis of 3-hydroxy-8-(2-(2-methoxyethoxy)ethoxy)-6H-benzo[c]chromen-6-one

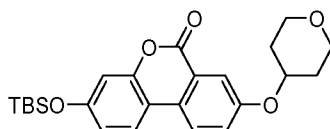


32 was prepared according to synthesis of **29** starting from (100 mg, 0.220mmol) and KHF_2 (70mg, 0.90mmol) to afford after purification by MPLC (SiO_2 , EtOAc/hexane from 0% to 30%) 3-hydroxy-8-(2-(2-methoxyethoxy)ethoxy)-6H-benzo[c]chromen-6-one (24mg, 32%) as a white solid as mixture of two compounds. ^1H NMR (400 MHz, CDCl_3) δ 7.75 – 7.56 (m, 2H), 7.34 (dd, $J = 42.4, 2.8$ Hz, 1H), 7.21 – 6.48 (m, 3H), 4.05 (dt, $J = 14.8, 4.4$ Hz, 2H), 3.92 – 3.85 (m, 2H), 3.80 (dt, $J = 6.1, 2.5$ Hz, 2H), 3.70 (ddd, $J = 4.4, 3.5, 1.5$ Hz, 2H), 3.46 (d, $J = 1.4$ Hz, 3H).

Synthesis of 3-hydroxy-8-((tetrahydro-2H-pyran-4-yl)oxy)-6H-benzo[c]chromen-6-one (**33**)

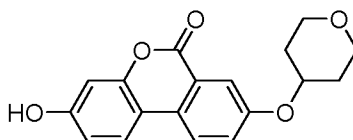


Step 1: Synthesis of 3-((*tert*-butyldimethylsilyl)oxy)-8-((tetrahydro-2H-pyran-4-yl)oxy)-6H-benzo[c]chromen-6-one



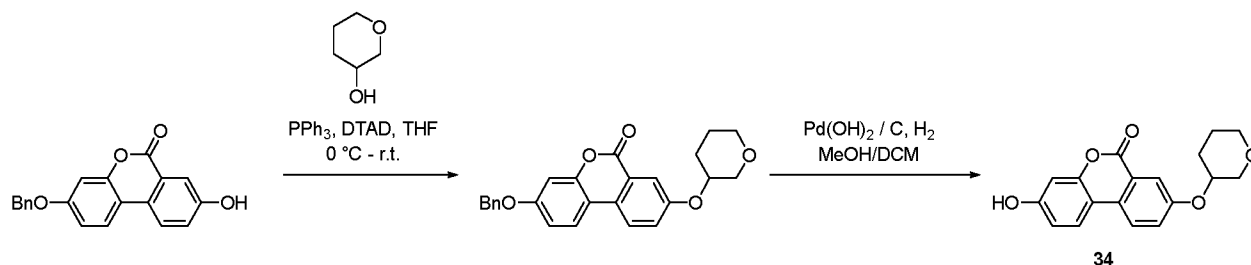
Compound was prepared according to synthesis of **29** starting from C2 (100mg, 0.29mmol) and tetrahydro-2H-pyran-4-ol (36mg, 0.35mmol) to afford 3-((*tert*-butyldimethylsilyl)oxy)-8-((tetrahydro-2H-pyran-4-yl)oxy)-6H-benzo[c]chromen-6-one (64mg, 51%) as yellowish oil. R_f = 0.67 (EtOAc/hexane 4/6). ^1H NMR (400 MHz, CDCl_3) δ 7.98 – 7.81 (m, 2H), 7.77 (dd, J = 7.3, 2.7 Hz, 1H), 7.42 – 7.27 (m, 1H), 6.96 – 6.80 (m, 2H), 4.61 (dtt, J = 44.2, 7.8, 3.9 Hz, 1H), 4.01 (ddd, J = 10.4, 5.9, 3.9 Hz, 2H), 3.62 (ddt, J = 11.9, 7.8, 3.7 Hz, 2H), 2.06 (d, J = 12.6 Hz, 2H), 1.83 (dtd, J = 12.5, 8.2, 3.9 Hz, 2H), 1.01 (d, J = 3.7 Hz, 9H), 0.32 – 0.20 (m, 6H).

Step 2: Synthesis of 3-hydroxy-8-((tetrahydro-2H-pyran-4-yl)oxy)-6H-benzo[c]chromen-6-one

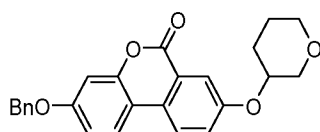


33 was prepared starting from 3-((*tert*-butyldimethylsilyl)oxy)-8-((tetrahydro-2H-pyran-4-yl)oxy)-6H-benzo[c]chromen-6-one (60 mg, 0.14 mmol) and KHF_2 (38mg, 0.49mmol) to afford 3-hydroxy-8-((tetrahydro-2H-pyran-4-yl)oxy)-6H-benzo[c]chromen-6-one (29mg, 66%) as a white solid. MS (ESI+): m/z = 313. ^1H NMR (400 MHz, DMSO) δ 10.30 – 10.11 (m, 1H), 8.23 – 7.98 (m, 2H), 7.66 – 7.28 (m, 2H), 7.09 – 6.68 (m, 2H), 4.74 (dtt, J = 25.7, 8.6, 4.0 Hz, 1H), 3.86 (dt, J = 10.3, 4.2 Hz, 2H), 3.52 (tdd, J = 11.6, 8.9, 2.7 Hz, 2H), 2.01 (dd, J = 13.2, 3.5 Hz, 2H), 1.62 (dtt, J = 14.1, 9.1, 4.6 Hz, 2H).

Synthesis of 3-hydroxy-8-((tetrahydro-2H-pyran-3-yl)oxy)-6H-benzo[c]chromen-6-one (**34**)

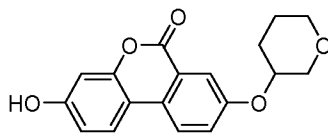


Step 1: Synthesis of 3-(benzyloxy)-8-((tetrahydro-2H-pyran-3-yl)oxy)-6H-benzo[c]chromen-6-one



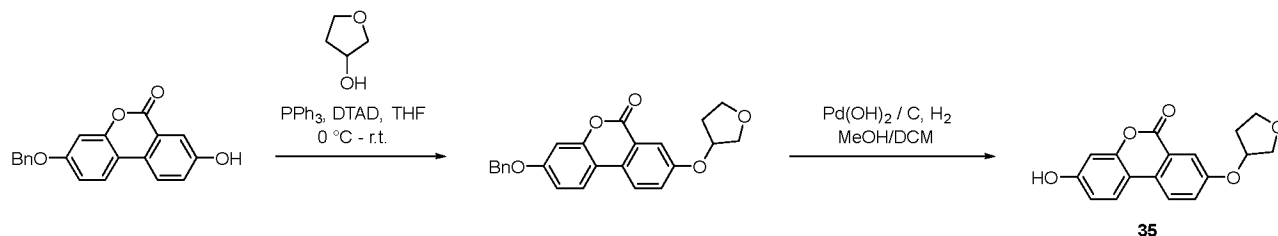
3-(benzyloxy)-8-hydroxy-6H-benzo[c]chromen-6-one (64mg, 0.20 mmol, 1.0 eq.) was dissolved in THF (0.7mL) in a 10 mL Biotage MW vial. Subsequently PPh_3 (79mg, 0.30 mmol, 1.5 eq.) and Tetrahydro-2H-pyran-3-ol (31mg, 0.30 mmol, 1.5 eq.) were added and the reaction mixture was cooled to 0 °C in an ice-bath in which it was stirred for 5min. Then a solution of Di-*tert*-butyl-diazene-1,2-dicarboxylate (69mg, 0.30 mmol, 1.5 eq.) (DTAD) in THF (0.1mL) was added dropwise to the reaction mixture. Upon complete addition the reaction mixture turned dark yellow and stirring was continued overnight at r.t.. After overnight stirring starting material was still present, therefore PPh_3 (79mg, 0.30 mmol, 1.5 eq.), Tetrahydro-2H-pyran-3-ol (31mg, 0.30 mmol, 1.5 eq.) and a solution of Di-*tert*-butyl-diazene-1,2-dicarboxylate (DTAD) in THF (0.1mL) were added to reaction mixture to bring the reaction to completion. After an additional 2h of stirring at room temperature the reaction mixture was concentrated under vacuum and loaded on silica to be purified by MPLC (SiO_2 , 12g, EtOAc in Hex 0-35%) to afford 3-(benzyloxy)-8-((tetrahydro-2H-pyran-3-yl)oxy)-6H-benzo[c]chromen-6-one (50mg, 62%) as a light yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 7.92 (d, J = 8.9 Hz, 1H), 7.86 (d, J = 8.9 Hz, 1H), 7.77 (d, J = 2.8 Hz, 1H), 7.46 – 7.31 (m, 5H), 6.97 (dd, J = 8.8, 2.6 Hz, 1H), 6.92 (d, J = 2.5 Hz, 1H), 5.12 (s, 2H), 4.47 (tt, J = 6.8, 3.5 Hz, 1H), 3.95 (ddd, J = 11.6, 3.2, 1.2 Hz, 1H), 3.75 (ddd, J = 10.6, 6.2, 3.9 Hz, 1H), 3.70 – 3.60 (m, 2H), 2.12 (tt, J = 11.8, 6.0 Hz, 1H), 1.89 (dddt, J = 31.0, 17.3, 8.0, 3.9 Hz, 3H), 1.70 – 1.59 (m, 1H).

Step 2: Synthesis of 3-hydroxy-8-((tetrahydro-2H-pyran-3-yl)oxy)-6H-benzo[c]chromen-6-one

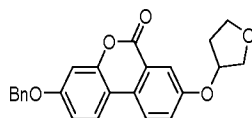


3-(benzyloxy)-8-((tetrahydro-2H-pyran-3-yl)oxy)-6H-benzo[c]chromen-6-one (50mg, 0.12mmol, 1.0 eq.) was dissolved in MeOH/DCM (5mL, 10/1) and Pd(OH)₂/C (20mg) was added in one portion. Then the reaction mixture was evacuated and backfilled with N₂ three times before putting it under hydrogen atmosphere (balloon). The reaction mixture was stirred for 2h and upon complete consumption of starting material (as indicated by TLC) filtered over silica and concentrated under vacuum to afford the crude product which was loaded on silica and purified by MPLC (SiO₂, 12g, EtOAc in Hex 0-50 %) to obtain 3-hydroxy-8-((tetrahydro-2H-pyran-3-yl)oxy)-6H-benzo[c]chromen-6-one (33mg, 0.11mmol, 89%) as a white solid. ¹H NMR (400 MHz, DMSO) δ 10.21 (s, 1H), 8.20 (d, *J* = 9.0 Hz, 1H), 8.09 (d, *J* = 8.8 Hz, 1H), 7.61 (d, *J* = 2.8 Hz, 1H), 7.53 (dd, *J* = 8.9, 2.8 Hz, 1H), 6.82 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.74 (d, *J* = 2.4 Hz, 1H), 4.57 (dt, *J* = 6.2, 3.2 Hz, 1H), 3.84 (dd, *J* = 11.6, 2.1 Hz, 1H), 3.64 (ddd, *J* = 10.8, 6.5, 3.7 Hz, 1H), 3.56 (dd, *J* = 11.7, 5.6 Hz, 2H), 2.05 (dd, *J* = 8.9, 4.9 Hz, 1H), 1.87 – 1.68 (m, 2H), 1.63 – 1.48 (m, 1H).

Synthesis of 3-hydroxy-8-((tetrahydrofuran-3-yl)oxy)-6H-benzo[c]chromen-6-one (**35**)



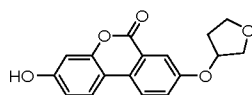
Step 1: Synthesis of 3-(benzyloxy)-8-((tetrahydrofuran-3-yl)oxy)-6H-benzo[c]chromen-6-one



3-(benzyloxy)-8-hydroxy-6H-benzo[c]chromen-6-one (100mg, 0.31mmol, 1.0 eq.) was dissolved in THF (1.1mL). Subsequently PPh₃ (124mg, 0.470 mmol, 1.5 eq.) and Tetrahydrofuran-3-ol (42mg, 0.47mmol, 1.5 eq.) were added and the reaction mixture was cooled to 0 °C in an ice-bath in which it was stirred for 5min. Then a solution of Di-*tert*-butyl-diazene-1,2-dicarboxylate (109mg, 0.470 mmol, 1.5 eq.) (DTAD) in THF (0.2mL) was added dropwise to the reaction

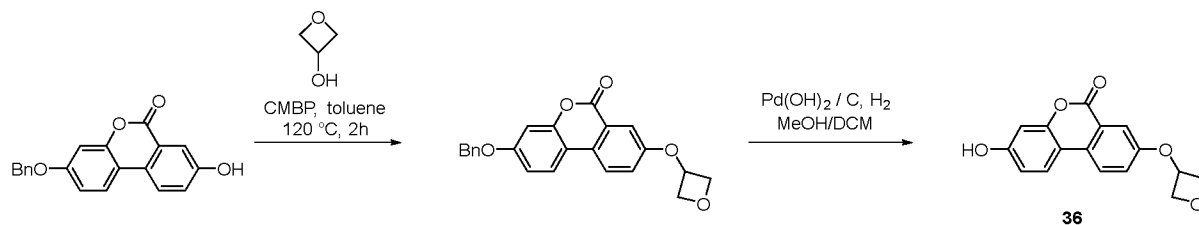
mixture. Upon complete addition the reaction mixture turned dark yellow and stirring was continued overnight at r.t. After overnight stirring starting material was still present, therefore PPh₃ (124mg, 0.470 mmol, 1.5 eq.), Tetrahydrofuran-3-ol (42mg, 0.47mmol, 1.5 eq.) and a solution of Di-*tert*-butyl-diazene-1,2-dicarboxylate (109mg, 0.470 mmol, 1.5 eq.) (DTAD) in THF (0.2mL) were added to reaction mixture to bring the reaction to completion. After an additional 2h of stirring at room temperature the reaction mixture was concentrated under vacuum and loaded on silica to be purified by MPLC (SiO₂, 12g, EtOAc in Hex 0-35%) to afford 3-(benzyloxy)-8-((tetrahydrofuran-3-yl)oxy)-6H-benzo[c]chromen-6-one (100mg, 82%) as a light yellow solid. The NMR after purification still showed a significant amount of reduced DTAD but the reaction was taken to the next step crude, therefore the NMR is not reported here.

Step 2: Synthesis of 3-hydroxy-8-((tetrahydrofuran-3-yl)oxy)-6H-benzo[c]chromen-6-one

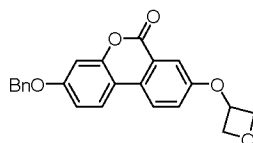


3-(benzyloxy)-8-((tetrahydrofuran-3-yl)oxy)-6H-benzo[c]chromen-6-one (100mg, 0.260 mmol, 1.0 eq.) was dissolved in MeOH/DCM (7mL, 10/1) and Pd(OH)₂/C (60mg) was added in one portion. Then the reaction mixture was evacuated and backfilled with N₂ three times before putting it under hydrogen atmosphere with the use of a balloon. The reaction mixture was stirred for 2h and upon complete consumption of starting material (as indicated by TLC) filtered over silica and concentrated under reduced pressure to give the crude product which was loaded on silica and purified by flash column chromatography (SiO₂, 12g, EtOAc in Hex 0-50 %) to give 3-hydroxy-8-((tetrahydrofuran-3-yl)oxy)-6H-benzo[c]chromen-6-one (65mg, 72%) as a white solid. ¹H NMR (400 MHz, DMSO) δ 10.21 (s, 1H), 8.22 (d, *J* = 8.8 Hz, 1H), 8.09 (d, *J* = 8.8 Hz, 1H), 7.57 (d, *J* = 2.7 Hz, 1H), 7.49 (dd, *J* = 8.9, 2.8 Hz, 1H), 6.83 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.75 (d, *J* = 2.4 Hz, 1H), 5.25 – 5.19 (m, 1H), 3.92 (dd, *J* = 10.2, 4.4 Hz, 1H), 3.88 – 3.83 (m, 2H), 3.78 (td, *J* = 8.4, 4.6 Hz, 1H), 2.36 – 2.20 (m, 1H), 2.02 (dd, *J* = 14.2, 7.5 Hz, 1H).

Synthesis of 3-hydroxy-8-(oxetan-3-yloxy)-6H-benzo[c]chromen-6-one (36)

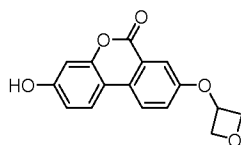


Step 1: Synthesis of 3-(benzyloxy)-8-(oxetan-3-yloxy)-6H-benzo[c]chromen-6-one



Cyanomehtylenetributylphosphorane (150mg, 0.630 mmol, 2.5 eq.) was added at r.t. to a solution of 3-(benzyloxy)-8-hydroxy-6H-benzo[c]chromen-6-one (80mg, 0.25mmol, 1.0 eq.) and oxetan-3ol (56mg, 0.75mmol, 3.0 eq.) in toluene (1.3mL) in one portion and the reaction mixture was heated to 120 °C for 2h in a sealed vial. After the full conversion of starting material, the reaction mixture was allowed to cool down to r.t., concentrated and loaded on silica to be purified by MPLC (SiO₂, 12g, EtOAc in Hex 0-30%) to afford 3-(benzyloxy)-8-(oxetan-3-yloxy)-6H-benzo[c]chromen-6-one (74mg, 79%) as a light yellow foam. ¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, J = 8.8 Hz, 1H), 7.88 (d, J = 8.9 Hz, 1H), 7.48 – 7.34 (m, 7H), 6.99 (dd, J = 8.8, 2.6 Hz, 1H), 6.94 (d, J = 2.5 Hz, 1H), 5.39 – 5.29 (m, 1H), 5.14 (s, 2H), 5.07 (ddd, J = 7.1, 6.0, 0.9 Hz, 2H), 4.79 (ddd, J = 7.4, 5.0, 1.0 Hz, 2H).

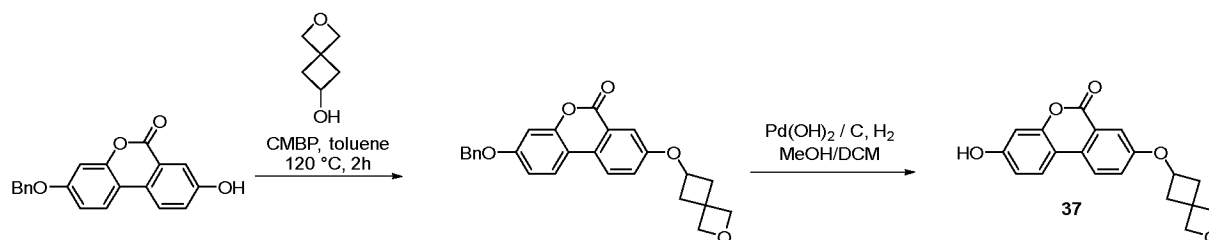
Step 2: Synthesis of 3-hydroxy-8-(oxetan-3-yloxy)-6H-benzo[c]chromen-6-one



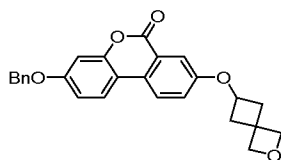
3-(benzyloxy)-8-(oxetan-3-yloxy)-6H-benzo[c]chromen-6-one (70mg, 0.19mmol, 1.0 eq.) was dissolved in MeOH/DCM (5mL, 10/1) and Pd(OH)₂/C (15mg) was added in one portion. Then the reaction mixture was evacuated and backfilled with N₂ three times before putting it under hydrogen atmosphere with the use of a balloon. The reaction mixture was stirred for 4h and upon complete consumption of starting material (as indicated by TLC) filtered over silica and concentrated under reduced pressure to give the crude product which was loaded on silica and purified by flash column

chromatography (SiO₂, 12g, EtOAc in Hex 0-50 %) to afford 3-hydroxy-8-(oxetan-3-yloxy)-6H-benzo[c]chromen-6-one (25mg, 0.09mmol, 47%) as a white solid. ¹H NMR (400 MHz, DMSO) δ 10.24 (s, 1H), 8.24 (d, J = 8.9 Hz, 1H), 8.10 (d, J = 8.8 Hz, 1H), 7.45 (dd, J = 8.8, 2.8 Hz, 1H), 7.35 (d, J = 2.8 Hz, 1H), 6.83 (dd, J = 8.7, 2.4 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H), 5.47 (q, J = 5.4, 4.8 Hz, 1H), 4.98 (t, J = 7.0 Hz, 2H), 4.59 (dd, J = 7.7, 5.1 Hz, 2H).

Synthesis of 8-((2-oxaspiro[3.3]heptan-6-yl)oxy)-3-hydroxy-6H-benzo[c]chromen-6-one (37)

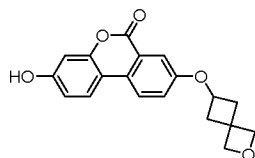


Step 1: Synthesis of 8-((2-oxaspiro[3.3]heptan-6-yl)oxy)-3-(benzyloxy)-6H-benzo[c]chromen-6-one



Cyanomehtylenetributylphosphorane (95mg, 0.39mmol, 2.5 eq.) was added at r.t. to a solution of 3-(benzyloxy)-8-hydroxy-6H-benzo[c]chromen-6-one (50mg, 0.16mmol, 1.0 eq.) and 2-oxaspiro[3.3]heptan-6-ol (39mg, 0.35mmol, 2.2 eq.) in toluene (3.0 mL) in one portion and the reaction mixture was heated to 120 °C for 2h in a sealed vial. After the full conversion of starting material, the reaction mixture was allowed to cool down to r.t., concentrated and loaded on silica to be purified by flash column chromatography (SiO₂, 12g, EtOAc in Hex 0-30%) to afford 8-((2-oxaspiro[3.3]heptan-6-yl)oxy)-3-(benzyloxy)-6H-benzo[c]chromen-6-one (40mg, 0.10 mmol, 61%) as a light yellow solid. ¹H NMR (400 MHz, DMSO) δ 8.26 (d, J = 8.9 Hz, 1H), 8.20 (d, J = 8.9 Hz, 1H), 7.54 – 7.32 (m, 7H), 7.09 (d, J = 2.5 Hz, 1H), 7.06 (dd, J = 8.7, 2.6 Hz, 1H), 5.22 (s, 2H), 4.77 (p, J = 6.8 Hz, 1H), 4.66 (s, 2H), 4.55 (s, 2H), 2.88 – 2.78 (m, 2H), 2.33 – 2.24 (m, 2H).

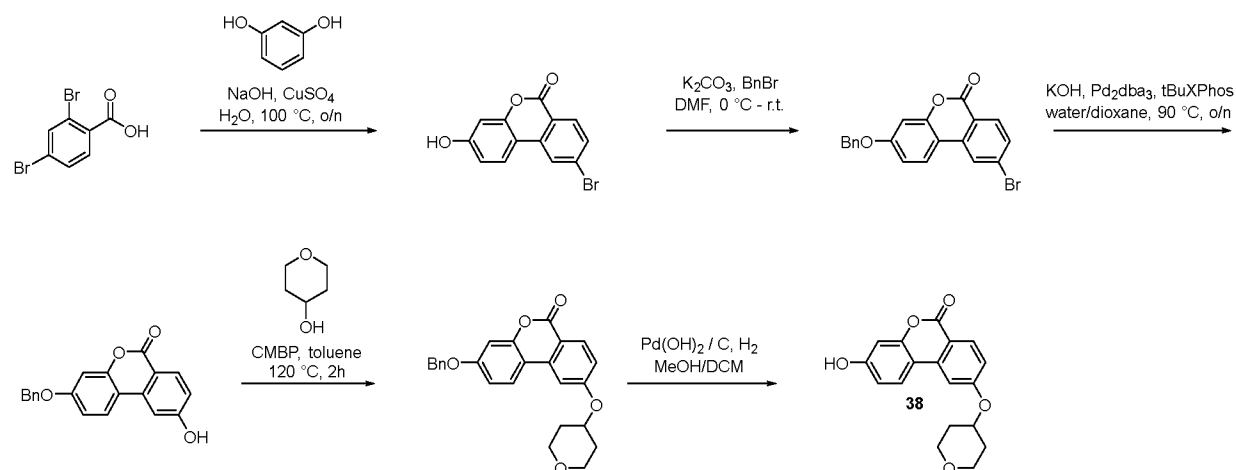
Step 2: Synthesis of 8-((2-oxaspiro[3.3]heptan-6-yl)oxy)-3-hydroxy-6H-benzo[c]chromen-6-one



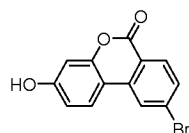
8-((2-oxaspiro[3.3]heptan-6-yl)oxy)-3-(benzyloxy)-6H-benzo[c]chromen-6-one (40mg, 0.10 mmol, 1.0 eq.) was dissolved in MeOH/DCM (5mL, 10/1) and Pd(OH)₂/C (14mg) was added in one portion. Then the reaction mixture was evacuated and backfilled with N₂ three times before putting it under hydrogen atmosphere with the use of a balloon. The reaction mixture was stirred for 4h and upon complete consumption of starting material (as indicated by TLC) filtered over silica and concentrated under vacuum to afford the crude product which was loaded on silica and purified by flash column chromatography (SiO₂, 12g, EtOAc in Hex 0-50 %) to give 8-((2-oxaspiro[3.3]heptan-6-yl)oxy)-3-hydroxy-6H-benzo[c]chromen-6-one (26mg, 0.08 mmol, 83%) as a white solid. MS (ESI⁺): m/z = 325. ¹H NMR (400 MHz, DMSO) δ 10.23 (s, 1H), 8.19 (d, J = 8.9 Hz, 1H), 8.08 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 2.8 Hz, 1H), 7.41 (dd, J = 8.8, 2.8 Hz, 1H), 6.82 (dd, J = 8.7, 2.4 Hz, 1H), 6.74 (d, J = 2.4 Hz, 1H), 4.76 (q, J = 6.8 Hz, 1H), 4.66 (s, 2H), 4.55 (s, 2H), 2.87 – 2.76 (m, 2H), 2.32 – 2.18 (m, 2H).

In a similar fashion, the 9-substituted analogue **38** was prepared according to the scheme below:

Synthesis of 3-hydroxy-9-((tetrahydro-2H-pyran-4-yl)oxy)-6H-benzo[c]chromen-6-one (**38**)

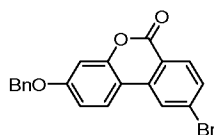


Step 1: Synthesis of 9-bromo-3-hydroxy-6H-benzo[c]chromen-6-one



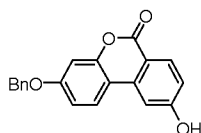
A mixture of 2,4-dibromobenzoic acid (5.00 g, 17.9mmol, 1.0 eq.), resorcinol (3.93g, 35.7 mmol, 2.0 eq.) and sodium hydroxide (1.71g, 42.9mmol, 2.4 eq.) in water (15ml) was heated under reflux for 60 minutes. After the addition of copper sulfate (5% aqueous solution, 10 mL), the mixture was refluxed again overnight and a precipitate was formed which was filtered off and washed with HCl (1M) then dried under vacuum to give 9-bromo-3-hydroxy-6H-benzo[c]chromen-6-one (2.91g, 56%) as an ochrey solid. ¹H NMR (400 MHz, DMSO) δ 10.44 (s, 1H), 8.47 (s, 1H), 8.19 (d, J = 8.7 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 6.86 – 6.78 (m, 1H), 6.73 (s, 1H).

Step 2: Synthesis of 3-(benzyloxy)-9-bromo-6H-benzo[c]chromen-6-one



To a suspension of 9-bromo-3-hydroxy-6H-benzo[c]chromen-6-one (2.00mg, 6.87mmol, 1.0 eq.) in DMF (35mL) was added in one portion K₂CO₃ (2.09g, 15.1mmol, 2.2 eq.). The suspension was cooled to 0 °C and stirred for 5min. Benzyl bromide (1.41g, 8.24mmol, 1.2 eq.) was added dropwise over a period of 5min and upon complete addition the reaction mixture was stirred at 0 °C for 10min before being allowed to warm up to room temperature over 2h. After the complete consumption of starting material (as indicated by TLC) the reaction mixture was quenched with half-saturated aqueous sodium bicarbonate solution. The precipitate was filtered over a Buchner funnel, washed with hexanes and dried to afford 3-(benzyloxy)-9-bromo-6H-benzo[c]chromen-6-one (1.49g, 61%) as a light brown solid. ¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, J = 8.7 Hz, 1H), 7.78 (d, J = 8.9 Hz, 1H), 7.41 – 7.28 (m, 6H), 6.91 – 6.88 (m, 2H), 6.85 (d, J = 2.5 Hz, 1H), 5.07 (s, 2H).

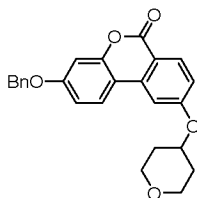
Step 3: Synthesis of 3-(benzyloxy)-9-hydroxy-6H-benzo[c]chromen-6-one



3-(benzyloxy)-9-bromo-6H-benzo[c]chromen-6-one (800mg, 2.10 mmol, 1.0 eq) was suspended in 1,4-dioxane (7mL) in a 20 mL Biotage MW vial. To this suspension was added Pd₂dba₃ (49mg,

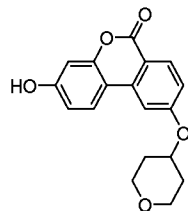
0.21mmol, 0.1 eq.) followed by tBuXPhos (200mg, 0.42mmol, 0.2 eq.). Subsequently the MW vial was sealed and degased with nitrogen for 10min. Then, a solution of KOH (471mg, 8.39mmol, 4.4 eq.) in H₂O (3mL) was added slowly to the reaction mixture, and put in a pre-heated oil bath at 90 °C for 3h. Upon complete consumption of starting material (as indicated by TLC) the reaction mixture was cooled to 0 °C and the pH adjusted to 1 with 6M aqueous HCl. The mixture was extracted with ethyl acetate (3x10 mL) and the combined organic phases were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude material was purified by MPLC (SiO₂, 40 g, EtOAc in Hexanes 0-30%) to afford 3-(benzyloxy)-9-hydroxy-6H-benzo[c]chromen-6-one (225mg, 37%) as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, J = 8.7 Hz, 1H), 7.78 (d, J = 8.9 Hz, 1H), 7.41 – 7.28 (m, 6H), 6.91 – 6.88 (m, 2H), 6.85 (d, J = 2.5 Hz, 1H), 5.07 (s, 2H).

Step 4: Synthesis of 3-(benzyloxy)-9-((tetrahydro-2H-pyran-4-yl)oxy)-6H-benzo[c]chromen-6-one



Cyanomehtylenetriethylphosphorane (227mg, 0.940 mmol, 2.5 eq.) was added at r.t. to a solution of 3-(benzyloxy)-9-hydroxy-6H-benzo[c]chromen-6-one (120mg, 0.380 mmol, 1.0 eq.) and tetrahydro-2H-pyran-4-ol (77mg, 0.71mmol, 2.0 eq.) in toluene (3.8mL) in one portion and the reaction mixture was heated to 120 °C for 2h in a sealed vial. After the full conversion of starting material, the reaction mixture was allowed to cool down to r.t., concentrated and loaded on silica to be purified by MPLC (SiO₂, 12g, EtOAc in Hex 0-30%) to afford 3-(benzyloxy)-9-((tetrahydro-2H-pyran-4-yl)oxy)-6H-benzo[c]chromen-6-one (135mg, 89%) as a light yellow foam. ¹H NMR (400 MHz, CDCl₃) δ 8.28 (d, J = 8.8 Hz, 1H), 7.86 (d, J = 8.9 Hz, 1H), 7.51 – 7.32 (m, 6H), 7.03 (dd, J = 8.9, 2.4 Hz, 1H), 6.97 (dd, J = 8.8, 2.6 Hz, 1H), 6.91 (d, J = 2.5 Hz, 1H), 5.13 (s, 2H), 4.73 (tt, J = 7.7, 3.8 Hz, 1H), 4.02 (ddd, J = 11.8, 6.3, 3.8 Hz, 2H), 3.65 (ddd, J = 11.5, 8.1, 3.3 Hz, 2H), 2.17 – 2.05 (m, 2H), 1.94 – 1.82 (m, 2H).

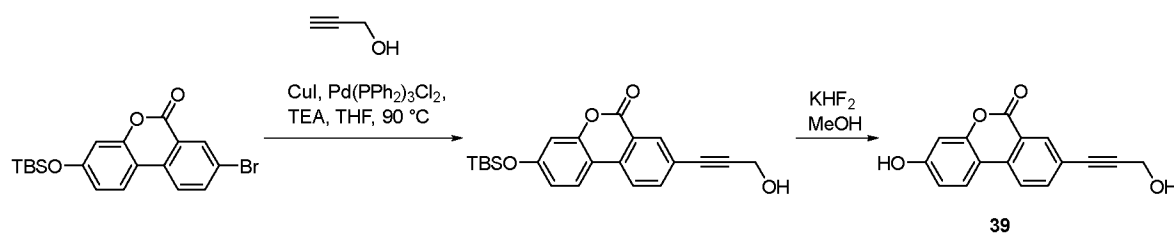
Step 5: Synthesis of 3-hydroxy-9-((tetrahydro-2H-pyran-4-yl)oxy)-6H-benzo[c]chromen-6-one



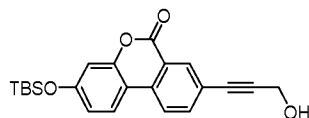
3-(benzyloxy)-9-((tetrahydro-2H-pyran-4-yl)oxy)-6H-benzo[c]chromen-6-one (135mg, 0.340 mmol, 1.0 eq.) was dissolved in MeOH/DCM (10 mL, 10/1) and Pd(OH)₂/C (70mg) was added in one portion. Then the reaction mixture was evacuated and backfilled with N₂ three times before putting it under hydrogen atmosphere (balloon). The reaction mixture was stirred for 4h and upon complete consumption of starting material (as indicated by TLC) filtered over silica and concentrated under vacuum to afford the crude product which was loaded on silica and purified by MPLC (SiO₂, 12g, EtOAc in Hex 0-50 %) to afford 3-hydroxy-9-((tetrahydro-2H-pyran-4-yl)oxy)-6H-benzo[c]chromen-6-one (40mg, 34%) as a white solid. ¹H NMR (400 MHz, DMSO) δ 10.33 (s, 1H), 8.25 (d, J = 8.9 Hz, 1H), 8.11 (d, J = 8.9 Hz, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.17 (dd, J = 8.9, 2.4 Hz, 1H), 6.83 (dd, J = 8.7, 2.4 Hz, 1H), 6.73 (d, J = 2.4 Hz, 1H), 4.97 (tt, J = 8.6, 4.1 Hz, 1H), 3.90 (dt, J = 11.7, 4.3 Hz, 2H), 3.56 (ddd, J = 11.8, 9.6, 2.7 Hz, 2H), 2.07 (dd, J = 11.3, 7.7 Hz, 2H), 1.66 (ddt, J = 13.7, 9.1, 4.6 Hz, 2H).

G) Ester “A” ring analogues with alkynyl substitution prepared by Sonogashira reaction

Synthesis of 3-hydroxy-8-(3-hydroxyprop-1-yn-1-yl)-6H-benzo[c]chromen-6-one (39)



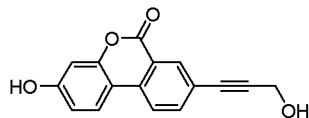
Step 1: Synthesis of 3-((*tert*-butyldimethylsilyl)oxy)-8-(3-hydroxyprop-1-yn-1-yl)-6H-benzo[c]chromen-6-one



To a solution of S8-bromo-3-((*tert*-butyldimethylsilyl)oxy)-6H-benzo[c]chromen-6-one (1.45g, 3.58mmol, 1.0 eq.) in THF (50 mL) in a 250 mL flask was subsequently added propargyl alcohol

(501mg, 8.94mmol, 2.5 eq.), Pd(PPh₃)₂Cl₂ (251mg, 0.360 mmol, 0.1 eq.) and CuI (68mg, 0.36mmol, 0.1 eq.) and the reaction was degased at r.t. with N₂ for 10min. Triethylamine (724mg, 7.15 mmol, 2.0 eq.) was added in one portion and the reaction mixture was put into a pre-heated oil-bath at 90 °C. Upon full conversion of the starting material (as indicated by TLC) the reaction mixture was allowed to cool to r.t. and quenched with water and extracted with EtOAc (2x 100 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude product was purified by MPLC (SiO₂, 80 g, EtOAc in Hex 0-40%) to afford 3-((*tert*-butyldimethylsilyl)oxy)-8-(3-hydroxyprop-1-yn-1-yl)-6H-benzo[*c*]chromen-6-one (490mg, 36%) as a brownish solid. ¹H NMR (400 MHz, CDCl₃) δ 8.41 (d, J = 1.8 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.79 (dd, J = 8.3, 1.8 Hz, 1H), 6.94 – 6.80 (m, 2H), 4.54 (d, J = 6.1 Hz, 2H), 1.00 (s, 9H), 0.26 (s, 6H).

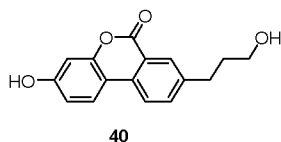
Step 2: Synthesis of 3-hydroxy-8-(3-hydroxyprop-1-yn-1-yl)-6H-benzo[*c*]chromen-6-one



3-((*tert*-butyldimethylsilyl)oxy)-8-(3-hydroxyprop-1-yn-1-yl)-6H-benzo[*c*]chromen-6-one (160mg, 0.420 mmol, 1.0 eq.) was dissolved in MeOH (2mL) and cooled to r.t. in an ice-bath and the resulting yellow solution was stirred for 10min. Then KHF₂ (66mg, 0.82mmol, 2.0 eq.) was added in on portion and the reaction was stirred at room temperature overnight. Upon complete consumption of the starting material (as indicated by TLC), the reaction mixture was filtered over a glass frit (Por. 4) and the filter residue was washed with MeOH and dried under vacuum to afford 3-hydroxy-8-(3-methoxyprop-1-yn-1-yl)-6H-benzo[*c*]chromen-6-one (112mg, 0.420 mmol, 99%) as a pale brown solid. ¹H NMR (400 MHz, DMSO) δ 10.45 (s, 1H), 8.26 (d, J = 8.4 Hz, 1H), 8.15 (d, J = 8.8 Hz, 1H), 8.12 (d, J = 1.8 Hz, 1H), 7.87 (dd, J = 8.4, 1.9 Hz, 1H), 6.85 (dd, J = 8.7, 2.4 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H), 5.41 (s, 1H), 4.35 (s, 2H).

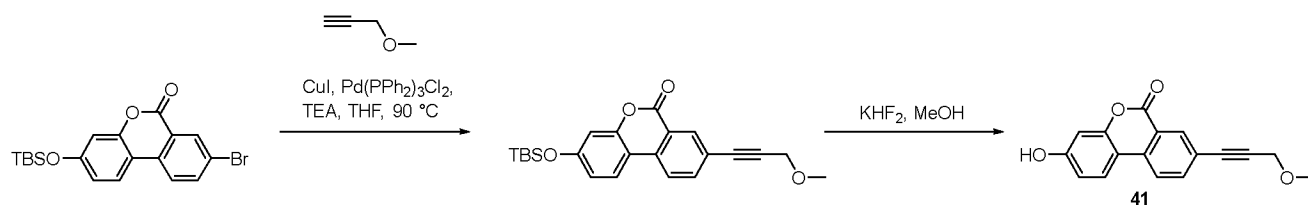
Additionally, the hydrogenation of the above compound was carried out as described below:

Step 3: Synthesis of 3-hydroxy-8-(3-hydroxypropyl)-6H-benzo[*c*]chromen-6-one (40)

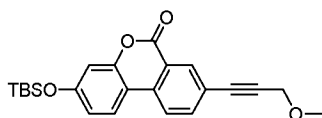


3-hydroxy-8-(3-methoxyprop-1-yn-1-yl)-6H-benzo[c]chromen-6-one (86mg, 0.32mmol, 1.0 eq.) and Pd(OH)₂/C (9mg, 0.07mmol, 0.2 eq.) in MeOH (5ml) was hydrogenated under atmospheric pressure overnight. The reaction mixture was filtered over a pad of celite and the solvent was evaporated concentrate under vacuum to afford 3-hydroxy-8-(3-hydroxypropyl)-6H-benzo[c]chromen-6-one (70 mg, 80%) as a white solid. MS (ESI⁺): m/z = 271. ¹H NMR (400 MHz, DMSO) δ 8.13 (d, J = 8.3 Hz, 1H), 8.04 (dd, J = 8.8, 2.2 Hz, 1H), 7.97 (d, J = 1.9 Hz, 1H), 7.70 (dd, J = 8.3, 2.0 Hz, 1H), 6.76 (dd, J = 8.7, 2.4 Hz, 1H), 6.64 (d, J = 2.5 Hz, 1H), 4.52 (s, 1H), 3.43 (t, J = 6.4 Hz, 2H), 2.81 – 2.71 (m, 2H), 1.86 – 1.73 (m, 2H).

Synthesis of 3-hydroxy-8-(3-methoxyprop-1-yn-1-yl)-6H-benzo[c]chromen-6-one (41)



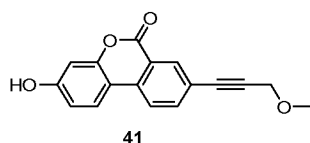
Step 1: Synthesis of 3-((*tert*-butyldimethylsilyl)oxy)-8-(3-methoxyprop-1-yn-1-yl)-6H-benzo[c]chromen-6-one



To a solution of 8-bromo-3-((*tert*-butyldimethylsilyl)oxy)-6H-benzo[c]chromen-6-one (370mg, 0.910 mmol, 1.0 eq.) in THF (3.04mL) in a 20 mL Biotage MW vial was subsequently added 3-methoxyprop-1-yne (224mg, 3.19 mmol, 3.5 eq.), Pd(PPh₃)₂Cl₂ (64mg, 0.09mmol, 0.1 eq.) and CuI (17mg, 0.09mmol, 0.1 eq.) and the reaction was degased at r.t. with N₂ for 10min. Triethylamine (277mg, 2.74 mmol, 3.0 eq.) was added in one portion and the reaction mixture was put into a pre-heated oil-bath at 90 °C. Upon full conversion of the starting material (as indicated by TLC) the reaction mixture was allowed to cool to r.t. and quenched with water and extracted

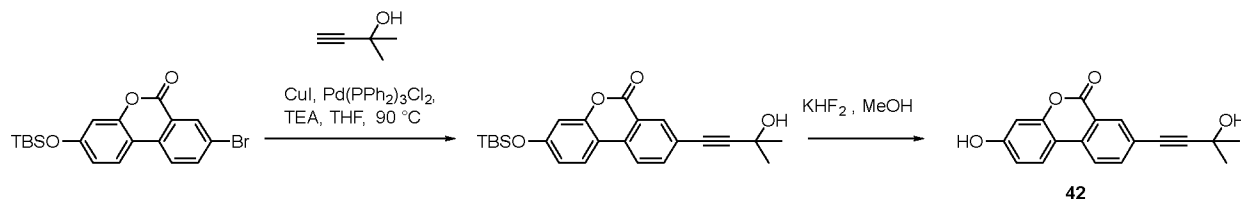
with EtOAc (2x 25mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude product was purified by MPLC (SiO₂, 40 g, EtOAc in Hex 0-40%) to afford 3-((*tert*-butyldimethylsilyl)oxy)-8-(3-methoxyprop-1-yn-1-yl)-6H-benzo[*c*]chromen-6-one (160mg 44%) as a brownish solid. ¹H NMR (400 MHz, CDCl₃) δ 8.42 (d, J = 1.8 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.80 (dd, J = 8.4, 1.8 Hz, 1H), 6.86 – 6.81 (m, 2H), 4.35 (s, 2H), 3.48 (s, 3H), 1.00 (s, 9H), 0.26 (s, 6H).

Step 2: Synthesis of 3-hydroxy-8-(3-methoxyprop-1-yn-1-yl)-6H-benzo[*c*]chromen-6-one

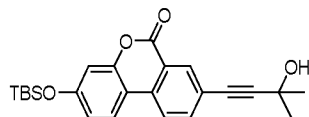


3-((*tert*-butyldimethylsilyl)oxy)-8-(3-methoxyprop-1-yn-1-yl)-6H-benzo[*c*]chromen-6-one (160mg, 0.410 mmol, 1.0 eq.) was dissolved in MeOH (2mL) and cooled to r.t. in an ice-bath and the resulting yellow solution was stirred for 10min. Then KHF₂ (63mg, 0.81mmol, 2.0 eq.) was added in on portion and the reaction was stirred overnight. Upon complete consumption of the starting material (as indicated by TLC) the reaction mixture was filtered over a glass frit (Por.4) and the filter residue was washed with MeOH and dried under vacuum to afford 3-hydroxy-8-(3-methoxyprop-1-yn-1-yl)-6H-benzo[*c*]chromen-6-one (85mg, 75%) as a pale brown solid. ¹H NMR (400 MHz, DMSO) δ 10.45 (s, 1H), 8.28 (d, J = 8.5 Hz, 1H), 8.20 – 8.13 (m, 2H), 7.91 (dd, J = 8.4, 1.9 Hz, 1H), 6.86 (dd, J = 8.7, 2.4 Hz, 1H), 6.76 (d, J = 2.4 Hz, 1H), 4.38 (s, 2H), 3.36 (s, 3H).

Synthesis of 3-hydroxy-8-(3-hydroxy-3-methylbut-1-yn-1-yl)-6H-benzo[*c*]chromen-6-one (42)

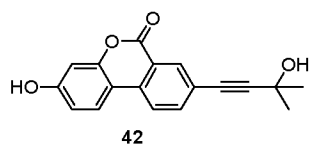


Step 1: Synthesis of 3-((*tert*-butyldimethylsilyl)oxy)-8-(3-hydroxy-3-methylbut-1-yn-1-yl)-6H-benzo[*c*]chromen-6-one



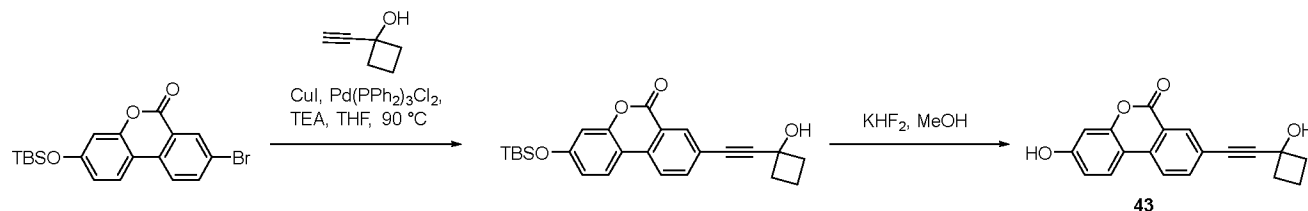
To a solution of 8-bromo-3-((tert-butyldimethylsilyl)oxy)-6H-benzo[c]chromen-6-one (370mg, 0.910 mmol, 1.0 eq.) in THF (3.0 mL) in a 20 mL Biotage MW vial was subsequently added 2-methylbut-3-yn-2-ol (269mg, 3.19mmol, 3.5 eq.), Pd(PPh₃)₂Cl₂ (64mg, 0.090 mmol, 0.1 eq.) and CuI (17mg, 0.090 mmol, 0.1 eq.) and the reaction was degased at r.t. with N₂ for 10min. Triethylamine (277mg, 2.74mmol, 3.0 eq.) was added in one portion and the reaction mixture was put into a pre-heated oil-bath at 90 °C. Upon full conversion of the starting material (as indicated by TLC) the reaction mixture was allowed to cool to r.t. and quenched with water and extracted with EtOAc (2x 25mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude product was purified by MPLC (SiO₂, 40 g, EtOAc in Hex 0-40%) to afford 3-((tert-butyldimethylsilyl)oxy)-8-(3-hydroxy-3-methylbut-1-yn-1-yl)-6H-benzo[c]chromen-6-one (233mg, 0.570 mmol, 63%) as a yellowish solid. ¹H NMR (400 MHz, CDCl₃) δ 8.41 (d, J = 1.8 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.78 (dd, J = 8.4, 1.9 Hz, 1H), 6.88 – 6.82 (m, 2H), 1.65 (s, 6H), 1.00 (s, 9H), 0.26 (s, 6H).

Step 2: Synthesis of 3-hydroxy-8-(3-hydroxy-3-methylbut-1-yn-1-yl)-6H-benzo[c]chromen-6-one

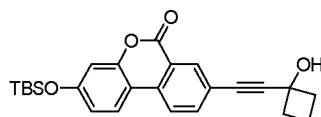


3-((tert-butyldimethylsilyl)oxy)-8-(3-hydroxy-3-methylbut-1-yn-1-yl)-6H-benzo[c]chromen-6-one (233mg, 0.570 mmol, 1.0 eq.) was dissolved in MeOH (3mL) and cooled to r.t. in an ice-bath and the resulting yellow solution was stirred for 10min. Then KHF₂ (89mg, 1.1mmol, 2.0 eq.) was added in on portion and the reaction was stirred overnight. Upon complete consumption of the starting material (as indicated by TLC) the reaction mixture was filtered over a glass frit (Por.4) and the filter residue was washed with MeOH and dried under vacuum to afford 3-hydroxy-8-(3-hydroxy-3-methylbut-1-yn-1-yl)-6H-benzo[c]chromen-6-one (120mg, 0.410 mmol, 72%) as a pale brown solid. ¹H NMR (400 MHz, DMSO) δ 10.44 (s, 1H), 8.25 (d, J = 8.5 Hz, 1H), 8.16 (d, J = 8.9 Hz, 1H), 8.10 (d, J = 1.8 Hz, 1H), 7.83 (dd, J = 8.4, 1.9 Hz, 1H), 6.86 (dd, J = 8.8, 2.4 Hz, 1H), 6.76 (d, J = 2.4 Hz, 1H), 5.54 (s, 1H), 3.32 (s, 6H).

Synthesis of 3-hydroxy-8-((1-hydroxycyclobutyl)ethynyl)-6H-benzo[c]chromen-6-one (**43**)

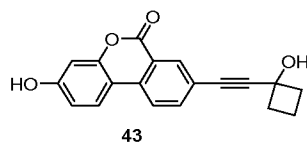


Step 1: Synthesis of 3-((*tert*-butyldimethylsilyl)oxy)-8-((1-hydroxycyclobutyl)ethynyl)-6H-benzo[c]chromen-6-one



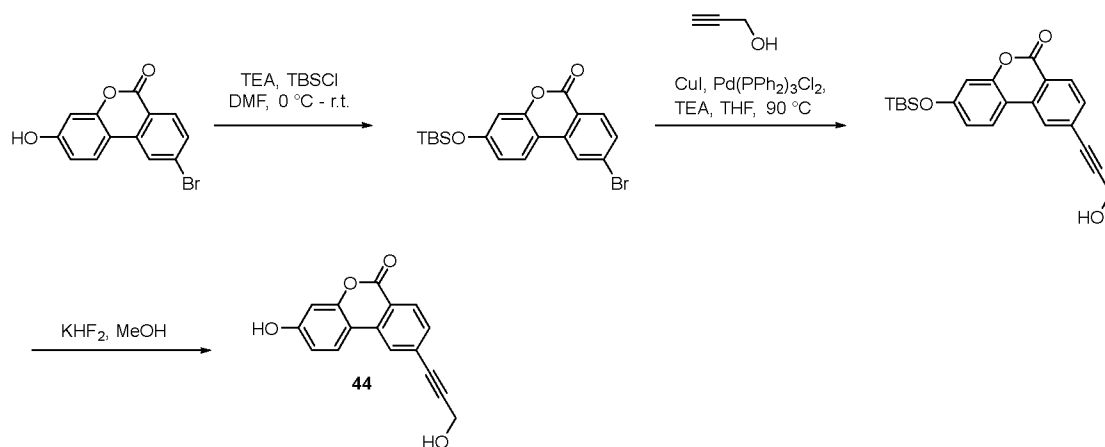
To a solution of 8-bromo-3-((*tert*-butyldimethylsilyl)oxy)-6H-benzo[c]chromen-6-one (250mg, 0.620 mmol, 1.0 eq.) in THF (2.06mL) in a 20 mL Biotage MW vial was subsequently added 1-ethynylcyclobutan-1-ol (208mg, 2.16mmol, 3.5 eq.), Pd(PPh₃)₂Cl₂ (43mg, 0.060 mmol, 0.1 eq.) and CuI (12mg, 0.060 mmol, 0.1 eq.) and the reaction was degased at r.t. with N₂ for 10min. Triethylamine (187mg, 1.85mmol, 3.00 eq.) was added in one portion and the reaction mixture was put into a pre-heated oil-bath at 90 °C. Upon full conversion of the starting material (as indicated by TLC) the reaction mixture was allowed to cool to r.t., quenched with water and extracted with EtOAc (2x 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude product was purified by MPLC (SiO₂, 40 g, EtOAc in Hex 0-40%) to afford 3-((*tert*-butyldimethylsilyl)oxy)-8-((1-hydroxycyclobutyl)ethynyl)-6H-benzo[c]chromen-6-one (195mg, 75%) as a yellowish solid. ¹H NMR (400 MHz, CDCl₃) δ 8.38 (d, J = 1.8 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.6 Hz, 1H), 7.76 (dd, J = 8.4, 1.9 Hz, 1H), 6.86 – 6.78 (m, 2H), 2.61 – 2.52 (m, 2H), 2.36 (td, J = 9.3, 2.8 Hz, 2H), 2.06 – 1.79 (m, 2H), 1.00 (s, 9H), 0.25 (s, 6H).

Step 2: Synthesis of 3-hydroxy-8-((1-hydroxycyclobutyl)ethynyl)-6H-benzo[c]chromen-6-one

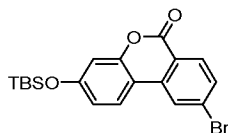


3-((*tert*-butyldimethylsilyl)oxy)-8-((1-hydroxycyclobutyl)ethynyl)-6H-benzo[*c*]chromen-6-one (195mg, 0.460 mmol, 1.0 eq.) was dissolved in MeOH (2mL) and cooled to r.t. in an ice-bath and the resulting yellow solution was stirred for 10min. Then KHF₂ (72mg, 0.93mmol, 2.0 eq.) was added in on portion and the reaction was stirred overnight. Upon complete consumption of the starting material (as indicated by TLC) the reaction mixture was filtered over a glass frit (Por.4) and the filter residue was washed with MeOH and dried under vacuum to afford 3-hydroxy-8-((1-hydroxycyclobutyl)ethynyl)-6H-benzo[*c*]chromen-6-one (100mg, 70%) as a white solid. ¹H NMR (400 MHz, DMSO) δ 10.44 (s, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.17 (d, *J* = 8.9 Hz, 1H), 8.13 (d, *J* = 1.8 Hz, 1H), 7.87 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.86 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.76 (d, *J* = 2.4 Hz, 1H), 5.95 (s, 1H), 2.41 (ddd, *J* = 9.2, 7.6, 4.4 Hz, 2H), 2.25 (td, *J* = 9.3, 2.7 Hz, 2H), 1.84 – 1.76 (m, 2H).

Synthesis of 3-hydroxy-9-(3-hydroxyprop-1-yn-1-yl)-6H-benzo[*c*]chromen-6-one (**44**)



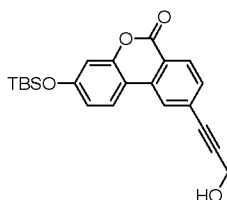
Step 1: Synthesis of 9-bromo-3-((*tert*-butyldimethylsilyl)oxy)-6H-benzo[*c*]chromen-6-one



9-bromo-3-hydroxy-6H-benzo[*c*]chromen-6-one (610mg, 2.10 mmol, 1.0 eq.) was suspended in DMF (10 mL) and triethylamine (636mg, 6.29mmol, 3.0 eq.) was added in one portion. The reaction mixture was cooled to 0 °C in an ice-bath and stirred at this temperature for 10min. Subsequently, TBSCl (411mg, 2.72mmol, 1.3 eq.) was added in one portion and the reaction mixture was allowed to warm to r.t. and stirred for an additional 2h. Upon full conversion of the

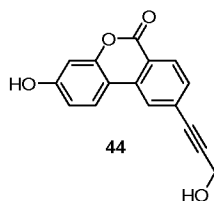
starting material (as indicated by TLC) the reaction mixture was quenched with half-saturated aqueous sodium bicarbonate solution, extracted with ethyl acetate and the combined organic phases dried over anhydrous Na_2SO_4 . The crude product was purified by MPLC (SiO_2 , 80 g, EtOAc in Hex 0-15%) to afford 9-bromo-3-((*tert*-butyldimethylsilyl)oxy)-6H-benzo[c]chromen-6-one (566mg, 67%) as a light brown solid. ^1H NMR (400 MHz, CDCl_3) δ 8.10 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 1.8 Hz, 1H), 7.75 (d, J = 8.5 Hz, 1H), 7.52 (dd, J = 8.5, 1.8 Hz, 1H), 6.84 – 6.67 (m, 2H), 0.90 (s, 9H), 0.17 (s, 6H).

Step 2: Synthesis of 3-((*tert*-butyldimethylsilyl)oxy)-9-(3-hydroxyprop-1-yn-1-yl)-6H-benzo[c]chromen-6-one



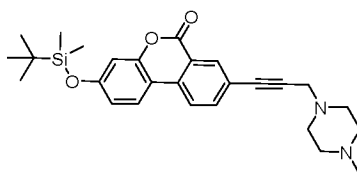
To a solution of 9-bromo-3-((*tert*-butyldimethylsilyl)oxy)-6H-benzo[c]chromen-6-one (250mg, 0.620 mmol, 1.0 eq.) in THF (2.0 mL) in a 20 mL Biotage MW vial was subsequently added propargyl alcohol (208mg, 2.16mmol, 3.5 eq.), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (43mg, 0.060 mmol, 0.1 eq.) and CuI (12mg, 0.060 mmol, 0.1 eq.) and the reaction was sparged at r.t. with N_2 for 10min. Triethylamine (187mg, 1.85mmol, 3.0 eq.) was added in one portion and the reaction mixture was put into a pre-heated oil-bath at 90 °C. Upon full conversion of the starting material (as indicated by TLC) the reaction mixture was allowed to cool to r.t., quenched with water and extracted with EtOAc (2x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by MPLC (SiO_2 , 40 g, EtOAc in Hex 0-40%) to afford 3-((*tert*-butyldimethylsilyl)oxy)-9-(3-hydroxyprop-1-yn-1-yl)-6H-benzo[c]chromen-6-one (176mg, 75%) as a yellowish solid. ^1H NMR (500 MHz, DMSO) δ 11.36 (s, 1H), 8.28 (s, 1H), 8.19 (dd, J = 8.8, 1.6 Hz, 1H), 8.13 (d, J = 8.2 Hz, 1H), 7.51 (d, J = 8.2 Hz, 1H), 6.80 (dd, J = 8.8, 2.4 Hz, 1H), 6.71 (d, J = 2.4 Hz, 1H), 5.63 (d, J = 124.9 Hz, 1H), 4.39 (s, 2H), 0.90 (s, 9H), 0.17 (s, 6H).

Step 2: Synthesis of 3-hydroxy-9-(3-hydroxyprop-1-yn-1-yl)-6H-benzo[c]chromen-6-one



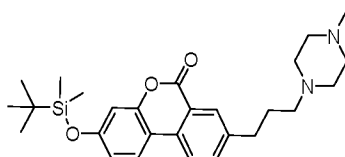
3-((*tert*-butyldimethylsilyl)oxy)-9-(3-hydroxyprop-1-yn-1-yl)-6H-benzo[c]chromen-6-one (176 mg, 0.460 mmol, 1.0 eq.) was dissolved in MeOH (2mL) and the resulting yellow solution was stirred for 10min. Then KHF₂ (72mg, 0.93mmol, 2.0 eq.) was added in on portion and the reaction was stirred overnight. Upon complete consumption of the starting material (as indicated by TLC) the reaction mixture was filtered over a glass frit (Por.4) and the filter residue was washed with MeOH and dried under vacuum to yield 3-hydroxy-8-((1-hydroxycyclobutyl)ethynyl)-6H-benzo[c]chromen-6-one (90mg, 0.34mmol, 73%) as a white solid. MS (ESI⁺): *m/z* = 267. ¹H NMR (500 MHz, DMSO) δ 11.36 (s, 1H), 8.28 (s, 1H), 8.19 (dd, *J* = 8.8, 1.6 Hz, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 6.80 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.71 (d, *J* = 2.4 Hz, 1H), 5.63 (d, *J* = 124.9 Hz, 1H), 4.39 (s, 2H).

Synthesis of 3-((*tert*-butyldimethylsilyl)oxy)-8-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)-6H-benzo[c]chromen-6-one



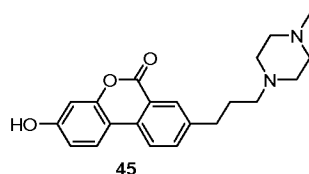
Mesyl Chloride (0.037 mL, 0.47 mmol) was added to a solution of 3-((*tert*-butyldimethylsilyl)oxy)-8-(3-hydroxyprop-1-yn-1-yl)-6H-benzo[c]chromen-6-one (140 mg, 0.360 mmol) and NEt₃ (0.150ml, 1.10mmol) in THF (5 mL) at 0°C and the reaction mixture was stirred at rt for 1h. TLC showed complete conversion of the starting material. *N*-methylpiperazine (111 mg, 1.10mmol) was added and the mixture was heated at 60°C overnight. A saturated solution of Ammonium chloride was added and the aqueous layer was extracted with EtOAc 3 times. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude product was purified by MPLC (SiO₂, MeOH/DCM 0% to 20%) to afford 3-((*tert*-butyldimethylsilyl)oxy)-8-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)-6H-benzo[c]chromen-6-one, which was used without further purification in the next step.

Synthesis of 3-((*tert*-butyldimethylsilyl)oxy)-8-(3-(4-methylpiperazin-1-yl)propyl)-6H-benzo[c]chromen-6-one



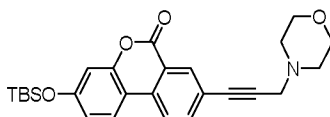
A suspension 3-((*tert*-butyldimethylsilyl)oxy)-8-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)-6H-benzo[c]chromen-6-one **10** (67mg, 0.14mmol) and Pd(OH)₂/C (20 mg, 0.030mmol) in MeOH (5ml) was hydrogenated under atmospheric pressure overnight. The reaction mixture was filtered over a pad of celite and the solvent was evaporated concentrate under vacuum to afford 3-((*tert*-butyldimethylsilyl)oxy)-8-(3-(4-methylpiperazin-1-yl)propyl)-6H-benzo[c]chromen-6-one (64 mg, 95%) as yellowish oil, which was used without further purification in the next step.

Synthesis of 3-hydroxy-8-(3-(4-methylpiperazin-1-yl)propyl)-6H-benzo[c]chromen-6-one (**45**)



45 was prepared starting from 3-((*tert*-butyldimethylsilyl)oxy)-8-(3-(4-methylpiperazin-1-yl)propyl)-6H-benzo[c]chromen-6-one (65 mg, 0.14 mmol) and KHF₂ (22mg, 0.28 mmol) to afford after purification by MPLC (SiO₂, MeOH/DCM 5% to 30%) 3-hydroxy-8-(3-(4-methylpiperazin-1-yl)propyl)-6H-benzo[c]chromen-6-one (36mg, 73%) as a yellowish solid. R_f = 0.4 (MeOH/DCM 30/70). ¹H NMR (400 MHz, CDCl₃) δ 8.04 (s, 1H), 7.73 (d, J = 8.5 Hz, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.51 (d, J = 6.5 Hz, 1H), 6.61 (d, J = 9.1 Hz, 1H), 6.53 (s, 1H), 2.86 – 2.48 (m, 12H), 2.39 (s, 3H), 1.99 (s, 2H).

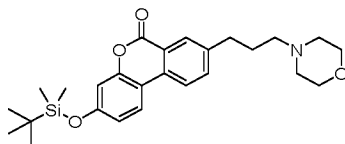
Synthesis of 3-((*tert*-butyldimethylsilyl)oxy)-8-(3-morpholinoprop-1-yn-1-yl)-6H-benzo[c]chromen-6-one



Mesyl Chloride (0.04ml, 0.51mmol) was added to a solution of 3-((*tert*-butyldimethylsilyl)oxy)-8-(3-hydroxyprop-1-yn-1-yl)-6H-benzo[c]chromen-6-one (150mg, 0.39mmol) and NEt₃

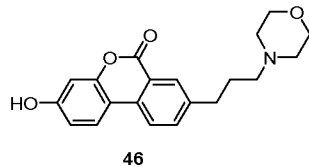
(0.160ml, 1.18mmol) in THF (5 mL) at 0°C and the reaction mixture was stirred at rt for 1h. TLC showed complete conversion of the starting material. Morpholine (0.100ml, 1.18 mmol) was added and the mixture was heated at 60°C overnight. A saturated solution of Ammonium chloride was added and the reaction mixture was extracted with EtOAc 3 times. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude product was purified by MPLC (SiO₂, MeOH/DCM 0% to 20%) to afford 3-((*tert*-butyldimethylsilyl)oxy)-8-(3-morpholinoprop-1-yn-1-yl)-6H-benzo[*c*]chromen-6-one (101mg, 57%), which was used without further purification in the next step.

Synthesis of 3-((*tert*-butyldimethylsilyl)oxy)-8-(3-morpholinopropyl)-6H-benzo[*c*]chromen-6-one



3-(3-((*tert*-butyldimethylsilyl)oxy)-6-oxo-6H-benzo[*c*]chromen-8-yl)prop-2-yn-1-yl methanesulfonate OTBS-morpholine (100mg, 0.220mmol) and Pd(OH)₂/C (31mg, 0.22mmol) in MeOH (5ml) was hydrogenated under atmospheric pressure overnight. The reaction mixture was filtered over a pad of celite and the solvent was concentrated under vacuum to afford 3-((*tert*-butyldimethylsilyl)oxy)-8-(3-morpholinopropyl)-6H-benzo[*c*]chromen-6-one (70mg, 69%) as a yellowish oil. ¹H NMR (400 MHz, CDCl₃) δ 8.16 (d, *J* = 1.9 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.87 (d, *J* = 9.4 Hz, 1H), 7.61 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.82 (h, *J* = 2.4 Hz, 2H), 3.71 (t, *J* = 4.7 Hz, 4H), 2.76 (d, *J* = 7.8 Hz, 2H), 2.43 (t, *J* = 4.6 Hz, 4H), 2.36 (dd, *J* = 8.4, 6.4 Hz, 2H), 1.87 (h, *J* = 7.4, 6.8 Hz, 2H), 0.99 (s, 9H), 0.24 (s, 6H).

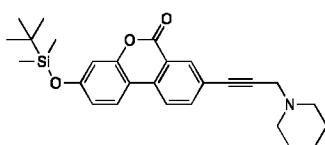
Synthesis of 3-hydroxy-8-(3-morpholinopropyl)-6H-benzo[*c*]chromen-6-one (46)



46 was prepared starting from 3-((*tert*-butyldimethylsilyl)oxy)-8-(3-morpholinopropyl)-6H-benzo[*c*]chromen-6-one (70mg, 0.15mmol) and KHF₂ (24mg, 0.31mmol) to afford after purification by MPLC (SiO₂, MeOH/DCM 5% to 30%) 3-hydroxy-8-(3-morpholinopropyl)-6H-

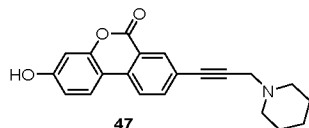
benzo[c]chromen-6-one (70 mg, 69%) as a yellowish solid. $R_f = 0.4$ (MeOH/DCM 30/70). ^1H NMR (400 MHz, DMSO) δ 10.31 (s, 1H), 8.18 (d, $J = 8.3$ Hz, 1H), 8.13 (d, $J = 8.9$ Hz, 1H), 8.01 (d, $J = 1.9$ Hz, 1H), 7.75 (dd, $J = 8.3, 2.0$ Hz, 1H), 6.83 (dd, $J = 8.7, 2.4$ Hz, 1H), 6.74 (d, $J = 2.4$ Hz, 1H), 3.57 (t, $J = 4.7$ Hz, 4H), 2.74 (t, $J = 7.6$ Hz, 2H), 2.35 – 2.31 (m, 4H), 2.28 (t, $J = 7.2$ Hz, 2H), 1.78 (p, $J = 7.4$ Hz, 2H).

Synthesis of 3-((*tert*-butyldimethylsilyl)oxy)-8-(3-(piperidin-1-yl)prop-1-yn-1-yl)-6H-benzo[c]chromen-6-one



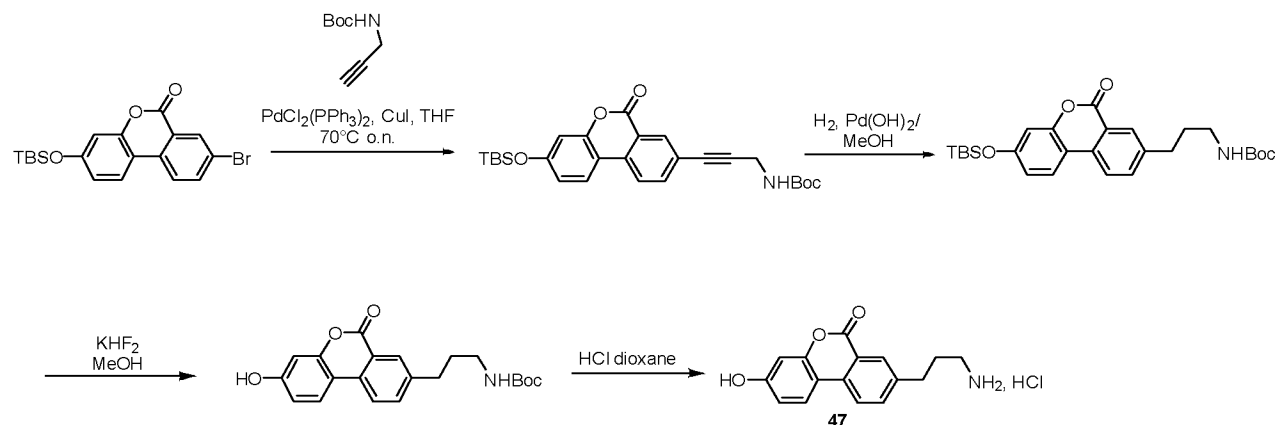
Mesyl Chloride (0.0980ml, 1.26mmol) was added to a solution of 3-((*tert*-butyldimethylsilyl)oxy)-8-(3-hydroxyprop-1-yn-1-yl)-6H-benzo[c]chromen-6-one (240mg, 0.630mmol) and NEt_3 (0.260ml, 1.89mmol) in THF (10 mL) at 0°C and the reaction mixture was stirred at rt for 1h. TLC showed complete conversion of the starting material. Piperidine (0.081ml, 0.82mmol) was added and the mixture was heated at 60°C overnight. A saturated solution of Ammonium chloride was added and the reaction mixture was extracted with EtOAc 3 times. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude product was purified by MPLC (SiO_2 , MeOH/DCM 0% to 20%) to afford 3-((*tert*-butyldimethylsilyl)oxy)-8-(3-(piperidin-1-yl)prop-1-yn-1-yl)-6H-benzo[c]chromen-6-one (66mg, 23%). ^1H NMR (400 MHz, CDCl_3) δ 8.41 (d, $J = 1.8$ Hz, 1H), 7.93 (d, $J = 8.4$ Hz, 1H), 7.88 (d, $J = 8.3$ Hz, 1H), 7.79 (dd, $J = 8.3, 1.8$ Hz, 1H), 6.85 (d, $J = 8.2$ Hz, 2H), 3.53 (s, 2H), 2.61 (s, 4H), 1.70 – 1.45 (m, 6H), 1.00 (s, 9H), 0.26 (s, 6H).

Synthesis of 3-hydroxy-8-(3-(piperidin-1-yl)prop-1-yn-1-yl)-6H-benzo[c]chromen-6-one (**47**)



47 was prepared starting from 3-((*tert*-butyldimethylsilyl)oxy)-8-(3-(piperidin-1-yl)prop-1-yn-1-yl)-6H-benzo[c]chromen-6-one (60mg, 0.13mmol) and KHF_2 (21mg, 0.27mmol) to afford after purification by MPLC (SiO_2 , EtOAc/cyclohexane 0% to 80%) to afford 3-hydroxy-8-(3-(piperidin-

1-yl)prop-1-yn-1-yl)-6H-benzo[c]chromen-6-one (37mg, 83%) as a yellowish solid. $R_f = 0.4$ (EtOAc/hexane 40%). ^1H NMR (400 MHz, CDCl_3) δ 7.70 – 7.62 (m, 2H), 7.59 (d, $J = 1.7$ Hz, 1H), 7.54 (dd, $J = 8.4, 1.8$ Hz, 1H), 6.82 (dd, $J = 8.7, 2.4$ Hz, 1H), 6.55 (d, $J = 2.4$ Hz, 1H), 3.36 (s, 2H), 2.77 (s, 4H), 1.80 (q, $J = 5.7$ Hz, 4H), 1.58 (b, 2H).



Synthesis of *tert*-butyl (3-(3-((*tert*-butyldimethylsilyl)oxy)-6-oxo-6H-benzo[c]chromen-8-yl)prop-2-yn-1-yl)carbamate

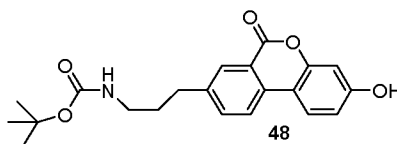
To a well degassed solution of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (41.8mg, 0.059mmol, 0.1eq) and CuI (11.3mg, 0.059mmol, 0.1eq) in THF (10 mL) and 8-bromo-3-((dimethyl(*tert*-butyl)silyl)oxy)-6H-benzo[c]chromen-6-one (250mg, 0.590mmol) and Prop-2-ynyl-carbamic acid *tert*-butyl ester (277mg, 1.79mmol, 3.0 eq) was added NEt_3 (0.330ml, 2.38mmol, 4.0 eq) and the mixture was heated at 70°C overnight. The reaction mixture was diluted with a saturated solution of NH_4Cl , and extracted with EtOAc. The organic layers was dried over sodium sulfate and concentrated under vacuum. The crude product was purified by MPLC (SiO_2 , EtOAc/hexane 0% to 20%) to afford *tert*-butyl (3-(3-((*tert*-butyldimethylsilyl)oxy)-6-oxo-6H-benzo[c]chromen-8-yl)prop-2-yn-1-yl)carbamate (190mg, 0.39mmol, 66 %) as a yellowish foam. $R_f = 0.4$ (EtOAc/hexane 20%). ^1H NMR (400 MHz, CDCl_3) δ 8.39 (d, $J = 1.7$ Hz, 1H), 7.93 (d, $J = 8.4$ Hz, 1H), 7.87 (dd, $J = 8.5, 0.8$ Hz, 1H), 7.77 (dd, $J = 8.3, 1.8$ Hz, 1H), 6.89 – 6.81 (m, 2H), 4.79 (s, 1H), 4.19 (d, $J = 5.6$ Hz, 2H), 1.48 (s, 9H), 1.00 (s, 9H), 0.26 (s, 6H).

Synthesis of *tert*-butyl (3-(3-((*tert*-butyldimethylsilyl)oxy)-6-oxo-6H-benzo[c]chromen-8-yl)propyl)carbamate

A suspension of *tert*-butyl (3-(3-((*tert*-butyldimethylsilyl)oxy)-6-oxo-6H-benzo[c]chromen-8-yl)prop-2-yn-1-yl)carbamate (190mg, 0.390mmol) and $\text{Pd}(\text{OH})_2/\text{C}$ 20% (56mg, 0.79mmol) was

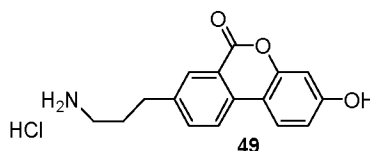
hydrogenated under atmospheric pressure in methanol, and stirred overnight. The reaction mixture was filtered over a pad of celite, and the solvent was evaporated under vacuum. The crude product was purified by MPLC (SiO₂, EtOAc/cyclohexane 0% to 20%) to afford *tert*-butyl (3-(3-((*tert*-butyldimethylsilyl)oxy)-6-oxo-6H-benzo[c]chromen-8-yl)propyl)carbamate (175mg, 91%) as a yellowish oil. *R*_f = 0.4 (EtOAc/hexane 20%). ¹H NMR (400 MHz, CDCl₃) δ 8.17 (d, *J* = 1.9 Hz, 1H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.88 (d, *J* = 9.3 Hz, 1H), 7.62 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.84 (dq, *J* = 4.5, 2.4 Hz, 2H), 4.57 (s, 1H), 3.18 (d, *J* = 7.0 Hz, 2H), 2.89 – 2.71 (m, 2H), 1.88 (p, *J* = 7.3 Hz, 2H), 1.45 (s, 9H), 1.00 (s, 9H), 0.26 (s, 6H).

Synthesis of *tert*-butyl (3-(3-hydroxy-6-oxo-6H-benzo[c]chromen-8-yl)propyl)carbamate (**48**)



48 was prepared starting from *tert*-butyl (3-(3-((*tert*-butyldimethylsilyl)oxy)-6-oxo-6H-benzo[c]chromen-8-yl)propyl)carbamate (170mg, 0.350mmol) and KHF₂ (55mg, 0.70mmol) to afford after purification by MPLC (SiO₂, EtOAc/cyclohexane 0% to 20%) *tert*-butyl (3-(3-hydroxy-6-oxo-6H-benzo[c]chromen-8-yl)propyl)carbamate (108mg, 0.290 mmol, 83%) as a white solid. *R*_f = 0.4 (EtOAc/hexane 20/100). ¹H NMR (400 MHz, DMSO) δ 10.27 (s, 1H), 8.15 (dd, *J* = 21.4, 8.5 Hz, 2H), 8.00 (d, *J* = 1.9 Hz, 1H), 7.73 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.87 (t, *J* = 5.4 Hz, 1H), 6.82 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.73 (d, *J* = 2.3 Hz, 1H), 2.94 (q, *J* = 6.6 Hz, 2H), 2.70 (t, *J* = 7.6 Hz, 2H), 1.72 (p, *J* = 7.3 Hz, 2H), 1.36 (s, 9H).

Synthesis of 8-(3-aminopropyl)-3-hydroxy-6H-benzo[c]chromen-6-one hydrochloride (**49**)

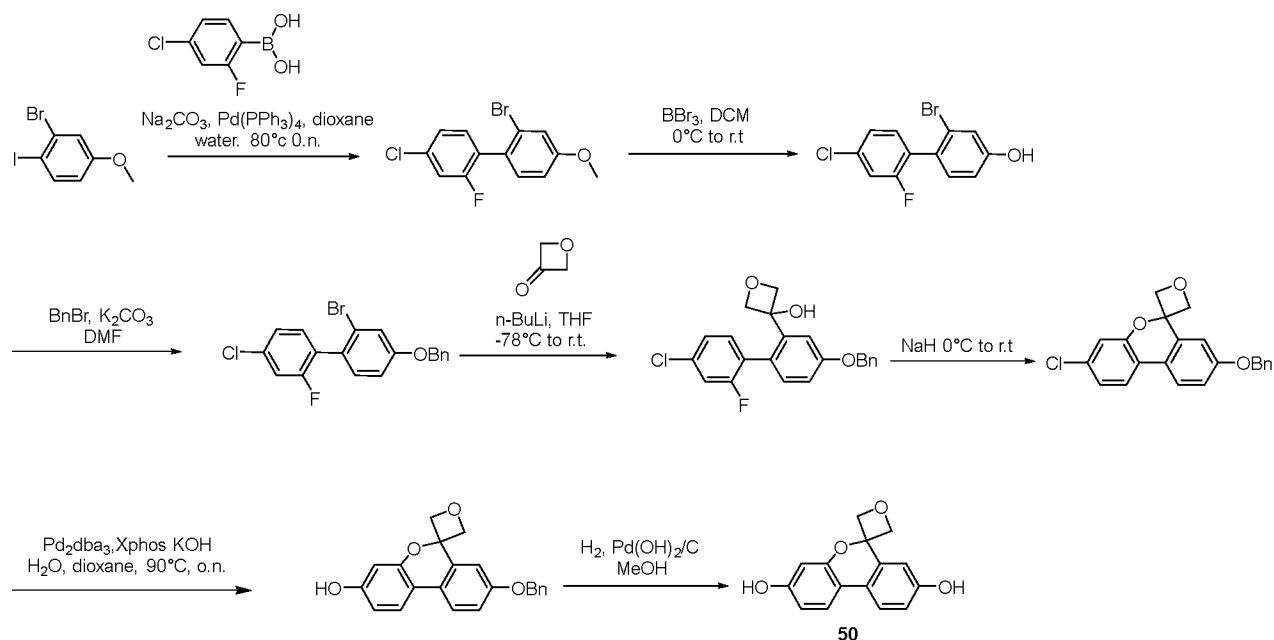


HCl (4M in Dioxane, 1.35 mL, 5.4mmol) was added to a solution of *tert*-butyl (3-(3-hydroxy-6-oxo-6H-benzo[c]chromen-8-yl)propyl)carbamate (100mg, 0.270mmol) in dioxane (0.5ml) at r.t. and the reaction mixture was stirred at r.t. overnight, and a precipitate was formed. The solvent

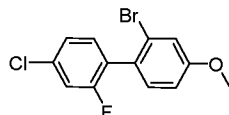
was concentrated under vacuum and the crude product was triturated in Et₂O, filtered, and dried to afford (3-aminopropyl)-3-hydroxy-6H-benzo[*c*]chromen-6-one hydrochloride (70mg, 86%) as a white solid. MS (ESI⁺): *m/z* = 270. ¹H NMR (400 MHz, DMSO) δ 10.36 (s, 1H), 8.22 (d, *J* = 8.3 Hz, 1H), 8.14 (d, *J* = 8.8 Hz, 1H), 8.05 (d, *J* = 1.9 Hz, 1H), 7.83 (s, 3H), 7.76 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.85 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.76 (dd, *J* = 2.4, 1.2 Hz, 1H), 2.81 (q, *J* = 7.7, 6.4 Hz, 4H), 1.98 – 1.85 (m, 2H).

H) Spirocycle (oxetane & azetidine) “A” ring analogies

Synthesis of spiro[benzo[*c*]chromene-6,3'-oxetane]-3,8-diol (**50**)



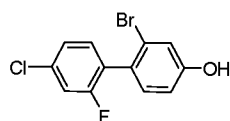
Step 1: Synthesis of 2-bromo-4'-chloro-2'-fluoro-4-methoxy-1,1'-biphenyl



2-bromo-1-iodo-4-methoxybenzene (4.00 g, 12.8 mmol) and (4-chloro-2-fluorophenyl) boronic acid (1.01g, 23.0 mmol) were dissolved in Dioxane (80 mL). Tetrakis(triphenylphosphine)palladium(0) (738mg, 0.640mmol) was added followed by a solution of Na₂CO₃ (2.70 g, 25.6mmol) and the reaction mixture was heated at 80°C overnight.

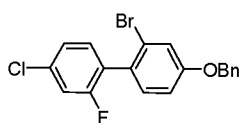
The reaction mixture was diluted with a saturated solution of sodium carbonate, and extracted with EtOAc twice. The combined organic layers were dried over sodium sulfate, and concentrated in vacuum. The crude product was purified by MPLC (SiO₂, 0 to 8% DCM/cyclohexane) to afford 2-bromo-4'-chloro-2'-fluoro-4-methoxy-1,1'-biphenyl (1.80 g, 45%) as a colorless oil. *R*_f = 0.2 (DCM/cyclohexane 3%). ¹H NMR (400 MHz, CDCl₃) δ 7.24 – 7.14 (m, 5H), 6.92 (dd, *J* = 8.5, 2.6 Hz, 1H), 3.84 (s, 3H).

Step 2: Synthesis of 2-bromo-4'-chloro-2'-fluoro-[1,1'-biphenyl]-4-ol



BBr₃ (1M in DCM, 6.97ml, 6.97mmol) was added at 0°C to a solution of 2-bromo-4'-chloro-2'-fluoro-4-methoxy-1,1'-biphenyl (1.10 g, 3.48mmol) in DCM (5 mL) and the reaction mixture was allowed to warm to r.t. overnight. Methanol (10 mL) was added at 0°C and the solvent was evaporated under vacuum. The crude product was diluted with a saturated solution of sodium bicarbonate and extracted with EtOAc. The combined organic layers were dried over sodium sulfate and concentrate under vacuum to afford 2-bromo-4'-chloro-2'-fluoro-[1,1'-biphenyl]-4-ol (1.10g), which was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.23 – 7.01 (m, 5H), 6.79 (dd, *J* = 8.4, 2.6 Hz, 1H).

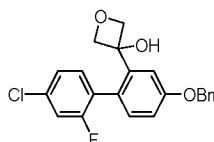
Step 3: Synthesis of 4-(benzyloxy)-2-bromo-4'-chloro-2'-fluoro-1,1'-biphenyl



Benzyl bromide (0.470ml, 3.98mmol) was added to a solution of 2-bromo-4'-chloro-2'-fluoro-[1,1'-biphenyl]-4-ol (1.00 g, 3.31mmol) and potassium carbonate (0.916g, 6.63mmol) in ACN (10 mL) and the mixture was heated at 60°C overnight. The crude was cooled to room temperature and extracted with Ethyl acetate from bicarbonate saturated solution. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude product was purified by MPLC (25 g silica cartridge, EtOAc/cyclhexane 0% to 10%) to afford 4-(benzyloxy)-2-bromo-4'-chloro-2'-fluoro-1,1'-biphenyl (1.10 g, 85 %) as colorless oil. ¹H NMR (400 MHz, CDCl₃) δ

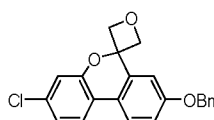
7.48 – 7.35 (m, 5H), 7.32 (d, $J = 2.6$ Hz, 1H), 7.23 – 7.15 (m, 4H), 6.99 (dd, $J = 8.5, 2.6$ Hz, 1H), 5.09 (s, 2H).

Step 4: Synthesis of 3-(4-(benzyloxy)-4'-chloro-2'-fluoro-[1,1'-biphenyl]-2-yl)oxetan-3-ol



*n*BuLi (1.6M in hexane, 2.58ml, 4.13mmol) was added dropwise at -78°C to a solution of 4-(benzyloxy)-2-bromo-4'-chloro-2'-fluoro-1,1'-biphenyl (900mg, 2.29mmol) in dry THF (8ml). The red pale solution was stirred at -78°C for 45min then a solution of oxetan-3-one (662mg, 9.19mmol) was added dropwise and the reaction was allowed to warm to room temperature over 5 h. The reaction mixture was quenched with NH_4Cl saturated solution and extracted with Ethyl acetate. The organic layers were dried over sodium sulfate. The crude product was purified by MPLC (25 g silica cartridge, EtOAc/cyclohexane 0% to 50%) to afford 3-(4-(benzyloxy)-4'-chloro-2'-fluoro-[1,1'-biphenyl]-2-yl)oxetan-3-ol (383mg, 85 %) as colorless oil. $R_f = 0.3$ (EtOAc/hexane 50/50). ^1H NMR (400 MHz, CDCl_3) δ 7.55 – 7.28 (m, 6H), 7.19 – 7.14 (m, 3H), 7.00 (dd, $J = 8.5, 2.6$ Hz, 1H), 6.85 (d, $J = 2.6$ Hz, 1H), 5.11 (s, 2H), 4.82 (s, 2H), 4.36 (s, 2H), 2.77 (s, 1H).

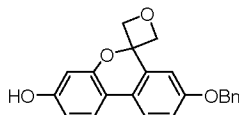
Step 5: Synthesis of 8-(benzyloxy)-3-chlorospiro[benzo[*c*]chromene-6,3'-oxetane



NaH (70.5mg, 1.76mmol, 60% dispersion in mineral oil) was added at 0°C to a solution of 3-(4-(benzyloxy)-4'-chloro-2'-fluoro-[1,1'-biphenyl]-2-yl)oxetan-3-ol (377mg, 0.980mmol) in DMF 4ml and the reaction was allowed to warm to room temperature overnight. The crude was extracted with 1/2 saturated solution of bicarbonate and ethyl acetate. The organic phase was dried over sodium sulfate and evaporated under vacuum. The crude product was purified by MPLC (25 g silica cartridge, EtOAc/cyclohexane 0% to 5%) to afford 8-(benzyloxy)-3-chlorospiro[benzo[*c*]chromene-6,3'-oxetane] (290mg, 81 %) as a yellow solid. $R_f = 0.3$ (EtOAc/hexane 10%). ^1H NMR (400 MHz, CDCl_3) δ 7.63 (d, $J = 8.7$ Hz, 1H), 7.54 (d, $J = 8.3$ Hz,

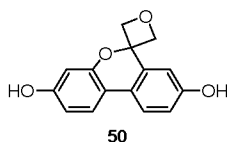
1H), 7.49 – 7.35 (m, 5H), 7.32 (d, J = 2.5 Hz, 1H), 7.08 (d, J = 2.1 Hz, 1H), 7.04 (dd, J = 8.7, 2.6 Hz, 1H), 7.01 (dd, J = 8.3, 2.1 Hz, 1H), 5.17 (s, 2H), 5.08 – 5.01 (m, 2H), 4.90 – 4.78 (m, 2H).

Step 6: Synthesis of 8-(benzyloxy)spiro[benzo[c]chromene-6,3'-oxetan]-3-ol

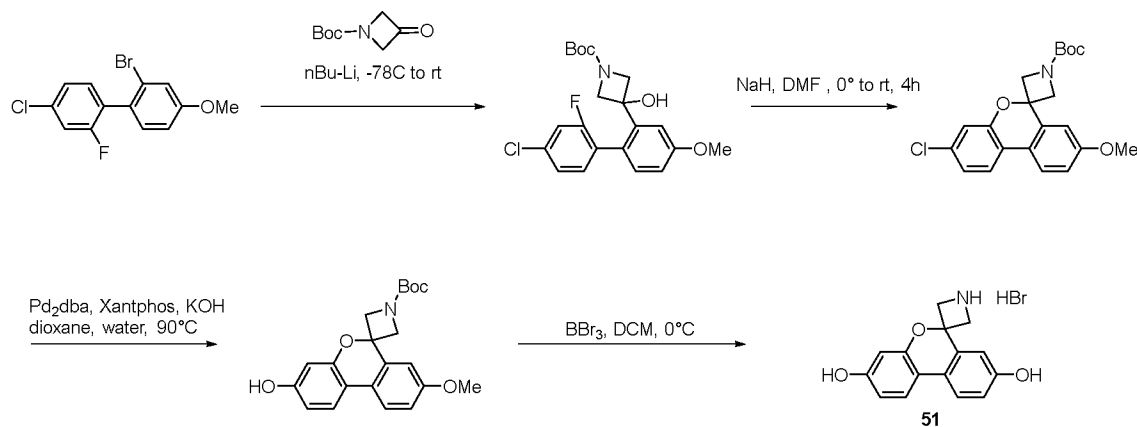


t-BuXPhos (9mg, 0.020mmol) was added to a suspension of Pd₂dba₃ (2.3mg, 0.099mmol) in Dioxane (1ml), degassed and stirred for 5minutes. 8-(benzyloxy)-3-chlorospiro[benzo[c]chromene-6,3'-oxetane] (45mg, 0.12mmol) was added followed by a solution of KOH (15mg, 0.27mmol) in water (0.3ml) at rt and the mixture was heated at 90°C overnight. Water was added and the mixture was extracted with EtOAc 3 times and the combined organic layers was dried over sodium sulfate, filtered and evaporated under vacuum. The crude product was purified by MPLC (25 g silica cartridge, EtOAc/cyclohexane 0% to 30%) to afford 8-(benzyloxy)spiro[benzo[c]chromene-6,3'-oxetan]-3-ol (30mg, 0.87mmol, 70 %) as a white solid. R_f = 0.3 (EtOAc/hexane 20%). MS (ESI⁺): m/z = 347. ¹H NMR (400 MHz, DMSO) δ 9.72 (s, 1H), 7.69 (d, J = 8.7 Hz, 1H), 7.60 (d, J = 8.3 Hz, 1H), 7.53 – 7.36 (m, 6H), 7.09 (dd, J = 8.6, 2.6 Hz, 1H), 6.56 – 6.43 (m, 2H), 5.21 (s, 2H), 4.86 – 4.80 (m, 4H).

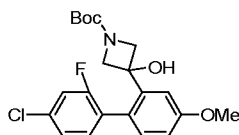
Step 7: Synthesis spiro[benzo[c]chromene-6,3'-oxetane]-3,8-diol



A suspension of 8-(benzyloxy)spiro[benzo[c]chromene-6,3'-oxetan]-3-ol (40mg, 0.12mmol) and Pd(OH)₂/C (16mg, 0.23mmol) in methanol (4ml) was hydrogenated under atmospheric pressure o.n. The reaction mixture was filtered over a pad of celite the solvent was evaporated and the product further purified by filtration over a pad of silica using DCM/methanol 10% to afford spiro[benzo[c]chromene-6,3'-oxetane]-3,8-diol (23mg, 0.09mmol, 78%) as a light yellow solid. MS (ESI⁺): m/z = 257. ¹H NMR (400 MHz, DMSO) δ 9.66 (d, J = 19.6 Hz, 2H), 7.57 (d, J = 8.5 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.09 (d, J = 2.4 Hz, 1H), 6.84 (dd, J = 8.4, 2.4 Hz, 1H), 6.51 – 6.44 (m, 2H), 4.83 (d, J = 7.3 Hz, 2H), 4.74 (d, J = 7.2 Hz, 2H).

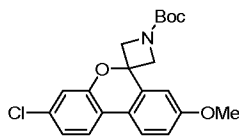
Synthesis of spiro[azetidine-3,6'-benzo[c]chromene]-3',8'-diol (**51**)

Step 1: Synthesis of tert-butyl 3-(4'-chloro-2'-fluoro-4-methoxy-[1,1'-biphenyl]-2-yl)-3-hydroxyazetidine-1-carboxylate



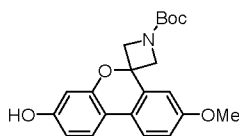
*n*BuLi (1.6M in hexane, 2.69ml, 4.31mmol) was added dropwise at -78°C to a solution of 4-(benzyloxy)-2-bromo-4'-chloro-2'-fluoro-1,1'-biphenyl (900mg, 2.29mmol) in dry THF (8ml). The red pale solution was stirred at -78°C for 45 min then a solution of tert-butyl 3-oxoazetidine-1-carboxylate (1.84g, 10.8mmol) in dry THF (5ml) was added dropwise and the reaction was allowed to warm to room temperature over 5 hours. The reaction mixture was quenched with NH₄Cl saturated solution and extracted with Ethyl acetate. The organic phases were dried over sodium sulfate. The crude product was purified by MPLC (80 g silica cartridge, EtOAc/cyclohexane 0% to 50%) to afford tert-butyl 3-(4'-chloro-2'-fluoro-4-methoxy-[1,1'-biphenyl]-2-yl)-3-hydroxyazetidine-1-carboxylate (400mg, 36%) as a mixture of two compounds as a colorless oil. *R*_f = 0.3 (EtOAc/hexane 50/50). ¹H NMR (400 MHz, CDCl₃) δ 7.32 (t, *J* = 8.2 Hz, 1H), 7.21 – 7.12 (m, 3H), 6.93 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.86 (d, *J* = 2.6 Hz, 1H), 4.18 – 3.97 (m, 1H), 3.95 – 3.87 (m, 1H), 3.86 (s, 3H), 3.73 (s, 2H), 2.70 (d, *J* = 14.5 Hz, 1H), 1.39 (s, 9H).

Step 2: Synthesis of tert-butyl 3'-chloro-8'-methoxyspiro[azetidine-3,6'-benzo[c]chromene]-1-carboxylate



NaH (12mg, 0.30mmol) was added at 0°C to a solution of tert-butyl 3-(4'-chloro-2'-fluoro-4-methoxy-[1,1'-biphenyl]-2-yl)-3-hydroxyazetidine-1-carboxylate (67mg, 0.16mmol) in DMF 3ml and the reaction mixture was stirred for for 3h. NH₄Cl saturated solution was added and the aqueous phase was extracted twice with Ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered and concentrated under vacuum. The crude was purified by MPLC (EtOAc/cyclohexane 0% to 8%) to give tert-butyl 3'-chloro-8'-methoxyspiro[azetidine-3,6'-benzo[c]chromene]-1-carboxylate (30mg, 47%) as a yellowish solid. ¹H NMR (400 MHz, CDCl₃) δ 7.63 (d, J = 8.5 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.09 – 6.93 (m, 4H), 4.31 (d, J = 9.5 Hz, 2H), 4.19 (s, 2H), 3.88 (s, 3H), 1.47 (s, 9H).

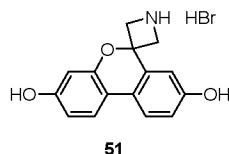
Step 3: Synthesis of tert-butyl 3'-hydroxy-8'-methoxyspiro[azetidine-3,6'-benzo[c]chromene]-1-carboxylate



3'-chloro-8'-methoxyspiro[azetidine-3,6'-benzo[c]chromene]-1-carboxylate (155mg, 0.400 mmol, 1.0 eq.) was dissolved in 1,4-dioxane (1.5mL) and Pd₂dba₃ (9mg, 0.04mmol, 0.1 eq.) as well as tBuXPhos (38mg, 0.080 mmol, 0.2 eq.) were added to the solution. Following the mixture was degassed using a N₂ balloon for 10min. Subsequently a solution of KOH (67mg, 1.2mmol, 3.0 eq.) in water (0.3mL) was added in on portion before putting the reaction mixture in a pre-heated oil-bath at 90 °C. Stirring was continued overnight and then the reaction was allowed to cool to r.t., quenched with water, the aq. phase extracted with ethyl acetate (3x10 mL) and the combined organic layers dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO₂, 20 g, EtOAc in Hex 0-30%) to yield tert-butyl 3'-hydroxy-8'-methoxyspiro [azetidine-3,6'-benzo[c]chromene]-1-carboxylate (120mg, 0.330 mmol, 81%) as a light yellow solid. R_f = 0.3 (EtOAc/hexane 20%) as yellowish solid. ¹H NMR (400 MHz, DMSO) δ 9.70 (s, 1H), 7.68 (d, J = 8.6 Hz, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.05

(d, $J = 2.6$ Hz, 1H), 7.00 (dd, $J = 8.6, 2.6$ Hz, 1H), 6.51 (dd, $J = 8.5, 2.4$ Hz, 1H), 6.45 (d, $J = 2.4$ Hz, 1H), 4.19 (d, $J = 9.6$ Hz, 2H), 4.10 (d, $J = 9.7$ Hz, 2H), 3.83 (s, 3H), 1.41 (s, 9H).

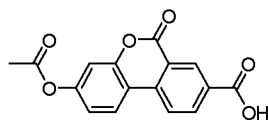
Step 4: Synthesis of spiro[azetidine-3,6'-benzo[*c*]chromene]-3',8'-diol hydrobromide



BBr_3 (0.54ml, 0.54mmol, 2.0 eq) was added to a solution of tert-butyl 3'-hydroxy-8'-methoxyspiro[azetidine-3,6'-benzo[*c*]chromene]-1-carboxylate (100mg, 0.270 mmol, 1.0 eq.) in DCM (5mL) at 0°C and the mixture was allowed to warm to room temperature overnight. Methanol was added to the mixture at 0°C was concentrated under vacuum and loaded on silica then purified by FC eluent MeOH/DCM 0% to 8% to give spiro[azetidine-3,6'-benzo[*c*]chromene]-3',8'-diol hydrobromide (40 mg, 44%) as a white solid. MS (ESI+): $m/z = 256$. ^1H NMR (400 MHz, DMSO) δ 9.76 (d, $J = 22.3$ Hz, 2H), 9.42 (s, 1H), 8.91 (s, 1H), 7.59 (t, $J = 8.7$ Hz, 2H), 7.06 (d, $J = 2.4$ Hz, 1H), 6.95 – 6.83 (m, 1H), 6.54 (dd, $J = 8.4, 2.4$ Hz, 1H), 6.49 (d, $J = 2.3$ Hz, 1H), 4.38 (dt, $J = 12.6, 6.8$ Hz, 2H), 4.24 (ddd, $J = 12.2, 7.4, 4.0$ Hz, 2H).

I) Ester “A” ring analogues with peptide substitution

Synthesis of 3-acetoxy-6-oxo-6*H*-benzo[*c*]chromene-8-carboxylic acid as the common intermediate

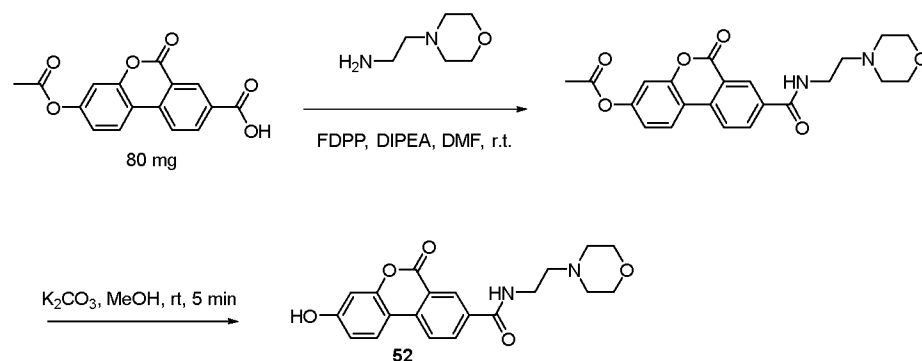


Acetylchlorid (0.36ml, 5.2mmol) was added at 0°C to a suspension of 3-hydroxy-6-oxo-6*H*-benzo[*c*]chromene-8-carboxylic acid (**2**) (600mg, 2.34mmol) in THF (8 mL) and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture is still a suspension (nothing solubilises). HCl 1M was added to the suspension and stirred 30 minutes at room temperature. The white suspension was filtered off and the solid was washed with cooled water and dried under vacuum to give (**17**) as a white solid (400 mg, 57%). ^1H NMR (400 MHz,

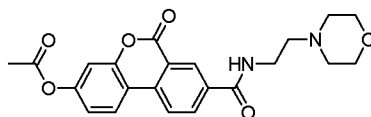
CDCl_3) δ 8.72 (d, $J = 1.8$ Hz, 1H), 8.53 (d, $J = 8.5$ Hz, 1H), 8.47 (d, $J = 8.8$ Hz, 1H), 8.39 (dd, $J = 8.4, 1.9$ Hz, 1H), 7.34 (d, $J = 2.2$ Hz, 1H), 7.26 (dd, $J = 8.7, 2.3$ Hz, 1H), 2.33 (s, 3H).

General procedure peptide coupling using FDPP and deprotection using potassium carbonate

Synthesis of 8-((2-morpholinoethyl)carbamoyl)-6-oxo-6H-benzo[c]chromen-3-yl acetate (**52**)



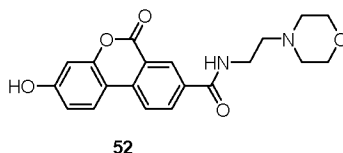
Step1: Synthesis of 8-((2-morpholinoethyl)carbamoyl)-6-oxo-6H-benzo[c]chromen-3-yl acetate



DIPEA (0.15ml, 0.86mmol) was added to a solution of 3-acetoxy-6-oxo-6H-benzo[c]chromene-8-carboxylic acid (80mg, 0.21mmol) in DMF (2 mL) followed by Pentafluorophenyldiphenylphosphinate (91mg, 0.24mmol) and the mixture was stirred 15 min then add 2-morpholinoethan-1-amine (28mg, 0.21mmol) dropwise and stirring continued for 1h. The reaction mixture was extracted with EtOAc and bicarbonate 1/2 saturated solution 3 times. The combined organic phases were dried over sodium sulfate and concentrated under vacuum. The crude was purified by MPLC (SiO_2 , MeOH/DCM from 0% to 10%) to afford 8-((2-morpholinoethyl)carbamoyl)-6-oxo-6H-benzo[c]chromen-3-yl acetate (45 mg, 51%)

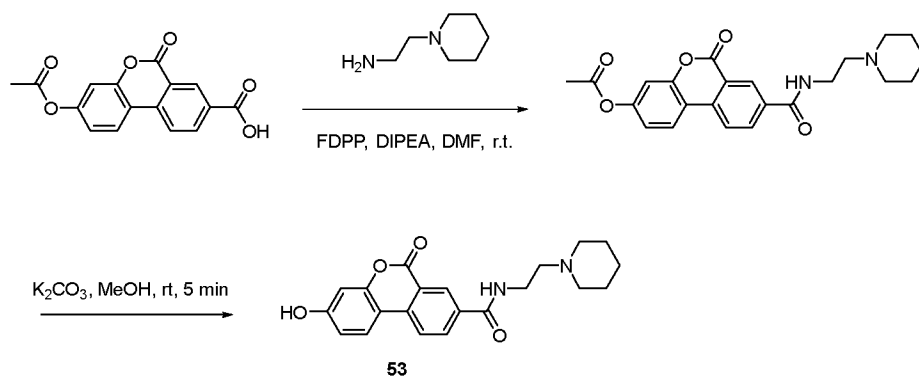
$R_f = 0.3$ (10% MeOH/DCM). ^1H NMR (400 MHz, CDCl_3) δ 8.69 (d, $J = 1.9$ Hz, 1H), 8.39 (dd, $J = 8.4, 2.0$ Hz, 1H), 8.17 (d, $J = 8.4$ Hz, 1H), 8.10 (d, $J = 8.7$ Hz, 1H), 7.20 (d, $J = 2.2$ Hz, 1H), 7.17 (dd, $J = 8.6, 2.3$ Hz, 1H), 7.00 (s, 1H), 3.78 (t, $J = 4.6$ Hz, 4H), 3.63 (q, $J = 5.6$ Hz, 2H), 2.68 (d, $J = 4.6$ Hz, 2H), 2.57 (s, 4H), 2.36 (s, 3H).

Step 2: Synthesis of 3-hydroxy-N-(2-morpholinoethyl)-6-oxo-6H-benzo[c]chromene-8-carboxamide

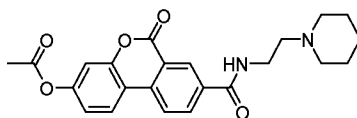


Potassium carbonate (36mg, 0.26mmol) was added at rt to solution of 8-((2-morpholinoethyl)carbamoyl)-6-oxo-6H-benzo[c]chromen-3-yl acetate (36mg, 0.088mmol) in MeOH and the reaction mixture was stirred at room temperature 10 min. The mixture was loaded on silica gel and purified by MPLC (SiO₂, MeOH/dichloromethane 0% to 10%) to afford 3-hydroxy-N-(2-morpholinoethyl)-6-oxo-6H-benzo[c]chromene-8-carboxamide UA0350 (23mg, 71%). R_f = 0.2 (10% MeOH/DCM). ¹H NMR (400 MHz, DMSO) δ 10.48 (s, 1H), 8.76 (t, J = 5.6 Hz, 1H), 8.68 (d, J = 1.9 Hz, 1H), 8.36 (d, J = 8.6 Hz, 1H), 8.29 (dd, J = 8.5, 1.9 Hz, 1H), 8.24 – 8.19 (m, 1H), 6.90 – 6.84 (m, 1H), 6.78 (d, J = 2.4 Hz, 1H), 3.58 (t, J = 4.6 Hz, 4H), 3.43 (q, J = 6.5 Hz, 2H), 2.43 (s, 4H) (2 missing protons are overshadowed by solvent).

Synthesis of 3-hydroxy-6-oxo-N-(2-(piperidin-1-yl)ethyl)-6H-benzo[c]chromene-8-carboxamide (53)

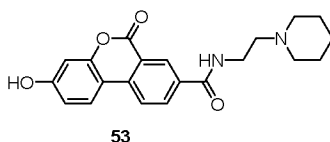


Step 1: Synthesis of 6-oxo-8-((2-(piperidin-1-yl)ethyl)carbamoyl)-6H-benzo[c]chromen-3-yl acetate



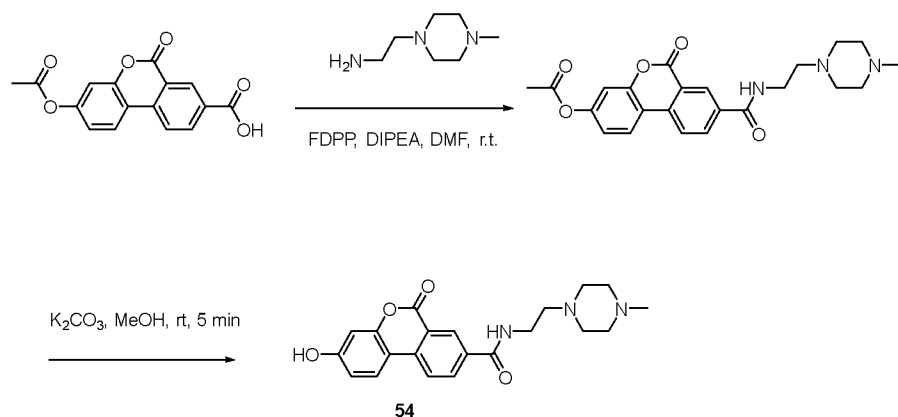
Compound was prepared according to general procedure starting from 3-acetoxy-6-oxo-6H-benzo[c]chromene-8-carboxylic acid (120mg, 0.320mmol), Pentafluorophenyl-diphenylphosphinate (136mg, 0.35mmol), 2-(piperidin-1-yl)ethan-1-amine (41mg, 0.32mmol) and DIPEA (0.224ml, 1.29mmol) to afford after purification by MPLC (SiO₂, MeOH/DCM 0% to 10%) 6-oxo-8-((2-(piperidin-1-yl)ethyl)carbamoyl)-6H-benzo[c]chromen-3-yl acetate 19 (65 mg, 49%) as a white solid. R_f = 0.3 (MeOH/DCM 10%). ¹H NMR (400 MHz, CDCl₃) δ 8.74 (d, J = 1.9 Hz, 1H), 8.40 (dd, J = 8.4, 1.9 Hz, 1H), 8.16 (d, J = 8.5 Hz, 1H), 8.09 (d, J = 8.7 Hz, 1H), 7.54 – 7.36 (m, 1H), 7.22 – 7.13 (m, 2H), 3.63 (q, J = 5.5 Hz, 2H), 2.68 (t, J = 5.8 Hz, 2H), 2.56 (s, 4H), 2.36 (s, 3H), 1.75 – 1.60 (m, 4H), 1.51 (s, 2H).

Step 2: Synthesis of 3-hydroxy-6-oxo-N-(2-(piperidin-1-yl)ethyl)-6H-benzo[c]chromene-8-carboxamide

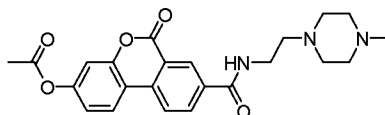


3-hydroxy-6-oxo-N-(2-(piperidin-1-yl)ethyl)-6H-benzo[c]chromene-8-carboxamide was prepared according to GP5 starting from 6-oxo-8-((2-(piperidin-1-yl)ethyl)carbamoyl)-6H-benzo[c]chromen-3-yl acetate 19 (49mg, 0.12mmol) and potassium carbonate (50mg, 0.36mmol) to afford after purification by MPLC (SiO₂, MeOH/DCM 5% to 35%) 3-hydroxy-6-oxo-N-(2-(piperidin-1-yl)ethyl)-6H-benzo[c]chromene-8-carboxamide **53** (15 mg, 34%) as a white solid. R_f = 0.3 (MeOH/DCM 20%). ¹H NMR (400 MHz, DMSO) δ 10.52 (s, 1H), 8.83 (s, 1H), 8.68 (d, J = 1.9 Hz, 1H), 8.36 (d, J = 8.6 Hz, 1H), 8.29 (dd, J = 8.5, 1.9 Hz, 1H), 8.22 (d, J = 8.8 Hz, 1H), 6.87 (dd, J = 8.7, 2.4 Hz, 1H), 6.78 (d, J = 2.4 Hz, 1H), 3.47 (d, J = 21.5 Hz, 5H), 1.65 – 1.19 (m, 9H).

Synthesis of- hydroxy-N-(2-(4-methylpiperazin-1-yl)ethyl)-6-oxo-6H-benzo[c]chromene-8-carboxamide (**54**)

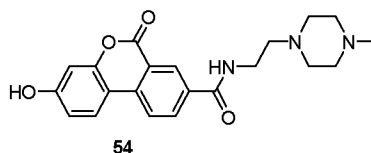


Step 1: Synthesis of 8-((2-(4-methylpiperazin-1-yl)ethyl)carbamoyl)-6-oxo-6H-benzo[c]chromen-3-yl acetate



Compound was prepared according to GP4 starting from 3-acetoxy-6-oxo-6H-benzo[c]chromene-8-carboxylic acid (120mg, 0.260mmol) Pentafluorophenyldiphenylphosphinate (113mg, 0.290mmol) and DIPEA (0.187ml, 1.070mmol) to afford after purification by MPLC (SiO₂, MeOH/DCM 0% to 10%) 8-((2-(4-methylpiperazin-1-yl)ethyl)carbamoyl)-6-oxo-6H-benzo[c]chromen-3-yl acetate **20** (73mg, 59%) as a white solid. $R_f = 0.3$ eluent (MeOH/DCM 10%). ¹NMR (400 MHz, CDCl₃) δ 8.68 (d, $J = 1.9$ Hz, 1H), 8.39 (dd, $J = 8.4, 2.0$ Hz, 1H), 8.16 (d, $J = 8.5$ Hz, 1H), 8.09 (d, $J = 8.7$ Hz, 1H), 7.19 (d, $J = 2.2$ Hz, 1H), 7.16 (dd, $J = 8.6, 2.3$ Hz, 1H), 7.11 (s, 1H), 3.62 (q, $J = 5.6$ Hz, 2H), 2.73 – 2.58 (m, 10H), 2.37 (d, $J = 5.2$ Hz, 6H).

Step 2: Synthesis of 3-hydroxy-N-(2-(4-methylpiperazin-1-yl)ethyl)-6-oxo-6H-benzo[c]chromene-8-carboxamide



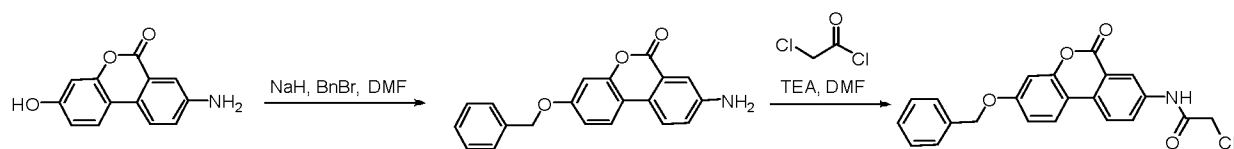
3-hydroxy-N-(2-(4-methylpiperazin-1-yl)ethyl)-6-oxo-6H-benzo[c]chromene-8-carboxamide was prepared according to GP5 starting from 8-((2-(4-methylpiperazin-1-yl)ethyl)carbamoyl)-6-oxo-6H-benzo[c]chromen-3-yl acetate **20** (60mg, 0.14mmol) and potassium carbonate (39mg,

0.28mmol) to afford after purification by MPLC (RP-C18, MeOH/water 0% to 95%) 3-hydroxy-N-(2-(4-methylpiperazin-1-yl)ethyl)-6-oxo-6H-benzo[c]chromene-8-carboxamide (27mg, 51%). $R_f = 0.1$ eluent (MeOH/DCM 30%). ^1H NMR (400 MHz, DMSO) δ 8.75 (t, $J = 5.6$ Hz, 1H), 8.68 (d, $J = 1.8$ Hz, 1H), 8.36 (d, $J = 8.6$ Hz, 1H), 8.29 (dd, $J = 8.5, 1.9$ Hz, 1H), 8.22 (d, $J = 8.9$ Hz, 1H), 8.18 (s, 1H), 6.88 (dd, $J = 8.7, 2.4$ Hz, 1H), 6.78 (d, $J = 2.4$ Hz, 1H), 3.47 – 3.40 (m, 2H), 2.48 – 2.30 (m, 10H), 2.20 (s, 3H).

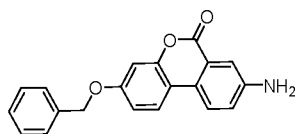
J) Ester “A” group analogs with inverse amide substitution

The syntheses of inverse amides was based on a common intermediate that is described below.

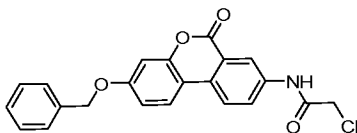
Synthesis of N-(3-(benzyloxy)-6-oxo-6H-benzo[c]chromen-8-yl)-2-chloroacetamide



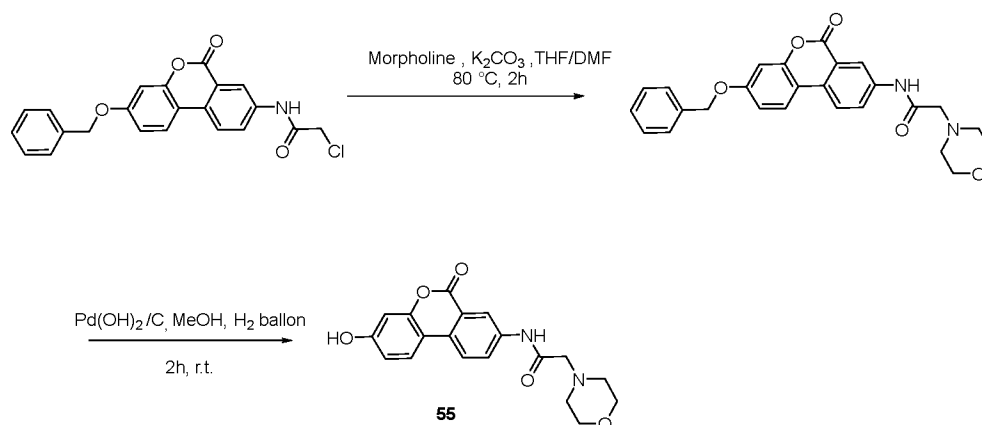
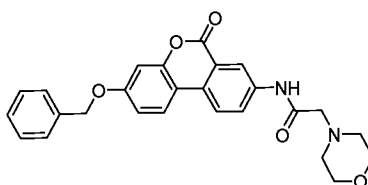
Step 1: Synthesis of 8-amino-3-(benzyloxy)-6H-benzo[c]chromen-6-one



8-amino-3-hydroxy-6H-benzo[c]chromen-6-one **15** (864mg, 3.80mmol) was dissolved in DMF (13 mL) then cooled to 0 °C. Subsequently NaH (152mg, 3.80mmol) was added in one portion. Upon stirring for 15min benzyl chloride (0.44ml, 3.80mmol) was added dropwise and the reaction mixture was allowed to warm to r.t. and stirring overnight was continued. Following the reaction was quenched with half-saturated NaHCO_3 solution and extracted with ethyl acetate (3x25ml). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by MPLC (SiO_2 , ethyl acetate/Hex 0 – 50%) to afford 8-amino-3-(benzyloxy)-6H-benzo[c]chromen-6-one (738mg, 61%) as an ochre colored solid. ^1H NMR (400 MHz, DMSO) δ 8.02 (dd, $J = 17.2, 8.7$ Hz, 2H), 7.51 – 7.34 (m, 6H), 7.14 (dd, $J = 8.7, 2.6$ Hz, 1H), 7.06 – 6.95 (m, 2H), 5.79 (s, 2H), 5.19 (s, 2H).

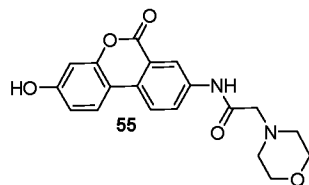
Step 2: Synthesis of N-(3-(benzyloxy)-6-oxo-6H-benzo[c]chromen-8-yl)-2-chloroacetamide

8-amino-3-(benzyloxy)-6H-benzo[c]chromen-6-one (738mg, 2.33mmol) was added to a solution of DMF (16ml) containing TEA (0.324ml, 2.56mmol). The mixture was stirred for 10 min at room temperature. Chloroacetylchloride (0.205ml, 2.33mmol) was added to the above mixture, maintaining the temperature between 0 and 5°C. The obtained solution was then stirred at room temperature for 4-6 h. The completion of reaction was monitored with TLC. The solution was then added onto crushed ice and the separated precipitates were filtered and dried under vacuum. The product was recrystallized from methanol to afford N-(3-(benzyloxy)-6-oxo-6H-benzo[c]chromen-8-yl)-2-chloroacetamide (833 mg, 91%) as a lightly yellowish solid. ¹H NMR (400 MHz, DMSO) δ 10.72 (s, 1H), 8.52 (d, J = 2.4 Hz, 1H), 8.31 (d, J = 8.8 Hz, 1H), 8.19 (d, J = 8.8 Hz, 1H), 8.03 (dd, J = 8.8, 2.4 Hz, 1H), 7.48 – 7.35 (m, 5H), 7.10 – 7.06 (m, 2H), 5.22 (s, 2H), 4.32 (s, 2H).

Synthesis of N-(3-(hydroxy)-6-oxo-6H-benzo[c]chromen-8-yl)-2-morpholinoacetamide (55)**Step 1: Synthesis of N-(3-(benzyloxy)-6-oxo-6H-benzo[c]chromen-8-yl)-2-morpholinoacetamide**

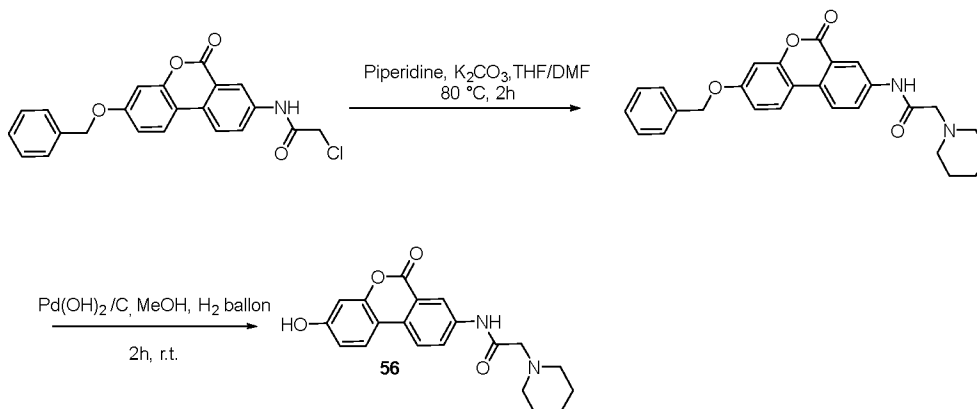
N-(3-(benzyloxy)-6-oxo-6H-benzo[c]chromen-8-yl)-2-chloroacetamide (60mg, 0.15mmol) was suspended in THF (5ml) and the potassium carbonate (42mg, 0.30mmol) was added in one portion. The minimum amount of DMF (2-3ml) were added dropwise in order to solubilize the suspension. Then morpholine (0.014 mL, 0.17 mmol) was added via syringe and the reaction was heated to 80 °C for 2h. Upon complete consumption of the starting material (as indicated by TLC) the reaction was allowed to cool down to r.t. and then the mixture was concentrated under reduced pressure. The crude product was purified by MPLC (SiO₂, MeOH in DCM 0-10%) to afford N-(3-(benzyloxy)-6-oxo-6H-benzo[c]chromen-8-yl)-2-morpholinoacetamide (46mg, 0.10 mmol, 68%) as a white solid. ¹H NMR (400 MHz, DMSO) δ 10.17 (s, 1H), 8.60 (d, J = 2.3 Hz, 1H), 8.29 (d, J = 8.9 Hz, 1H), 8.21 (d, J = 8.7 Hz, 1H), 8.13 (dd, J = 8.8, 2.4 Hz, 1H), 7.50 – 7.35 (m, 5H), 7.11 – 7.06 (m, 2H), 5.23 (s, 2H), 3.66 (t, J = 4.7 Hz, 4H), 3.19 (s, 2H), 2.55 – 2.52 (m, 4H).

Step 2: Synthesis of N-(3-hydroxy-6-oxo-6H-benzo[c]chromen-8-yl)-2-morpholinoacetamide

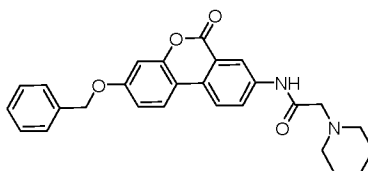


A solution of N-(3-(benzyloxy)-6-oxo-6H-benzo[c]chromen-8-yl)-2-morpholinoacetamide (40mg, 0.090mmol) and Pd(OH)₂/C (7mg, 0.009 mmol) in MeOH (2ml) and DCM (2ml) was stirred under hydrogen at atmospheric pressure overnight. The reaction mixture was filtered over a pad of celite and the solvent was evaporated under vacuum to give N-(3-hydroxy-6-oxo-6H-benzo[c]chromen-8-yl)-2-morpholinoacetamide (25mg, 78%) as an off-white solid. ¹H NMR (400 MHz, DMSO) δ 10.26 (s, 1H), 10.14 (s, 1H), 8.57 (d, J = 2.3 Hz, 1H), 8.23 (d, J = 9.0 Hz, 1H), 8.10 (d, J = 8.8 Hz, 2H), 6.83 (dd, J = 8.7, 2.5 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H), 3.65 (t, J = 4.8 Hz, 4H), 3.18 (s, 2H). (clean, but 4 aliphatic protons are overshadowed by solvent)

Synthesis of N-(3-(hydroxy)-6-oxo-6H-benzo[c]chromen-8-yl)-2-(piperidin-1-yl)acetamide (56)

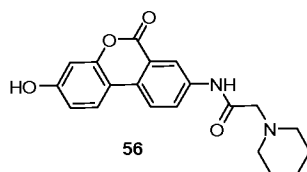


Step 1: Synthesis of N-(3-(benzyloxy)-6-oxo-6H-benzo[c]chromen-8-yl)-2-(piperidin-1-yl)acetamide



N-(3-(benzyloxy)-6-oxo-6H-benzo[c]chromen-8-yl)-2-chloroacetamide (200mg, 0.510 mmol) was suspended in THF (5ml) and the potassium carbonate (140mg, 1.02mmol) was added in one portion. The minimum amount of DMF (5-6ml) were added in order to solubilize the suspension. Then piperidine (0.055 mL, 0.56 mmol) was added dropwise via syringe and the reaction was heated to 80 °C for 2h. Upon complete consumption of the starting material (as indicated by TLC) the reaction was allowed to cool down to r.t. and then the mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography (MeOH in DCM 0-10%) to obtain N-(3-(benzyloxy)-6-oxo-6H-benzo[c]chromen-8-yl)-2-(piperidin-1-yl)acetamide (154mg, 0.51 mmol, 69%) as a white solid. ¹H NMR (400 MHz, DMSO) δ 10.10 (s, 1H), 8.61 (d, J = 2.3 Hz, 1H), 8.28 (d, J = 8.9 Hz, 1H), 8.20 (d, J = 8.8 Hz, 1H), 8.12 (dd, J = 8.8, 2.4 Hz, 1H), 7.53 – 7.37 (m, 5H), 7.13 – 7.05 (m, 2H), 5.23 (s, 2H), 3.13 (s, 2H), 2.47 (d, J = 5.0 Hz, 4H), 1.58 (p, J = 5.6 Hz, 4H), 1.41 (q, J = 6.0 Hz, 2H).

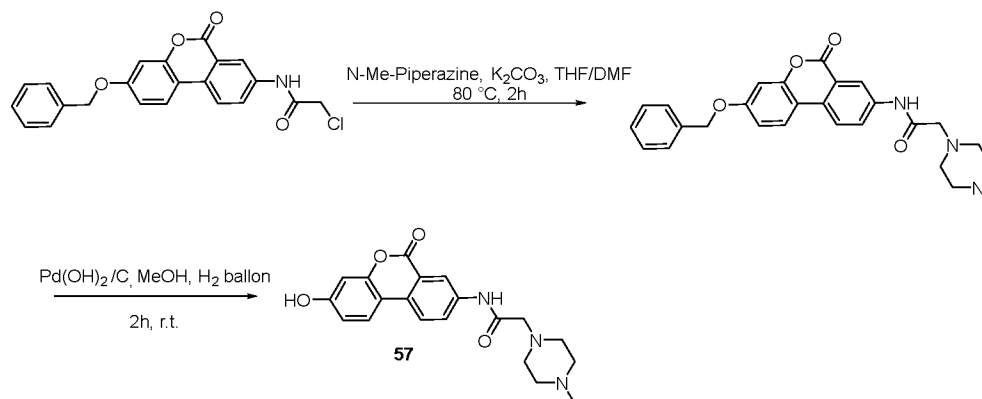
Step 2: Synthesis N-(3-hydroxy-6-oxo-6H-benzo[c]chromen-8-yl)-2-(piperidin-1-yl)acetamide



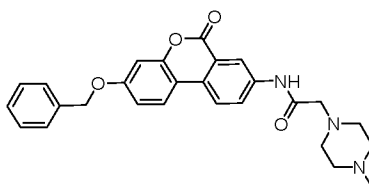
A solution of N-(3-(benzyloxy)-6-oxo-6H-benzo[c]chromen-8-yl)-2-(piperidin-1-yl)acetamide (154mg, 0.350mmol) and Pd(OH)₂/C (34mg, 0.035mmol) in MeOH (3ml) and DCM (3ml) was stirred under hydrogen at atmospheric pressure overnight. The reaction mixture was filtered over a pad of celite and the solvent was evaporated under vacuum to give N-(3-hydroxy-6-oxo-6H-benzo[c]chromen-8-yl)-2-(piperidin-1-yl)acetamide (95 mg, 77%) as a dark yellow solid. ¹H NMR (400 MHz, DMSO) δ 10.07 (s, 1H), 8.58 (d, J = 2.3 Hz, 1H), 8.21 (d, J = 8.9 Hz, 1H), 8.09 (dd, J = 8.8, 2.8 Hz, 2H), 6.83 (dd, J = 8.7, 2.4 Hz, 1H), 6.74 (d, J = 2.4 Hz, 1H), 3.12 (s, 2H), 2.47 (d, J = 5.6 Hz, 4H), 1.59 (q, J = 5.6 Hz, 4H), 1.41 (q, J = 6.2 Hz, 2H).

MS (ESI⁺): m/z = 353

Synthesis of N-(3-(hydroxy)-6-oxo-6H-benzo[c]chromen-8-yl)-2-(4-methylpiperazin-1-yl)acetamide (57)

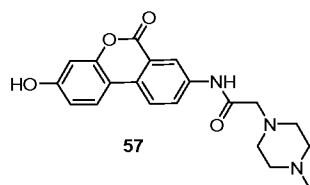


Step 1: Synthesis of N-(3-(benzyloxy)-6-oxo-6H-benzo[c]chromen-8-yl)-2-(piperidin-1-yl)acetamide



N-(3-(benzyloxy)-6-oxo-6H-benzo[c]chromen-8-yl)-2-chloroacetamide (200mg, 0.510mmol) was suspended in THF (5ml) and the potassium carbonate (140mg, 1.02mmol) was added in one portion. The minimum amount of DMF (5-6ml) were added in order to solubilize the suspension. Then 1-methylpiperazine (0.062 mL, 0.56 mmol) was added dropwise via syringe and the reaction was heated to 80 °C for 2h. Upon complete consumption of the starting material (as indicated by TLC) the reaction was allowed to cool down to r.t. and then the mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography (MeOH in DCM 0-20%) to obtain N-(3-(benzyloxy)-6-oxo-6H-benzo[c]chromen-8-yl)-2-(piperidin-1-yl)acetamide (148mg, 64%) as a white solid. ¹H NMR (400 MHz, DMSO) δ 10.21 (s, 1H), 8.59 (d, J = 2.3 Hz, 1H), 8.29 (d, J = 8.9 Hz, 1H), 8.20 (d, J = 8.8 Hz, 1H), 8.11 (dd, J = 8.8, 2.3 Hz, 1H), 7.55 – 7.30 (m, 5H), 7.14 – 7.03 (m, 2H), 5.23 (s, 2H), 3.17 (s, 2H), 2.68 – 2.66 (m, 8H), 2.39 (s, 3H).

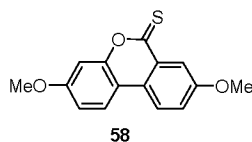
Step 2: Synthesis of N-(3-hydroxy-6-oxo-6H-benzo[c]chromen-8-yl)-2-(4-methylpiperazin-1-yl)acetamide



A solution of N-(3-(benzyloxy)-6-oxo-6H-benzo[c]chromen-8-yl)-2-(piperidin-1-yl)acetamide (148mg, 0.320mmol) Pd(OH)₂/C (40mg, 0.032mmol) in MeOH (3ml) and DCM (3ml) was stirred under hydrogen at atmospheric pressure overnight. The reaction mixture was filtered over a pad of celite and the solvent was evaporated under vacuum to give N-(3-hydroxy-6-oxo-6H-benzo[c]chromen-8-yl)-2-(4-methylpiperazin-1-yl)acetamide (69 mg, 58%) as a pale yellow solid. MS (ESI⁺): m/z = 368.

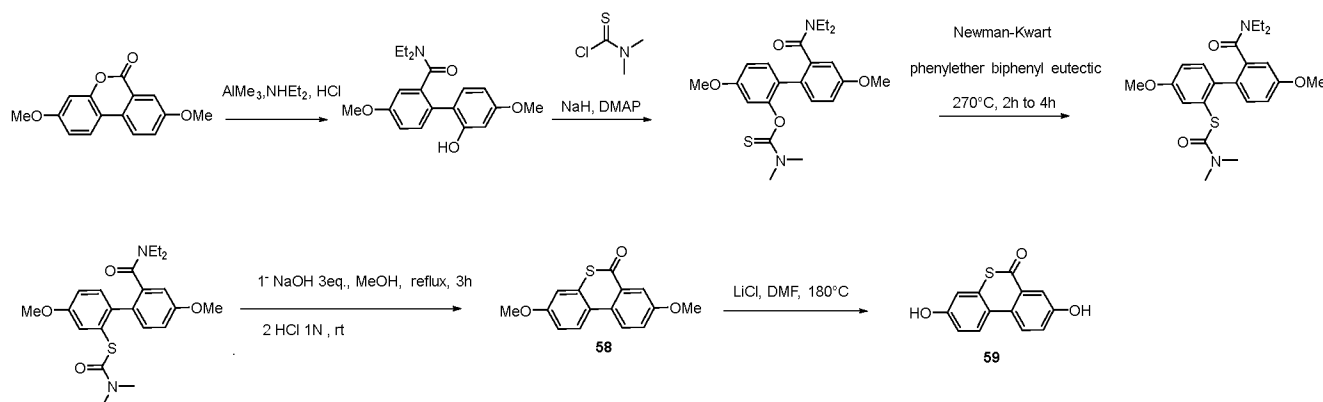
K) Thionoester “A” group analogues

Synthesis of 3,8-dimethoxy-6H-benzo[c]chromene-6-thione (58)



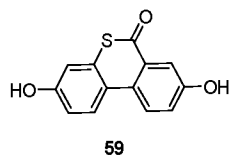
A mixture of 3,8-dimethoxy-6H-benzo[c]chromen-6-one (previously described above) (140 mg, 0.154mmol) and lawesson's reagent (552mg, 1.34mmol) were refluxed in toluene o.n.. The reaction was monitored by TLC which showed that reaction is not complete so lawesson's reagent (884 mg, 2.19mmol) were added and reflux continued overnight. The reaction mixture was filtered off and the solvent was evaporated under vacuum. The crude was purified by MPLC (SiO₂, EtOAc/cyclohexane 0% to 25%) to afford 3,8-dimethoxy-6H-benzo[c]chromene-6-thione (110 mg, 74%,) as a yellow solid. *R_f* = 0.4 (EtOAc/hexane 20%) yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.21 (d, *J* = 2.8 Hz, 1H), 7.92 (dd, *J* = 8.9, 6.7 Hz, 2H), 7.39 (dd, *J* = 8.9, 2.8 Hz, 1H), 7.03 (d, *J* = 2.6 Hz, 1H), 6.99 – 6.95 (dd, 1H), 3.96 (s, 3H), 3.88 (s, 3H).

Synthesis of 3,8-dihydroxy-6H-benzo[c]thiochromen-6-one (59)



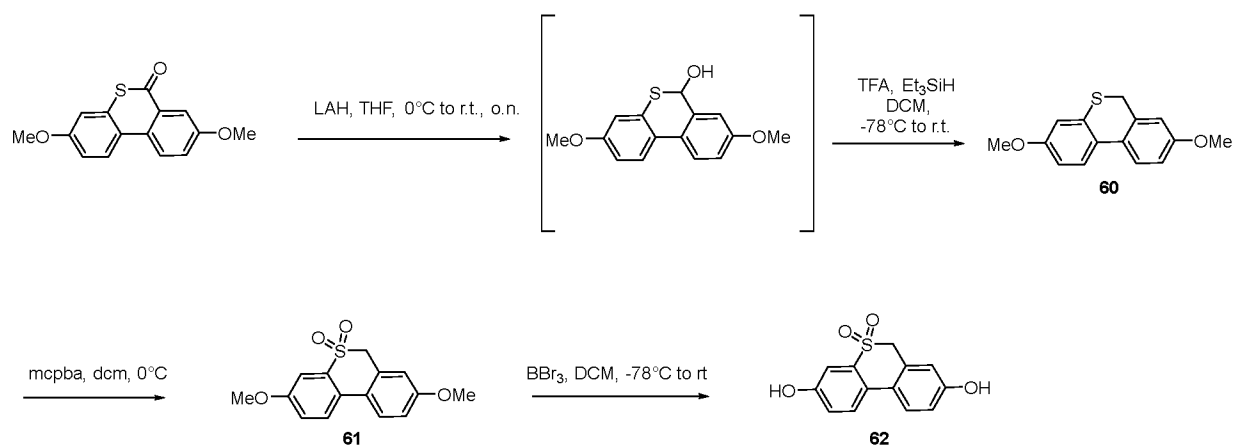
58 was prepared in 4 steps from **17** according to a described procedure in *Org. Lett.*, Vol. 7, No. 3, 2005, 411- 414. The product was obtained as a white solid. The analytical data fully matched to the one that was previously reported in the literature.

Step 5: Synthesis of 3,8-dihydroxy-6H-benzo[c]thiochromen-6-one

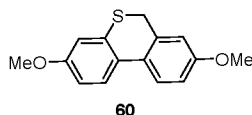


In a sealed tube, a mixture of Lithium Chloride (65mg, 1.5mmol) and 3,8-dimethoxy-6H-benzo[c]thiochromen-6-one (70mg, 0.26mmol) in DMF (1 mL) was heated at 130°C for 2 days. The solvent was evaporated under vacuum and the crude was loaded on silica gel and was purified by MPLC (SiO₂, Methanol/Dichloromethane 0% to 10%) to afford 3,8-dihydroxy-6H-benzo[c]thiochromen-6-one (28mg, 45%), as a yellow solid. ¹H NMR (400 MHz, DMSO) δ 10.19 (s, 2H), 8.32 (dd, J = 15.6, 9.1 Hz, 2H), 7.53 (d, J = 2.8 Hz, 1H), 7.31 (dd, J = 8.9, 2.9 Hz, 1H), 6.92 (dd, J = 8.9, 2.6 Hz, 1H), 6.87 (d, J = 2.5 Hz, 1H).

Synthesis of 3,8-dihydroxy-6H-benzo[c]thiophene 5,5-dioxide (62)



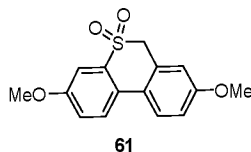
Step 1: Synthesis of 3,8-dimethoxy-6H-benzo[c]thiophene (60)



LAH (35mg, 0.91mmol) was added to solution of 3,8-dimethoxy-6H-benzo[c]thiochromen-6-one (250mg, 0.910mmol) in DCM (10 mL) at 0°C and the mixture was stirred overnight at room temperature. workup: add 10ml Et₂O followed by 0.05ml of MeOH, NaOH 1N 0.025ml then water 3 drops and stirring continued for 15min. Na₂SO₄ was added and the reaction mixture was filtered off and concentrated under vacuum. The crude was dissolved in DCM (5ml) and cooled down to -78°C, TFA (0.354 mL, 4.59 mmol) was added dropwise and stirred 60min at -78°C, then EtSi₃H (0.290ml, 1.84mmol) was added and the reaction was allowed to warm to room temperature overnight. The reaction mixture was washed with Na₂CO₃ saturated solution and the organic layer was dried over sodium sulfate and concentrated under vacuum to afford 230 mg of crude material,

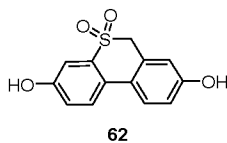
which was triturated in Et₂O to afford 3,8-dimethoxy-6H-benzo[c]thiochromene (160mg, 67%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, J = 8.7 Hz, 1H), 7.54 (d, J = 8.6 Hz, 1H), 6.94 (d, J = 2.7 Hz, 1H), 6.89 (dd, J = 8.6, 2.7 Hz, 1H), 6.81 (dd, J = 8.7, 2.7 Hz, 1H), 6.77 (d, J = 2.7 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.81 (s, 2H).

Step 2: Synthesis of 3,8-dimethoxy-6H-benzo[c]thiochromene 5,5-dioxide (**61**)



m-CPBA (150mg, 0.62mmol) was added to a solution of 3,8-dimethoxy-6H-benzo[c]thiochromene (80mg, 0.31mmol) in dichloromethane (4ml) at 0°C and the mixture was allowed to warm to room temperature over 2h. 1M Na₂S₂O₃ solution was added to the reaction mixture. The aqueous phase was extracted with EtOAc and the organic phase was washed with bicarbonate saturated solution twice. The organic phase was dried over sodium sulfate. The organic phase was concentrated under vacuum and filtered over a pad of celite using EtOAc then concentrated to afford 3,8-dimethoxy-6H-benzo[c]thiochromene 5,5-dioxide (66 mg, 73%) as a yellowish solid. ¹H NMR (400 MHz, CDCl₃) δ 7.71 (dd, J = 8.7, 4.4 Hz, 2H), 7.52 (d, J = 2.8 Hz, 1H), 7.20 (dd, J = 8.8, 2.7 Hz, 1H), 7.01 (dd, J = 8.7, 2.7 Hz, 1H), 6.83 (d, J = 2.7 Hz, 1H), 4.36 (s, 2H), 3.91 (s, 3H), 3.86 (s, 3H).

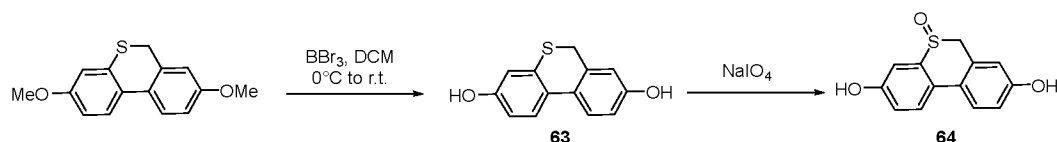
Step 3: Synthesis of 3,8-dihydroxy-6H-benzo[c]thiochromene 5,5-dioxide (**62**)



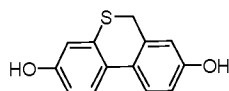
BBr₃ (0.76ml, 0.76mmol) was added to a solution of 3,8-dimethoxy-6H-benzo[c]thiochromene 5,5-dioxide (55mg, 0.19mmol) in DCM 2ml at -70°C and the mixture was allowed to warm to room temperature overnight. TLC showed 2 spots. Methanol was added to the mixture at 0°C was concentrated under vacuum and loaded on silica then purified by MPLC (SiO₂, MeOH/DCM 0% to 8%) to afford 3,8-dihydroxy-6H-benzo[c]thiochromene 5,5-dioxide (23mg, 46%) as a yellowish solid. ¹H NMR (400 MHz, DMSO) δ 10.29 (s, 1H), 9.87 (s, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.71 (d,

J = 8.6 Hz, 1H), 7.24 (d, J = 2.6 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.86 (dd, J = 8.5, 2.6 Hz, 1H), 6.82 (d, J = 2.6 Hz, 1H), 4.65 (s, 2H).

Synthesis of 3,8-dihydroxy-6H-benzo[c]thiochromene 5-oxide (64)

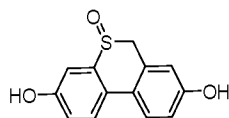


Step 1: Synthesis of 6H-benzo[c]thiochromene-3,8-diol (63)



BBr_3 (0.81ml, 0.81mmol) was added at 0°C to a solution of 3,8-dimethoxy-6H-benzo[c]thiochromene (70mg, 0.27mmol) in DCM 4ml and allowed to warm to room temperature overnight. The reaction mixture was poured into methanol at 0°C and stirred for 10 minutes then the solvent was evaporated under vacuum. The crude was filtered over a pad of silica to afford 6H-benzo[c]thiochromene-3,8-diol (40 mg, 64%) as a grey solid. $R_f = 0.75$ (EtOAc/hexane 50/50). ^1H NMR (400 MHz, DMSO) δ 9.56 (s, 1H), 9.50 (s, 1H), 7.56 (d, J = 8.6 Hz, 1H), 7.44 (d, J = 8.5 Hz, 1H), 6.75 – 6.64 (m, 4H), 5.76 (s, 1H), 3.78 (s, 2H).

Step 2: Synthesis of 3,8-dihydroxy-6H-benzo[c]thiochromene 5-oxide (64)

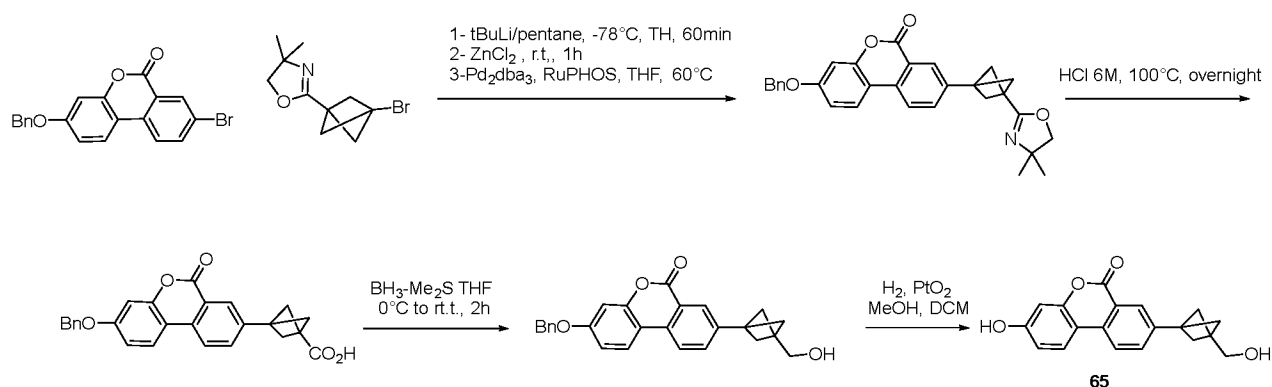


A solution of NaIO_4 (26mg 0.12mmol) in water 0.3 mL was added to a solution of 6H-benzo[c]thiochromene-3,8-diol (28mg, 0.12mmol) in MeOH 1.5ml at r.t and the mixture stirred o.n. A precipitate was formed. TLC showed still starting material. Hence, 0.2 eq of NaIO_4 dissolved in water 0.2 mL was added and stirring continued; reaction not complete but stopped. DCM was added to dissolve the precipitate and the crude was loaded on silica and purified by MPLC (SiO_2 , MeOH/ DCM 0% to 8%) to afford 3,8-dihydroxy-6H-benzo[c]thiochromene 5-oxide (16mg, 53%) as a grey solid. $R_f = 0.3$ (MeOH/ DCM 5%). ^1H NMR (400 MHz, DMSO) δ

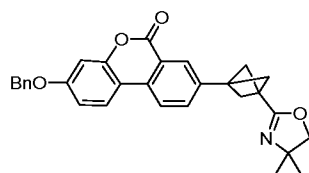
10.05 (s, 1H), 9.72 (s, 1H), 7.64 (dd, $J = 32.7, 8.5$ Hz, 2H), 7.11 (d, $J = 2.6$ Hz, 1H), 7.00 (dd, $J = 8.5, 2.6$ Hz, 1H), 6.83 (d, $J = 6.7$ Hz, 2H), 4.21 (dd, $J = 90.8, 14.2$ Hz, 2H).

l) Ester "A" group with bicyclopentane substitution

Synthesis of 3-hydroxy-8-(3-(hydroxymethyl)bicyclo[1.1.1]pentan-1-yl)-6H-benzo[c]chromen-6-one (65)



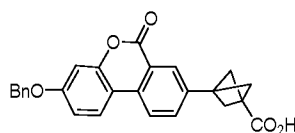
Step 1: Synthesis of 3-(benzyloxy)-8-(3-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)bicyclo[1.1.1]pentan-1-yl)-6H-benzo[c]chromen-6-one



To a cooled -78°C solution of 2-(3-bromobicyclo[1.1.1]pentan-1-yl)-4,4-dimethyl-4,5-dihydrooxazole (192mg, 0.788mmol) in anhydrous 2.7 mL was added carefully dropwise *tert*-butyllithium (1.7 M in pentane, 0.95ml, 1.63mmol). The reaction mixture was stirred at -78°C for 60 min. A solution of ZnCl_2 [0.5M in THF] (1.78ml, 0.89 mmol) was added dropwise. The reaction mixture was allowed to reach room temperature for 60 min. The resulting zincate solution was slowly added dropwise to a mixture of 3-(benzyloxy)-8-bromo-6H-benzo[c]chromen-6-one (200mg, 0.525mmol), RuPhos (49mg, 0.105mmol) and Tris(dibenzylideneacetone)dipalladium (48mg, 0.052mmol) under N_2 atmosphere at room temperature. The reaction vessel was sealed and heated at 60°C for 12 hrs. The reaction mixture was concentrated under reduced pressure and the

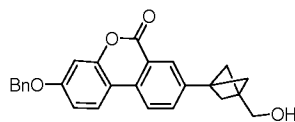
resulting residue was absorbed on SiO₂. Purification of the residue by MPLC (SiO₂, EtOAc/cyclohexane 0% to 20%) to give 3-(benzyloxy)-8-(3-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)bicyclo[1.1.1]pentan-1-yl)-6H-benzo[c]chromen-6-one (90mg, 0.19mmol, 37%). ¹H NMR (500 MHz, CDCl₃) δ 8.18 (d, J = 1.9 Hz, 1H), 7.94 (t, J = 8.4 Hz, 2H), 7.64 (dd, J = 8.2, 1.9 Hz, 1H), 7.45 – 7.35 (m, 5H), 6.99 (dd, J = 8.8, 2.6 Hz, 1H), 6.93 (d, J = 2.6 Hz, 1H), 5.14 (s, 2H), 3.97 (s, 2H), 2.40 (s, 6H), 1.31 (s, 6H).

Step 2: Synthesis of 3-(3-(benzyloxy)-6-oxo-6H-benzo[c]chromen-8-yl)bicyclo[1.1.1]pentane-1-carboxylic acid



A suspension of 3-(benzyloxy)-8-(3-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)bicyclo[1.1.1]pentan-1-yl)-6H-benzo[c]chromen-6-one (110mg, 0.236mmol) in 6M HCl was heated at 100°C o.n. in a sealed tube. The reaction mixture was cooled down to r.t. then filtered and washed with water and dried under high vacuum. The crude was purified by FC eluent MeOH/DCM 0 % to 8% to give 3-(3-(benzyloxy)-6-oxo-6H-benzo[c]chromen-8-yl)bicyclo[1.1.1]pentane-1-carboxylic acid (70 mg, 72%) as a beige solid. LCMS no mass TLC/MS 413. R_f = 0.5 (10% MeOH/DCM). ¹H NMR (400 MHz, DMSO) δ 12.45 (s, 1H), 8.29 (dd, J = 13.3, 8.6 Hz, 2H), 8.00 (d, J = 1.9 Hz, 1H), 7.81 (dd, J = 8.3, 1.9 Hz, 1H), 7.53 – 7.32 (m, 5H), 7.13 – 7.06 (m, 2H), 5.24 (s, 2H), 2.33 (s, 6H).

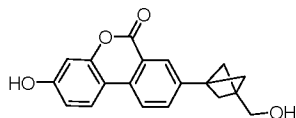
Step 3: Synthesis of 3-(benzyloxy)-8-(3-(hydroxymethyl)bicyclo[1.1.1]pentan-1-yl)-6H-benzo[c]chromen-6-one



Borane dimethyl sulfide complex (0.22ml, 0.44mmol, 2 M in THF, 3.0 eq) was added to a solution of 3-(3-(benzyloxy)-6-oxo-6H-benzo[c]chromen-8-yl)bicyclo[1.1.1]pentane-1-carboxylic acid (60mg, 0.15mmol, 1.0 eq) at 0°C in THF 2ml and stirring continued for 2h from 0°C to rt. MeOH was added and the crude was loaded on silica and purified by FC eluent MeOH/DCM 0% to 5% to give 3-(benzyloxy)-8-(3-(hydroxymethyl)bicyclo[1.1.1]pentan-1-yl)-6H-benzo[c]chromen-6-one (47 mg, 0.12mmol, 81%) as a beige solid. R_f = 0.6 (MeOH/DCM 5%). ¹H NMR (400 MHz,

CDCl₃) δ 8.19 (d, J = 1.9 Hz, 1H), 7.94 (dd, J = 8.6, 3.3 Hz, 2H), 7.65 (dd, J = 8.3, 1.9 Hz, 1H), 7.42 (dtdd, J = 14.5, 8.7, 6.9, 1.8 Hz, 5H), 6.99 (dd, J = 8.8, 2.6 Hz, 1H), 6.94 (d, J = 2.5 Hz, 1H), 5.30 (s, 1H), 5.14 (s, 2H), 3.74 (s, 2H), 2.07 (s, 6H).

Step 4: Synthesis of 3-hydroxy-8-(3-(hydroxymethyl)bicyclo[1.1.1]pentan-1-yl)-6H-benzo[c]chromen-6-one

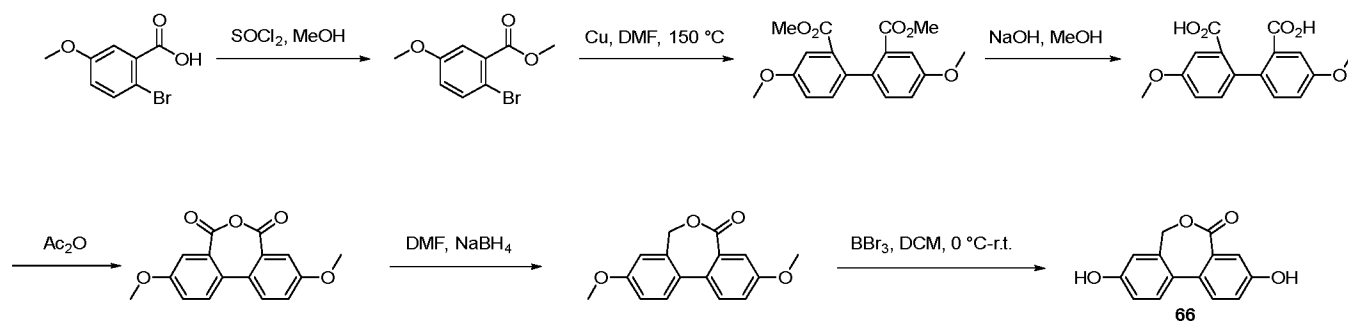


3-(benzyloxy)-8-(3-(hydroxymethyl)bicyclo[1.1.1]pentan-1-yl)-6H-benzo[c]chromen-6-one (45mg, 0.11mmol) was dissolved in MeOH 3ml and DCM 1ml. PtO₂ (6.4mg, 0.023mmol) was added and the mixture was hydrogenated under atmospheric pressure for 5h. The reaction mixture was filtered over a pad of celite and concentrated under vacuum. The crude was purified by FC MeOH/DCM 0% to 10% to give 3-hydroxy-8-(3-(hydroxymethyl)bicyclo[1.1.1]pentan-1-yl)-6H-benzo[c]chromen-6-one (1.5mg, 0.069mmol, 62%) as a white solid. R_f = 0.3 (EtOAc/hexane 50%); R_f = 0.5 (MeOH/DCM 10%). ¹H NMR (400 MHz, DMSO) δ 10.31 (s, 1H), 8.21 (d, J = 8.3 Hz, 1H), 8.14 (d, J = 8.8 Hz, 1H), 7.94 (d, J = 1.9 Hz, 1H), 7.74 (dd, J = 8.2, 1.9 Hz, 1H), 6.84 (dd, J = 8.7, 2.4 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H), 4.58 (t, J = 5.5 Hz, 1H), 3.48 (d, J = 5.6 Hz, 2H), 1.96 (s, 6H).

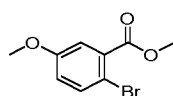
2. Synthesis of 7-membered Urolithin A analogues

A) Lactones and ethers “A” group analogues

Synthesis of 3,9-dihydroxydibenzo[c,e]oxepin-5(7H)-one (66)

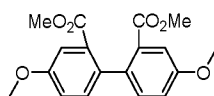


Step 1: Synthesis of 2-bromo-5-methoxybenzoate



2-bromo-5-methoxybenzoic acid (11.6g, 50.0 mmol, 1.00 eq.) was dissolved in MeOH (250 mL) and the resulting solution was cooled down to 0 °C in an ice-bath. Stirring at 0 °C was continued for 10min and then SOCl₂ (17.8g, 150 mmol, 3.00eq.) was added dropwise via a dropping funnel. The reaction was allowed to warm up to r.t. and as soon as no more starting material could be observed (overnight stirring) all the volatiles were evaporated and the crude residue taken up in diethyl ether and filtered through silica. The filtrate was concentrated under vacuo to afford pure methyl 2-bromo-5-methoxybenzoate (12.3g, 49.9mmol, 99%) as a colorless oil that solidified upon storage. NMR matched precedent literature.

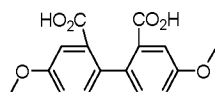
Step 2: Synthesis of dimethyl 4,4'-dimethoxy-[1,1'-biphenyl]-2,2'-dicarboxylate



2-bromo-5-methoxybenzoate (12.3g, 50 mmol, 1.00 eq.) was dissolved in DMF (60 mL) and copper powder (12.7g, 200 mmol, 4.00 eq.) was added to the solution in one portion. Subsequently the reaction mixture was heated to 150 °C overnight. After overnight stirring the reaction was allowed to cool to r.t. and diluted with a copious amount of water and extracted with diethyl ether (3x100 mL). The combined organic layers were washed with water and brine, dried over Na₂SO₄, filtered through silica and concentrated in vacuo. The crude product was purified by flash column chromatography (SiO₂, 330 g, EtOAc in Hex 0-30%) to give dimethyl 4,4'-dimethoxy-[1,1'-

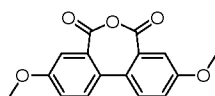
biphenyl]-2,2'-dicarboxylate (7.5g, 23mmol, 91%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.49 (d, J = 2.7 Hz, 2H), 7.11 (d, J = 8.3 Hz, 2H), 7.06 (dd, J = 8.4, 2.7 Hz, 2H), 3.88 (s, 6H), 3.63 (s, 6H).

Step 3: Synthesis of 4,4'-dimethoxy-[1,1'-biphenyl]-2,2'-dicarboxylic acid



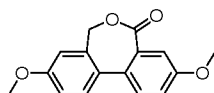
dimethyl 4,4'-dimethoxy-[1,1'-biphenyl]-2,2'-dicarboxylate (7.5g, 23mmol, 1.0 eq.) was dissolved in MeOH (90 mL) and a 2M aq. solution of NaOH (57mL, 110 mmol, 5.0 eq.) was added dropwise via an addition funnel. The reaction was refluxed over the weekend before being allowed to cool to r.t. upon which the reaction mixture was concentrated under vacuo. The remaining organic layer was slightly diluted with water and washed with DCM to remove all organic impurities. The layers were separated and the aqueous layer was transferred into a conical flask and with stirring acidified to pH1 with 2M KHSO_4 . Stirring was continued for 30min and the formed precipitate was filtered, washed with water and dried under high vacuum to obtain 4,4'-dimethoxy-[1,1'-biphenyl]-2,2'-dicarboxylic acid (6.64g, 22.0 mmol, 97%) as a free-flowing white solid. ^1H NMR (400 MHz, DMSO) δ 12.43 (s, 2H), 7.33 (d, J = 2.6 Hz, 2H), 7.14 – 7.01 (m, 4H), 3.82 (s, 6H).

Step 4: Synthesis of 3,9-dimethoxydibenzo[c,e]oxepine-5,7-dione



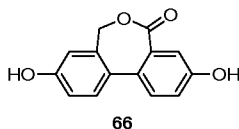
4,4'-dimethoxy-[1,1'-biphenyl]-2,2'-dicarboxylic acid (2.60 g, 10.1mmol, 1.0 eq.) was suspended in Ac_2O (50 mL) and the suspension was stirred overnight. The reaction was monitored by LCMS and after overnight stirring the starting material completely disappeared. Then the reaction mixture was filtered and washed with diethyl ether to facilitate drying. The filter cake was dried under high vacuum to yield 3,9-dimethoxydibenzo[c,e]oxepine-5,7-dione (2.87g, 10.1mmol, 99%). The NMR matched with the one reported in the literature.

Step 5: Synthesis of 3,9-dimethoxydibenzo[c,e]oxepin-5(7H)-one



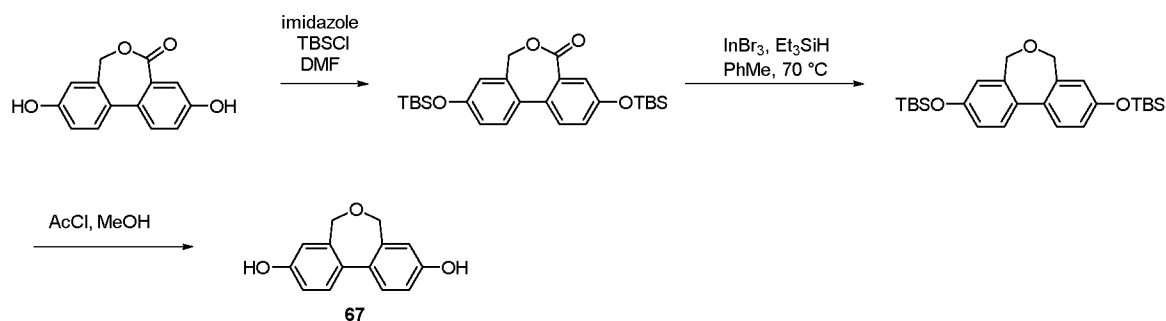
3,9-dimethoxydibenzo[c,e]oxepine-5,7-dione (150mg, 0.530 mmol, 1.0 eq.) was suspended in DMF (5mL) and cooled to 0 °C before sodium borohydride (20mg, 0.53mmol, 1.0 eq.) was added slowly. After two hours the reaction mixture was poured into aq. HCl (6M, 5mL) which was then subsequently diluted with water (10 mL) and stirred overnight. The product was precipitated overnight and was filtered before being taken up in DCM (25mL) and washed with water (3x10 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered, concentrated in vacuo, filtered through basic alumina with DCM and dried to afford 3,9-dimethoxydibenzo[c,e]oxepin-5(7H)-one (85mg, 0.31mmol, 60%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, J = 8.6 Hz, 1H), 7.50 – 7.44 (m, 2H), 7.19 (dd, J = 8.7, 2.8 Hz, 1H), 7.05 (dd, J = 8.6, 2.7 Hz, 1H), 6.97 (d, J = 2.7 Hz, 1H), 4.98 (d, J = 28.5 Hz, 2H), 3.90 (s, 3H), 3.87 (s, 3H).

Step 5: Synthesis of 3,9-dihydroxydibenzo[c,e]oxepin-5(7H)-one

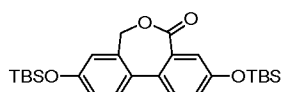


3,9-dimethoxydibenzo[c,e]oxepin-5(7H)-one (75mg, 0.28mmol, 1.0 eq.) was dissolved in DCM (6mL) and cooled down to 0 °C in an ice-bath and stirring was continued for 5min. Then BBr₃ (0.83ml, 1M in DCM, 0.83mmol, 3.00 eq.) was added dropwise to the reaction mixture. Upon complete addition the mixture was left in the ice bath and was allowed to warm to r.t. over the course of 2h. When no more starting material could be observed the reaction mixture was dropwise added into 0 °C cold methanol (10 mL) and stirred for an additional 10min. Then the mixture was concentrated and loaded on silica to be purified by flash column chromatography (SiO₂, 12g, MeOH in DCM 0-5%) 3,9-dihydroxydibenzo[c,e]oxepin-5(7H)-one (19mg, 0.8mmol, 28%) as white solid. ¹H NMR (400 MHz, MeOD) δ 7.49 (dd, J = 8.5, 7.3 Hz, 2H), 7.28 (d, J = 2.7 Hz, 1H), 7.14 (dd, J = 8.6, 2.7 Hz, 1H), 6.97 (dd, J = 8.4, 2.6 Hz, 1H), 6.93 (d, J = 2.6 Hz, 1H), 4.96 (d, J = 19.5 Hz, 2H).

Synthesis of 5,7-dihydrodibenzo[c,e]oxepine-3,9-diol (67)

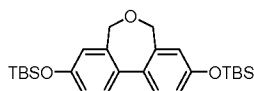


Step 1: Synthesis of 3,9-bis((tert-butyldimethylsilyl)oxy)dibenzo[c,e]oxepin-5(7H)-one



TBSCl (174mg, 1.15mmol, 2.2 eq.) was dissolved in DCM (9mL) and the resulting solution was cooled to 0 °C in an ice-bath and stirred for 5min. Then imidazole (89mg, 1.3mmol, 2.5 eq.) was slowly added in portions and upon complete addition stirring was continued for 15min. Subsequently 3,9-dihydroxydibenzo[c,e]oxepin-5(7H)-one (127mg, 0.520 mmol, 1.0 eq.) was added to the reaction mixture which became heterogenous upon addition of the substrate. Therefore DMF (1mL) was added in order to homogenize the mixture. Stirring at r.t. was continued overnight before the DCM was removed at the rotary evaporator and the remaining DMF solution was quenched with copious amounts of water and extracted with diethyl ether (3x10 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give the crude product which was further purified by MPLC (SiO₂, 40 g, EtOAc in Hex 0-20%) to afford 3,9-bis((tert-butyldimethylsilyl)oxy)dibenzo[c,e]oxepin-5(7H)-one (199mg, 0.42mmol 82%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.47 – 7.38 (m, 3H), 7.10 (dd, J = 8.6, 2.6 Hz, 1H), 6.97 (dd, J = 8.4, 2.6 Hz, 1H), 6.90 (d, J = 2.6 Hz, 1H), 4.88 (d, 2H), 1.01 (d, J = 1.9 Hz, 18H), 0.25 (d, J = 8.8 Hz, 12H).

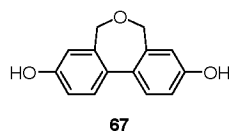
Step 2: Synthesis of 3,9-bis((tert-butyldimethylsilyl)oxy)-5,7-dihydrodibenzo[c,e]oxepine



3,9-bis((tert-butyldimethylsilyl)oxy)dibenzo[c,e]oxepin-5(7H)-one (200mg, 0.430 mmol, 1.0 eq.) was dissolved in toluene (5mL) and Et₃SiH (0.27ml, 1.7mmol, 4.0 eq.) was added in one portion. The reaction mixture was heated to 70 °C in a pre-heated oil-bath. Upon stirring for 5min at 70 °C InBr₃ (15mg, 0.04mmol, 0.10 eq.) was added in one portion. A quick color change to orange as

well as the evolution of gas could be observed and stirring was continued for 1h und the TLC did not show any more starting material. The reaction mixture was cooled down, filtered and the precipitate washed with DCM. The filtrate was loaded on silica and the crude was purified by flash column chromatography (SiO₂, 25g, DCM in Hex 0-10%) to yield 3,9-bis((tert-butyldimethylsilyl)oxy)-5,7-dihydrodibenzo[c,e]oxepine (194mg, 0.430 mmol, 99%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.36 (d, J = 8.3 Hz, 2H), 6.94 (dd, J = 8.3, 2.5 Hz, 2H), 6.90 (d, J = 2.5 Hz, 2H), 4.31 (s, 4H), 1.01 (s, 18H), 0.24 (s, 12H).

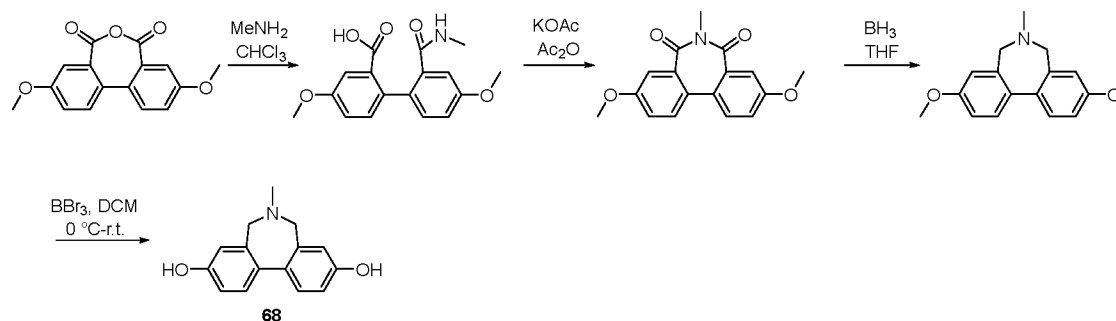
Step 3: Synthesis of 5,7-dihydrodibenzo[c,e]oxepine-3,9-diol

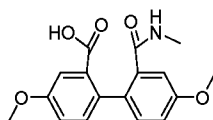


3,9-bis((tert-butyldimethylsilyl)oxy)-5,7-dihydrodibenzo[c,e]oxepine (194mg, 0.430 mmol, 1.0 eq.) was dissolved in MeOH (12mL) and the reaction mixture was cooled to 0 °C and AcCl (167mg, 2.12mmol, 5.0 eq.) were added dropwise via syringe. Upon complete addition, the reaction mixture was allowed to r.t. and stirring was continued over the weekend. The reaction was quenched with water and extracted into diethyl ether (3x15mL) and the combined organic layers were washed with NaHCO₃ and brine, dried over Na₂SO₄ and filtered through silica with diethyl ether washings and then concentrated to give pure 5,7-dihydrodibenzo[c,e]oxepine-3,9-diol (71mg, 0.31mmol, 73%) as a white solid. ¹H NMR (400 MHz, DMSO) δ 9.55 (s, 2H), 7.30 (d, J = 8.2 Hz, 2H), 6.87 (dd, J = 8.2, 2.6 Hz, 2H), 6.84 (d, J = 2.5 Hz, 2H), 4.13 (s, 4H).

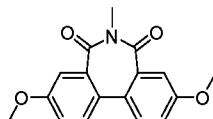
B) Amine “A” group analogues

Synthesis of 6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepine-3,9-diol (**68**)

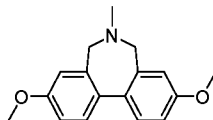


Step 1: Synthesis of 4,4'-dimethoxy-2'-(methylcarbamoyl)-[1,1'-biphenyl]-2-carboxylic acid

3,9-dimethoxydibenzo[c,e]oxepine-5,7-dione (569mg, 2.00 mmol, 1.0 eq.) was dissolved in CHCl_3 (20 mL) and to the resulting solution a 2M solution of MeNH_2 (1.20 mL, 2.40 mmol, 1.2 eq.) was added in one portion. Upon addition of the MeNH_2 a precipitate formed and the complete disappearance of starting material could be observed via LCMS. The precipitate was filtered over a glass frit (Por.4) and the filter residue was dried under vacuo to afford pure 4,4'-dimethoxy-2'-(methylcarbamoyl)-[1,1'-biphenyl]-2-carboxylic acid (631mg, 2.00 mmol, 99%) as a light brown solid. LCMS showed clean product which was carried on further to the next step.

Step 2: Synthesis of 3,9-dimethoxy-6-methyl-5H-dibenzo[c,e]azepine-5,7(6H)-dione

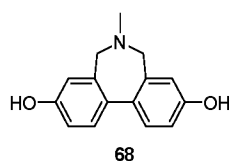
4,4'-dimethoxy-2'-(methylcarbamoyl)-[1,1'-biphenyl]-2-carboxylic acid (631mg, 2.00 mmol, 1.00 eq.) were suspended in Ac_2O (20 mL) and KOAc (393mg, 4.00 mmol, 2.00 eq.) were added in one portion. The reaction was stirred overnight and LCMS showed the complete conversion of starting material, therefore the suspension was filtered and the filter residue was dried under high vacuum to afford 3,9-dimethoxy-6-methyl-5H-dibenzo[c,e]azepine-5,7(6H)-dione (595mg, 2.00 mmol, 99%). ^1H NMR (400 MHz, CDCl_3) δ 7.51 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 2.8 Hz, 2H), 7.16 (dd, J = 8.7, 2.8 Hz, 2H), 3.90 (s, 6H), 3.54 (s, 3H).

Step 3: Synthesis of 3,9-dimethoxy-6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepine

3,9-dimethoxy-6-methyl-5H-dibenzo[c,e]azepine-5,7(6H)-dione (541mg, 1.82mmol, 1.0 eq.) was suspended in THF (15mL) and at r.t. $\text{BH}_3 \cdot \text{THF}$ (7.28mL, 7.28mmol, 1M, 4.0 eq.) was added dropwise over the course of 5min. Upon complete addition, the reaction was heated to reflux and

stirred overnight. Following the reaction was quenched with MeOH (200 mL) and stirring at 50 °C was continued for 30min. Subsequently the volatiles were evaporated and the crude material was purified by MPLC (SiO₂, 40 g, MeOH in EtOAc 0-50%) to obtain 3,9-dimethoxy-6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepine (485mg, 1.80 mmol, 99%) as an orange-brown solid. ¹H NMR (400 MHz, CDCl₃) δ 7.38 (d, J = 8.4 Hz, 2H), 6.97 (dd, J = 8.4, 2.7 Hz, 2H), 6.91 (d, J = 2.7 Hz, 2H), 3.86 (s, 6H), 3.37 (s, 4H), 2.48 (s, 3H).

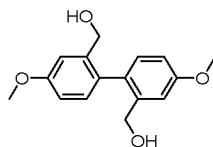
Step 4: Synthesis of 6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepine-3,9-diol



3,9-dimethoxy-6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepine (376mg, 1.40 mmol, 1.0 eq.) was dissolved in DCM (10 mL) and cooled down to 0 °C in an ice-bath and stirring was continued for 5min. Then BBr₃ (6.28ml, 1M in DCM, 6.28mmol, 4.5 eq.) was added dropwise to the reaction mixture. Upon complete addition the mixture was left in the ice bath and was allowed to warm to r.t. over the course of 2h. When no more starting material could be observed the reaction mixture was dropwise added into 0 °C cold methanol (10 mL) and stirred for an additional 10 min. Then the mixture was concentrated and loaded on silica to be purified by flash column chromatography (SiO₂, 40 g, MeOH in DCM 0-5%) 6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepine-3,9-diol (190mg, 0.790 mmol, 56%) as pale orange solid. ¹H NMR (400 MHz, DMSO) δ 10.92 – 10.62 (m, 2H), 7.37 (d, J = 8.2 Hz, 2H), 7.10 – 6.93 (m, 4H), 3.16 (s, 4H), 2.83 (d, J = 4.6 Hz, 3H).

Synthesis of 2,2'-bis(bromomethyl)-4,4'-dimethoxy-1,1'-biphenyl as a common intermediate

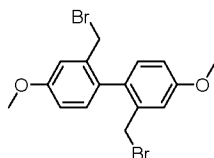
Step 1: Synthesis of (4,4'-dimethoxy-[1,1'-biphenyl]-2,2'-diyl)dimethanol



LiAlH₄ (251mg, 6.61mmol) was added carefully to a solution of 4,4'-dimethoxy-[1,1'-biphenyl]-2,2'-dicarboxylic acid (previously described above) (1.00 g, 3.30mmol) in THF (8ml) at 0°C then refluxed for 4h (reaction monitored by TLC). After Fieser workup 850 mg of (4,4'-dimethoxy-[1,1'-biphenyl]-2,2'-diyl)dimethanol (810mg, 2.90 mmol, 89%) as a white solid. ¹H NMR (400

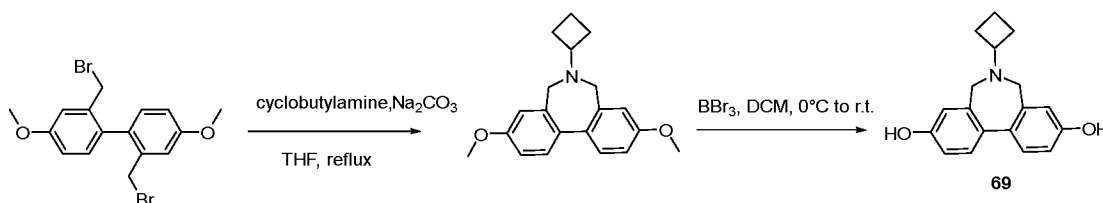
MHz, CDCl_3) δ 7.08 – 7.03 (m, 4H), 6.87 (dd, J = 8.3, 2.8 Hz, 2H), 4.40 – 4.28 (m, 4H), 3.86 (s, 6H), 2.20 (s, 2H).

Step 2: Synthesis of 2,2'-bis(bromomethyl)-4,4'-dimethoxy-1,1'-biphenyl

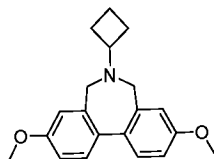


To a solution of (4,4'-dimethoxy-[1,1'-biphenyl]-2,2'-diyl)dimethanol (0.800 g, 2.92 mmol) and CBr_4 (4.84g, 14.6mmol) in CH_2Cl_2 (40 mL) cooled to 0 °C under an argon atmosphere was added portion-wise a solution of PPh_3 (3.06 g, 11.7mmol) in CH_2Cl_2 (20 mL). The reaction was stirred at room temp for 48 hrs, then concentrated and the crude product purified by MPLC on silica gel (EtOAc/ hexane: 0% to 10%) to give 2,2'-bis(bromomethyl)-4,4'-dimethoxy-1,1'-biphenyl (0.88 g, 2.20 mmol, 75%) as colorless oil. R_f = 0.5 (EtOAc/cyclohexane 10%). ^1H NMR (400 MHz, CDCl_3) δ 7.17 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 2.7 Hz, 2H), 6.91 (dd, J = 8.4, 2.7 Hz, 2H), 4.31 (d, J = 10.0 Hz, 2H), 4.17 (d, J = 10.0 Hz, 2H), 3.87 (s, 6H).

Synthesis of 6-cyclobutyl-6,7-dihydro-5H-dibenzo[c,e]azepine-3,9-diol (69)



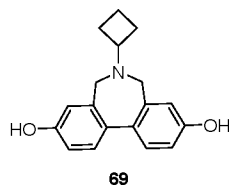
Step 1: Synthesis of 6-cyclobutyl-3,9-dimethoxy-6,7-dihydro-5H-dibenzo[c,e]azepine



Cyclobutylamine (28mg, 0.39mmol) was added to a suspension of 2,2'-bis(bromomethyl)-4,4'-dimethoxy-1,1'-biphenyl (130mg, 0.325mmol) and sodium carbonate (138mg, 130mmol) in THF 2 mL and the mixture was refluxed for 3h in THF. The reaction mixture was filtered off and the solvent was removed under vacuum to give 6-cyclobutyl-3,9-dimethoxy-6,7-dihydro-5H-dibenzo[c,e]azepine (100mg, 0.323mmol, 99%) as colorless oil. R_f = 0.3 (EtOAc). ^1H NMR (400

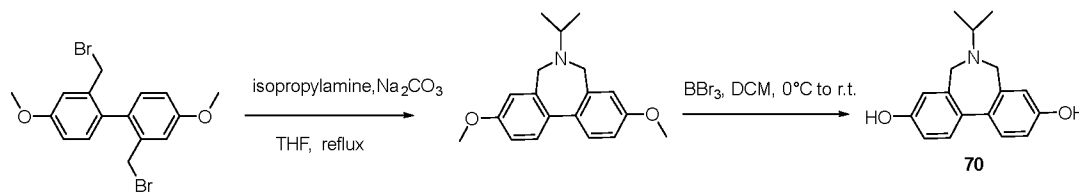
MHz, CDCl₃) δ 7.36 (d, J = 8.4 Hz, 2H), 6.95 (dd, J = 8.4, 2.7 Hz, 2H), 6.87 (d, J = 2.7 Hz, 2H), 3.86 (s, 6H), 3.28 (s, 4H), 3.12 (p, J = 8.0 Hz, 1H), 2.21 – 2.12 (m, 2H), 2.05 (d, J = 9.6 Hz, 2H), 1.82 – 1.65 (m, 2H).

Step 2: Synthesis of 6-cyclobutyl-6,7-dihydro-5H-dibenzo[c,e]azepine-3,9-diol

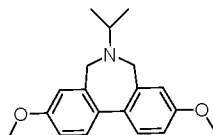


BBr₃ (0.87ml, 0.87mmol, 1.0M in DCM) was added to a solution of 6-cyclobutyl-3,9-dimethoxy-6,7-dihydro-5H-dibenzo[c,e]azepine (90mg, 0.29mmol) in dry DCM 3ml at 0°C and stirring continued overnight. Methanol 2ml was added at 0°C and the mixture was evaporated under vacuum. The crude product purified by flash chromatography on silica gel (Methanol/DCM: 0% to 10%) to give 6-cyclobutyl-6,7-dihydro-5H-dibenzo[c,e]azepine-3,9-diol hydrobromide (35mg, 0.97mmol, 33%) as a beige solid. R_f = 0.3 (MeOH/DCM 8%). MS (ESI⁺): m/z = 282. ¹H NMR (400 MHz, DMSO) δ 10.72 (s, 1H), 9.85 (s, 2H), 7.37 (d, J = 9.0 Hz, 2H), 6.99 (dd, J = 5.9, 2.8 Hz, 4H), 3.89 (s, 2H), 3.74 (d, J = 8.7 Hz, 1H), 3.51 (s, 2H), 2.37 – 2.21 (m, 4H), 1.75 (dt, J = 28.5, 10.0 Hz, 2H).

Synthesis of 6-isopropyl-6,7-dihydro-5H-dibenzo[c,e]azepine-3,9-diol (70)



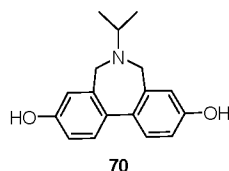
Step 1: Synthesis 6-isopropyl-3,9-dimethoxy-6,7-dihydro-5H-dibenzo[c,e]azepine



Isopropylamine (27mg, 0.45mmol) was added to a suspension of 2,2'-bis(bromomethyl)-4,4'-dimethoxy-1,1'-biphenyl (150mg, 0.375mmol) and sodium carbonate (159mg, 1.50mmol) in THF (2 mL) and the mixture was refluxed for 3h in THF. The reaction mixture was filtered off and the solvent was removed under vacuum to 6-isopropyl-3,9-dimethoxy-6,7-dihydro-5H-

dibenzo[*c,e*]azepine (110mg, 0.323mmol, 99%) as colourless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.44 – 7.33 (m, 2H), 6.99 (d, $J = 7.3$ Hz, 4H), 3.87 (s, 6H), 3.65 (s, 4H), 3.14 – 3.00 (m, 1H), 1.38 (d, $J = 6.4$ Hz, 6H).

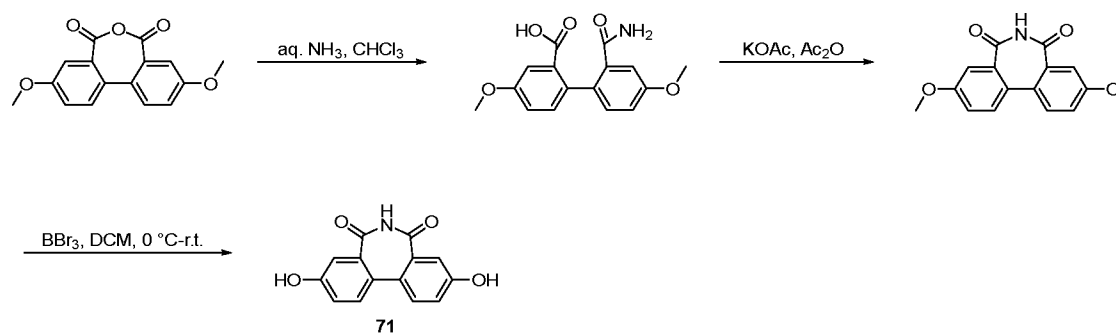
Step 2: Synthesis of 6-isopropyl-6,7-dihydro-5H-dibenzo[*c,e*]azepine-3,9-diol



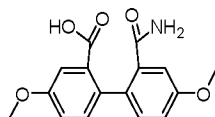
BBr_3 (1.87ml, 1.87mmol, 1.0M in DCM) was added to a solution of 6-isopropyl-3,9-dimethoxy-6,7-dihydro-5H-dibenzo[*c,e*]azepine (111mg, 0.370mmol) in dry DCM 3ml at 0°C and stirring continued overnight. Methanol 2ml was added at 0°C and the mixture was evaporated under vacuum. The crude product purified by flash chromatography on silica gel (Methanol/DCM: 0% to 10%) to give 6-isopropyl-6,7-dihydro-5H-dibenzo[*c,e*]azepine-3,9-diol (35mg, 0.97mmol, 35%) as a beige solid. $R_f = 0.3$ (MeOH/DCM 8%). ^1H NMR (400 MHz, DMSO) δ 10.19 (s, 1H), 9.84 (s, 2H), 7.37 (d, $J = 8.3$ Hz, 2H), 7.05 (d, $J = 2.6$ Hz, 2H), 6.99 (dd, $J = 8.4, 2.5$ Hz, 2H), 3.92 (s, $J = 4.3$ Hz, 4H), 3.63 – 3.51 (m, 1H), 1.40 (d, $J = 6.5$ Hz, 6H).

C) Imide “A” group analogues

Synthesis of 3,9-dihydroxy-5H-dibenzo[*c,e*]azepine-5,7(6H)-dione (71)

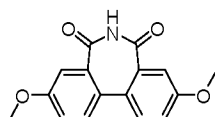


Step 1: Synthesis of 2'-carbamoyl-4,4'-dimethoxy-[1,1'-biphenyl]-2-carboxylic acid



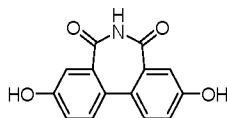
3,9-dimethoxydibenzo[c,e]oxepine-5,7-dione (100mg, 0.350 mmol, 1.0 eq.) was suspended in 25% aq. NH_3 solution (0.70 mL, 0.42mmol, 1.2 eq.) for 30min until the complete disappearance of the starting material was confirmed by LCMS (too polar to be monitored by TLC). The reaction mixture was filtered over a glass frit (Por.4) and the filter residue was dried under vacuo to afford pure 2'-carbamoyl-4,4'-dimethoxy-[1,1'-biphenyl]-2-carboxylic acid (106mg, 0.350 mmol, 99%) as a white solid. LCMS showed clean product after filtration and the product was used without further purification in the next step.

Step 2: Synthesis of 3,9-dimethoxy-5H-dibenzo[c,e]azepine-5,7(6H)-dione



2'-carbamoyl-4,4'-dimethoxy-[1,1'-biphenyl]-2-carboxylic acid (106mg, 0.350 mmol, 1.0 eq.) was suspended in Ac_2O (4mL) and KOAc (69mg, 0.70 mmol, 2.0 eq.) was added in one portion. The reaction mixture was stirred at r.t. overnight before being filtered over a small glass frit (Por.4). The precipitate was dried under vacuo to afford 3,9-dimethoxy-5H-dibenzo[c,e]azepine-5,7(6H)-dione (65mg, 0.23mmol, 65%) as a white solid. ^1H NMR (400 MHz, DMSO) δ 11.69 (s, 1H), 7.71 (dd, J = 8.7, 1.5 Hz, 2H), 7.40 – 7.36 (m, 2H), 7.31 (dt, J = 8.8, 2.4 Hz, 2H), 3.86 (s, 6H).

Step 3: Synthesis of 3,9-dihydroxy-5H-dibenzo[c,e]azepine-5,7(6H)-dione



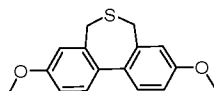
3,9-dimethoxy-5H-dibenzo[c,e]azepine-5,7(6H)-dione (100mg, 0.350 mmol, 1.0 eq.) was dissolved in DCM (2mL) and cooled down to 0 °C in an ice-bath and stirring was continued for 5min. Then BBr_3 (1.41ml, 1M in DCM, 1.41mmol, 4.0 eq.) was added dropwise to the reaction mixture. Upon complete addition the mixture was left in the ice bath and was allowed to warm to r.t. over the course of 2h. When no more starting material could be observed the reaction mixture was dropwise added into 0 °C cold methanol (10 mL) and stirred for an additional 10min. Then

the mixture was concentrated and loaded on silica to be purified by flash column chromatography (SiO₂, 12g, MeOH in DCM 0-5%) 3,9-dihydroxy-5H-dibenzo[c,e]azepine-5,7(6H)-dione (56mg, 0.22mmol, 62%) as white solid. ¹H NMR (400 MHz, DMSO) δ 9.66 (s, 2H), 7.13 (d, J = 2.6 Hz, 1H), 7.03 (s, 1H), 7.00 (d, J = 8.3 Hz, 1H), 6.93 (s, 1H), 6.90 (dd, J = 8.3, 2.6 Hz, 1H), 6.87 – 6.84 (m, 2H), 6.77 (dd, J = 8.2, 2.6 Hz, 1H).

D) Thioether and sulfone “A” group analogues

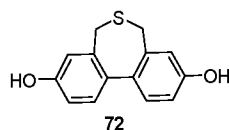
Synthesis 5,7-dihydrodibenzo[c,e]thiepine-3,9-diol (**72**)

Step 1: Synthesis 3,9-dimethoxy-5,7-dihydrodibenzo[c,e]thiepine



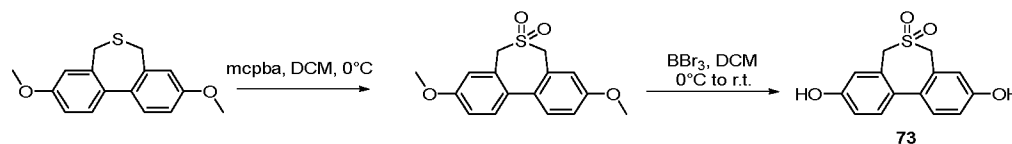
A mixture of 2,2'-bis(bromomethyl)-4,4'-dimethoxy-1,1'-biphenyl (procedure described above) (220mg, 0.55mmol) and sodium sulphidehydrate (69mg, 0.71mmol) in DMF (3 mL) was heated at 100 °C for 20 min. After cooling, the mixture was poured into water (10 mL), and the precipitate was filtered and washed with water (2 X 3 mL). The precipitate was taken up in CHCl₃ (15 mL), the solution was dried over Na₂SO₄, and the solvent was evaporated in vacuo to give 3,9-dimethoxy-5,7-dihydrodibenzo[c,e]thiepine (140mg, 0.510 mmol, 93%) as a yellowish solid. ¹H NMR (400 MHz, CDCl₃) δ 7.19 (d, J = 8.4 Hz, 2H), 6.91 (dd, J = 8.3, 2.7 Hz, 2H), 6.87 (d, J = 2.6 Hz, 2H), 3.86 (s, 6H), 3.56 (d, J = 12.7 Hz, 2H), 3.27 (s, 2H).

Step 2: Synthesis 5,7-dihydrodibenzo[c,e]thiepine-3,9-diol

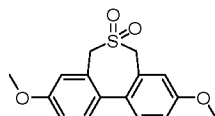


A solution of BBr₃ (0.59ml, 0.59mmol, 1M in DCM) was added at -78°C to a solution of 3,9-dimethoxy-5,7-dihydrodibenzo[c,e]thiepine (54mg, 0.20mmol) in DCM 2ml dcm and stirring continued overnight at room temperature. Methanol (5ml) was added at 0°C and the solvent was removed in vacuo. The crude was purified by MPLC (SiO₂, MeOH/DCM from 0% to 8%) to afford 5,7-dihydrodibenzo[c,e]thiepine-3,9-diol (18mg, 0.074mmol, 37%) as a beige solid. R_f = 0.3 (MeOH/DCM 5%). ¹H NMR (400 MHz, DMSO) δ 9.46 (s, 2H), 7.09 – 6.91 (m, 2H), 6.78 – 6.67 (m, 4H), 3.28 (s, 4H).

Synthesis of 3,9-dihydroxy-5,7-dihydrodibenzo[c,e]thieline 6,6-dioxide (73)

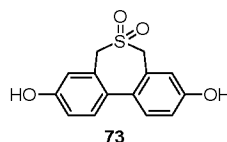


Step 1: Synthesis of 3,9-dimethoxy-5,7-dihydrodibenzo[c,e]thieline 6,6-dioxide



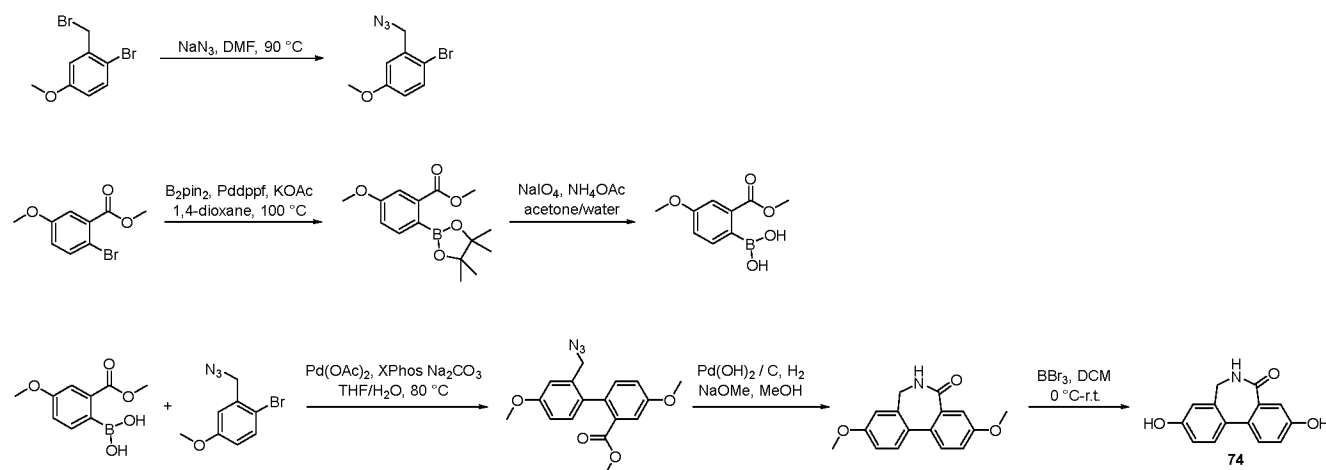
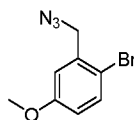
MCPBA (170mg, 0.690mmol) was added to 3,9-dimethoxy-5,7-dihydrodibenzo[c,e]thieline (90mg, 0.33mmol) in DCM (2ml) at 0°C and the reaction mixture was stirred at room temperature overnight. Na₂S₂O₃ 1M solution was added and the mixture stirred for 10 minutes, then NaHCO₃ saturated solution was added and the mixture was extracted twice with NaHCO₃ saturated solution. The organic phase was dried over sodium sulfate, filtered and evaporated under vacuum. The crude was purified by MPLC (SiO₂, EtOAc/cyclohexane 0% to 30%) to afford 3,9-dimethoxy-5,7-dihydrodibenzo[c,e]thieline 6,6-dioxide (90mg, 0.30 mmol, 89%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.38 (d, J = 8.4 Hz, 2H), 7.03 (dd, J = 8.4, 2.6 Hz, 2H), 6.99 (d, J = 2.6 Hz, 2H), 4.07 – 3.93 (q, 4H), 3.88 (s, 6H).

Step 2: Synthesis of 3,9-dihydroxy-5,7-dihydrodibenzo[c,e]thieline 6,6-dioxide

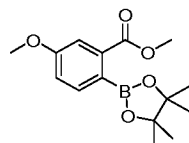


A solution of BBr₃ (1.0ml, 1.0 mmol, 1M in DCM, 3.5 eq.) was added at 0°C to a solution 3,9-dimethoxy-5,7-dihydrodibenzo[c,e]thieline 6,6-dioxide (90mg, 0.30 mmol, 1.0 eq.) in DCM (2mL) and stirring continued overnight at room temperature. Methanol (5mL) was added at 0°C and the solvent was removed in vacuo. The crude was purified by MPLC (EtOAc/Hex from 0% to 70%) to afford 3,9-dihydroxy-5,7-dihydrodibenzo[c,e]thieline 6,6-dioxide (46mg, 0.17mmol, 56%) as a beige solid. R_f = 0.3 (MeOH/DCM 5%). ¹H NMR (400 MHz, DMSO) δ 9.76 (s, 2H), 7.26 (d, J = 8.1 Hz, 2H), 6.94 – 6.83 (m, 4H), 4.29 (d, J = 13.7 Hz, 2H), 3.73 (d, J = 13.7 Hz, 2H).

E) Amides “A” group analogues

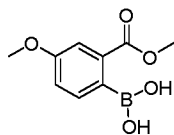
Synthesis of 3,9-dihydroxy-6,7-dihydro-5H-dibenzo[c,e]azepin-5-one (74)**Step 1:** Synthesis of 2-(azidomethyl)-1-bromo-4-methoxybenzene

1-bromo-2-(bromomethyl)-4-methoxybenzene (5.00 g, 17.9mmol, 1.0 eq.) was dissolved in DMF (60 mL) and NaN_3 (5.81g, 89.3mmol, 5.0 eq.) were added in one portion. Then the reaction mixture was heated to 90 °C and stirring was continued overnight. After overnight stirring the reaction mixture was allowed to cool to r.t., quenched with water (300 mL) and extracted with cyclohexane (3x75mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuo to afford pure 2-(azidomethyl)-1-bromo-4-methoxybenzene (4.32g, 17.8mmol, 99%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.47 (d, J = 8.8 Hz, 1H), 6.95 (d, J = 3.0 Hz, 1H), 6.76 (dd, J = 8.8, 3.0 Hz, 1H), 4.45 (s, 2H), 3.81 (s, 3H).

Step 2: Synthesis of 5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

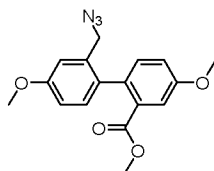
Methyl 2-bromo-5-methoxybenzoate (10.0, 40.8mmol, 1.0 eq.) was dissolved in 1,4-dioxane (140 mL). To this solution was added B₂pin₂ (11.4g, 44.9mmol, 1.1 eq.), Pd(dppf)Cl₂ (1.49g, 2.04mmol, 0.1 eq.) and KOAc (12.0 g, 122mmol, 3.0 eq.) and the reaction mixture was thoroughly degassed for 10min using a N₂ balloon before putting the reaction mixture in a pre-heated oil-bath to 85 °C for overnight stirring. Upon complete consumption of the starting material, the reaction mixture was allowed to cool to r.t. and then quenched with water. The layers were separated and the aq. phase was extracted with ethyl acetate (2x100 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuo. The crude product was purified by MPLC (SiO₂, 240 g, EtOAc in Hex 0-15%) to yield methyl 5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (9.51g, 32.6mmol, 78%) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.27 (d, *J* = 6.1 Hz, 1H), 7.09 (s, 1H), 6.88 (dd, *J* = 8.1, 2.6 Hz, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 1.23 (s, 12H).

Step 3: Synthesis of (4-methoxy-2-(methoxycarbonyl)phenyl)boronic acid



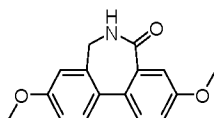
5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (1.33g, 4.55mmol, 1.0 eq.) was dissolved in a mixture of acetone (23mL) and water (23mL) and NH₄OAc (1.05g, 13.7mmol, 3.0 eq.) as well as NaIO₄ (2.92, 13.7mmol, 3.0 eq.) were added in one portion. Upon complete addition the mixture warmed up slightly and stirring was continued overnight. After the disappearance of the starting material (as indicated by TLC) the reaction mixture was filtered and the white precipitate was washed with acetone and the mother liquor concentrated to give pure (4-methoxy-2-(methoxycarbonyl)phenyl)boronic acid (590mg, 2.81mmol, 62%) as a white solid. Analytical data matched with the literature.

Step 4: Synthesis of 2'-(azidomethyl)-4,4'-dimethoxy-[1,1'-biphenyl]-2-carboxylate



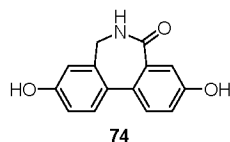
A 20 mL Biotage MW vial was charged with (4-methoxy-2-(methoxycarbonyl)phenyl)boronic acid (563mg, 2.68mmol, 1.10 eq.), 2-(azidomethyl)-1-bromo-4-methoxybenzene (590mg, 2.44mmol, 1.0 eq.), Pd(OAc)₂ (27 mg, 0.12mmol, 0.05 eq.), XPhos (116mg, 0.24mmol, 0.1 eq.) and all reagents were dissolved in THF (15 mL). The reaction mixture was degassed by using a N₂ balloon for 10min and afterwards a solution of Na₂CO₃ (775 mg, 7.31mmol, 3.0 eq.) in water (5mL) was added dropwise at r.t. Upon complete addition the reaction mixture was heated to 80 °C in an oil-bath and stirring was continued overnight. After overnight stirring the reaction mixture was allowed to cool to r.t. and quenched with water, the layers were separated and the aqueous layer was extracted with ethyl acetate (2x10 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuo. The crude product was purified by MPLC (SiO₂, 25g, EtOAc in Hex 0-20 %) to give methyl 2'-(azidomethyl)-4,4'-dimethoxy-[1,1'-biphenyl]-2-carboxylate (367mg, 1.12mmol, 46%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.47 (d, *J* = 2.7 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.08 (dd, *J* = 8.4, 2.8 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.96 (d, *J* = 2.6 Hz, 1H), 6.87 (dd, *J* = 8.4, 2.7 Hz, 1H), 4.09 (d, *J* = 3.1 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.63 (s, 3H).

Step 5: Synthesis of 3,9-dimethoxy-6,7-dihydro-5H-dibenzo[c,e]azepin-5-one



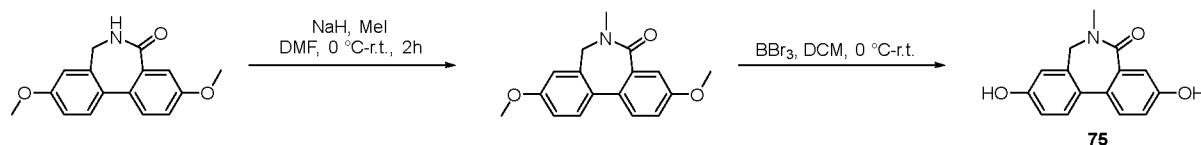
2'-(azidomethyl)-4,4'-dimethoxy-[1,1'-biphenyl]-2-carboxylate (50mg, 0.15mmol, 1.0 eq.) was dissolved in MeOH (8mL) and Pd(OH)₂/C (16mg, 0.02mmol, 0.15 eq.) as well as NaOMe (33mg, 0.15mmol, 1.0 eq.) were added to the solution which was degassed with N₂ three times followed by a hydrogen atmosphere exchange for three times. The reaction mixture was stirred overnight at r.t. before being filtered over a pad of celite and purified by MPLC (SiO₂, EtOAc in Hex 0-30%) to afford 3,9-dimethoxy-6,7-dihydro-5H-dibenzo[c,e]azepin-5-one (22mg, 0.08mmol, 53%) as a white solid. ¹H NMR (400 MHz, DMSO) δ 8.53 (s, 1H), 7.45 (t, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 2.8 Hz, 1H), 7.11 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.94 (dd, *J* = 12.2, 3.8 Hz, 2H), 3.84 (dd, *J* = 9.5, 3.6 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.18 (d, *J* = 14.8 Hz, 1H).

Step 6: Synthesis of 3,9-dihydroxy-6,7-dihydro-5H-dibenzo[c,e]azepin-5-one

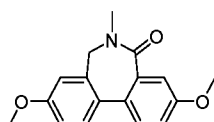


3,9-dimethoxy-6,7-dihydro-5H-dibenzo[c,e]azepin-5-one (64 mg, 0.24mmol, 1.0 eq.) was dissolved in DCM (2mL) and cooled down to 0 °C in an ice-bath and stirring was continued for 5min. Then BBr₃ (0.95ml, 1M in DCM, 0.95mmol, 4.0 eq.) was added dropwise to the reaction mixture. Upon complete addition the mixture was left in the ice bath and was allowed to warm to r.t. over the course of 2h. When no more starting material could be observed the reaction mixture was dropwise added into 0 °C cold methanol (10 mL) and stirred for an additional 10min. Then the mixture was concentrated and loaded on silica to be purified by flash column chromatography (SiO₂, 12g, MeOH in DCM 0-5%) to afford 3,9-dihydroxy-6,7-dihydro-5H-dibenzo[c,e]azepin-5-one (25mg, 0.10 mmol, 44%) as an orange solid. ¹H NMR (400 MHz, DMSO) δ 8.39 (t, *J* = 6.1 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 2.6 Hz, 1H), 6.97 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.80 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.71 (d, *J* = 2.3 Hz, 1H), 3.80 (ddd, *J* = 35.6, 14.6, 6.1 Hz, 2H).

Synthesis of 3,9-dihydroxy-6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepin-5-one (75)



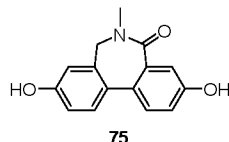
Step 1: Synthesis of 3,9-dimethoxy-6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepin-5-one



3,9-dimethoxy-6,7-dihydro-5H-dibenzo[c,e]azepin-5-one (80mg, 0.30 mmol, 1.0 eq.) was dissolved in DMF (3.0 mL) and the solution was cooled to 0 °C in an ice-bath and stirring was continued for 10min before adding 60% NaH in petroleum oil (14 mg, 0.36mmol, 1.2 eq.) in one portion. The reaction was stirred until the evolution of hydrogen gas completely ceased upon which MeI (0.13g, 0.89mmol, 3.0 eq.) was added dropwise. Afterwards the reaction was allowed to warm up to r.t. and stirred for 3h until the starting material disappeared (as indicated by TLC). The reaction was quenched with ice-water (10 mL) and the aqueous solution was extracted with diethyl ether (3x10 mL) and the organic layers were washed with water and brine, dried over Na₂SO₄ and

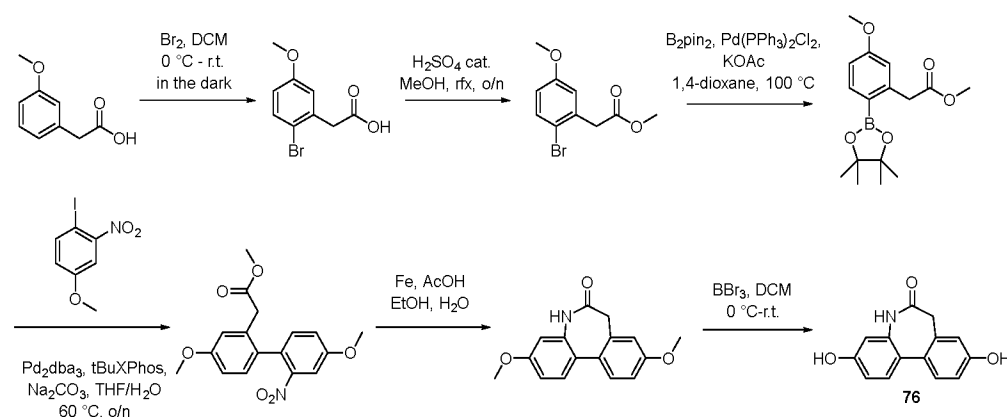
concentrated to afford 3,9-dimethoxy-6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepin-5-one (84mg, 0.30 mmol, 99%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.35 (dd, $J = 16.3, 8.4$ Hz, 2H), 7.14 (d, $J = 2.7$ Hz, 1H), 6.96 (dd, $J = 8.5, 2.7$ Hz, 1H), 6.90 – 6.81 (m, 2H), 4.10 – 3.75 (m, 2H), 3.10 (s, 3H), 3.00 (s, 3H), 2.90 (s, 3H).

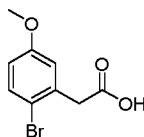
Step 2: Synthesis of 3,9-dihydroxy-6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepin-5-one



3,9-dimethoxy-6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepin-5-one (84 mg, 0.84mmol, 1.0 eq.) was dissolved in DCM (1mL) and cooled down to 0 °C in an ice-bath and stirring was continued for 5min. Then BBr_3 (1.20mL, 1M in DCM, 1.20 mmol, 4.0 eq.) was added dropwise to the reaction mixture. Upon complete addition the mixture was left in the ice bath and was allowed to warm to r.t. over the course of 2h. When no more starting material could be observed the reaction mixture was dropwise added into 0 °C cold methanol (10 mL) and stirred for an additional 10min. Then the mixture was concentrated and loaded on silica to be purified by flash column chromatography (SiO_2 , 12g, MeOH in DCM 0-5%) to afford 3,9-dihydroxy-6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepin-5-one (40mg, 0.16mmol, 52%) as light orange solid. ^1H NMR (400 MHz, DMSO) δ 9.65 (s, 2H), 7.35 (dd, $J = 16.3, 8.4$ Hz, 2H), 7.14 (d, $J = 2.7$ Hz, 1H), 6.96 (dd, $J = 8.5, 2.7$ Hz, 1H), 6.90 – 6.81 (m, 2H), 4.20 – 3.85 (m, 2H), 3.02 (s, 3H).

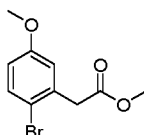
Synthesis of 3,9-dihydroxy-5,7-dihydro-6H-dibenzo[b,d]azepin-6-one (76)



Step 1: Synthesis of 2-(2-bromo-5-methoxyphenyl)acetic acid

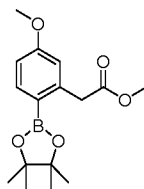
Bromine (1.92g, 12.0 mmol, 1.0 eq.) was added dropwise to a solution of 2-(3-methoxyphenyl)acetic acid (2.00 g, 12.0 mmol, 1.0 eq.) in DCM (40 mL) at 0 °C. Upon complete addition of the bromine, the reaction was allowed to warm to r.t. and stirred overnight while being covered from light using aluminum foil. The dark red solution was discolored with sodium thiosulfate solution (1M), washed with water (50 mL) and separated. The aqueous layer was extracted into DCM (2x25mL) and the combined organic layers dried over Na₂SO₄, filtered and evaporated to dryness to afford 2-(2-bromo-5-methoxyphenyl)acetic acid (2.80 g, 11.0 mmol, 95%) as a pale red solid.

¹H NMR (400 MHz, CDCl₃) δ 10.07 (s, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 6.85 (d, *J* = 3.0 Hz, 1H), 6.72 (dd, *J* = 8.8, 3.0 Hz, 1H), 3.79 (s, 2H), 3.78 (s, 3H).

Step 2: Synthesis of 2-(2-bromo-5-methoxyphenyl)acetate

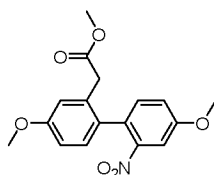
2-(2-bromo-5-methoxyphenyl)acetic acid (6.63g, 27.1mmol, 1.0 eq.) was dissolved in MeOH (90 mL) and a catalytic amount of concentrated sulfuric acid (0.2mL) was added to the mixture which was then refluxed for 4h before being cooled to r.t., quenched with water and extracted into ethyl acetate (3x100 mL). The organic layers were washed with sat. sodium bicarbonate solution and brine and dried with Na₂SO₄ and concentrated under vacuo. The crude product was purified by MPLC (SiO₂, 240 g, EtOAc in Hex 0-20%) to afford methyl 2-(2-bromo-5-methoxyphenyl)acetate (6.44g, 24.9mmol, 92%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.47 (d, *J* = 8.8 Hz, 1H), 6.87 (d, *J* = 3.0 Hz, 1H), 6.74 (dd, *J* = 8.8, 3.0 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 2H), 3.75 (s, 3H).

Step 3: Synthesis of 2-(5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate



Methyl 2-(2-bromo-5-methoxyphenyl)acetate (2.00 g, 7.72mmol, 1.0 eq.) was dissolved in 1,4-dioxane (150 mL) and there to was added B₂pin₂ (3.53g, 13.9mmol, 1.8 eq.), Pd(PPh₃)₂Cl₂ (542mg, 0.770 mmol, 0.1 eq.) and KOAc (3.03g, 30.9mmol, 4.0 eq.). The resulting reaction mixture was degassed for 10min using a N₂ balloon before being put into a pre-heated oil-bath at 100 °C overnight. After overnight stirring the mixture was allowed to cool to r.t. and quenched with sat. aq. NH₄Cl solution which was extracted into ethyl acetate (3x75mL). The combined organic layers were dried over anhydrous Na₂SO₄, concentrated under vacuo and the crude purified by MPLC (SiO₂, 120 g, EtOAc in Hex 0-20%) to afford methyl 2-(5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (1.32g, 4.31mmol, 56%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, *J* = 8.3 Hz, 1H), 6.80 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.74 (d, *J* = 2.5 Hz, 1H), 3.96 (s, 2H), 3.81 (s, 3H), 3.66 (s, 3H), 1.30 (s, 12H).

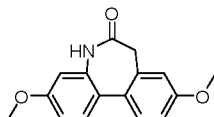
Step 4: Synthesis of 2-(4,4'-dimethoxy-2'-nitro-[1,1'-biphenyl]-2-yl)acetate



Methyl 2-(5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (670mg, 2.19mmol, 1.0 eq.) and 1-iodo-4-methoxy-2-nitrobenzene (733mg, 2.63mmol, 1.2 eq.) were dissolved in THF (2mL) and to this solution was added Pd₂dba₃ (100mg, 0.110 mmol, 0.05 eq.) as well as tBuXPhos (93mg, 0.22mmol, 0.1 eq.). The resulting mixture was degassed for 10min using a N₂ ballon before the dropwise addition of a solution of Na₂CO₃ (696mg, 6.56mmol, 3.0 eq.) in water (4mL). Following the reaction mixture was heated to 60 °C overnight (until starting material completely disappeared on TLC) before being allowed to cool to r.t., quenched with sat. aq. NH₄Cl solution, extracted with ethyl acetate (3x50 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuo. The resulting crude material was purified by MPLC (SiO₂, 40 g, EtOAc in Hex 0-35%) to afford methyl 2-(4,4'-dimethoxy-2'-nitro-[1,1'-biphenyl]-2-yl)acetate (490mg, 1.48mmol, 68%) as a green oil. ¹H NMR (400 MHz, CDCl₃) δ 7.48 (d, *J* = 2.7 Hz, 1H), 7.23 (d, *J* = 8.5 Hz,

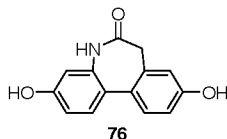
1H), 7.14 (dd, $J = 8.5, 2.7$ Hz, 1H), 7.03 (d, $J = 8.4$ Hz, 1H), 6.92 (d, $J = 2.6$ Hz, 1H), 6.83 (dd, $J = 8.4, 2.7$ Hz, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 3.59 (s, 3H), 3.48 – 3.33 (m, 2H).

Step 5: Synthesis of 3,9-dimethoxy-5,7-dihydro-6H-dibenzo[b,d]azepin-6-one



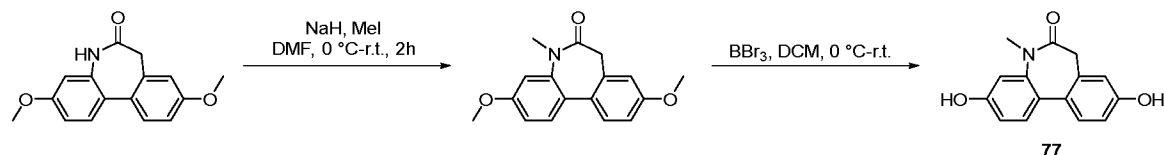
Methyl 2-(4,4'-dimethoxy-2'-nitro-[1,1'-biphenyl]-2-yl)acetate (485mg, 1.46mmol, 1.0 eq.) was dissolved in H₂O (3mL), AcOH (2mL) and EtOH (3mL) and powdered Fe (818mg, 14.6mmol, 10.0 eq.) was added to the mixture, which was stirred for 2h until the TLC showed no more starting material. Then reaction mixture was filtered over a pad of celite and concentrated under reduced pressure (AcOH was removed by azeotropic distillation with cyclohexane) and purified by MPLC (SiO₂, 40 g, EtOAc in Hex 0-85%) to afford 3,9-dimethoxy-5,7-dihydro-6H-dibenzo[b,d]azepin-6-one (150mg, 0.560 mmol, 38%) as a white solid. ¹H NMR (400 MHz, DMSO) δ 9.93 (s, 1H), 7.50 (d, $J = 8.7$ Hz, 1H), 7.44 (d, $J = 9.0$ Hz, 1H), 7.00 – 6.94 (m, 2H), 6.85 (dd, $J = 8.7, 2.6$ Hz, 1H), 6.72 (d, $J = 2.6$ Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H).

Step 6: Synthesis of 3,9-dihydroxy-5,7-dihydro-6H-dibenzo[b,d]azepin-6-one

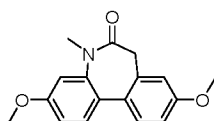


3,9-dimethoxy-5,7-dihydro-6H-dibenzo[b,d]azepin-6-one (70 mg, 0.26mmol, 1.0 eq.) was dissolved in DCM (2mL) and cooled down to 0 °C in an ice-bath and stirring was continued for 5min. Then BBr₃ (1.30ml, 1M in DCM, 1.30 mmol, 5.0 eq.) was added dropwise to the reaction mixture. Upon complete addition the mixture was left in the ice bath and was allowed to warm to r.t. over the course of 2h. When no more starting material could be observed the reaction mixture was dropwise added into 0 °C cold methanol (10 mL) and stirred for an additional 10min. Then the mixture was concentrated and loaded on silica to be purified by flash column chromatography (SiO₂, 12g, MeOH in DCM 0-5%) to afford 3,9-dihydroxy-5,7-dihydro-6H-dibenzo[b,d]azepin-6-one (35mg, 0.15mmol, 56%) as a light yellow solid. ¹H NMR (400 MHz, DMSO) δ 9.82 (s, 1H), 9.56 (s, 2H), 7.33 (d, $J = 8.5$ Hz, 1H), 7.27 (d, $J = 8.4$ Hz, 1H), 6.77 (dd, $J = 8.4, 2.5$ Hz, 1H), 6.69 (d, $J = 2.5$ Hz, 1H), 6.63 (dd, $J = 8.5, 2.5$ Hz, 1H), 6.55 (d, $J = 2.5$ Hz, 1H), 3.20 (s, 2H).

Synthesis of 3,9-dihydroxy-5-methyl-5,7-dihydro-6H-dibenzo[b,d]azepin-6-one (77)

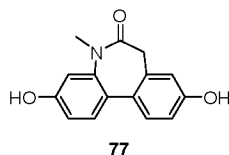


Step 1: Synthesis of 3,9-dimethoxy-5-methyl-5,7-dihydro-6H-dibenzo[b,d]azepin-6-one



3,9-dimethoxy-5,7-dihydro-6H-dibenzo[b,d]azepin-6-one (85mg, 0.32mmol, 1.0 eq.) was dissolved in DMF (3.2mL) and the solution was cooled to 0 °C in an ice-bath and stirring was continued for 10min before adding 60% NaH in petroleum oil (14mg, 0.36mmol, 1.2 eq.) in one portion. The reaction was stirred until the evolution of hydrogen gas completely ceased upon which MeI (0.060 g, 0.38mmol, 1.2 eq.) was added dropwise. Afterwards the reaction was allowed to warm up to r.t. and stirred for 3h until the starting material disappeared (as indicated by TLC). The reaction was quenched with ice-water (10 mL) and the aqueous solution was extracted with diethyl ether (3x10 mL) and the organic layers were washed with water and brine, dried over Na₂SO₄ and concentrated to afford 3,9-dimethoxy-5-methyl-5,7-dihydro-6H-dibenzo[b,d]azepin-6-one (60mg, 0.21mmol, 67%) as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.46 (dd, *J* = 8.4, 5.6 Hz, 2H), 6.98 – 6.85 (m, 4H), 3.89 (s, 3H), 3.86 (s, 3H), 3.56 – 3.39 (dd, 2H), 3.33 (s, 3H).

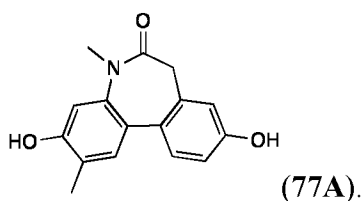
Step 1: Synthesis of 3,9-dihydroxy-5-methyl-5,7-dihydro-6H-dibenzo[b,d]azepin-6-one



3,9-dimethoxy-5,7-dihydro-6H-dibenzo[b,d]azepin-6-one (58 mg, 0.20 mmol, 1.0 eq.) was dissolved in DCM (2mL) and cooled down to 0 °C in an ice-bath and stirring was continued for 5min. Then BBr₃ (0.82ml, 1M in DCM, 0.82mmol, 4.0 eq.) was added dropwise to the reaction mixture. Upon complete addition the mixture was left in the ice bath and was allowed to warm to r.t. over the course of 2h. When no more starting material could be observed the reaction mixture

was dropwise added into 0 °C cold methanol (10 mL) and stirred for an additional 10min. Then the mixture was concentrated and loaded on silica to be purified by flash column chromatography (SiO₂, 12g, MeOH in DCM 0-5%) to afford 3,9-dihydroxy-5-methyl-5,7-dihydro-6H-dibenzo[b,d]azepin-6-one (30mg, 0.12mmol, 57%) as light orange solid. ¹H NMR (400 MHz, DMSO) δ 9.74 (s, 1H), 9.57 (s, 1H), 7.31 (dd, *J* = 8.4, 2.3 Hz, 2H), 6.82 – 6.71 (m, 4H), 3.31 – 3.20 (m, 2H), 3.15 (s, 3H).

Compound **77A** was prepared by employing the appropriate methyl substituted iodophenyl intermediate in the Pd coupling step of the above synthesis of **76**, which provides the methyl substituted analog of **76**. The remaining steps are analogous to those employed to provide compound **77**, i.e. amide methylation followed by deprotection.



Example 2: Synthesis of additional representative compounds

Reactions were not carried out under an inert atmosphere unless specified, and all solvents and commercial reagents were used as received.

Purification by chromatography refers to purification using the COMBIFLASH® Companion purification system or the Biotage SP1 purification system. Where products were purified using an Isolute® SPE Si II cartridge, 'Isolute SPE Si cartridge' refers to a pre-packed polypropylene column containing unbonded activated silica with irregular particles with average size of 50 µm and nominal 60Å porosity. Fractions containing the required product (identified by TLC and/or LCMS analysis) were pooled, the organic fraction recovered by evaporation, to give the final product. Where thin layer chromatography (TLC) has been used, it refers to silica-gel TLC plates, typically 3 × 6 cm silica-gel on aluminium foil plates with a fluorescent indicator (254 nm), (e.g. Fluka 60778). Microwave experiments were carried out using a Biotage Initiator 60™ which uses a single-mode resonator and dynamic field tuning. Temperatures from 40-250 °C can be achieved, and pressures of up to 30 bar can be reached.

NMR spectra were obtained on a Bruker Avance 400 MHz, 5mm QNP probe H, C, F, P, single Z gradient, two channel instrument running TopSpin 2.1 or on a Bruker Avance III 400

MHz, 5mm BBFO Plus probe, single Z gradient, two channel instrument running TopSpin 3.0.

Analytical LC-MS Conditions

Method 1: Experiments were performed on a Waters Acquity SQD2 mass spectrometer linked to a Waters Acquity UPLC binary pump / PDA detector. The spectrometer had an electrospray source operating in positive and negative ion mode. Additional detection was achieved using an Acquity UPLC HSS C18 1.7 μ m, 100 x 2.1 mm column maintained at 40°C and a 0.4 mL/minute flow rate. The initial solvent system was 95% water containing 0.1% formic acid (solvent A) and 5% MeCN containing 0.1% formic acid (solvent B) for the first 0.4 minute followed by a gradient up to 5% solvent A and 95%.

Method 2: Experiments were performed on a Waters Acquity SQD2 mass spectrometer linked to a Waters Acquity UPLC binary pump / PDA detector. The spectrometer had an electrospray source operating in positive and negative ion mode. Additional detection was achieved using an Acquity UPLC BEH Shield RP18 1.7 μ m 100 x 2.1mm. column maintained at 40°C and a 0.4 mL/minute flow rate. The initial solvent system was 95% water containing 0.03% aqueous ammonia (solvent A) and 5% MeCN containing 0.03% aqueous ammonia (solvent B) for the first 0.4 minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 5.4 min. The final solvent system was held constant for a further 0.8 min.

Method 3: Experiments were performed on a Waters Acquity ZQ mass spectrometer linked to a Waters Acquity UPLC binary pump / PDA detector. The spectrometer had an electrospray source operating in positive and negative ion mode. Additional detection was achieved using an Acquity UPLC BEH C18 1.7 μ m, 100 x 2.1 mm column maintained at 40°C and a 0.4 mL/minute flow rate. The initial solvent system was 95% water containing 0.1% formic acid (solvent A) and 5% MeCN containing 0.1% formic acid (solvent B) for the first 0.4 minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 5.6 min. The final solvent system was held constant for a further 0.8 min.

Method 4: Experiments were performed on a Waters Acquity ZQ mass spectrometer linked to a Waters Acquity UPLC binary pump/PDA detector. The spectrometer had an electrospray source operating in positive and negative ion mode. Additional detection was achieved using an Acquity UPLC BEH C18 1.7 μ m, 100 x 2.1 mm column maintained at 40°C and a 0.4 mL/minute flow rate. The initial solvent system was 95% water containing 0.03%

aqueous ammonia (solvent A) and 5% MeCN containing 0.03% aqueous ammonia (solvent B) for the first 0.4 minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 4 min. The final solvent system was held constant for a further 0.8 min.

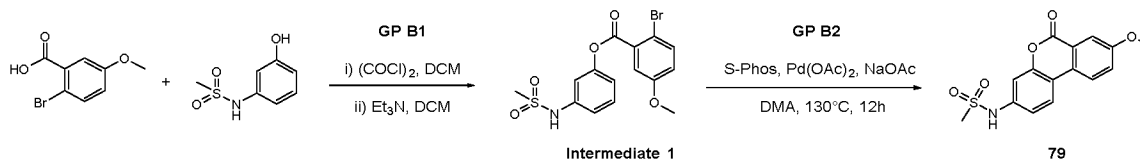
Method 5: Experiments were performed on a Waters Acquity ZQ mass spectrometer linked to a Waters Acquity H-class UPLC with DAD detector and QDa. The spectrometer had an electrospray source operating in positive and negative ion mode. Additional detection was achieved using an Acquity UPLC CSH 1.7 μ m, 50 x 2.1 mm column maintained at 40°C and a 1.0 mL/minute flow rate. The initial solvent system was 97% water containing 0.1% formic acid (solvent A) and 3% MeCN containing 0.1% formic acid (solvent B) for the first 0.4 minute followed by a gradient up to 1% solvent A and 99% solvent B over the next 1.4 min. The final solvent system was held constant for a further 0.5 min.

Method 6: Experiments were performed on a Waters Acquity ZQ mass spectrometer linked to a Waters Acquity H-class UPLC with DAD detector and QDa. The spectrometer had an electrospray source operating in positive and negative ion mode. Additional detection was achieved using an Acquity BEH UPLC 1.7 μ m, 50 x 2.1 mm column maintained at 40°C and a 0.8 mL/minute flow rate. The initial solvent system was 97% of 7.66 mM ammonia in water (solvent A) and 3% of 7.66 mM ammonia in MeCN containing (solvent B) for the first 0.4 minutes followed by a gradient up to 3% solvent A and 97% solvent B over the next 1.6 min. The final solvent system was held constant for a further 0.5 min.

A) Ester “A” group analogues

General Procedure B

N-(8-Methoxy-6-oxo-6*H*-benzo[*c*]chromen-3-yl)methanesulfonamide (79)



GP B1

3-(Methylsulfonamido)phenyl 2-bromo-5-methoxybenzoate (Intermediate 1)

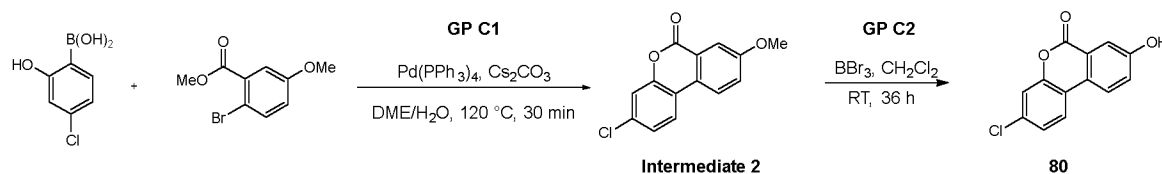
To a suspension of 2-bromo-5-methoxybenzoic acid (642 mg, 2.78 mmol) in DCM (10 mL) was added oxalyl chloride (0.27 mL, 3.06 mmol) dropwise and 1 drop of DMF. The solution was stirred at RT for 1 h and the solvent was removed *in vacuo*. The resultant mixture was re-dissolved in DCM (5 mL) and a suspension of *N*-(3-hydroxyphenyl)methanesulfonamide (520 mg, 2.78 mmol) in DCM (5 mL) was added followed by TEA (0.58 mL, 4.17 mmol). The resulting mixture was stirred for 4 h, then diluted with DCM and washed with saturated aq. NH_4Cl . The organic extracts were filtered through PTFE and concentrated *in vacuo* and the crude product was purified by chromatography on silica (ISCO 12 g) using 0-50% EtOAc in cyclohexane as eluant to give the product 3-(methylsulfonamido)phenyl 2-bromo-5-methoxybenzoate as colourless oil (1 g, 90%). LCMS (Method 5): R_t 1.43 min; m/z 398.0/400.0 $[\text{M}-\text{H}]^-$. ^1H NMR (400 MHz, CDCl_3) δ 7.61 (1H, d, $J=8.9$ Hz), 7.52 (1H, d, $J=3.1$ Hz), 7.41 (1H, t, $J=8.1$ Hz), 7.19-7.08 (3H, m), 6.98 (1H, dd, $J=8.9, 3.1$ Hz), 6.77 (1H, s), 3.87 (3H, s), 3.07 (6H, s).

GP B2

N-(8-Methoxy-6-oxo-6*H*-benzo[*c*]chromen-3-yl)methanesulfonamide (79)

A mixture of 3-(methylsulfonamido)phenyl 2-bromo-5-methoxybenzoate (Intermediate 1) (900 mg, 2.26 mmol), SPhos (92 mg, 0.225 mmol), palladium(II)acetate (50 mg, 0.225 mmol) and sodium acetate (369 mg, 4.5 mmol) in DMA (45 mL) was placed in a sealed tube, degassed and purged with argon (x3). The mixture was heated to 130°C for 3 h then cooled and diluted with water (400 mL) and extracted into DCM (3 x 50 mL) and the combined organic extracts were washed with brine and evaporated *in vacuo* at 80°C to remove residual DMA. The crude mixture was recrystallised from MeCN to give the product *N*-(8-methoxy-6-oxo-6*H*-benzo[*c*]chromen-3-yl)methanesulfonamide as a cream solid (200 mg, 27%). LCMS (Method 3): $R_t=3.85$ min; $m/z=320.0$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz: $\text{DMSO}-d_6$) δ 10.22 (1H, s), 8.30 (1H, d, $J=8.6$ Hz), 8.25 (1H, d, $J=9.2$ Hz), 7.65 (1H, d, $J=2.8$ Hz), 7.54 (1H, dd, $J=8.9, 2.8$ Hz), 7.22-7.19 (2H, m), 3.92 (3H, s), 3.11 (3H, s).

3-Chloro-8-hydroxy-6*H*-benzo[*c*]chromen-6-one (80)

**GP C1****3-Chloro-8-methoxy-6H-benzo[c]chromen-6-one (Intermediate 2)**

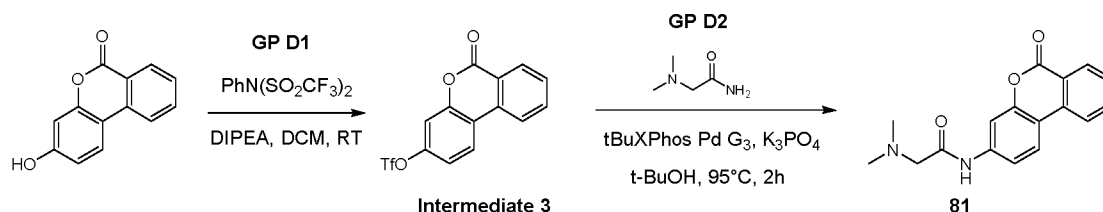
To a solution of 4-chloro-2-hydroxyphenylboronic acid (253 mg, 1.47 mmol) in DME (8.0 mL) and water (2.0 mL) was added methyl 2-bromo-5-methoxybenzoate (300 mg) and cesium carbonate (1.60 g, 4.90 mmol) followed by tetrakis(triphenylphosphine)palladium(0) (141 mg, 0.122 mmol). The reaction mixture was heated at 120°C in a microwave for 30 mins. The mixture was diluted with EtOAc (100 mL) and washed with water (10 mL) and brine (10 mL). The organic layer was passed through a phase separator and concentrated *in vacuo*. Purification of the residue by chromatography on silica eluting with 5-15% EtOAc in cyclohexane followed by trituration in MeOH and drying in a vacuum oven afforded the title compound as a white solid (112 mg, 35%). LCMS (Method 1). R_t =5.51 min; m/z =261.0, 263.1 $[M+H]^+$. ^1H NMR (400 MHz: $CDCl_3$) δ 7.99 (1H, d, J =8.8 Hz), 7.91 (1H, d, J =8.3 Hz), 7.81 (1H, d, J =2.8 Hz), 7.44-7.36 (2H, m), 7.31 (1H, dd, J =8.6, 2.0 Hz), 3.95 (3H, s);

GP C2**3-Chloro-8-hydroxy-6H-benzo[c]chromen-6-one (80)**

To a solution of 3-chloro-8-methoxy-6H-benzo[c]chromen-6-one (Intermediate 2) (70 mg, 0.268 mmol) in dry DCM (10 mL) under nitrogen was added dropwise a solution of boron tribromide in DCM (1.0 M, 5.4 mL, 5.36 mmol). The reaction mixture was stirred at RT for 3 days. Water (20 mL) was added and the mixture was diluted with DCM (10 mL). The mixture was stirred at RT for 10 mins. The resulting precipitate was filtered off and the aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were passed through a phase separation cartridge and concentrated under reduced pressure. The precipitate was dissolved in MeOH/DCM and concentrated *in vacuo*. Purification of the combined residues by chromatography on silica eluting with 2-4% MeOH in DCM afforded the title compound as a white solid (28 mg, 42%). LCMS (Method 1): R_t =4.55 min; m/z =247.1, 249.0 $[M+H]^+$. ^1H NMR (400 MHz: $DMSO-d_6$) δ 10.54 (1H, s), 8.35-8.31 (2H, m), 7.63-7.61 (2H, m), 7.51-7.42 (2H, m).

General Procedure D

2-(Dimethylamino)-N-(6-oxo-6H-benzo[c]chromen-3-yl)acetamide (81)



GP D1

6-Oxo-6H-benzo[c]chromen-3-yl trifluoromethanesulfonate (Intermediate 3)

A mixture of 6-hydroxy-6H-benzo[c]chromen-6-one (2.50 g, 11.78 mmol), *N*-phenyl-*bis*(trifluoromethanesulfonimide) (5.05 g, 14.1 mmol) and DIPEA (4.1 mL, 23.6 mmol) in DCM (50 mL) was stirred under nitrogen at RT. A catalytic amount of DMAP was added and the mixture stirred for 48 h. The resulting red solution was washed with 1M HCl (50 mL) and the DCM layer was dried (PTFE frit) and evaporated. The crude residue was recrystallised from DCM/cyclohexane to give the product as a cream solid. The mother liquors were purified by chromatography on silica using 20-100% DCM in cyclohexane as eluant. This afforded additional product 1.22 g (total yield 2.86 g, 71%). LCMS (Method 5): R_t =1.60 min (no m/z detected – poor ionization). ^1H NMR (CDCl_3) δ 8.43 (1H, dd, J =1.3, 8.0 Hz), 8.16 (1H, d, J =8.9 Hz), 8.11 (1H, d, J =8.0 Hz), 7.92-7.87 (1H, m), 7.69-7.64 (1H, m), 7.34 (1H, d, J =2.3 Hz), 7.30 (1H, dd, J =2.5, 8.9 Hz).

GP D2

2-(Dimethylamino)-N-(6-oxo-6H-benzo[c]chromen-3-yl)acetamide (81)

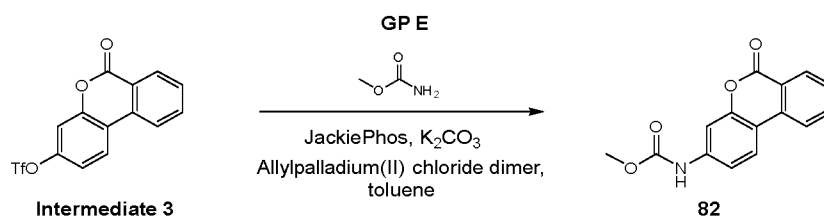
A mixture of 6-oxo-6H-benzo[c]chromen-3-yl trifluoromethanesulfonate (Intermediate 3) (344 mg, 1.0 mmol), 2-(dimethylamino)acetamide (153 mg, 1.5 mmol), tBuXPhos-Pd-G3 (24 mg, 0.03 mmol) and potassium phosphate tribasic (318 mg, 1.5 mmol) in a septum-sealed vial was degassed (evacuation and flush with argon 3 cycles). Warm degassed (argon sparged) tert-butanol (8.5 mL) was added *via* syringe and the mixture was then heated at 95°C for 2 h. The cooled mixture was diluted with water (15 mL) and the resulting mixture was filtered and dried *in vacuo* to afford a grey solid. This was taken into DCM (15 mL) and filtered through a 2 g

flash Si (II) cartridge which was then further eluted with 2% MeOH in DCM to give the title compound (125 mg, 42%) a white solid. LCMS (Method 3): $R_t=2.72$ min; $m/z=296.9$ $[M+H]^+$.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.14 (1H, s), 8.37 (1H, d, $J=8.1$ Hz), 8.29 (1H, d, $J=8.8$ Hz), 8.23 (1H, dd, $J=1.1, 7.9$ Hz), 7.96-7.90 (1H, m), 7.88 (1H, d, $J=2.1$ Hz), 7.68 (1H, dd, $J=2.1, 8.7$ Hz), 7.66-7.60 (1H, m), 3.13 (2H, s), 2.30 (6H, s).

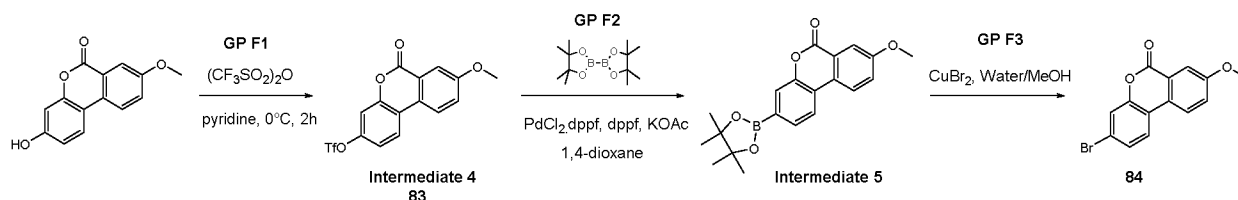
General Procedure E

Methyl (6-oxo-6H-benzo[c]chromen-3-yl)carbamate (82)



A mixture of 6-oxo-6H-benzo[c]chromen-3-yl trifluoromethanesulfonate (Intermediate 3) (250 mg, 0.73 mmol), methyl carbamate (82 mg, 1.09 mmol), allylpalladium(II)chloride dimer (2.7 mg, 0.007 mmol), JackiePhos (29 mg, 0.036 mmol) and K_2CO_3 (301 mg, 2.18 mmol) in toluene (6.0 mL) was sparged with argon for 5 min. The reaction vessel was then sealed, and the mixture was heated at 110°C for 1 h. The cooled reaction mixture was diluted with DCM (20 mL) and water (20 mL), which gave a suspension in the aqueous phase. The organic phase was separated, and the aqueous phase was washed with DCM (20 mL). The aqueous phase was filtered and the dark solid recovered was taken into 6% MeOH in DCM. This solution was filtered through a 5 g flash Si (II) cartridge which was then further eluted with 6% MeOH in DCM to afford the title compound (129 mg, 65%) as a white solid. LCMS (Method 3): $R_t=4.05$ min; $m/z=269.9$ $[M+H]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.12 (1H, s), 8.32 (1H, d, $J=8.1$ Hz), 8.28 (1H, d, $J=8.8$ Hz), 8.22 (1H, dd, $J=1.1, 7.9$ Hz), 7.95-7.89 (1H, m), 7.65-7.58 (2H, m), 7.45 (1H, dd, $J=2.1, 8.7$ Hz), 3.72 (3H, s).

General Procedure F

3-Bromo-8-methoxy-6H-benzo[c]chromen-6-one (84)**GP F1****8-Methoxy-6-oxo-6H-benzo[c]chromen-3-yl trifluoromethanesulfonate (83) (Intermediate 4)**

3-Hydroxy-8-methoxy-6H-benzo[c]chromen-6-one (1 g, 4.13 mmol) was dissolved in pyridine (10 mL) and the mixture was cooled in ice-water. Trifluoromethanesulfonic anhydride (1 mL, 6.19 mmol) was added dropwise and the resulting brown mixture was stirred at 0°C to RT for 2 h. The mixture was concentrated *in vacuo* and the residue was dissolved in DCM and washed with 1M HCl, brine, dried (PTFE frit) and concentrated *in vacuo*. The resultant residue was passed through a silica pad (12 g) and the product was eluted with 50-100% DCM in cyclohexane to give the compound as white crystals (1.2 g, 80%). ¹H NMR (400 MHz, CDCl₃) δ 8.56 (1H, d, J=9.1 Hz), 8.48 (1H, d, J=8.8 Hz), 7.80 (1H, d, J=2.5 Hz), 7.75 (1H, d, J=2.8 Hz), 7.65 (1H, dd, J=2.8, 8.8 Hz), 7.59 (1H, dd, J=2.7, 9.0 Hz), 4.00 (3H, s); LCMS (Method 1): R_t=5.64 min; m/z=375.0 [M+H]⁺.

GP F2**8-Methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6H-benzo[c]chromen-6-one (Intermediate 5)**

A mixture of 8-methoxy-6-oxo-6H-benzo[c]chromen-3-yl trifluoromethanesulfonate (Intermediate 4) (1.0 g, 2.67 mmol), potassium acetate (393 mg, 4.0 mmol), [1,1-bis(diphenylphosphino)ferrocene] dichloropalladium(II) complex with DCM (65 mg, 0.08 mmol), 1,1-bis(diphenylphosphino)ferrocene (44 mg, 0.08 mmol) and dioxane (20 mL) was sparged with argon. Bis(pinacolato)diboron (746 mg, 2.94 mmol) was added and after a further period of degassing, the mixture was heated at 90°C under argon for 19 h. The cooled mixture was partitioned between ether (25 mL) and water (25 mL) and the phases were separated, and the aqueous phase extracted with ether (2 x 25 mL). The combined organic extract was washed with saturated brine, dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified by flash

chromatography on a 20 g Si-(II) cartridge eluting with DCM then 10% EtOAc in DCM. The product obtained was triturated with cyclohexane (10 mL) then dried *in vacuo* to afford the title compound (0.76 g, 81%) as an off white solid. LCMS (Method 5): R_t =1.65 min; m/z =353.1 $[M+H]^+$ and R_t =1.11 min; m/z =271.1 $[M-Pin+H]^+$.

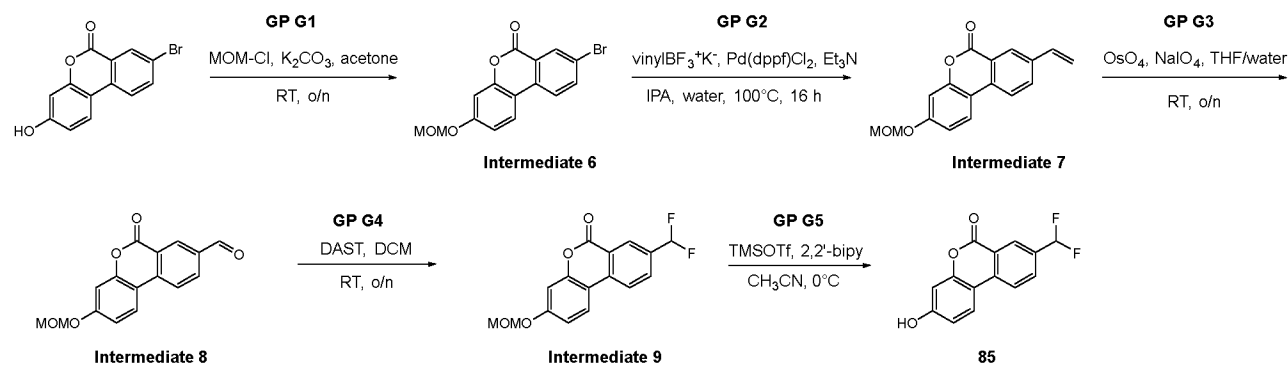
GP F3

3-Bromo-8-methoxy-6*H*-benzo[*c*]chromen-6-one (84)

A suspension of 8-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6*H*-benzo[*c*]chromen-6-one (Intermediate 5) (352 mg, 1.0 mmol) in MeOH (10 mL) was treated with a solution of copper(II)bromide (670 mg, 3.0 mmol) in water (10 mL). The resulting mixture was heated at reflux for 16 h then cooled. The cold mixture was extracted with ether (2 x 25 mL) then DCM (2 x 25 mL) and the combined organic phase was filtered through a hydrophobic frit then concentrated *in vacuo*. The residue was purified by flash chromatography on a 5 g Si-(II) cartridge and eluted with [1:1] DCM/cyclohexane then DCM to afford the title compound (240 mg, 78%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (1H, d, J =8.9 Hz), 7.84 (1H, d, J =8.7 Hz), 7.80 (1H, d, J =3.0 Hz), 7.53 (1H, d, J =1.9 Hz), 7.46-7.39 (2H, m), 3.95 (3H, s); LCMS (Method 5), R_t =1.53 min; m/z =304.8, 306.8 $[M+H]^+$.

Procedure G

8-(Difluoromethyl)-3-(methoxymethoxy)-6*H*-benzo[*c*]chromen-6-one (85)



GP G1

8-Bromo-3-(methoxymethoxy)-6*H*-benzo[*c*]chromen-6-one (Intermediate 6)

8-Bromo-3-hydroxy-6*H*-benzo[*c*]chromen-6-one (1.0 g, 3.44 mmol), K_2CO_3 (1.42 g, 10.31 mmol) and chloromethyl methyl ether (0.39 mL, 5.15 mmol) were suspended in acetone (10 mL)

and the mixture was stirred for 3 h. An additional aliquot of chloromethyl methyl ether (0.39 mL, 5.15 mmol) was added and the mixture stirred for 2 h. The mixture was concentrated *in vacuo* and dispersed between DCM and water. The DCM layer was washed with brine, dried (PTFE frit) and evaporated to give the product as a white solid (1 g, 86%). ¹H NMR (400 MHz, CDCl₃) δ 8.50 (1H, s), 7.9 -7.88 (3H, m), 7.07-7.02 (2H, m), 5.25-5.24 (2H, m), 3.51 (3H, s).

GP G2

3-(Methoxymethoxy)-8-vinyl-6*H*-benzo[*c*]chromen-6-one (Intermediate 7)

A mixture of 8-bromo-3-(methoxymethoxy)-6*H*-benzo[*c*]chromen-6-one (Intermediate 6) (1 g, 2.98 mmol), potassium vinyltrifluoroborate (520 mg, 3.88 mmol), TEA (1.2 mL, 8.95 mmol) and [1,1'-*bis*(diphenylphosphino)ferrocene]dichloropalladium(II) complex with DCM (122 mg, 0.15 mmol) in isopropanol (20 mL) and water (10 mL) was placed in a sealed tube, evacuated and purged with argon (x3). The mixture was heated at 90°C under argon for 2 h. The cooled mixture was concentrated *in vacuo* and the residue dispersed between EtOAc and water. The EtOAc layer was washed with brine, dried (PTFE frit) and concentrated *in vacuo*. The resultant residue was purified by chromatography on silica using 0-50% DCM in cyclohexane as eluant to give the product as a white solid (705 mg, 71%). ¹H NMR (400 MHz, CDCl₃) δ 8.37 (1H, d, *J*=1.9 Hz), 7.98 (1H, d, *J*=8.5 Hz), 7.94 (1H, d, *J*=8.7 Hz), 7.84 (1H, dd, *J*=2.0, 8.4 Hz), 7.07-7.02 (2H, m), 6.81 (1H, dd, *J*=10.9, 17.6 Hz), 5.91 (1H, d, *J*=17.6 Hz), 5.40 (1H, d, *J*=11.0 Hz), 5.25 (2H, s), 3.51 (3H, s).

GP G3

3-(Methoxymethoxy)-6-oxo-6*H*-benzo[*c*]chromene-8-carbaldehyde (Intermediate 8)

To a solution of 3-(methoxymethoxy)-8-vinyl-6*H*-benzo[*c*]chromen-6-one (Intermediate 7) (700 mg, 2.48 mmol) in THF (40 mL) was added osmium tetroxide (0.25 mL, 0.025 mmol) followed by a solution of sodium periodate (1.59 g, 7.44 mmol), and the resulting solution was stirred for 18 h, which gave a white suspension. The mixture was concentrated *in vacuo* and the residue portioned between DCM and water, and the DCM layer was washed with aqueous sodium sulfite, brine then dried (PTFE frit) to give a white solid (700 mg, quant.). ¹H NMR (400 MHz, CDCl₃) δ 10.11 (1H, s), 8.83 (1H, d, *J*=1.8 Hz), 8.30 (1H, dd, *J*=1.8, 8.4 Hz), 8.16 (1H, d, *J*=8.4

Hz), 8.04-8.00 (1H, m), 7.10-7.07 (2H, m), 5.27 (2H, s), 3.52 (3H, s); LCMS (Method 6): R_t =1.41 min; m/z =284.2 $[M+1]^+$.

GP G4

8-(Difluoromethyl)-3-(methoxymethoxy)-6H-benzo[c]chromen-6-one (Intermediate 9)

A suspension of 3-(methoxymethoxy)-6-oxo-6H-benzo[c]chromene-8-carbaldehyde (Intermediate 8) (190 mg, 0.67 mmol) in DCM (3 mL) was placed under argon. DAST (0.26 mL, 2.01 mmol) was added dropwise and the resulting mixture was stirred for 18 h at RT. The resulting solution was neutralised with saturated aqueous NaHCO_3 and the DCM layer was washed with brine, dried (PTFE frit) and concentrated *in vacuo*. The residue was purified by chromatography on silica using 0-70% DCM in cyclohexane as eluant to give the product as a pale-yellow solid (175 mg, 85%). ^1H NMR (400 MHz, CDCl_3 , 258114) δ 8.49 (1H, d, J =1.1 Hz), 8.12 (1H, d, J =8.4 Hz), 7.98 (1H, d, J =8.5 Hz), 7.96-7.92 (1H, m), 7.09-7.05 (2H, m), 6.76 (1H, t, J =56.1 Hz), 5.26 (2H, s), 3.51 (3H, s); LCMS (Method 6): R_t =1.55 min (no m/z detected – poor ionization).

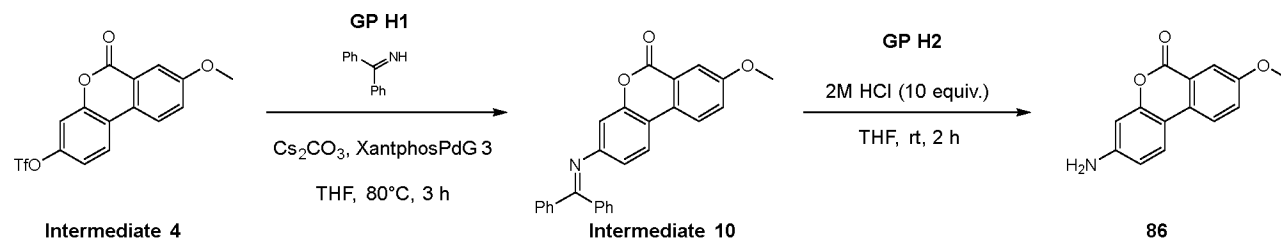
GP G5

8-(Difluoromethyl)-3-hydroxy-6H-benzo[c]chromen-6-one (85)

A solution of 8-(difluoromethyl)-3-(methoxymethoxy)-6H-benzo[c]chromen-6-one (Intermediate 9) (65 mg, 0.21 mmol) and 2,2'-bipyridyl in MeCN was placed in a sealed tube under argon and cooled in ice-water. Trifluoromethyl trifluoromethane sulfonate (0.08 mL, 0.42 mmol) was added and the solution was stirred for 18 h. The resultant mixture was stirred with water (0.5 mL) for 30 min. then concentrated *in vacuo*, and the residue was partitioned between EtOAc and water. The EtOAc layer was washed with brine, dried (PTFE frit) and concentrated *in vacuo*. The crude residue was purified by chromatography on silica using 0-5% MeOH in DCM as eluant to give the product as a pale-yellow solid. The product was further purified by chromatography on silica using 0-50% EtOAc in cyclohexane as eluant to give the title compound as a white solid (25 mg, 45% yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.50 (1H, s), 8.41 (1H, d, J =8.5 Hz), 8.35 (1H, d, J =1.1 Hz), 8.21 (1H, d, J =8.9 Hz), 8.04 (1H, d, J =8.4 Hz), 7.21 (1H, t, J =55.6 Hz), 6.88 (1H, dd, J =2.4, 8.7 Hz), 6.78 (1H, d, J =2.4 Hz). LCMS (Method 3): R_t =4.03 min; m/z =260.9 $[M-H]^-$.

Procedure H

3-Amino-8-methoxy-6H-benzo[c]chromen-6-one (86)



GP H1

3-((Diphenylmethylene)amino)-8-methoxy-6H-benzo[c]chromen-6-one (Intermediate 10)

A glass vial was charged with a mixture of 8-methoxy-6-oxo-6H-benzo[c]chromen-3-yl trifluoromethanesulfonate (Intermediate 4) (300 mg, 0.802 mmol), benzophenone imine (0.20 mL, 1.20 mmol), cesium carbonate (392 mg, 1.20 mmol) and XPhos-Pd-G3 (76 mg, 0.080 mmol) in THF (4.0 mL). The reaction mixture was evacuated and purged with nitrogen (x 3) and was heated at 80°C for 2 h. The cooled mixture was partitioned between EtOAc (x 2) and water and the combined organic extract was washed with brine, dried (MgSO_4) and concentrated *in vacuo*. The resultant residue was purified by chromatography on silica using 5-95% EtOAc in cyclohexane as eluant to give the product as a white solid (250 mg, 77%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.23 (1H, d, $J=9.0$ Hz), 8.05 (1H, d, $J=8.5$ Hz), 7.61 (1H, d, $J=2.8$ Hz), 7.72-7.66 (2H, m), 7.53-7.46 (4H, m), 7.36-7.31 (2H, m), 7.33 (1H, ob. s), 7.27-7.21 (2H, m), 6.79 (1H, d, $J=2.0$ Hz), 6.73 (1H, dd, $J=2.0, 8.4$ Hz), 3.89 (3H, s). LCMS (Method 5): $R_t=1.94$ min; $m/z=406.3$ $[\text{M}+\text{H}]^+$.

GP H1

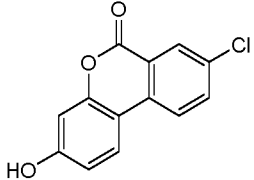
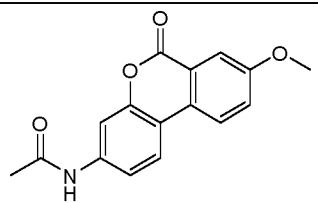
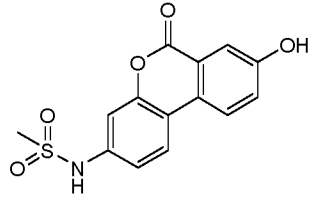
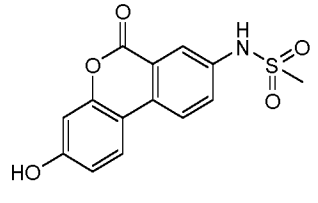
3-Amino-8-methoxy-6H-benzo[c]chromen-6-one (86)

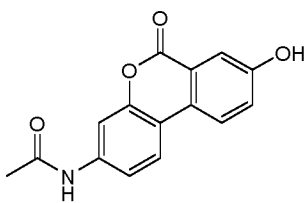
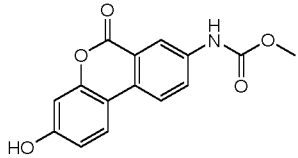
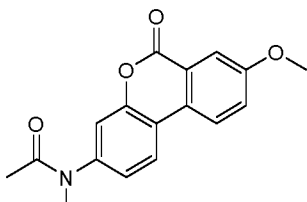
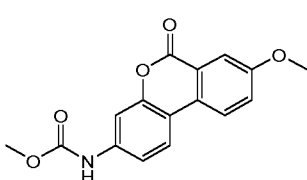
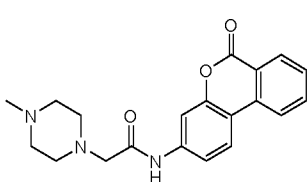
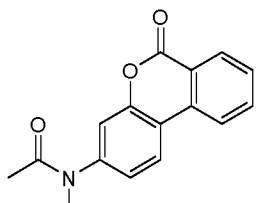
A solution of 3-((diphenylmethylene)amino)-8-methoxy-6H-benzo[c]chromen-6-one (Intermediate 10) (250 mg, 0.617 mmol) in THF (3.0 mL) was treated with 2 M HCl (3.1 mL) and allowed to stir at RT for 10 mins. A precipitate was collected by filtration, which was then dissolved in MeOH and applied to a MeOH-equilibrated SCX-2 cartridge; after washing with MeOH/DCM the title compound was eluted using 7M NH_3 in MeOH to give the product as a beige solid (50 mg, 34%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.15 (1H, d, $J=8.8$ Hz), 7.94 (1H, d,

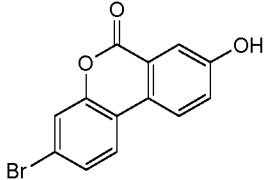
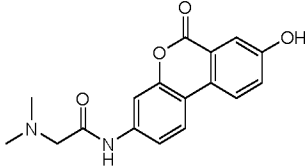
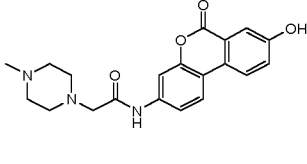
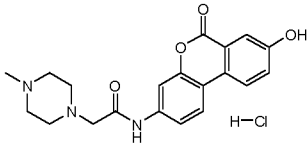
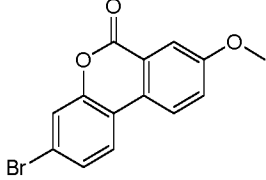
J=8.6 Hz), 7.61 (1H, d, J=2.8 Hz), 7.49 (1H, dd, J=2.8, 8.8 Hz), 6.67 (1H, dd, J=2.3, 8.6 Hz), 6.54 (1H, d, J=2.3 Hz), 5.82 (2H, s), 3.92 (3H, s); LCMS (Method 1): R_t =3.91 min; m/z =242.3[M+H]⁺.

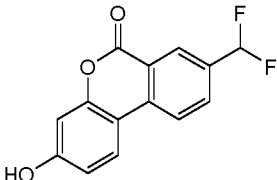
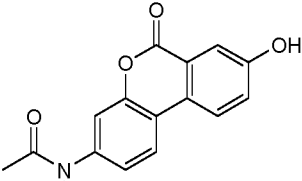
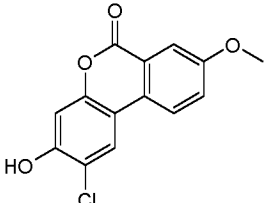
The following examples in Table A were prepared using similar methods those described above by utilizing the general procedures (GP) indicated.

Table A.

Ex.	Structure	General procedure	¹ H NMR data (400 MHz, DMSO- <i>d</i> ₆) δ	LCMS m/z (M+H)	HPLC R_t (min)/QC Method
(87)		A	10.48 (1H, s), 8.36 (1H, d, J=8.8 Hz), 8.23 (1H, d, J=8.8 Hz), 8.17 (1H, d, J=2.3 Hz), 7.98 (1H, dd, J=2.4, 8.7 Hz), 6.91 (1H, dd, J=2.4, 8.7 Hz), 6.82 (1H, d, J=2.3 Hz)	245.1, 247.1	4.52 / 1
(92)		A/D	10.29 (1H, s), 8.24 (2H, dd, J=8.9, 28.4 Hz), 7.78 (1H, d, J=2.0 Hz), 7.64 (1H, d, J=2.7 Hz), 7.55-7.46 (2H, m), 3.91 (3H, s), 2.10 (3H, s)	284.0	3.72 / 3
(94)		A/D/C2	10.38-10.35 (1H, m), 10.15 (1H, s), 8.21-8.17 (2H, m), 7.55 (1H, d, J=2.6 Hz), 7.36 (1H, dd, J=2.7, 8.7 Hz), 7.20-7.17 (2H, m), 3.09 (3H, s)	305.8	3.06 / 3
(99)		A/D2	10.29 - 10.19 (2H, m), 8.25 (1H, d, J=8.7 Hz), 8.10 (1H, d, J=8.9 Hz), 8.00 (1H, d, J=2.4 Hz), 7.69 (1H, dd, J=2.4, 8.7 Hz), 6.84 (1H, dd, J=2.4, 8.7 Hz), 6.76-6.75 (1H, m), 3.07-3.06 (3H, m)	305.9	3.07 / 3

(100)		A/D/C2	10.27 (1H, s), 8.19-8.12 (2H, m), 7.75 (1H, d, J=2.0 Hz), 7.54 (1H, d, J=2.6 Hz), 7.46 (1H, dd, J=2.0, 8.7 Hz), 7.35 (1H, dd, J=2.7, 8.7 Hz), 2.09 (3H, s)	269.9	2.94 / 3
(101)		A/E	10.26 (1H, s), 10.07 (1H, s), 8.35 (1H, d, J=2.3 Hz), 8.20 (1H, d, J=8.9 Hz), 8.07 (1H, d, J=8.9 Hz), 7.92 (1H, dd, J=2.4, 8.8 Hz), 6.83 (1H, dd, J=2.4, 8.7 Hz), 6.74 (1H, d, J=2.4 Hz), 3.71 (3H, s)	285.9	3.38 / 3
(102)		A/E	8.41 (1H, d, J=8.9 Hz), 8.35 (1H, d, J=8.5 Hz), 7.68 (1H, d, J=2.8 Hz), 7.57 (1H, dd, J=2.8, 8.9 Hz), 7.50 (1H, s), 7.38 (1H, dd, J=2.1, 8.5 Hz), 3.93 (3H, s), 3.24 (3H, s), 1.92 (3H, s)	297.9	3.84 / 3
(103)		A/E	10.06 (1H, s), 8.27 (1H, d, J=8.9 Hz), 8.20 (1H, d, J=8.8 Hz), 7.64 (1H, d, J=2.8 Hz), 7.58 (1H, d, J=2.0 Hz), 7.53 (1H, dd, J=2.8, 8.9 Hz), 7.42 (1H, dd, J=2.1, 8.7 Hz), 3.91 (3H, s), 3.72 (3H, s)	299.8	4.18 / 3
(104)		A/D	10.09 (1H, s), 8.35 (1H, d, J=8.1 Hz), 8.30 (1H, d, J=8.8 Hz), 8.23 (1H, dd, J=1.0, 7.9 Hz), 7.96-7.91 (1H, m), 7.85 (1H, d, J=2.0 Hz), 7.66-7.60 (2H, m), 3.17 (2H, s), 2.54 (br s, part obscured by solvent), 2.39 (4H, br s), 2.18 (3H, s)	352.0	3.76 / 4
(105)		E	8.46 (1H, d, J=8.1 Hz), 8.42 (1H, d, J=8.3 Hz), 8.27 (1H, dd, J=1.2, 7.9 Hz), 8.01-7.95 (1H, m), 7.74-7.68 (1H, m), 7.52 (1H, d, J=1.7 Hz), 7.41 (1H, dd, J=2.2, 8.5 Hz),	268.0	3.77 / 4

			3.25 (3H, s), 1.94 (3H, br s)		
(106)		F/C2	10.5 (1H, s), 8.29 (1H, d, J=8.8 Hz), 8.19 (1H, d, J=8.6 Hz), 7.68 (1H, d, J=2.0 Hz), 7.57 (1H, d, J=2.7 Hz), 7.55 (1H, dd, J=2.0, 8.6 Hz), 7.38 (1H, dd, J=2.7, 8.8 Hz)	288.9	4.02 / 4
(107)		F/D2 (from bromide Ex 35)	10.34 (1H, s), 10.06 (1H, s), 8.19 (1H, d, J=8.9 Hz), 8.15 (1H, d, J=8.8 Hz), 7.84 (1H, d, J=1.9 Hz), 7.63 (1H, dd, J=1.9, 8.6 Hz), 7.55 (1H, d, J=2.6 Hz), 7.35 (1H, dd, J=2.6, 8.7 Hz), 4.34 (1H, t, J=5.0 Hz), 3.48-3.40 (1H, m), 3.12 (2H, s), 2.29 (6H, s), 1.06 (1.8 H, t, J=7.0 Hz)	313.0	2.99 / 4
(108)		F/D2 (from bromide Ex 35)	10.34 (1H, s), 10.01 (1H, s), 8.20 (1H, d, J=8.9 Hz), 8.16 (1H, d, J=8.9 Hz), 7.81 (1H, d, J=2.1 Hz), 7.59-7.53 (2H, m), 7.35 (1H, dd, J=2.7, 8.8 Hz), 3.16 (2H, s), 2.53 (br s obscured by solvent), 2.40 (4H, br s), 2.18 (3H, s)	368.0	2.27 / 3
(108)*		F/D2 (from bromide Ex 35)	11.30-10.20 (3H, m), 8.25-8.16 (2H, m), 7.82 (1H, d, J=1.9 Hz), 7.58-7.53 (2H, m), 7.38, 1H, dd, J=2.7, 8.8 Hz), 4.15-3.0 (br m, signals obscured by water), 2.80 (3H, s)	368.0	2.80 / 4
(111)		F	(CDCl ₃) 8.00 (1H, d, J=8.9 Hz), 7.84 (1H, d, J=8.7 Hz), 7.80 (1H, d, J=2.8 Hz), 7.53 (1H, d, J=1.9 Hz), 7.46-7.39 (2H, m), 3.95 (3H, s)	304.8, 306.8	5.30 / 3

(85)		A/G	(CDCl ₃) 10.50 (1H, s), 8.41 (1H, d, J=8.7 Hz), 8.35 (1H, d, J=0.8 Hz), 8.21 (1H, d, J=8.9 Hz), 8.06-8.02 (1H, m), 7.21 (1H, t, J=55.5 Hz), 6.88 (1H, dd, J=2.4, 8.7 Hz), 6.78 (1H, d, J=2.4 Hz)	260.9	4.03 / 3
(112)		A/E	10.46 (s, 1H), 8.32-8.26 (m, 2H), 7.58 (d, J=2.6 Hz, 1H), 7.46 (s, 1H), 7.41-7.33 (m, 2H), 3.22 (s, 3H), 1.90 (s, 3H).	283.9	3.06 / 3
(113)		A	11.05 (1H, br s), 8.35 (1H, s), 8.33 (1H, ob d J=8.4 Hz), 7.64 (1H, d J=2.8 Hz), 7.53 (1H, dd J=2.8, 8.8 Hz), 6.97 (1H, s), 3.94 (3H, s)	276.9	3.00 / 4

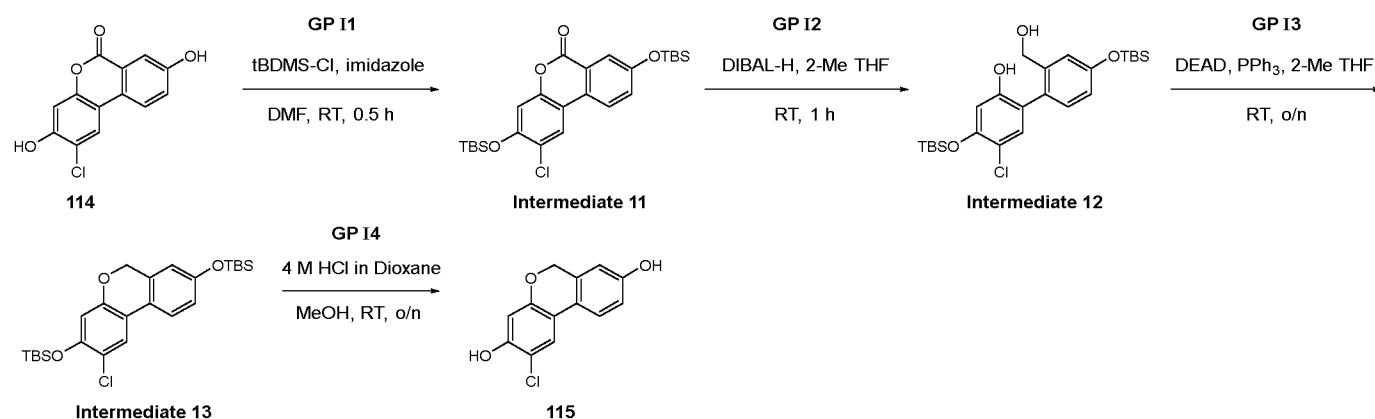
*=salt was prepared following treatment with 1.1 eq aqueous HCl and lyophilization. NMR spectra were obtained in *d*₆-DMSO unless otherwise stated.

B) Ether and amide “A” group analogues

Procedure I

2-Chloro-3,8-dihydroxy-6H-benzo[c]chromen-6-one (114) and

2-Chloro-6H-benzo[c]chromene-3,8-diol (115)



2-Chloro-3,8-dihydroxy-6H-benzo[c]chromen-6-one (114)

2-Chloro-3,8-dihydroxy-6H-benzo[c]chromen-6-one was prepared from **113** using General Procedure C2. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.25 (1H, br s), 8.24 (1H, s), 8.19 (1H, d J=8.8 Hz), 7.51 (1H, d J=2.6 Hz), 7.31 (1H, dd J=2.7, 8.7 Hz), 6.91 (1H, s); LCMS (Method 3): R_t=3.52 min; m/z=260.9 [M-H]⁺.

GP I1

3,8-bis((Tert-butyldimethylsilyl)oxy)-2-chloro-6H-benzo[c]chromen-6-one (Intermediate 11)

A suspension of 2-chloro-3,8-dihydroxy-6H-benzo[c]chromen-6-one (**114**) (2.37 g, 9.04 mmol) in DMF (15 mL) was treated with imidazole (2.46 g, 36.14 mmol) then TBDMSCl and the resulting mixture stirred at RT for 18 h. The reaction was partitioned between EtOAc (x 3) and water and the combined organic extract was washed with brine, dried (PTFE frit) and concentrated *in vacuo*. The resultant residue was purified by chromatography on silica using 0-25% DCM in cyclohexane as eluant to give the product as a white solid (2.0 g, 45%). ¹H NMR (400 MHz, CDCl₃) δ 7.94 (1H, s), 7.85 (1H, d J=8.7 Hz), 7.76 (1H, d J=2.6 Hz), 7.31 (1H, dd J=2.7, 8.7 Hz), 6.89 (1H, s), 1.05 (9H, s), 1.01 (9H, s), 0.28 (6H, s), 0.26 (6H, s).

GP I2

4,4'-bis((Tert-butyldimethylsilyl)oxy)-5-chloro-2'-(hydroxymethyl)-[1,1'-biphenyl]-2-ol (Intermediate 12)

To a solution of 3,8-bis((tert-butyldimethylsilyl)oxy)-2-chloro-6H-benzo[c]chromen-6-one (Intermediate 11) (385 mg, 0.784 mmol) in 2-Me THF (10 mL) was added dropwise, DIBAL-H (1.0 M in THF; 1.60 mL, 1.60 mmol) and the resulting solution was stirred at RT for 1 h. The mixture was cooled in an ice bath then quenched by addition of 15% aqueous NaOH (0.1 mL) followed by water (0.16 mL). After stirring for 30 mins Na₂SO₄ was added and the resultant mixture stirred for 18 h at RT. The mixture was filtered through Celite® and the pad washed with DCM, and the combined organic layer concentrated *in vacuo* to give a yellow solid (388 mg, quant.). ¹H NMR (400 MHz, CDCl₃) δ 7.24 (1H, s), 7.04 (1H, d J=8.3 Hz), 6.98 (1H, s), 6.88 (1H, s), 6.79 (1H, d J=7.7 Hz), 6.42 (1H, s), 4.27 (2H, m), 1.23 (1H, m), 1.02 (9H, s), 0.98 (9H, s), 0.20 (6H, s), 0.19 (6H, s).

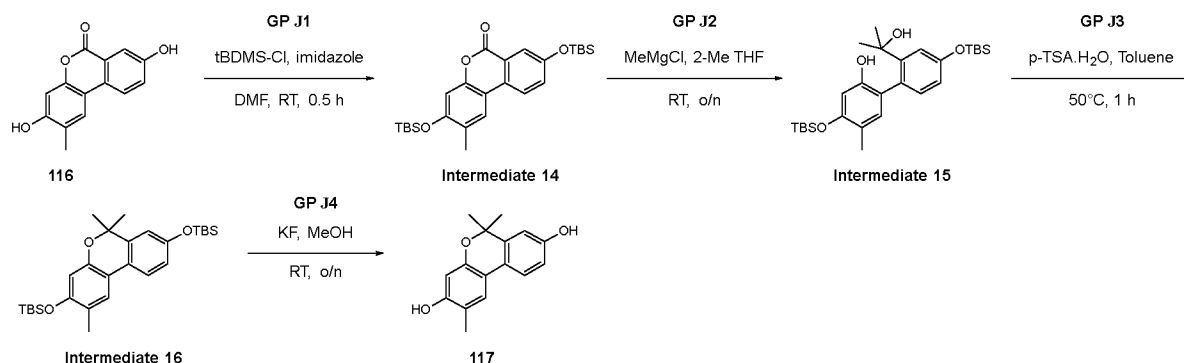
GP I3**((2-Chloro-6H-benzo[c]chromene-3,8-diyl)bis(oxy))bis(tert-butyldimethylsilane)****(Intermediate 13)**

To a solution of 4,4'-bis((tert-butyldimethylsilyl)oxy)-5-chloro-2'-(hydroxymethyl)-[1,1'-biphenyl]-2-ol (Intermediate 12) (388 mg, 0.783 mmol) and triphenylphosphine (308 mg, 1.17 mmol) in 2-Me THF (5.0 mL) was added dropwise DEAD (0.18 mL), and the mixture was stirred for 30 min at RT. The resulting solution was concentrated *in vacuo* and purified by chromatography on silica using 0-50% EtOAc in cyclohexane as eluant to give the semi-pure product. LCMS analysis gave desired product plus ~70% of the fully de-protected diol. The crude reaction mixture was taken on to the next stage without purification.

GP I4**2-Chloro-6H-benzo[c]chromene-3,8-diol (115)**

A solution of crude ((2-chloro-6H-benzo[c]chromene-3,8-diyl)bis(oxy))bis(tert-butyl dimethyl silane) (Intermediate 13) (0.783 mmol) in MeOH (5.0 mL) was treated with 4 M HCl in dioxane (1.96 mL, 7.83 mmol) and the reaction was allowed to stir at RT for 18 h. The resultant mixture was concentrated *in vacuo*, and the residue was partitioned between DCM (x 2) and water. The combined organic extract was washed with brine, dried (Na₂SO₄) and concentrated *in vacuo* and the crude residue was purified by chromatography on silica using 0-50% EtOAc in cyclohexane as eluant to give the title compound as a pale-yellow solid (60 mg, 31% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.22 (1H, br s), 9.60 (1H, br s), 7.66 (1H, s), 7.54 (1H, d J=8.3 Hz), 6.74 (1H, d J=7.5 Hz), 6.62 (1H, s), 6.53 (1H, s), 4.99 (2H, s); LCMS (Method 3): R_t=3.57 min; m/z=246.9 [M-H]⁺.

Procedure J**3,8-Dihydroxy-2-methyl-6H-benzo[c]chromen-6-one (116) and
2,6,6-Trimethyl-6H-benzo[c]chromene-3,8-diol (117)**



3,8-Dihydroxy-2-methyl-6H-benzo[c]chromen-6-one (116)

3,8-Dihydroxy-2-methyl-6H-benzo[c]chromen-6-one was prepared using General Procedures A and C2. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.15 (2H, br s), 8.11 (1H, d $J=8.9$ Hz), 7.92 (1H, s), 7.50 (1H, d $J=2.7$ Hz), 7.31 (1H, dd $J=2.7, 8.7$ Hz), 6.74 (1H, s), 2.21 (3H, s); LCMS (Method 3): $R_t=3.45$ min; $m/z=242.9$ $[\text{M}+1]^+$.

GP J1

3,8-bis((Tert-butyldimethylsilyl)oxy)-2-methyl-6H-benzo[c]chromen-6-one (Intermediate 14)

3,8-bis((tert-butyldimethylsilyl)oxy)-2-methyl-6H-benzo[c]chromen-6-one was prepared from 3,8-dihydroxy-2-methyl-6H-benzo[c]chromen-6-one (**120**) using General Procedure I1

^1H NMR (400 MHz, CDCl_3) δ 7.89 (1H, d $J=8.7$ Hz), 7.76 (1H, d $J=2.7$ Hz), 7.71 (1H, s), 7.28 (1H, dd $J=2.6, 8.8$ Hz), 6.78 (1H, s), 2.29 (3H, s), 1.03 (9H, s), 1.01 (9H, s), 0.27 (6H, s), 0.26 (6H, s).

GP J2

4,4'-bis((Tert-butyldimethylsilyl)oxy)-2'-(2-hydroxypropan-2-yl)-5-methyl-[1,1'-biphenyl]-2-ol (Intermediate 15)

To a solution of 3,8-bis((tert-butyldimethylsilyl)oxy)-2-methyl-6H-benzo[c]chromen-6-one (Intermediate 14) (300 mg, 0.637 mmol) in 2-Me THF (6.0 mL) was added MeMgCl (3.0 M in THF; 0.64 mL, 1.92 mmol) and the resulting solution was stirred at RT for 18 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (x 2) prior to drying (Na_2SO_4) and concentrating *in vacuo* to give the title compound as a colourless oil (320 mg, quant.). ^1H NMR (400 MHz, CDCl_3) δ 7.10 (1H, d $J=2.5$ Hz), 6.94 (1H, d $J=8.2$ Hz), 6.86

(1H, s), 6.75 (1H, dd J=2.5, 8.2 Hz), 6.43 (1H, s), 5.08 (1H, s), 2.13 (3H, s), 2.04 (1H, s), 1.53 (3H, s), 1.42 (3H, s), 1.03 (9H, s), 1.01 (9H, s), 0.26 (3H, s), 0.25 (3H, s), 0.24 (6H, s).

GP J3

((2,6,6-Trimethyl-6H-benzo[c]chromene-3,8-diyl)bis(oxy))bis(tert-butyldimethylsilane) (Intermediate 16)

A solution of 4,4'-bis((tert-butyldimethylsilyl)oxy)-2'-(2-hydroxypropan-2-yl)-5-methyl-[1,1'-biphenyl]-2-ol (Intermediate 15) (320 mg, 0.637 mmol) in toluene (5.0 mL) was treated with PTSA.H₂O and the resulting mixture was heated for 1 h at 50°C. The resulting solution was purified directly by chromatography on silica using DCM as eluant to give the product as a colourless oil (280 mg, 90%). ¹H NMR (400 MHz, CDCl₃) δ 7.48 (1H, d J=8.4 Hz), 6.38 (1H, s), 6.77 (1H, dd J=2.4, 8.4 Hz), 6.68 (1H, d J=2.4 Hz), 6.39 (1H, s), 2.19 (3H, s), 1.57 (6H, s), 1.02 (9H, s), 0.99 (9H, s), 0.23 (6H, s), 0.21 (6H, s). LCMS (Method 3): R_t=3.57 min; m/z=246.9 [M-H]⁻.

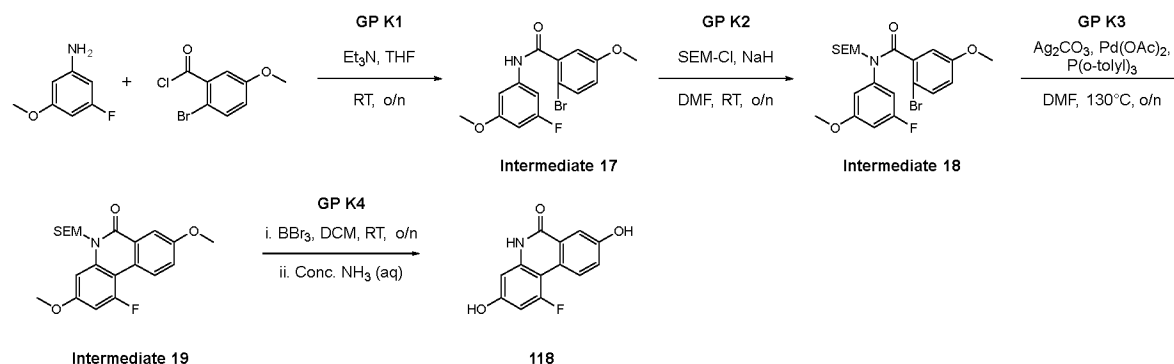
GP J4

2,6,6-Trimethyl-6H-benzo[c]chromene-3,8-diol (117)

A suspension of ((2,6,6-trimethyl-6H-benzo[c]chromene-3,8-diyl)bis(oxy))bis(tert-butyl dimethylsilane) (Intermediate 16) (270 mg, 0.557 mmol) in MeOH (5.0 mL) was treated with solid KF (97 mg, 1.67 mmol) and the resulting suspension stirred at RT for 18 h. The resultant mixture was absorbed on to HMN and purified by chromatography on silica using 0-30% EtOAc in cyclohexane as eluant to give semi-pure product as a pale-yellow oil (121 mg). Further purification by trituration from a mixture of DCM and n-pentane gave the title compound as a white solid (91 mg, 64%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.40 (1H, s), 9.32 (1H, s), 7.47 (1H, d J=8.4 Hz), 7.38 (1H, s), 6.71 (1H, dd J=2.3, 8.4 Hz), 6.66 (1H, d J=2.3 Hz), 6.31 (1H, s), 2.09 (3H, s), 1.50 (6H, s); LCMS (Method 3): R_t=3.80 min; m/z=257.1 [M+H]⁺.

Procedure K

1-Fluoro-3,8-dihydroxyphenanthridin-6(5H)-one (118)



GP K1

2-Bromo-N-(3-fluoro-5-methoxyphenyl)-5-methoxybenzamide (Intermediate 17)

To a solution of 2-bromo-5-methoxybenzoyl chloride (694 mg, 2.78 mmol) in THF (15 mL) was added triethylamine (0.58 mL, 4.17 mmol) followed by 5-methoxyaniline (393 mg, 2.78 mmol). The resulting solution was stirred at RT for 18 h then partitioned between water and DCM (x 2) and the combined organic extract was dried and concentrated *in vacuo*. The residue was purified by chromatography on silica using 0-100% DCM in cyclohexane as eluant to give the title compound as a pale-yellow solid (700 mg, 71% yield). LCMS (Method 6): $R_t=1.53$ min; $m/z=354.2/356.2$ $[\text{M}+\text{H}]^+$.

GP K2

2-Bromo-N-(3-fluoro-5-methoxyphenyl)-5-methoxy-N-((2-(trimethylsilyl)ethoxy)methyl)benzamide (Intermediate 18)

A solution of 2-bromo-N-(3-fluoro-5-methoxyphenyl)-5-methoxybenzamide (Intermediate 17) (300 mg, 1.09 mmol) in dry DMF (3.0 mL) was treated with NaH (60wt%; 87 mg, 2.18 mmol) and stirred at RT for 30 mins until gas evolution had ceased. SEM-Cl (0.72 mL, 3.27 mmol) was added to the reaction mixture and stirring was continued for 18 h at RT. The resulting solution was diluted with water (100 mL) then extracted with EtOAc (x 3) and the combined organic extract was washed with brine then dried and concentrated *in vacuo*. The residue was purified by chromatography on silica using 0-30% EtOAc in cyclohexane as eluant to give the title compound as a pale-yellow solid (430 mg, 97% yield). LCMS (Method 6): $R_t=1.89$ min; $m/z=482.3/484.3$ $[\text{M}+\text{H}]^+$.

GP K3**1-Fluoro-3,8-dimethoxy-5-((2-(trimethylsilyl)ethoxy)methyl)phenanthridin-6(5H)-one (Intermediate 19)**

A microwave vial was charged with a solution of 2-bromo-N-(3-fluoro-5-methoxyphenyl)-5-methoxy-N-((2-(trimethylsilyl)ethoxy)methyl) benzamide (Intermediate 18) (830 mg, 1.71 mmol) in dry DMF (8.0 mL). AgCO_3 (945 mg, 3.43 mmol), $\text{Pd}(\text{OAc})_2$ (58 mg, 0.257 mmol) and tri(o-tolyl)phosphine (156 mg, 0.514 mmol) was added and the resultant mixture de-gassed under Argon prior to being heated for 18 h at 130°C. The cooled reaction mixture was filtered through Celite® then partitioned between water and EtOAc (x 3) and the combined organic extract was washed with brine then dried and concentrated *in vacuo*. The resultant residue was purified by chromatography on silica using 0-50% EtOAc in cyclohexane as eluant to give the semi-pure product (270 mg). Further purification by trituration from a mixture of DCM and n-pentane gave purer material but an additional purification by chromatography on silica using 0-20% EtOAc in cyclohexane as eluant was required to give pure title compound as a white solid (186 mg, 27%). ^1H NMR (400 MHz, CDCl_3) δ 8.52 (1H, dd J=2.5, 9.1 Hz), 7.98 (1H, d J=3.0 Hz), 7.33 (1H, m), 7.04 (1H, m), 6.66 (1H, dd J=2.5, 14.9 Hz), 5.83 (2H, s), 3.95 (3H, s), 3.90 (3H, s), 3.76 (2H, t J=7.9 Hz), 0.97 (2H, t, J=8.1 Hz), -0.02 (9H, s).

GP K4**1-Fluoro-3,8-dihydroxyphenanthridin-6(5H)-one (118)**

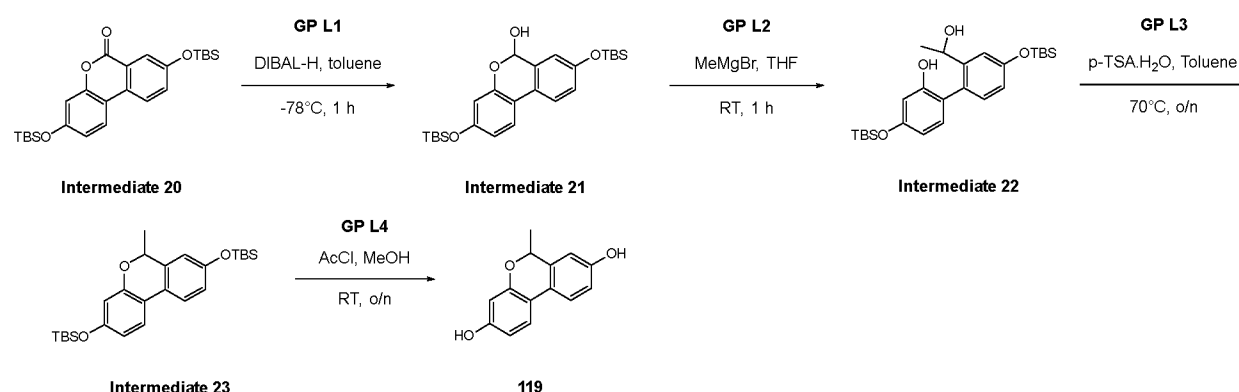
A solution of 1-fluoro-3,8-dimethoxy-5-((2-(trimethylsilyl)ethoxy)methyl)phenanthridin-6(5H)-one (Intermediate 19) (86 mg, 0.213 mmol) in DCM (2.0 mL) was treated dropwise with BBr_3 and the resulting mixture was stirred for 18 h at RT. The reaction mixture was quenched carefully with water then azeotroped with MeOH (x 4) which gave the intermediate hydroxy methyl amide, from partial de-protection of the SEM protecting group, as a yellow solid. LCMS (Method 6): R_t =1.09 min; m/z =276.0 $[\text{M}+1]^+$.

The intermediate hydroxymethyl amide was treated with concentrated aqueous ammonia (3.0 mL) and the resultant turbid solution stirred for 3 h at RT then azeotroped with MeOH (x 4) which gave the crude product as a grey solid. Further purification by reverse-phase

chromatography on C18-silica using 3-97% MeCN in water (+0.1% formic acid) gave pure title compound as a grey-white solid following lyophilisation (52 mg, 84%). ^1H NMR (400 MHz, DMSO- d_6) δ 11.60 (1H, br s), 10.05 (2H, br s), 8.28 (1H, d $J=9.2$ Hz), 7.66 (1H, d $J=2.3$ Hz), 7.25 (1H, m), 6.64 (1H, s), 6.49 (1H, d $J=15.3$ Hz); LCMS (Method 3): $R_t=2.98$ min; $m/z=246.0$ $[\text{M}+1]^+$.

Procedure L

6-Methyl-6H-benzo[c]chromene-3,8-diol (119)



GP L1

3,8-bis((Tert-butyldimethylsilyl)oxy)-6H-benzo[c]chromen-6-one (Intermediate 20)

3,8-bis((Tert-butyldimethylsilyl)oxy)-6H-benzo[c]chromen-6-one was prepared using General Procedure II. ^1H NMR (400 MHz, CDCl₃) δ 7.89 (d, $J = 8.8$ Hz, 1H), 7.85 – 7.80 (m, 1H), 7.76 (d, $J = 2.6$ Hz, 1H), 7.29 (dd, $J = 8.7, 2.7$ Hz, 1H), 6.86 – 6.80 (m, 2H), 1.02 (s, 9H), 0.98 (s, 9H), 0.26 (s, 6H), 0.24 (s, 6H).

GP L2

3,8-bis((Tert-butyldimethylsilyl)oxy)-6H-benzo[c]chromen-6-ol (Intermediate 21)

To a solution of 3,8-bis((tert-butyldimethylsilyl)oxy)-6H-benzo[c]chromen-6-one (Intermediate 20) (912 mg, 2.0 mmol) in toluene (20 mL) under inert atmosphere and at -78°C was very slowly added DIBAL-H (1M in toluene, 2.10 mL, 2.10 mmol). Stirring was continued at -78°C for 1 h. The reaction mixture was quenched by addition of water at -78°C according to the Fieser work-up followed by the regular Fieser work-up. Filtration through silica and removal of the solvents *in vacuo* afforded the desired lactol as a white solid, which was used in the next step without further purification (921 mg, quant.). ^1H NMR (400 MHz, CDCl₃) δ 7.60 (dd, $J = 8.9, 6.9$ Hz,

2H), 6.93 (dd, $J = 8.5, 2.5$ Hz, 1H), 6.83 (d, $J = 2.6$ Hz, 1H), 6.62 – 6.58 (m, 2H), 6.26 (s, 1H), 1.00 (s, 9H), 0.98 (s, 9H), 0.25 – 0.18 (m, 12H).

GP L3

4,4'-bis((Tert-butyldimethylsilyl)oxy)-2'-(1-hydroxyethyl)-[1,1'-biphenyl]-2-ol

(Intermediate 22)

To a solution of 3,8-bis((tert-butyldimethylsilyl)oxy)-6H-benzo[c]chromen-6-ol (Intermediate 21) (458 mg, 1 mmol) in dry THF (10 mL) under inert atmosphere and at 0°C was added MeMgBr (3M in Et₂O, 1.0 mL). Stirring was continued at 0°C for 1 h. The reaction mixture was quenched with water (100 mL) and the mixture extracted with Et₂O; the ethereal extracts were dried over Na₂SO₄, filtered through silica with Et₂O washings and then concentrated *in vacuo*. The crude residue was used in the next step without further purification (475 mg, quant.).

¹H NMR (400 MHz, CDCl₃) δ 7.15 (d, $J = 2.6$ Hz, 0.4H), 7.12 (d, $J = 2.6$ Hz, 0.6H), 7.07 (s, 0.4H), 7.04 (s, 0.6H), 6.96 (d, $J = 8.1$ Hz, 0.4H), 6.90 (d, $J = 8.5$ Hz, 0.6H), 6.86 – 6.78 (m, 1H), 6.52 – 6.43 (m, 2H), 4.79 (q, $J = 6.4$ Hz, 0.4H), 4.73 (q, $J = 6.5$ Hz, 0.6H), 1.36 (d, $J = 6.4$ Hz, 1.2H), 1.30 (d, $J = 6.4$ Hz, 1.8H), 1.01 (s, 7.2H), 1.00 (s, 10.8H), 0.25 (s, 4.8H), 0.24 (s, 7.2H).

GP L4

((6-Methyl-6H-benzo[c]chromene-3,8-diyl)bis(oxy))bis(tert-butyldimethylsilane)

(Intermediate 23)

To a solution of 4,4'-bis((tert-butyldimethylsilyl)oxy)-2'-(1-hydroxyethyl)-[1,1'-biphenyl]-2-ol (Intermediate 22) (470 mg, 0.98 mmol) in toluene (10 mL) was added PTSA monohydrate (19.0 mg, 0.19 mmol) and the resulting mixture was heated at 70°C overnight. The reaction mixture was filtered through silica with DCM washings and concentrated *in vacuo*. The residue was purified by column chromatography (silica, 0-25% DCM/cyclohexane) to afford the desired ether as a white solid (411 mg, 90%). ¹H NMR (400 MHz, CDCl₃) δ 7.48 (dd, $J = 8.5, 4.1$ Hz, 2H), 6.80 (dd, $J = 8.4, 2.5$ Hz, 1H), 6.61 (dd, $J = 2.4, 0.8$ Hz, 1H), 6.52 (dd, $J = 8.4, 2.4$ Hz, 1H), 6.47 (d, $J = 2.4$ Hz, 1H), 5.17 (q, $J = 6.5$ Hz, 1H), 1.00 (s, 9H), 0.98 (s, 9H), 0.92 – 0.84 (m, 3H), 0.21 (s, 6H), 0.20 (s, 6H).

GP L5

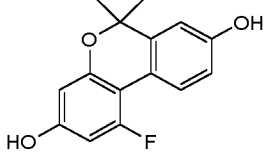
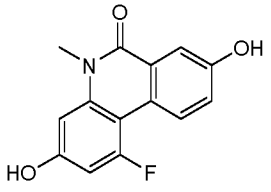
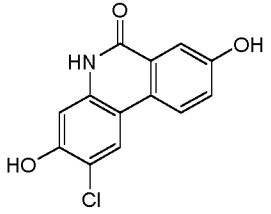
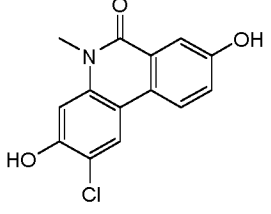
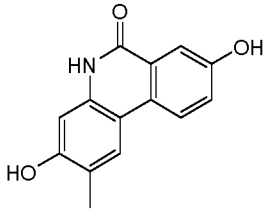
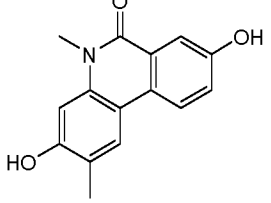
6-Methyl-6H-benzo[c]chromene-3,8-diol (119)

To a solution of ((6-methyl-6H-benzo[c]chromene-3,8-diyl)bis(oxy))bis(tert-butyl)dimethylsilane) (Intermediate 23) (411 mg, 0.90 mmol) in dry MeOH (10 mL) at 0°C was slowly added acetyl chloride (96 mL, 1.35 mmol) and the resulting mixture was stirred overnight. The solvents were removed *in vacuo* and the residue purified by column chromatography (silica, 0-100% EtOAc/cyclohexane) to provide the title compound as a white solid (202 mg, 98%). ¹H NMR (400 MHz, DMSO) δ 9.47 (s, 1H), 9.45 (s, 1H), 7.49 (t, J = 8.7 Hz, 2H), 6.73 (dd, J = 8.4, 2.5 Hz, 1H), 6.60 (d, J = 2.4 Hz, 1H), 6.43 (dd, J = 8.4, 2.4 Hz, 1H), 6.30 (d, J = 2.4 Hz, 1H), 5.14 (q, J = 6.5 Hz, 1H), 1.44 (d, J = 6.5 Hz, 3H).

The following examples in Table 2 were prepared using similar methods to those described above by utilizing the general procedures (GP) indicated.

Table 2.

Ex.	Structure	General procedure	¹ H NMR data (400 MHz, DMSO- <i>d</i> ₆) δ	LCMS m/z (M+H)	HPLC R _t (min)/QC Method
(120)		I	9.42 (2H, br s), 7.46 (1H, d J=8.4 Hz), 7.39 (1H, s), 6.72 (1H, m), 6.59 (1H, s), 6.36 (1H, s), 4.91 (2H, s), 2.10 (3H, s)		3.46 / 3
(121)		I	9.79 (2H, br s), 7.60 (1H, d J=8.1 Hz), 6.77 (1H, dd J=2.5, 8.5 Hz), 6.67 (1H, d J=2.4 Hz), 6.30 (1H, dd J=2.3, 13.5 Hz), 6.24 (1H, m), 4.95 (2H, s)	231.1 [M-H] ⁻	3.41 / 3
(122)		J	analytical data in progress		

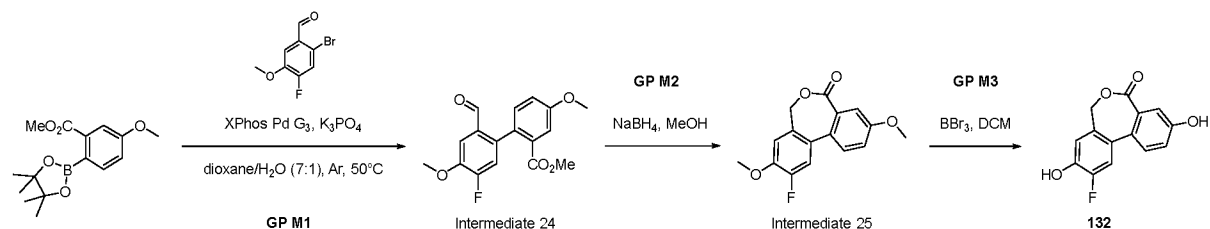
(123)		J	9.76 (2H, v br s), 7.64 (1H, d J=8.2 Hz), 6.78-6.72 (1H, obs m), 6.74 (1H, s), 6.27 (1H, dd J=2.3, 13.7 Hz), 6.18 (1H, m), 1.50 (6H, s)	259.0 [M-H] ⁻	3.78 / 3
(124)		K	10.18 (2H, br s), 8.32 (1H, d J=9.2 Hz), 7.73 (1H, d J=2.4 Hz), 7.25 (1H, m), 6.75 (1H, s), 6.62 (1H, d J=15.3 Hz), 3.64 (3H, s)	260.0	2.32 / 4
(125)		K	11.51 (1H, br s), 10.58 (1H, br s), 10.04 (1H, br s), 8.21 (1H, d J=8.9 Hz), 8.19 (1H, s), 7.58 (1H, d J=2.7 Hz), 7.21 (1H, d J=2.7, 8.8 Hz), 6.95 (1H, s)	259.9 [M-H] ⁻	3.12 / 3
(126)		K	10.52 (1H, v br s), 10.07 (1H, br s), 8.30 (1H, s), 8.26 (1H, d J=8.9 Hz), 7.64 (1H, d J=2.6 Hz), 7.22 (1H, d J=2.6, 8.7 Hz), 7.04 (1H, s), 3.62 (3H, s)	276.0	3.34 / 3
(127)		K	11.34 (1H, s), 9.81 - 9.76 (2H, br s), 8.15 (1H, d, J=9.0 Hz), 7.90 (1H, s), 7.57 (1H, d, J=2.7 Hz), 7.20 (1H, dd, J=2.7, 8.7 Hz), 6.77 (1H, s), 2.19 (3H, s)	242.0	3.05 / 3
(128)		K	9.87 (2H, br s), 8.19 (1H, d J= Hz), 8.03 (1H, s), 7.64 (1H, d J=2.7 Hz), 7.21 (1H, d J=2.7, 8.8 Hz), 6.88 (1H, s), 3.62 (3H, s), 2.24 (3H, s)	256.0	3.26 / 3

(129)		L	9.57-9.26 (2H, br s), 9.59 (1H, br s), 7.47 (1H, d J=8.4 Hz), 7.39 (1H, s), 6.73 (1H, dd J=2.4, 8.4 Hz), 6.59 (1H, d J=2.3 Hz), 6.35 (1H, s), 5.09 (1H, q J=6.5 Hz), 2.10 (3H, s), 1.43 (1H, d J=6.5 Hz)	242.0	3.63 / 4
(130)		L	10.18 (1H, br s), 9.59 (1H, br s), 7.66 (1H, s), 7.55 (1H, d J=8.5 Hz), 6.74 (1H, dd J=2.5, 8.4 Hz), 6.61 (1H, d J=2.4 Hz), 6.51 (1H, s), 5.18 (1H, q J=6.5 Hz), 1.43 (1H, d J=6.5 Hz)	263.9	3.76 / 3
(131)		L	10.31-9.25 (2H, 2 x br s), 7.62 (1H, d J=8.3 Hz), 6.76 (1H, dd J=2.5, 8.5 Hz), 6.66 (1H, d J=2.5 Hz), 6.28 (1H, dd J=2.3, 13.6 Hz), 6.23-6.20 (1H, m), 5.18 (1H, q J=6.5 Hz), 1.45 (1H, d J=6.5 Hz)	245.0 [M-H] ⁻	2.87 / 4

NMR spectra were obtained in DMSO-*d*₆ unless otherwise stated.

Procedure M

10-fluoro-3,9-dihydroxydibenzo[*c,e*]oxepin-5(7H)-one (132)



GP M1

Methyl 5'-fluoro-2'-formyl-4,4'-dimethoxy-[1,1'-biphenyl]-2-carboxylate (Intermediate 24)

A mixture of 2-bromo-4-fluoro-5-methoxybenzaldehyde (250 mg, 1.07 mmol), methyl 5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (345 mg, 1.18 mmol), and potassium phosphate (683 mg, 3.22 mmol) in dioxane (4 mL) and water (0.4 mL) was placed in a tube and degassed by purging with argon for 10 min. XPhos-Pd-G3 (45 mg, 0.05 mmol) was then added and the mixture was sealed, degassed and purged with argon. The mixture was heated at 50°C for 1h. The resulting cooled mixture was diluted with water then extracted with EtOAc (x 3) and the combined organic extract was washed with brine then dried and concentrated *in vacuo*. The residue was purified by chromatography on silica using 0-25% EtOAc in cyclohexane as eluant to give the title compound as a pale-brown oil (280 mg, 82% yield). ¹H NMR (400 MHz, CDCl₃) δ 9.66 (1H, s), 7.59 (1H, d, J=8.8 Hz), 7.55 (1H, d, J=2.8 Hz), 7.19 (1H, d, J=8.4 Hz), 7.14 - 7.08 (1H, m), 6.97 (1H, d, J=11.2 Hz), 3.99 (3H, s), 3.91 (3H, s), 3.67 (3H, s).

GP M2

10-Fluoro-3,9-dimethoxydibenzo[c,e]oxepin-5(7H)-one (Intermediate 25)

To a solution of methyl 5'-fluoro-2'-formyl-4,4'-dimethoxy-[1,1'-biphenyl]-2-carboxylate (Intermediate 24) (270 mg, 0.85 mmol) in MeOH (4 mL) was added sodium borohydride (32 mg, 0.85 mmol) portionwise. The solution was stirred for 30 min then quenched with water and evaporated. The resulting mixture was diluted with water and EtOAc; this led to a large precipitate at the interface which was isolated by filtration and dissolved in a large volume of ethyl acetate and the combined organic extract was concentrated *in vacuo*. The solid residue was dissolved in CHCl₃/MeOH and evaporated to half volume, whereupon the product crystallised as a white solid; the mother liquors were adsorbed onto HMN and purified by chromatography on silica using 0-5% EtOAc in DCM as eluant to give additional product. The two batches of product were combined to give the title compound as a white solid (150 mg, 61% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.47 (1H, d, J=2.7 Hz), 7.44 (1H, d, J=8.6 Hz), 7.33 (1H, d, J=11.9 Hz), 7.21 (1H, dd, J=2.7, 8.8 Hz), 7.04 (1H, d, J=8.2 Hz), 5.03 - 4.89 (2H, m), 3.96 (3H, s), 3.91 (3H, s).

GP M3

10-fluoro-3,9-dihydroxydibenzo[c,e]oxepin-5(7H)-one (132)

10-Fluoro-3,9-dimethoxydibenzo[c,e]oxepin-5(7H)-one (Intermediate 25) (145 mg, 0.5 mmol) was suspended in DCM (10 mL) and boron tribromide (2 mL, 1 M soln in DCM, 2.0 mmol) was added dropwise at RT. The resulting yellow solution was stirred overnight to give a yellow suspension. The mixture was cooled in ice-water and isopropanol (5 mL) was added dropwise to quench the reaction. The solvents were removed in vacuo. The resulting beige powder was dissolved in MeOH and adsorbed onto HMN and purified by chromatography on silica using 0-30% EtOAc in DCM to give the impure product which was re-purified on silica using 0-5% MeOH in DCM as eluant to give the title compound as an off-white solid (25 mg, 19%).
¹H NMR (400 MHz, DMSO-*d*₆) δ 10.59 - 9.60 (2H, m), 7.50 (1H, d, J=4.6 Hz), 7.47 (1H, d, J=8.3 Hz), 7.19 (1H, d, J=2.7 Hz), 7.16 (1H, d, J=8.9 Hz), 7.11 (1H, dd, J=2.7, 8.6 Hz), 5.10 - 4.74 (2H, m). LCMS (Method 3): R_t=2.96 min; m/z=259.0 [M-H]⁺.

Additional compounds are prepared in accordance with methods adapted from the above procedures.

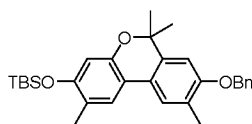
Example 3: Synthesis of additional representative compounds of the invention

All reactions were performed with oven-dried glassware and under an inert atmosphere (nitrogen) unless otherwise stated. All solvents were used as purchased unless otherwise stated. Commercial reagents were used as purchased without further purification. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.

Thin-layer chromatography was carried out using Merck Kieselgel 60 F254 (230–400 mesh) fluorescent treated silica and were visualized under UV light (254 and 366 nm) and/or by staining with aqueous potassium permanganate solution. ¹H NMR spectra were recorded in deuterated solvents on Bruker spectrometer at 400 MHz or Nanalysis NMReady-60PRO spectrometer at 60 MHz, with residual protic solvent as the internal standard. ¹³C NMR spectra were recorded in deuterated solvents on Bruker spectrometer at 100 MHz, with the central peak of the deuterated solvent as the internal standard. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) are given in Hertz (Hz) rounded to the nearest 0.1 Hz. The ¹H NMR spectra are reported as δ/ppm downfield from tetramethylsilane (multiplicity, number of protons, coupling constant J/Hz). The ¹³C NMR spectra are reported as δ/ppm. TLC-MS data was obtained on Advion Expression CMS coupled with Plate Express TLC-plate Reader. Medium

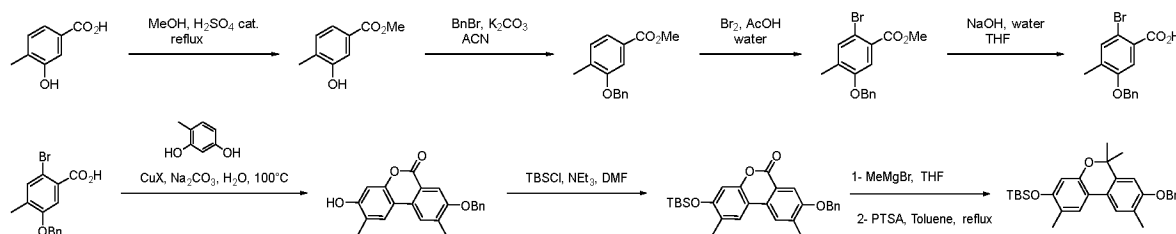
pressure liquid chromatography (MPLC) was performed on a Biotage Isolera Four with built-in UV-detector and fraction collector with Interchim silica gel columns.

1. Synthesis of ((8-(benzyloxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-yl)oxy)(tert-butyl)dimethylsilane

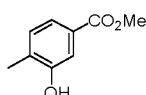


((8-(benzyloxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-yl)oxy)(tert-butyl)dimethylsilane was prepared in 7 steps from 3-hydroxy-4-methylbenzoic acid

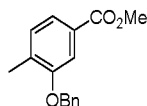
Scheme 1.



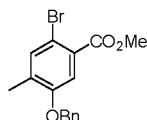
Step 1: Synthesis of methyl 3-hydroxy-4-methylbenzoate



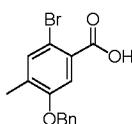
sulfuric acid (1.3 g, 0.70 mL, 0.2 Eq, 13 mmol) was added to a suspension of 3-hydroxy-4-methylbenzoic acid (10 g, 1 Eq, 66 mmol) in methanol (2.1 g, 0.16 L, 0.4 molar, 1 Eq, 66 mmol) and the mixture was refluxed o.n. Methanol was evaporated under vacuum and the crude was extracted with EtOAc and Na₂CO₃ saturated solution. The organic phase was washed with water, dried over sodium sulfate and concentrated under vacuum to give methyl 3-hydroxy-4-methylbenzoate (8.7 g, 52 mmol, 80 %) as a white solid. ¹H NMR (400 MHz, DMSO) δ 9.73 (d, *J* = 0.5 Hz, 1H), 7.39 (d, *J* = 1.7 Hz, 1H), 7.31 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.19 (d, *J* = 7.7 Hz, 1H), 3.80 (s, 3H), 2.17 (d, *J* = 0.6 Hz, 3H).

Step 2: synthesis of methyl 3-(benzyloxy)-4-methylbenzoate

methyl 3-hydroxy-4-methylbenzoate (8.7 g, 1 Eq, 52 mmol) was dissolved in acetonitrile (2.1 g, 0.13 L, 0.4 molar, 1 Eq, 52 mmol). potassium carbonate (7.2 g, 1 Eq, 52 mmol) was added followed by benzyl bromide (9.0 g, 6.2 mL, 1 Eq, 52 mmol) and the mixture was heated at 50°C o.n. Water was added and the aqueous phase was extracted with EtOAc. The organic phase was washed successively with water and brine, dried over sodium sulfate and evaporated under vacuum to give methyl 3-(benzyloxy)-4-methylbenzoate (10.9 g, 42.5 mmol, 81 %) as a yellowish solid. ¹H NMR (400 MHz, CDCl₃) δ 7.61 – 7.57 (m, 2H), 7.51 – 7.30 (m, 6H), 7.23 – 7.19 (m, 1H), 5.14 (s, 2H), 3.91 (s, 3H), 2.33 (d, *J* = 0.7 Hz, 3H).

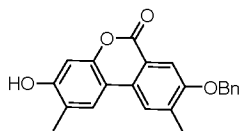
Step 3: Synthesis of methyl 5-(benzyloxy)-2-bromo-4-methylbenzoate

bromine (8.16 g, 2.63 mL, 1.2 Eq, 51.0 mmol) was added to a RT suspension of methyl 3-(benzyloxy)-4-methylbenzoate (10.9 g, 1 Eq, 42.5 mmol) in acetic acid (51.1 g, 48.7 mL, 20 Eq, 851 mmol) and water (38.3 g, 38.3 mL, 50 Eq, 2.13 mol) and the resulting mixture was heated to 60 °C overnight. After cooling to room temperature, Ice was added and the reaction mixture was stirred at room temperature for 2h. The precipitate was filtered off and rinsed with cold water, dried under vacuum to give methyl 5-(benzyloxy)-2-bromo-4-methylbenzoate (13 g, 39 mmol, 91 %) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.46 – 7.32 (m, 7H), 5.09 (s, 2H), 3.92 (s, 3H), 2.27 (d, *J* = 0.8 Hz, 3H).

Step 4: Synthesis of 5-(benzyloxy)-2-bromo-4-methylbenzoic acid

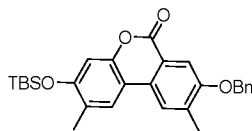
methyl 5-(benzyloxy)-2-bromo-4-methylbenzoate (3000.00 mg, 1 Eq, 8.950 mmol) was dissolved in methanol (286.8 mg, 17.90 mL, 0.5 molar, 1 Eq, 8.950 mmol), THF (645.4 mg, 44.75 mL, 0.2 molar, 1 Eq, 8.950 mmol) at room temperature. then cooled down to 0°C. A solution of LiOH (643.0 mg, 3 Eq, 26.85 mmol) in water (161.3 mg, 17.90 mL, 0.5 molar, 1 Eq, 8.950 mmol) was added dropwise and stirring continued overnight. Methanol and THF were evaporated under vacuum. The crude obtained was extracted with ethyl acetate and HCl 1M twice. The combined organic phases were washed with brine once, dried over sodium sulfate and concentrated under vacuum to give 5-(benzyloxy)-2-bromo-4-methylbenzoic acid (2.7 g, 8.4 mmol, 94 %) as a white solid. ¹H NMR (400 MHz, DMSO) δ 13.26 (s, 1H), 7.52 (d, J = 0.9 Hz, 1H), 7.48 – 7.44 (m, 2H), 7.43 – 7.38 (m, 3H), 7.36 – 7.31 (m, 1H), 5.17 (s, 2H), 2.26 – 2.19 (m, 3H).

Step 5: Synthesis of 8-(benzyloxy)-3-hydroxy-2,9-dimethyl-6H-benzo[c]chromen-6-one



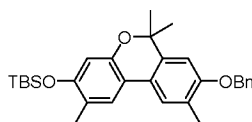
sodium carbonate (2.970 g, 3.0 Eq, 28.02 mmol) was dissolved in water (168.3 mg, 46.70 mL, 0.2 molar, 1 Eq, 9.341 mmol) at room temperature. 4-methylbenzene-1,3-diol (2.319 g, 2.0 Eq, 18.68 mmol) was added portionwise and heated at 60°C for 30 minutes. 5-(benzyloxy)-2-bromo-4-methylbenzoic acid (3000 mg, 1 Eq, 9.341 mmol) was added portionwise and stirring continued T 60°C for 1h. CuI (1.245 g, 0.7 Eq, 6.539 mmol) was added and the reaction mixture was heated at the same temperature overnight. A precipitate was formed after addition of CuI. The precipitate was filtered of and washed successively with water and HCl 1M. the solid was dried under high vacuum to give 8-(benzyloxy)-3-hydroxy-2,9-dimethyl-6H-benzo[c]chromen-6-one (1.8 g, 5.2 mmol, 56 %) as a beige solid. ¹H NMR (400 MHz, DMSO) δ 10.16 (s, 1H), 8.12 (s, 1H), 7.97 (s, 1H), 7.63 (s, 1H), 7.51 (d, J = 7.0 Hz, 2H), 7.42 (t, J = 7.4 Hz, 2H), 7.36 – 7.32 (m, 1H), 6.74 (s, 1H), 5.26 (s, 2H), 2.39 (s, 3H), 2.21 (s, 3H).

Step 6: synthesis 8-(benzyloxy)-3-((tert-butyldimethylsilyl)oxy)-2,9-dimethyl-6H-benzo[c]chromen-6-one



8-(benzyloxy)-3-hydroxy-2,9-dimethyl-6H-benzo[c]chromen-6-one (1.7 g, 1 Eq, 4.9 mmol) was dissolved in DMF (0.36 g, 49 mL, 0.1 molar, 1 Eq, 4.9 mmol) at room temperature. triethylamine (1.2 g, 1.7 mL, 2.5 Eq, 12 mmol) was added and the mixture was cooled down to 0°C. TBDMS-Cl (0.89 g, 1.2 Eq, 5.9 mmol) was added and stirring continued at r.t. o.n. Reaction mixture was extracted with HCl 1M and EtOAc. The combined organic phases were washed with successively with water and brine, dried over sodium sulfate and concentrated under vacuum. The crude material was purified by flash column chromatography on silica (0-50% EtOAc in Hex) to afford 8-(benzyloxy)-3-((tert-butyldimethylsilyl)oxy)-2,9-dimethyl-6H-benzo[c]chromen-6-one (1.18 g, 2.56 mmol, 52 %). $R_f = 0.7$ (EtOAc/Cyclohexane 20%). ^1H NMR (400 MHz, CDCl_3) δ 7.80 (d, $J = 1.0$ Hz, 1H), 7.78 (s, 1H), 7.73 (s, 1H), 7.51 – 7.47 (m, 2H), 7.45 – 7.39 (m, 2H), 7.38 – 7.33 (m, 1H), 6.79 (s, 1H), 5.20 (s, 2H), 2.46 (d, $J = 0.8$ Hz, 3H), 2.30 (d, $J = 0.7$ Hz, 3H), 1.04 (s, 9H), 0.28 (s, 6H).

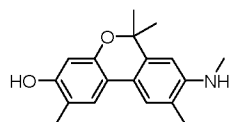
Step 7: synthesis ((8-(benzyloxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-yl)oxy)(tert-butyl)dimethylsilane



8-(benzyloxy)-3-((tert-butyldimethylsilyl)oxy)-2,9-dimethyl-6H-benzo[c]chromen-6-one (1170 mg, 1 Eq, 2.540 mmol) was dissolved in THF (183.2 mg, 25.40 mL, 0.1 molar, 1 Eq, 2.540 mmol) and the reaction was cooled to 0 °C in an ice-bath. Following methylmagnesium bromide (1.333 g, 3.725 mL, 3 molar, 4.4 Eq, 11.18 mmol) was added in one portion. The reaction was stirred at 0 °C for 10min before being allowed to warm to room temperature. Stirring at room temperature was continued for 1h before the reaction was quenched with water and extracted with EtOAc (3x). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under vacuo. The crude was dissolved in EtOAc 20 mL, PTOSH (48.31 mg, 0.1 Eq, 254.0 μmol) was added in one portion and the mixture was heated at 60°C for 1h. The reaction mixture was extracted

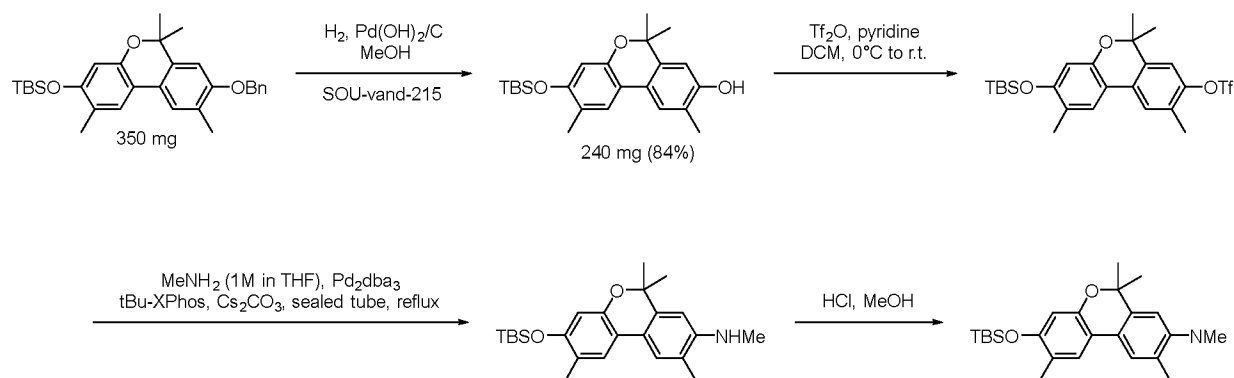
with EtOAc and sodium bicarbonate saturated solution once, dried over sodium sulfate and concentrated under vacuum to give ((8-(benzyloxy)-2,6,6,9-tetramethyl-6H-benzo[*c*]chromen-3-yl)oxy)(tert-butyl)dimethylsilane (1100 mg, 2.317 mmol, 91.23 %) as brownish solid. $R_f = 0.6$ (EtOAc/Cyclohexane 20%). ^1H NMR (400 MHz, CDCl_3) δ 7.57 – 7.46 (m, 2H), 7.45 – 7.38 (m, 2H), 7.37 – 7.30 (m, 1H), 7.21 (s, 1H), 6.85 (d, $J = 0.9$ Hz, 1H), 6.44 (s, 1H), 5.14 (s, 2H), 2.24 (d, $J = 0.8$ Hz, 3H), 2.14 (s, 3H), 1.51 (s, 3H), 1.40 (s, 3H), 1.03 (s, 9H), 0.26 (s, 3H), 0.25 (s, 3H).

2. Synthesis of 2,6,6,9-tetramethyl-8-(methylamino)-6H-benzo[*c*]chromen-3-ol (2a)

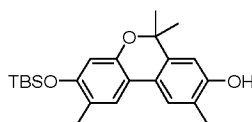


2a was synthesized in 4 steps starting from ((8-(benzyloxy)-2,6,6,9-tetramethyl-6H-benzo[*c*]chromen-3-yl)oxy)(tert-butyl)dimethylsilane.

Scheme 2.

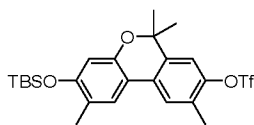


Step 1: synthesis of 3-((tert-butyl(dimethyl)silyl)oxy)-2,6,6,9-tetramethyl-6H-benzo[*c*]chromen-8-ol



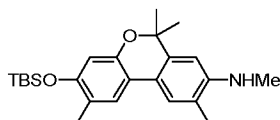
((8-(benzyloxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-yl)oxy)(tert-butyl)dimethylsilane (400 mg, 1 Eq, 843 μ mol) was dissolved in methanol (27.0 mg, 8.43 mL, 0.1 molar, 1 Eq, 843 μ mol) and dichloromethane (71.6 mg, 4.21 mL, 0.2 molar, 1 Eq, 843 μ mol). palladium hydroxide on carbon (118 mg, 20% Wt, 0.2 Eq, 169 μ mol) was added in one portion and the suspension was hydrogenated under atmospheric pressure overnight. After completion, the reaction mixture was filtered over a pad of celite. p-Toluenesulfonic acid monohydrate (16.0 mg, 12.9 μ L, 0.1 Eq, 84.3 μ mol) was added then the mixture was concentrated and loaded on silica to be purified by flash column chromatography (SiO₂, 12g, MeOH in DCM 0-5% to give 3-((tert-butyldimethylsilyl)oxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-ol (150 mg, 390 μ mol, 46.3 %) as a white solid. ¹H NMR (400 MHz, DMSO) δ 9.35 (s, 1H), 7.49 (s, 1H), 7.44 (s, 1H), 6.67 (s, 1H), 6.26 (s, 1H), 2.15 (s, 3H), 2.13 (s, 3H), 1.47 (s, 6H), 0.98 (s, 9H), 0.20 (s, 6H).

Step 2: synthesis of 3-((tert-butyldimethylsilyl)oxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-yl trifluoromethanesulfonate



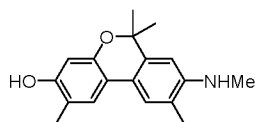
triflic anhydride (165 mg, 98.8 μ L, 1.5 Eq, 585 μ mol) was added dropwise to a solution of 3-((tert-butyldimethylsilyl)oxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-ol (150 mg, 1 Eq, 390 μ mol) and pyridine (309 mg, 315 μ L, 10 Eq, 3.90 mmol) at 0°C in DCM 10 mL and the mixture was stirred for 3h at room temperature. The reaction was monitored by TLC eluent EtOAc/cyclohexane 10%. Dichloromethane was evaporated under vacuum and the crude was extracted with HCl 1M and EtOAc. The organic phase was washed with water once, dried over sodium sulfate and concentrated under vacuum to give 3-((tert-butyldimethylsilyl)oxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-yl trifluoromethanesulfonate (140 mg, 271 μ mol, 69.5 %) used to the next step without further purification. R_f 0.6 (EtOAc/Cyclohexane 40 %).

Step 3: synthesis of 3-((tert-butyldimethylsilyl)oxy)-N,2,6,6,9-pentamethyl-6H-benzo[c]chromen-8-amine



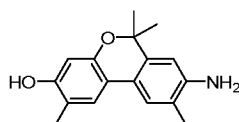
t-Bu XPhos (23 mg, 0.4 Eq, 54 μmol) was added to a suspension of Tris(dibenzylideneacetone)dipalladium (25 mg, 0.2 Eq, 27 μmol) in dioxane 8ml and the mixture was stirred 5 minute at rt. 3-((tert-butyldimethylsilyl)oxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-yl trifluoromethanesulfonate (70 mg, 1 Eq, 0.14 mmol), methanamine (63 mg, 1.0 mL, 2 molar, 15 Eq, 2.0 mmol) and cesium carbonate (427mg, 1.31mmol) were successively added and the reaction mixture was refluxed for 3hours. Water was added and the mixture extracted with EA 3 times. The combined organic phases were dried over sodium sulfate, filtered and concentrated under vacuum. The crude was loaded on silica and purified by FC eluent EA/cyclohexane 0% to 5% to 10% 20% to give 3-((tert-butyldimethylsilyl)oxy)-N,2,6,6,9-pentamethyl-6H-benzo[c]chromen-8-amine (40 mg, 0.10 mmol, 74 %) as yellowish oil. Product contaminated with ligand. R_f 0.5 (EtOAc/Cyclohexane 20 %). MS (ESI+): m/z = 397.24 found 398.3.

Step 4: synthesis of 2,6,6,9-tetramethyl-8-(methylamino)-6H-benzo[c]chromen-3-ol (**2a**)



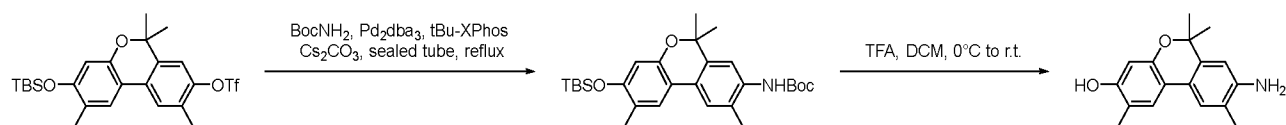
3-((tert-butyldimethylsilyl)oxy)-N,2,6,6,9-pentamethyl-6H-benzo[c]chromen-8-amine (40 mg, 1 Eq, 0.10 mmol) was dissolved in dry methanol (3.2 mg, 2.0 mL, 0.05 molar, 1 Eq, 0.10 mmol)hydrogen chloride Methanol solution (34 mg, 0.40 mL, 1.25 molar, 5 Eq, 0.50 mmol) was added at r.t. and the mixture was stirred o.n. Solvent was evaporated and the crude was loaded on silica purified By FC: eluent MeOH/DCM 0% to 20% to give 2,6,6,9-tetramethyl-8-(methylamino)-6H-benzo[c]chromen-3-ol (10 mg, 35 μmol , 35 %). R_f 0.5 (MeOH/DCM 10 %) ^1H NMR (400 MHz, DMSO) δ 9.17 (s, 1H), 7.32 (s, 1H), 7.29 (s, 1H), 6.32 (s, 1H), 6.28 (s, 1H), 2.75 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 1.48 (s, 6H).

3. Synthesis of 8-amino-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-ol (**2**)

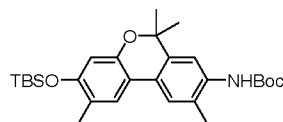


2 is prepared in 2 steps from **3** 3-((tert-butyldimethylsilyl)oxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-yl trifluoromethanesulfonate

Scheme 3.

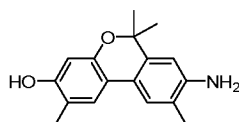


Step 1: synthesis of tert-butyl (3-((tert-butyldimethylsilyl)oxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-yl)carbamate



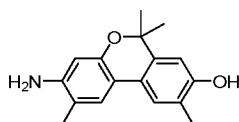
t-Bu XPhos (29.6 mg, 0.2 Eq, 69.7 μmol) was added to a suspension of Tris(dibenzylideneacetone)dipalladium (31.9 mg, 0.1 Eq, 34.8 μmol) in dioxane 8ml and the mixture was stirred 5 minute at rt. 3-((tert-butyldimethylsilyl)oxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-yl trifluoromethanesulfonate (180 mg, 1 Eq, 348 μmol), Tert-butryl carbamate (163 mg, 4 Eq, 1.39 mmol) and cesium carbonate (427mg, 1.31mmol) were added and the reaction mixture was refluxed for 1hours. water was added and the mixture extracted with EA 3 times. The combined organic phases were dried over sodium sulfate, filtered and concentrated under vacuum and the crude was loaded on silica and purified by FC eluent EA/cyclohexane 0% to 20% to give tert-butyl (3-((tert-butyldimethylsilyl)oxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-yl)carbamate (70 mg, 0.14 mmol, 42 %) as a yellowish solid. R_f 0.5 (EtOAc/Cyclohexane 20 %) ^1H NMR (400 MHz, CDCl_3) δ 7.72 (s, 1H), 7.39 (d, J = 1.1 Hz, 2H), 6.39 (s, 1H), 6.27 (s, 1H), 2.28 (s, 3H), 2.20 (s, 3H), 1.61 (s, 6H), 1.55 (s, 9H), 1.01 (s, 9H), 0.24 (s, 6H).

Step 2: Synthesis of 8-amino-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-ol (**2**)



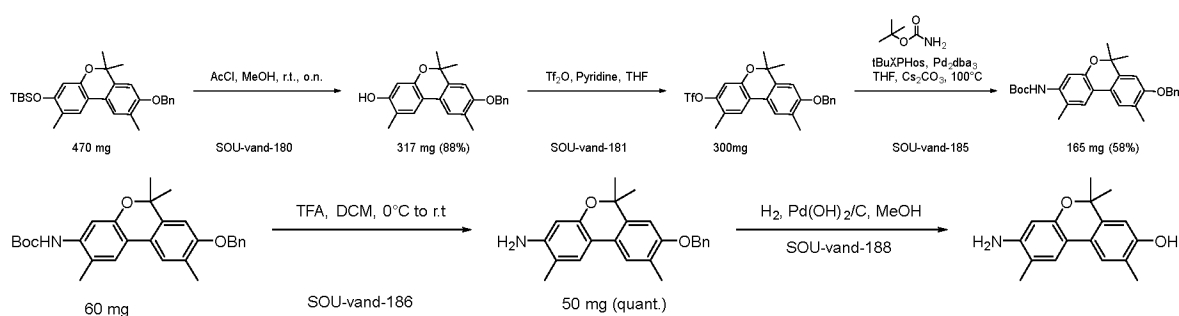
tert-butyl (3-((tert-butyldimethylsilyl)oxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-yl) carbamate (20 mg, 1 Eq, 41 μ mol) was dissolved in DCM (2 mL) and cooled down to 0°C. TFA (0.28 g, 0.19 mL, 60 Eq, 2.5 mmol) was added dropwise and stirring continued o.n. The reaction mixture was extracted with EtOAc and NaHCO₃ saturated solution twice. The combined organic phases were dried over sodium sulfate, filtered and concentrated under vacuum and the crude was loaded on silica and purified by FC eluent MeOH/DCM 0% to 5% to 10% 20% to give 8-amino-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-ol (10 mg, 37 μ mol, 90 %) as a whit solid. ¹H NMR (400 MHz, DMSO) δ 9.18 (s, 1H), 7.31 (s, 1H), 7.25 (s, 1H), 6.52 (s, 1H), 6.27 (s, 1H), 2.08 (s, 6H), 1.44 (s, 6H).

4. Synthesis of 3-amino-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-ol (1)

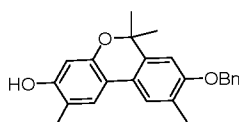


1 is prepared in 5 steps from ((8-(benzyloxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-yl)oxy)(tert-butyl)dimethylsilane

Scheme 4.



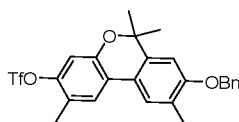
Step 1: Synthesis 8-(benzyloxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-ol



((8-(benzyloxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-yl)oxy)(tert-butyl)dimethylsilane (470 mg, 1 Eq, 990 μ mol) dissolved in methanol dry (31.7 mg, 9.90 mL, 0.1 molar, 1 Eq, 990 μ mol) and DCM (84.1 mg, 4.95 mL, 0.2 molar, 1 Eq, 990 μ mol) (SM not soluble in MeOH) acetyl chloride (155 mg, 141 μ L, 2 Eq, 1.98 mmol) was added dropwise and stirring continued o.n. tlc showed no more sm. The solvent was evaporated under vacuum and the crude was extracted with EA and Sodium bicarbonate saturated solution. The organic phase was dried over sodium sulfate and concentrated under vacuum to give 8-(benzyloxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-ol (317 mg, 879 μ mol, 88.8 %) as a brownish solid used to the next step without further purification

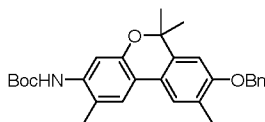
^1H NMR (400 MHz, DMSO) δ 9.36 (d, J = 1.5 Hz, 1H), 7.49 (d, J = 7.7 Hz, 3H), 7.44 – 7.38 (m, 3H), 7.32 (td, J = 6.9, 1.5 Hz, 1H), 6.91 (s, 1H), 6.30 (d, J = 1.7 Hz, 1H), 5.15 (s, 2H), 2.21 (s, 3H), 2.10 (s, 3H), 1.49 (s, 6H).

Step 2: synthesis of 8-(benzyloxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-yl trifluoromethanesulfonate



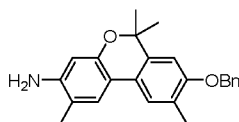
triflicanhydride (352 mg, 211 μ L, 1.5 Eq, 1.25 mmol) was added dropwise to a solution of 8-(benzyloxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-ol (300 mg, 1 Eq, 832 μ mol) and pyridine (658 mg, 673 μ L, 10 Eq, 8.32 mmol) at 0°C in DCM 10 mL and the mixture was stirred for 3h at room temperature. DCM was evaporated under vacuum and the crude was extracted with NH₄Cl saturated solution and EA. The organic phase was washed with water once, dried over sodium sulfate and concentrated under vacuum. The crude was purified By FC eluent EA/cyclohexane 0% to 15% to give 8-methoxy-6-oxo-6H-benzo[c]chromen-3-yl trifluoromethanesulfonate (550mg, 1.47 mmol, 42%). ^1H NMR (400 MHz, CDCl₃) δ 7.53 (s, 1H), 7.49 – 7.31 (m, 6H), 6.83 (s, 1H), 6.71 (s, 1H), 5.12 (s, 2H), 2.36 (d, J = 0.6 Hz, 3H), 2.33 (d, J = 0.8 Hz, 3H), 1.58 (s, 6H).

Step 3: synthesis of tert-butyl (8-(benzyloxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-yl)carbamate



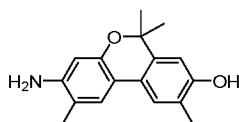
t-Bu XPhos (36.2 mg, 0.14 Eq, 85.3 μ mol) was added to a suspension of Tris(dibenzylideneacetone)dipalladium (39.0 mg, 0.07 Eq, 42.6 μ mol) in Toluene 6.5ml and the mixture was stirred 5 minute at rt. 8-(benzyloxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-yl trifluoromethanesulfonate (300 mg, 1 Eq, 609 μ mol), Tert-butryl carbamate (428 mg, 6 Eq, 3.65 mmol) and cesium carbonate (427mg, 1.31mmol) were added and the reaction mixture was refluxed for 1hours. Water was added and the mixture extracted with EA 3 times. The combined organic phases were dried over sodium sulfate, filtered and concentrated under vacuum. and the crude was loaded on silica and purified by FC eluent EA/cyclohexane 0% to 5% to 10% 20% to give tert-butyl (8-(benzyloxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-yl) carbamate (60 mg, 0.13 mmol, 21 %). R_f 0.5 (EtOAc/Cyclohexane 20 %). MS (APCI+): m/z = 460.

Step 4: synthesis of tert-butyl 8-(benzyloxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-amine



TFA (0.74 g, 0.50 mL, 50 Eq, 6.5 mmol) was added to a solution of tert-butyl (8-(benzyloxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-yl) carbamate (60 mg, 1 Eq, 0.13 mmol) in DCM (11 mg, 1.3 mL, 0.1 molar, 1 Eq, 0.13 mmol) at 0°C and stirred at rt for 1h. Solvent was evaporated under vacuum and the crude was partitioned between EtOAc and sodium bicarbonate saturated solution. The aqueous phase was extracted 3 times with EtOAc. The combined organic phases were dried over sodium sulfate and concentrated under vacuum to give 8-(benzyloxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-amine (50 mg, 0.14 mmol, 110 %) as brownish oil which was used as a crude for next step. MS (APCI+): m/z = 360.

Step 5: synthesis of 3-amino-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-ol (**1**)

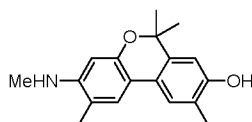


8-(benzyloxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-amine (50 mg, 1 Eq, 0.14 mmol) was dissolved in methanol (4.5 mg, 4.6 mL, 0.03 molar, 1 Eq, 0.14 mmol) and DCM (12 mg, 1.4 mL, 0.1 molar, 1 Eq, 0.14 mmol). palladium hydroxide on carbon (9.8 mg, 20% Wt, 0.1 Eq, 14 μ mol) was added and the mixture was hydrogenated under atmospheric pressure for 2h. The crude was filtered over a pad of celite and the crude was purified by FC eluent EtOAc/cyH 0% to 80% to give 3-amino-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-ol (20 mg, 74 μ mol, 53 %).

Rf 0.4 (EtOAc/Cyclohexane 20 %).

^1H NMR (400 MHz, DMSO) δ 9.14 (s, 1H), 7.30 (s, 1H), 7.24 (s, 1H), 6.62 (s, 1H), 6.12 (s, 1H), 4.85 (s, 2H), 2.13 (d, J = 0.7 Hz, 3H), 2.04 – 1.87 (m, 3H), 1.44 (s, 6H). MS: m/z : 270 $[\text{M}+\text{H}]^+$.

5. Synthesis of 2,6,6,9-tetramethyl-3-(methylamino)-6H-benzo[c]chromen-8-ol (8)

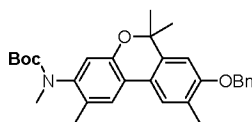


8 is prepared in 4 steps from tert-butyl (8-(benzyloxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-yl) carbamate

Scheme 5.



Step 1: synthesis of tert-butyl (8-(benzyloxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-yl)(methyl)carbamate

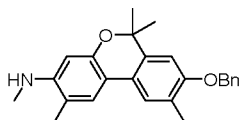


sodium hydride (17 mg, 60% Wt, 2 Eq, 435 μ mol) was added to a solution of tert-butyl (8-(benzyloxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-yl)carbamate (100 mg, 1 Eq, 218 μ mol)

in DMF 4 mL at 0°C. Then methyl iodide (92.7 mg, 40.8 μ L, 3 Eq, 653 μ mol) was added and stirring continued for 1h. NH₄Cl Saturated solution and the aqueous phase was extracted with EtOAc. The organic phase was washed with water, dried over sodium sulfate. The solvent was concentrated under vacuum to give m(crude) = 100mg used to the next step without further purification.

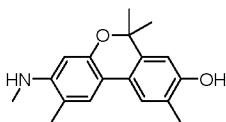
¹H NMR (400 MHz, CDCl₃) δ 7.74 – 7.43 (m, 3H), 7.44 – 7.35 (m, 2H), 7.33 (d, J = 7.3 Hz, 1H), 6.77 – 6.68 (m, 1H), 6.21 (s, 1H), 5.09 (s, 1H), 2.96 (d, J = 0.5 Hz, 3H), 2.89 (d, J = 0.7 Hz, 3H), 2.31 (s, 3H), 1.59 (s, 9H).

Step 2: synthesis 8-(benzyloxy)-N,2,6,6,9-pentamethyl-6H-benzo[c]chromen-3-amine



of tert-butyl (8-(benzyloxy)-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-yl)(methyl)carbamate 100mg (crude) was dissolved in DCM 3ml and treated with TFA (496 mg, 335 μ L, 20 Eq, 4.35 mmol) at 0°C for 1h then allowed to warm to room temperature overnight. NaHCO₃ saturated solution was added and the aqueous phase was extracted with EtOAc twice. The combined organic phases were dried over sodium sulfate and concentrated under vacuum. The crude material was purified by flash column chromatography on silica (0-50% EtOAc in Hex) to give 8-(benzyloxy)-N,2,6,6,9-pentamethyl-6H-benzo[c]chromen-3-amine (70 mg, 0.19 mmol, 86 %). R_f = 0.5 (EtOAc/Cyclohexane 20 %). m/z = 373.20 Found 374.2.

Step 3: synthesis 2,6,6,9-tetramethyl-3-(methyamino)-6H-benzo[c]chromen-8-ol (**8**)

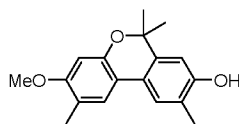


8-(benzyloxy)-N,2,6,6,9-pentamethyl-6H-benzo[c]chromen-3-amine (70 mg, 1 Eq, 0.19 mmol) was hydrogenated under atmospheric pressure in presence of palladium hydroxide on carbon (13 mg, 20% Wt, 0.1 Eq, 19 μ mol) in MeOH (6.0 mg, 3.7 mL, 0.05 molar, 1 Eq, 0.19 mmol) o.n. The

crude material was purified by flash column chromatography on silica (0-50% EtOAc in Hex) to give 2,6,6,9-tetramethyl-3-(methylamino)-6H-benzo[*c*]chromen-8-ol (21 mg, 74 μ mol, 40 %) as a white solid. R_f = 0.5 (EtOAc/Cyclohexane 50%).

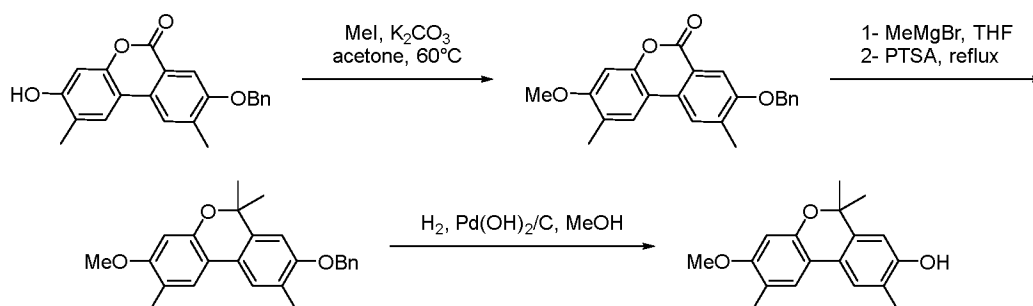
^1H NMR (400 MHz, DMSO) δ 9.14 (s, 1H), 7.31 (s, 1H), 7.28 (s, 1H), 6.63 (s, 1H), 5.96 (s, 1H), 5.08 (q, J = 4.8 Hz, 1H), 2.69 (d, J = 4.9 Hz, 3H), 2.13 (d, J = 0.7 Hz, 3H), 2.05 (d, J = 0.7 Hz, 3H), 1.46 (s, 6H). MS: m/z : 284 $[\text{M}+\text{H}]^+$.

6. *Synthesis of 3-methoxy-2,6,6,9-tetramethyl-6H-benzo[*c*]chromen-8-ol (6)*

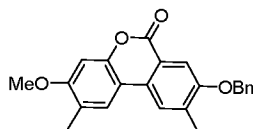


6 was prepared in 4 steps from 8-(benzyloxy)-3-hydroxy-2,9-dimethyl-6H-benzo[*c*]chromen-6-one

Scheme 6.



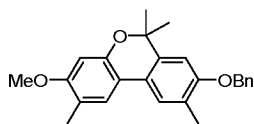
Step1: synthesis of 8-(benzyloxy)-3-methoxy-2,9-dimethyl-6H-benzo[*c*]chromen-6-one



8-(benzyloxy)-3-hydroxy-2,9-dimethyl-6H-benzo[*c*]chromen-6-one (700 mg, 1 Eq, 2.02 mmol) was dissolved in acetone (117 mg, 40.4 mL, 0.05 molar, 1 Eq, 2.02 mmol) at room temperature. potassium carbonate (1.12 g, 4 Eq, 8.08 mmol) was added followed by methyl iodide (1.43 g, 632 μ L, 5 Eq, 10.1 mmol) and the mixture was refluxed overnight. Water was added and the aqueous

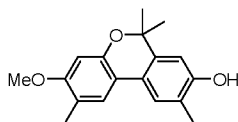
phase extracted with EtOAc 3 times. dried over sodium sulfate and concentrated under vacuum to give a yellowish solid which was triturated in EtOAc to give 8-(benzyloxy)-3-methoxy-2,9-dimethyl-6H-benzo[c]chromen-6-one (680 mg, 1.89 mmol, 93.4 %) as a beige solid. ^1H NMR (400 MHz, CDCl_3) δ 7.82 – 7.79 (m, 1H), 7.78 (s, 1H), 7.71 (d, $J = 1.0$ Hz, 1H), 7.55 – 7.46 (m, 2H), 7.45 – 7.38 (m, 2H), 7.37 – 7.31 (m, 1H), 6.80 (s, 1H), 5.20 (s, 2H), 3.88 (s, 3H), 2.47 (d, $J = 0.8$ Hz, 3H), 2.30 (d, $J = 0.8$ Hz, 3H).

Step 2: synthesis of 8-(benzyloxy)-3-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromene



8-(benzyloxy)-3-methoxy-2,9-dimethyl-6H-benzo[c]chromen-6-one (350 mg, 1 Eq, 971 μmol) was dissolved in THF (70.0 mg, 13.9 mL, 0.07 molar, 1 Eq, 971 μmol) and methylmagnesium bromide (579 mg, 1.62 mL, 3 molar, 5 Eq, 4.86 mmol) was added dropwise at rt. stirring continued o.n. The rm was poured into HCl 1M and extracted twice with EtOAc, dried over sodium sulfate and concentrated under vacuum to give open intermediate 170 mg. Open intermediate was heated in toluene in presence of PTSOH (18.5 mg, 0.1 Eq, 97.1 μmol) for 1 h. The reaction mixture was extracted with EtOAc and Sodium bicarbonate saturated solution. the combined organic phases were dried over sodium sulfate and concentrated under vacuum. The crude was loaded on silica and purified by FC eluent MeOH/DCM 0% to 5% to 10% 20% to give 8-amino-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-ol (10 mg, 37 μmol , 90 %) as a whit solid. ^1H NMR (400 MHz, CDCl_3) δ 7.47 – 7.43 (m, 3H), 7.43 – 7.37 (m, 3H), 7.35 – 7.32 (m, 1H), 6.71 (s, 1H), 6.45 (s, 1H), 5.10 (s, 2H), 3.82 (s, 3H), 2.32 (d, $J = 0.7$ Hz, 3H), 2.21 (d, $J = 1.0$ Hz, 3H), 1.59 (s, 6H).

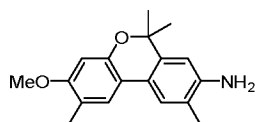
Step 3: synthesis of 3-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-ol (**6**)



A suspension of 8-(benzyloxy)-3-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromene (240 mg, 1 Eq, 641 μmol) and palladium hydroxide on carbon (18.0 mg, 0.2 Eq, 128 μmol) in methanol (20.5 mg, 6.41 mL, 0.1 molar, 1 Eq, 641 μmol) was hydrogenated under atmospheric pressure for 2

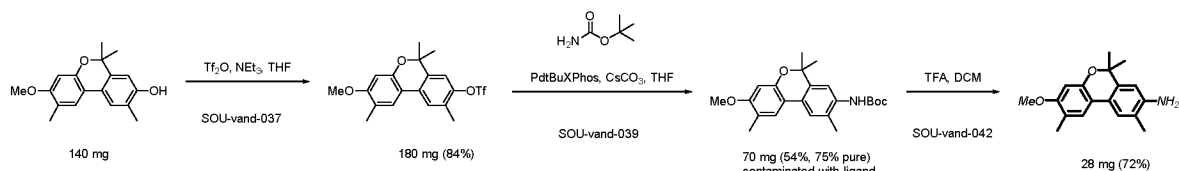
hours. The reaction mixture was filtered over a pad of celite. The open intermediate was heated in toluene in presence of p-Toluenesulfonic acid monohydrate (18.3 mg, 14.7 μ L, 0.15 Eq, 96.1 μ mol) for 30 min. sodium bicarbonate saturated solution aqueous phase was extracted with EtOAc twice. The combined organic phases were dried over sodium sulfate and concentrated under vacuum. The crude was loaded on silica and purified by FC eluent EtOAc/Cyclohexane 0% to 20% to give 3-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-ol (170 mg, 598 μ mol, 93.3 %). R_f 0.7 (EtOAc/Cyclohexane 20 %). ^1H NMR (400 MHz, DMSO) δ 9.32 (s, 1H), 7.73 – 7.45 (m, 1H), 7.43 (s, 1H), 6.67 (s, 1H), 6.46 (s, 1H), 3.75 (s, 3H), 2.15 (s, 3H), 2.12 (s, 3H), 1.48 (s, 6H).

7. Synthesis of 3-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-amine (4)

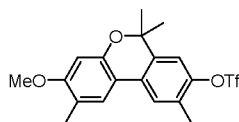


4 was prepared in 3 steps from 3-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-ol (**6**)

Scheme 7.



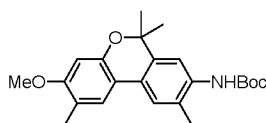
Step 1: Synthesis of 3-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-yl trifluoromethanesulfonate



Triflic anhydride (360 mg, 215 μ L, 2.5 Eq, 1.27 mmol) was added dropwise to a solution of 3-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-ol (145 mg, 1 Eq, 510 μ mol) and pyridine (403 mg, 412 μ L, 10 Eq, 5.10 mmol) at 0°C in DCM 10 mL and the mixture was stirred for 3h at room temperature. Dichloromethane was evaporated under vacuum and the crude was extracted

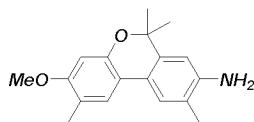
with NH_4Cl saturated solution and EA. The organic phase was washed with water once, dried over sodium sulfate and concentrated under vacuum. The crude was purified By FC eluent EA/cyclohexane 0% to 15% to give 8-methoxy-6-oxo-6H-benzo[c]chromen-3-yl trifluoromethanesulfonate (550mg, 1.47 mmol, 42%) as a yellowish foam. R_f 0.6 (EtOAc/Cyclohexane 40 %) used as a crude to the next step without further purification.

Step 2: synthesis of tert-butyl (3-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-yl) carbamate



t-Bu XPhos (22.8 mg, 0.16 Eq, 53.8 μmol) was added to a suspension of Tris(dibenzylideneacetone)dipalladium (24.6 mg, 0.08 Eq, 26.9 μmol) in Toluene 6.5ml and the mixture was stirred 5 minutes at rt. 3-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-yl trifluoromethanesulfonate (140 mg, 1 Eq, 336 μmol), Tert-butryl carbamate (197 mg, 5 Eq, 1.68 mmol) and cesium carbonate (427mg, 1.31mmol) were added and the reaction mixture was refluxed for 1hours. Water was added and the mixture extracted with EA 3 times. The combined organic phases were dried over sodium sulfate, filtered and concentrated under vacuum.and the crude was loaded on silica and purified by FC eluent EA/cylohexane 0% to 5% to 10% 20% to give tert-butyl (3-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-yl)carbamate (70 mg, 0.18 mmol, 54 %) contaminated with tBuXPhos. MS (APCI+): m/z = 384. R_f = 0.5 (EtOAc/Cyclohexane 20 %) as a brownish solid.

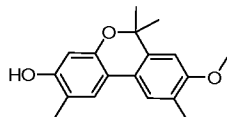
Step 3: synthesis of 3-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-amine (4)



TFA (0.31 g, 0.21 mL, 20 Eq, 2.7 mmol) was added to a mixture of tert-butyl (3-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-yl)carbamate (70 mg, 75% Wt, 1 Eq, 0.14 mmol) in DCM (12 mg, 2.7 mL, 0.05 molar, 1 Eq, 0.14 mmol) at 0°C and stirring continued at r.t for 3h. DCM was evaporated under reduced pressure and the crude was extracted with EtOAc/ NaHCO_3 . The organic phase was dried over sodium sulfate. The crude was purified biotage eluent EtOAc/cyclohexane

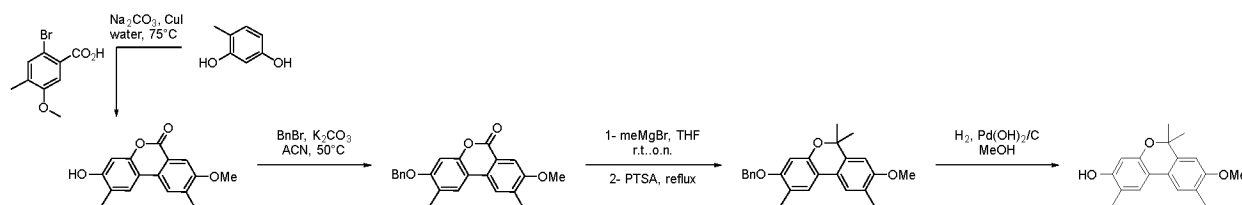
0% to 30% to give 3-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-amine (28 mg, 99 μ mol, 72 %) as a white solid. R_f = 0.2 (EtOAc/Cyclohexane 20 %). ^1H NMR (400 MHz, DMSO) δ 7.41 (s, 1H), 7.31 (s, 1H), 6.56 (s, 1H), 6.43 (s, 1H), 5.30 (s, 2H), 3.73 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H), 1.46 (s, 6H). MS: m/z : 270 $[\text{M}+\text{H}]^+$.

8. Synthesis of 8-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-ol (5)

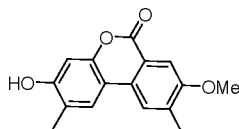


5 was prepared from methyl resorcinol in 4 steps.

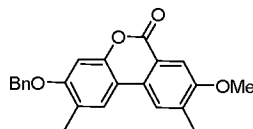
Scheme 8.



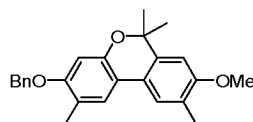
Step 1: synthesis of 3-hydroxy-8-methoxy-2,9-dimethyl-6H-benzo[c]chromen-6-one



4-methylbenzene-1,3-diol (2.026 g, 2.0 Eq, 16.32 mmol) was dissolved in water (147.1 mg, 40.80 mL, 0.2 molar, 1 Eq, 8.161 mmol) and sodium carbonate (2.595 g, 3.0 Eq, 24.48 mmol) was added and the mixture heated to 60 °C until everything had dissolved. Then 2-bromo-5-methoxy-4-methylbenzoic acid (2000 mg, 1 Eq, 8.161 mmol) was added and stirring at 75 °C was continued for 4h. copper(I) iodide (777.1 mg, 0.5 Eq, 4.080 mmol) was added in one portion and the reaction was stirred for 12h. at 75°C. the precipitate was filtered off and the cake washed successively with water and with HCl 1M then dried under vacuum overnight to give 3-hydroxy-8-methoxy-2,9-dimethyl-6H-benzo[c]chromen-6-one (1.6 g, 5.9 mmol, 73 %) as a beige solid. ^1H NMR (400 MHz, DMSO) δ 10.12 (s, 1H), 8.07 (s, 1H), 7.94 (s, 1H), 7.51 (s, 1H), 6.73 (s, 1H), 3.90 (s, 3H), 2.33 (s, 3H), 2.21 (s, 3H).

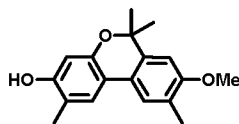
Step 2: synthesis of 3-(benzyloxy)-8-methoxy-2,9-dimethyl-6H-benzo[c]chromen-6-one

3-hydroxy-8-methoxy-2,9-dimethyl-6H-benzo[c]chromen-6-one (1500 mg, 1 Eq, 5.550 mmol) was dissolved in acetone (322.3 mg, 55.50 mL, 0.1 molar, 1 Eq, 5.550 mmol). benzyl bromide (854.3 mg, 594.1 μ L, 0.9 Eq, 4.995 mmol) was added and the mixture was heated at 70°C overnight. The suspension was filtered off and the filtrate was evaporated under vacuum and the precipitate was triturated in Et₂O and filtered to give 3-(benzyloxy)-8-methoxy-2,9-dimethyl-6H-benzo[c]chromen-6-one (1.72 g, 4.77 mmol, 86.0 %) as a brownish solid. ¹H NMR (400 MHz, DMSO) δ 8.17 (s, 1H), 8.08 (s, 1H), 7.56 (s, 1H), 7.52 – 7.47 (m, 2H), 7.42 (t, J = 7.4 Hz, 2H), 7.40 – 7.31 (m, 1H), 7.08 (s, 1H), 5.23 (s, 2H), 3.92 (s, 3H), 2.36 (s, 3H), 2.30 (s, 3H).

Step3: Synthesis of 3-(benzyloxy)-8-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromene

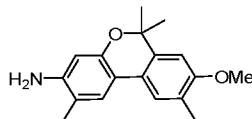
3-(benzyloxy)-8-methoxy-2,9-dimethyl-6H-benzo[c]chromen-6-one (200 mg, 1 Eq, 555 μ mol) was dissolved in THF (40.0 mg, 7.93 mL, 0.07 molar, 1 Eq, 555 μ mol) and methylmagnesium bromide (304 mg, 851 μ L, 3 molar, 4.6 Eq, 2.55 mmol) was added dropwise at rt. stirring continued o.n. The rm was poured into HCl 1M and extracted twice with EtOAc, dried over sodium sulfate and concentrated under vacuum to give open intermediate 170 mg. Open intermediate was heated at 70°C in toluene in presence of PTSOH (10.6 mg, 0.1 Eq, 55.5 μ mol) for 1h. Toluene was evaporated and the crude was extracted with NaHCO₃ saturated solution, dried over sodium sulfate to give 3-(benzyloxy)-8-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromene (160 mg, 427 μ mol, 77.0 %) as a brownish oil. MS (APCI+): m/z = 375. ¹H NMR (400 MHz, CDCl₃) δ 7.55 – 7.29 (m, 7H), 6.65 (s, 1H), 6.53 (s, 1H), 5.06 (s, 2H), 3.86 (s, 3H), 2.28 (d, J = 0.7 Hz, 3H), 2.26 (d, J = 0.7 Hz, 3H), 1.62 (s, 6H).

Step 4: synthesis of 8-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-ol (**5**)



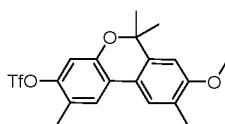
A suspension of 3-(benzyloxy)-8-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromene (800 mg, 1 Eq, 2.14 mmol) and palladium hydroxide on carbon (300 mg, 20% Wt, 0.2 Eq, 427 μ mol) in MeOH (5 mL) was hydrogenated under atmospheric pressure over 2h. The suspension was filtered over a pad of celite and the solvent was evaporated under vacuum to give 8-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-ol (600 mg, 2.11 mmol, 98.8 %) as a white foam. R_f 0.5 EA/Hexane 10/90. ^1H NMR (400 MHz, CDCl_3) δ 14.11 (s, 1H), 12.22 (d, J = 0.9 Hz, 1H), 12.18 (s, 1H), 11.55 (s, 1H), 11.07 (s, 1H), 8.57 (s, 3H), 8.08 (s, 2H), 6.92 (d, J = 0.7 Hz, 3H), 6.86 (d, J = 0.7 Hz, 3H), 6.28 (s, 6H).

9. Synthesis of 8-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-amine (**3**)



3 was prepared from **6** in 3 steps.

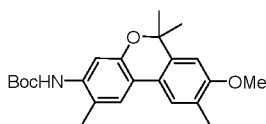
Step 1: synthesis of 8-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-yl trifluoromethanesulfonate



Triflicanhydride (570 mg, 342 μ L, 2.5 Eq, 2.02 mmol) was added dropwise to a solution of 8-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-ol (230 mg, 1 Eq, 809 μ mol) and pyridine (640 mg, 654 μ L, 10 Eq, 8.09 mmol) at 0°C in DCM 10 mL and the mixture was stirred for 3h at room temperature. DCM was evaporated under vacuum and the crude was extracted with NH_4Cl saturated solution and EA. The organic phase was washed with water once, dried over sodium sulfate and concentrated under vacuum. The crude was purified By FC eluent EA/cyclohexane 0%

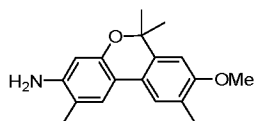
to 15% to give 8-methoxy-6-oxo-6H-benzo[c]chromen-3-yl trifluoromethanesulfonate (550mg, 1.47 mmol, 42%) as a white solid. R_f 0.6 (EA/cyclohexane 40%) used as a crude.

Step 2: synthesis of tert-butyl (8-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-yl) carbamate



t-BuXPhos (42.8 mg, 0.14 Eq, 101 μ mol) was added to a suspension of Tris(dibenzylideneacetone)dipalladium (46.2 mg, 0.07 Eq, 50.4 μ mol) in Toluene 6.5ml and the mixture was stirred 5 minute at rt. 8-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-yl trifluoromethanesulfonate (300 mg, 1 Eq, 720 μ mol), Tert-butyl carbamate (338 mg, 4 Eq, 2.88 mmol) and cesium carbonate (427mg, 1.31mmol) were added and the reaction mixture was refluxed overnight. NH_4Cl saturated solution was added and the mixture extracted with EA 3 times. The combined organic phases were dried over sodium sulfate, filtered and concentrated under vacuum and the crude was loaded on silica and purified by FC eluent EA/cyclohexane 0% to 5% to 10% 20% to give tert-butyl (8-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-yl) carbamate (145 mg, 378 μ mol, 52.5 %) contaminated with tBuXPhos. The product was used to the next step without further purification. R_f 0.5 (EA/cyclohexane 20%).

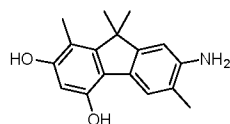
Step 3: synthesis of 8-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-amine **3**



tert-butyl (8-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-yl)carbamate (70 mg, 1 Eq, 0.18 mmol) was dissolved in dry DCM (16 mg, 12 μ L, 1 Eq, 0.18 mmol) and cooled to 0°C then TFA (0.21 g, 0.14 mL, 10 Eq, 1.8 mmol) was added dropwise and stirring continued at rt for 2h. Na_2CO_3 sat. sol. was added and the mixture extracted with EA twice. The combined organic phases were dried over sodium sulfate, filtered and concentrated under vacuum. The crude was loaded on silica and purified by FC eluent EA/cyclohexane 0% to 5% to 10% 20% to give 8-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-amine (20 mg, 71 μ mol, 39 %). R_f 0.2

(EA/cyclohexane 20%). ^1H NMR (400 MHz, DMSO) δ 7.38 (s, 1H), 7.28 (s, 1H), 6.76 (s, 1H), 6.13 (s, 1H), 4.90 (s, 2H), 3.79 (s, 3H), 2.32 – 2.09 (s, 3H), 2.04 (s, 3H), 1.50 (s, 6H).

10. Synthesis of 7-amino-1,6,9,9-tetramethyl-9H-fluorene-2,4-diol (14a)



14a was prepared from tert-butyl (3-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-yl) carbamate in one step by treatment with BBr_3 via a rearrangement involving the formation of a carbocation.

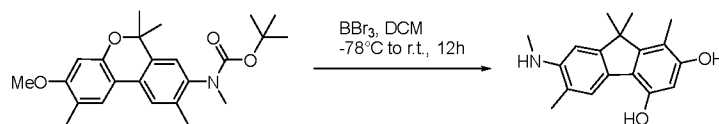
Scheme 9.



BBr_3 (235.2 mg, 938.7 μL , 1 molar, 4 Eq, 938.7 μmol) was added to a suspension of tert-butyl (3-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-yl)carbamate (90.00 mg, 1 Eq, 234.7 μmol) in DCM (19.93 mg, 4.694 mL, 0.05 molar, 1 Eq, 234.7 μmol) at -78°C over 5 min and the mixture was allowed to warm to r.t o.n. The reaction mixture was quenched with NaHCO_3 saturated solution and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over sodium sulfate and the organic residue was subjected to column chromatography biotage FC EtOAc/cyclohexane 0% to 20% to give MeOH/DCM 0% to 20% to give 7-amino-1,6,9,9-tetramethyl-9H-fluorene-2,4-diol (20 mg, 74 μmol , 32 %) as a white solid. R_f 0.5 (MeOH/DCM 10 %). ^1H NMR (400 MHz, DMSO) δ 9.13 (s, 1H), 8.89 (s, 1H), 7.40 (s, 1H), 6.62 (s, 1H), 6.32 (s, 1H), 4.78 (s, 2H), 2.16 (s, 3H), 2.06 (s, 3H), 1.39 (d, $J = 2.1$ Hz, 6H).

11. Synthesis of 2,6,6,9-tetramethyl-8-(methylamino)-6H-benzo[c]chromen-3-ol (14)

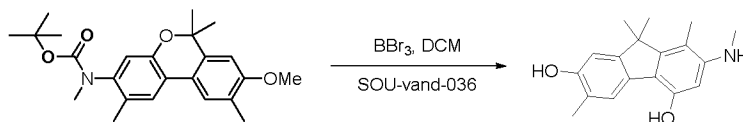
Scheme 10.



BBr_3 (100.8 mg, 402.5 μL , 1 molar, 4 Eq, 402.5 μmol) was added to a suspension of tert-butyl (3-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-8-yl)(methyl)carbamate (40.00 mg, 1 Eq, 100.6 μmol) in DCM (8.546 mg, 1.006 mL, 0.1 molar, 1 Eq, 100.6 μmol) at -78°C over 5 min and the mixture was allowed to warm to r.t o.n. The reaction mixture was quenched with NaHCO_3 saturated solution and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over sodium sulfate and the organic residue was subjected to column chromatography biotage FC EtOAc/cyclohexane 0% to 20% to give MeOH/DCM 0% to 20% to give 2,6,6,9-tetramethyl-8-(methylamino)-6H-benzo[c]chromen-3-ol (19 mg, 67 μmol , 67 %) as a brownish solid. R_f 0.5 (MeOH/DCM 10 %). ^1H NMR (400 MHz, DMSO) δ 9.15 (s, 1H), 8.91 (s, 1H), 7.45 (s, 1H), 6.50 (s, 1H), 6.33 (s, 1H), 4.86 (s, 1H), 2.78 (s, 3H), 2.17 (s, 3H), 2.09 (s, 3H), 1.44 (s, 3H), 1.43 (s, 3H). MS (APCI+): m/z = 284.

12. Synthesis of 3,8,9,9-tetramethyl-7-(methylamino)-9H-fluorene-2,5-diol (15)

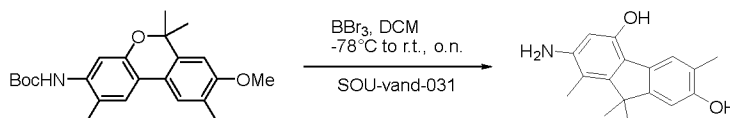
Scheme 11.



BBr_3 (0.11 g, 0.45 mL, 1 molar, 3 Eq, 0.45 mmol) was added to a suspension of tert-butyl (8-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-yl)(methyl)carbamate (60 mg, 1 Eq, 0.15 mmol) in DCM (13 mg, 3.0 mL, 0.05 molar, 1 Eq, 0.15 mmol) at -78°C over 2 min and the mixture was allowed to warm to r.t o.n. The reaction mixture was quenched with NaHCO_3 saturated solution, and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over sodium sulfate and the organic residue was subjected to column chromatography biotage FC MeOH/DCM 0% to 20% to give 3,8,9,9-tetramethyl-7-(methylamino)-9H-fluorene-2,5-diol (20 mg, 71 μmol , 47 %) as a white solid. R_f 0.5 (MeOH/DCM 10 %). ^1H NMR (400 MHz, DMSO) δ 9.14 (s, 1H), 8.88 (s, 1H), 7.49 (s, 1H), 6.75 (s, 1H), 6.03 (s, 1H), 4.88 (s, 1H), 2.77 – 2.70 (m, 3H), 2.16 (s, 3H), 2.14 (s, 3H), 1.44 (s, 3H), 1.44 (s, 3H). MS (APCI+): m/z = 284.

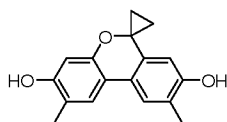
13. Synthesis of 7-amino-3,8,9,9-tetramethyl-9H-fluorene-2,5-diol (13)

Scheme 12.



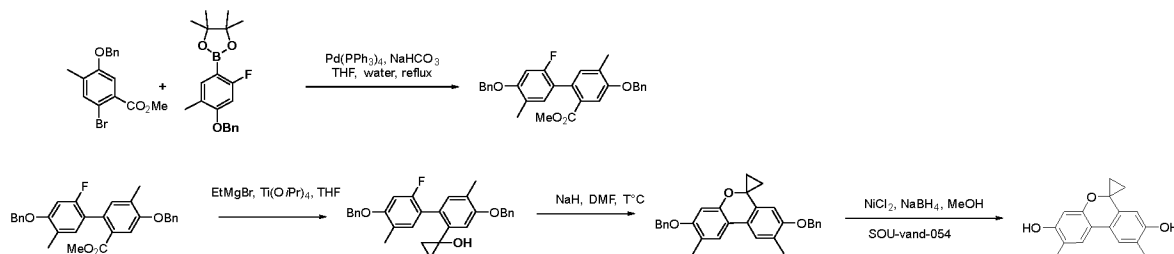
BBr_3 (0.18 g, 0.73 mL, 1 molar, 4 Eq, 0.73 mmol) was added to a suspension of tert-butyl (8-methoxy-2,6,6,9-tetramethyl-6H-benzo[c]chromen-3-yl)carbamate (70 mg, 1 Eq, 0.18 mmol) in DCM (13 mg, 3.0 mL, 0.05 molar, 1 Eq, 0.15 mmol) at -78°C over 2 min and the mixture was allowed to warm to r.t. o.n. The reaction mixture was quenched with NaHCO_3 saturated solution and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over sodium sulfate and the organic residue was subjected to column chromatography biotage FC MeOH/DCM 0% to 20% to give 7-amino-3,8,9,9-tetramethyl-9H-fluorene-2,5-diol (20 mg, 74 μmol , 41 %) as a white solid. R_f 0.5 (MeOH/DCM 10 %). ^1H NMR (400 MHz, DMSO) δ 9.00 (s, 1H), 8.82 (s, 1H), 7.44 (s, 1H), 6.70 (s, 1H), 6.13 (s, 1H), 4.66 (s, 2H), 2.11 (d, $J = 0.7$ Hz, 3H), 2.09 (s, 3H), 1.39 (s, 6H). MS (APCI+): $m/z = 270$.

14. Synthesis of 2,9-dimethylspiro[benzo[c]chromene-6,1'-cyclopropane]-3,8-diol (7)

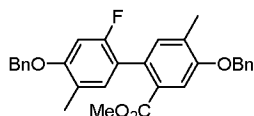


7 was prepared from intermediate methyl 5-(benzyloxy)-2-bromo-4-methylbenzoate and 2-(4-(benzyloxy)-2-fluoro-5-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane synthesized according in 4 steps.

Scheme 13.

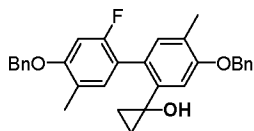


Step 1: synthesis of methyl 4,4'-bis(benzyloxy)-2'-fluoro-5,5'-dimethyl-[1,1'-biphenyl]-2-carboxylate



methyl 5-(benzyloxy)-2-bromo-4-methylbenzoate (1000 mg, 1 Eq, 2.983 mmol), 2-(4-(benzyloxy)-2-fluoro-5-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.225 g, 1.2 Eq, 3.580 mmol) and 1,2-Bis(diphenylphosphino)ethane palladium(II)dichloride (171.8 mg, 0.1 Eq, 298.3 μ mol) were suspended in THF (215.1 mg, 29.83 mL, 0.1 molar, 1 Eq, 2.983 mmol) and degassed with Nitrogen for 5 minutes. A solution of sodium bicarbonate (551.4 mg, 2.2 Eq, 6.563 mmol) in water (10 g, 10 mL, 0.3 molar, 1.0 Eq, 3.0 mmol) was added at r.t. and the mixture was refluxed o.n. After cooling to room temperature, NH_4Cl saturated solution was added and the aqueous phase was extracted with EA twice. The combined organic phases were dried over sodium sulfate, concentrated under vacuum and the organic residue was subjected to column chromatography biotage FC EA/cyclohexane 0% to 10% to give methyl 4,4'-bis(benzyloxy)-2'-fluoro-5,5'-dimethyl-[1,1'-biphenyl]-2-carboxylate (870 mg, 1.85 mmol, 62.0 %) as a white solid. R_f 0.3 (EA/cyclohexane 5 %). ^1H NMR (400 MHz, CDCl_3) δ 7.60 – 7.32 (m, 11H), 7.15 (t, J = 0.9 Hz, 1H), 7.08 (dq, J = 8.6, 0.9 Hz, 1H), 6.68 (dd, J = 11.7, 1.2 Hz, 1H), 5.18 (s, 2H), 5.11 (s, 2H), 3.73 (d, J = 1.1 Hz, 3H), 2.36 (d, J = 0.8 Hz, 3H), 2.30 (d, J = 1.2 Hz, 3H).

Step 2: Synthesis of 1-(4,4'-bis(benzyloxy)-2'-fluoro-5,5'-dimethyl-[1,1'-biphenyl]-2-yl) cyclopropan-1-ol

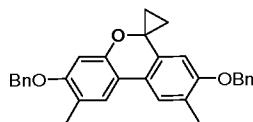


Under nitrogen atmosphere, Ethylmagnesium bromide solution/1M THF (1.70 g, 12.8 mL, 1 molar, 15 Eq, 12.8 mmol) was added dropwise over 5 minutes at 0°C to a solution of methyl 4,4'-bis(benzyloxy)-2'-fluoro-5,5'-dimethyl-[1,1'-biphenyl]-2-carboxylate (400 mg, 1 Eq, 850 μ mol) and Titanium tetraisopropoxide (747 mg, 0.78 mL, 97% Wt, 3 Eq, 2.55 mmol) in THF (61.3 mg,

10.6 mL, 0.08 molar, 1 Eq, 850 μmol). The reaction was then stirred at 0°C for 30min: TLC showed no more SM. The mixture was quenched with HCl 1 M. After filtration, the solution was extracted with 3x30 mL of EtOAc, washed with distilled water, and dried over MgSO_4 , followed by filtration and concentration. The organic residue was subjected to column chromatography biotage FC EtOAc/cyclohexane 0% to 20% to give 1-(4,4'-bis(benzyloxy)-2'-fluoro-5,5'-dimethyl-[1,1'-biphenyl]-2-yl)cyclopropan-1-ol (170 mg, 363 μmol , 42.7 %)

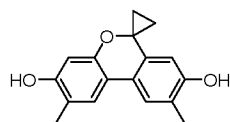
R_f 0.2 (EA/cyclohexane 10%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.52 – 7.33 (m, 10H), 7.16 (s, 1H), 7.06 (dd, $J = 8.9, 0.9$ Hz, 1H), 7.02 (d, $J = 0.9$ Hz, 1H), 6.72 (d, $J = 12.0$ Hz, 1H), 5.15 (s, 2H), 5.11 (s, 2H), 2.29 (d, $J = 0.7$ Hz, 3H), 2.26 (d, $J = 0.9$ Hz, 3H), 0.99 – 0.79 (m, 2H), 0.65 – 0.55 (m, 2H).

Step 3: Synthesis of 3,8-bis(benzyloxy)-2,9-dimethylspiro[benzo[c]chromene-6,1'-cyclopropane]



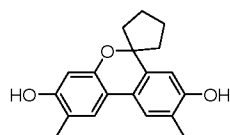
A solution of 1-(4,4'-bis(benzyloxy)-2'-fluoro-5,5'-dimethyl-[1,1'-biphenyl]-2-yl)cyclopropan-1-ol (170.00 mg, 1 Eq, 362.81 μmol) in DMF (4 mL) was heated at 110 °C. Sodium hydride (61mg, 1.53 mmol, 5 eq., 60% in oil) was added to was added in one portion and heating continued for 5 min. TLC showed no more SM. The reaction mixture was diluted with EtOAc and poured in a solution of ice and NaHCO_3 saturated solution. The aqueous phase was extracted with EtOAc twice and the combined organic phases were dried over sodium sulfate and evaporated under vacuum. The crude was purified by FC eluent EtOAc/cyclohexane 0% to 20% to give 3,8-bis(benzyloxy)-2,9-dimethylspiro[benzo[c]chromene-6,1'-cyclopropane] (50 mg, 0.11 mmol, 31 %) as colourless oil. R_f 0.4 (EA/cyclohexane 5%). ^1H NMR (400 MHz, DMSO) δ 7.64 – 7.57 (m, 1H), 7.57 – 7.53 (m, 1H), 7.51 – 7.43 (m, 4H), 7.40 (td, $J = 7.1, 1.0$ Hz, 4H), 7.35 – 7.30 (m, 2H), 6.64 (s, 1H), 6.54 (s, 1H), 5.13 (s, 2H), 5.09 (s, 2H), 2.23 (d, $J = 0.7$ Hz, 3H), 2.19 (d, $J = 0.7$ Hz, 3H), 1.24 – 1.16 (m, 2H), 1.11 (t, $J = 3.4$ Hz, 2H).

Step 4: synthesis 2,9-dimethylspiro[benzo[c]chromene-6,1'-cyclopropane]-3,8-diol (7)



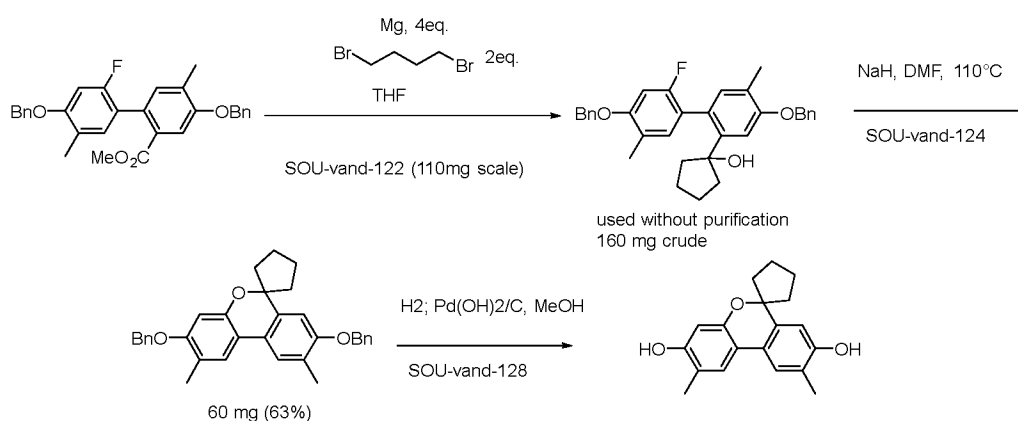
3,8-bis(benzyloxy)-2,9-dimethylspiro[benzo[c]chromene-6,1'-cyclopropane] (50.00 mg, 1.00 Eq, 111.5 μmol) was dissolved in MeOH (4 mL). Nickelous chloride hexahydrate (264.9 mg, 10 Eq, 1.115 mmol) was added. Sodium tetrahydroborate (84.34 mg, 78.89 μL , 20 Eq, 2.229 mmol) was carefully added portionwise (gas evolution). TLC showed no more starting material. The mixture was filtered off and the crude was loaded on silica gel and purified by FC eluent MeOH/DCM 0% to 4% to give 2,9-dimethylspiro[benzo[c]chromene-6,1'-cyclopropane]-3,8-diol (20 mg, 75 μmol , 67 %) as a white solid. R_f 0.4 (MeOH/DCM 4%). ^1H NMR (400 MHz, DMSO) δ 9.36 (s, 1H), 9.25 (s, 1H), 7.41 (s, 1H), 7.41 (s, 1H), 6.32 (s, 1H), 6.25 (s, 1H), 2.14 (s, 3H), 2.10 (s, 3H), 1.22 – 1.10 (m, 2H), 0.98 – 0.87 (m, 2H). MS: m/z : 269 $[\text{M}+\text{H}]^+$.

15. Synthesis of 2,9-dimethylspiro[benzo[c]chromene-6,1'-cyclopentane] (9)

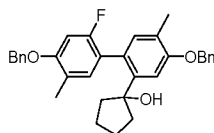


9 was prepared from intermediate methyl 4,4'-bis(benzyloxy)-2'-fluoro-5,5'-dimethyl-[1,1'-biphenyl]-2-carboxylate in 3 steps.

Scheme 14.

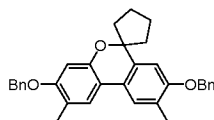


Step 1: Synthesis of 1-(4,4'-bis(benzyloxy)-2'-fluoro-5,5'-dimethyl-[1,1'-biphenyl]-2-yl) cyclopentan-1-ol



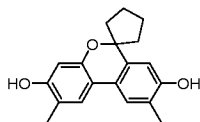
To a dry magnesium (39.7 mg, 4.8 Eq, 1.6322 mmol) in dry diethyl ether (25.20 mg, 6.8007 mL, 0.05 molar, 1 Eq, 340.03 μ mol) was added 1,4-dibromobutane (440.52 mg, 242.0 μ L, 6 Eq, 2.0402 mmol) at rt and the reaction mixture was stirred for 2h. to this turbid solution was added a solution of methyl 4,4'-bis(benzyloxy)-2'-fluoro-5,5'-dimethyl-[1,1'-biphenyl]-2-carboxylate (160.00 mg, 1 Eq, 340.03 μ mol) in dry THF 1ml and the reaction stirred for 5h. tlc showed still some sm (a polar product was formed, TLC MS showed M-18). The reaction was quenched with NH₄Cl saturated solution and extracted with EtOAc dried over sodium sulfate and evaporated under vacuum to give methyl 4,4'-bis(benzyloxy)-2'-fluoro-5,5'-dimethyl-[1,1'-biphenyl]-2-carboxylate (160.00 mg, 1 Eq, 340.03 μ mol) crude used to the next step without further purification. R_f = 0.2 (EA/cyclohexane 10%).

Step 2: Synthesis 3,8-bis(benzyloxy)-2,9-dimethylspiro[benzo[c]chromene-6,1'-cyclopentane]



In a round bottom flask, 1-(4,4'-bis(benzyloxy)-2'-fluoro-5,5'-dimethyl-[1,1'-biphenyl]-2-yl)cyclopentan-1-ol (100 mg, 1 Eq, 201 μ mol) was dissolved in dry DMF 3ml and heated at 120°C then NaH (40 mg, 60% Wt, 5 Eq, 1.01 mmol) was added portionwise and stirring continued at 120°C for 10min. The mixture was cooled down to room temperature, NaHCO₃ saturated solution was added and the aqueous phase was extracted with EA twice. The combined organic phases were dried over sodium sulfate and concentrated under vacuum. The crude was loaded on silica gel and purified by FC eluent EtOAc/Cy_h 0% to 10% to give 3,8-bis(benzyloxy)-2,9-dimethylspiro[benzo[c]chromene-6,1'-cyclopentane] (60 mg, 0.13 mmol, 63 %) as a white solid. R_f 0.6 (EA/cyclohexane 10%). MS (APCI+): m/z = 476. ¹H NMR (400 MHz, CDCl₃) δ 7.51 – 7.42 (m, 6H), 7.39 (td, J = 7.4, 1.7 Hz, 4H), 7.33 (td, J = 7.0, 1.8 Hz, 2H), 6.72 (s, 1H), 6.52 (s, 1H), 5.10 (s, 2H), 5.05 (s, 2H), 2.32 (d, J = 0.7 Hz, 3H), 2.27 (d, J = 0.9 Hz, 3H), 2.25 – 2.15 (m, 2H), 2.03 – 1.82 (m, 4H), 1.81 – 1.70 (m, 2H).

Step 3: Synthesis of 2,9-dimethylspiro[benzo[c]chromene-6,1'-cyclopentane]-3,8-diol (**9**)

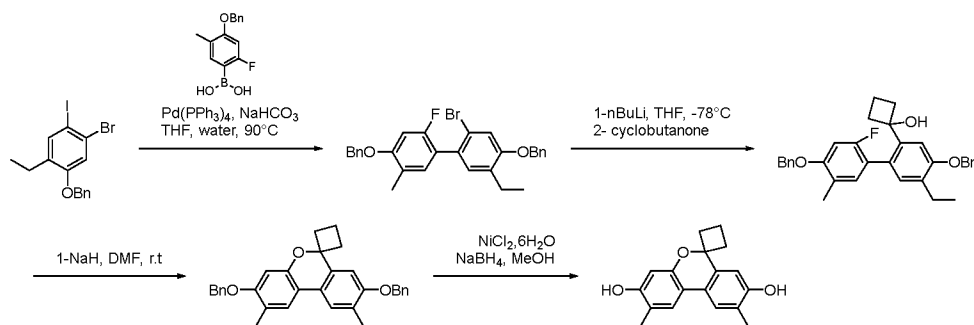


3,8-bis(benzyloxy)-2,9-dimethylspiro[benzo[c]chromene-6,1'-cyclopentane] (60 mg, 1 Eq, 0.13 mmol) was dissolved in methanol (4.0 mg, 2.5 mL, 0.05 molar, 1 Eq, 0.13 mmol) at room temperature. palladium hydroxide on carbon (18 mg, 20% Wt, 0.2 Eq, 25 μ mol) was added and the suspension was hydrogenated under atmospheric pressure over 4 h. The suspension was filtered over a pad of celite and the solvent was concentrated under vacuum. The crude was loaded on silica gel and purified by FC eluent MeOH/DCM 0% to 10% to give 3,8-bis(benzyloxy)-2,9-dimethylspiro[benzo[c]chromene-6,1'-cyclopentane] (60 mg, 0.13 mmol, 63 %) as a white solid. R_f 0.4 (MeOH/DCM 10%). MS: m/z : 297 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 9.27 (s, 1H), 9.25 (s, 1H), 7.37 (d, J = 2.0 Hz, 2H), 6.66 (s, 1H), 6.28 (s, 1H), 2.14 (d, J = 0.7 Hz, 3H), 2.09 (s, 3H), 2.05 – 2.00 (m, 2H), 1.91 – 1.67 (m, 6H).

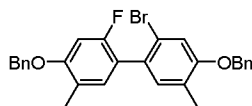
16. Synthesis of 9-ethyl-2-methylspiro[benzo[c]chromene-6,1'-cyclobutane]-3,8-diol (11)

11 was prepared from 1-(benzyloxy)-5-bromo-2-ethyl-4-iodobenzene and (4-(benzyloxy)-2-fluoro-5-methylphenyl)boronic acid (see patent 1amazentis) in 4 steps.

Scheme 15.

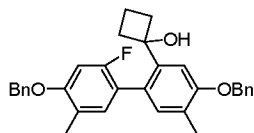


Step 1: Synthesis of 4,4'-bis(benzyloxy)-2-bromo-5-ethyl-2'-fluoro-5'-methyl-1,1'-biphenyl



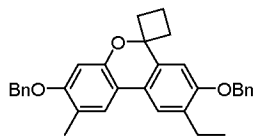
1-(benzyloxy)-5-bromo-4-iodo-2-methylbenzene (370mg, 0.918mmol) and (4-(benzyloxy)-2-fluoro-5-methylphenyl)boronic acid (334mg, 1.29mmol, 1.4eq.) were dissolved in dioxane (10 mL). Tetrakis(triphenylphosphine)palladium(o) (85mg, 0.073mmol, 0.08 eq.) was added and the solution was degassed for 5 min. then sodium bicarbonate saturated solution (1.8ml, 1.84mmol, 2eq.) was added dropwise and the mixture was heated at 90°C overnight. Water was added and the mixture was extracted with EtOAc twice. The combined organic phases were dried over sodium sulfate and concentrated under vacuum. The crude was purified by FC biotage EA/CyH 0% to 5% to give 4,4'-bis(benzyloxy)-2-bromo-2'-fluoro-5,5'-dimethyl-1,1'-biphenyl (340mg, 0.692mmol, 75%) as colorless oil. R_f 0.3 (EA/cyclohexane 10%). ^1H NMR (400 MHz, CDCl_3) δ 7.50 – 7.31 (m, 10H), 7.19 (s, 1H), 7.12 – 7.06 (m, 1H), 7.06 – 7.02 (m, 1H), 6.70 (d, J = 11.4 Hz, 1H), 5.09 (s, 4H), 2.95 – 2.54 (m, 2H), 1.21 (t, J = 7.5 Hz, 3H).

Step 2: Synthesis of 4,4'-bis(benzyloxy)-2-bromo-5,5'-diethyl-2'-fluoro-1,1'-biphenyl



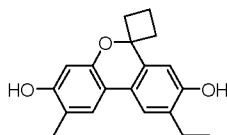
nBuLi (53.28 mg, 519.78 μL , 1.6 molar, 1.8 Eq, 831.65 μmol) was added to a solution of 4,4'-bis(benzyloxy)-2-bromo-5,5'-diethyl-2'-fluoro-1,1'-biphenyl (240.00 mg, 1 Eq, 462.03 μmol) in THF (7ml) at -78°C. The mixture was stirred for 30 min at -78°C then 1-Oxocyclobutane (161.9 mg, 173 μL , 5 Eq, 2.3101 mmol) was added dropwise and the mixture was allowed to warm to rt. over 6h. NH_4Cl saturated solution was added and the mixture was extracted with EtOAc twice. The combined organic phases were dried over sodium sulfate and concentrated under vacuum. The crude was purified by FC eluent EtOAc/cyclohexane 0% to 20% to give 1-(4,4'-bis(benzyloxy)-5,5'-diethyl-2'-fluoro-[1,1'-biphenyl]-2-yl)cyclobutan-1-ol (80 mg, 0.16 mmol, 34 %). The next step where the desired product could eventually be isolated. R_f 0.3 (EA/cyclohexane 20%) ^1H NMR (400 MHz, CDCl_3) δ 7.58 – 7.28 (m, 10H), 7.08 (d, J = 8.9 Hz, 1H), 6.97 (s, 1H), 6.89 (s, 1H), 6.68 (d, J = 11.7 Hz, 1H), 5.13 (s, 2H), 5.08 (d, J = 2.1 Hz, 2H), 2.70 (dq, J = 9.9, 7.5 Hz, 4H), 2.26 (m, 2H), 2.06 (m, 3H), 1.85 – 1.71 (m, 1H), 1.22 (td, J = 7.5, 5.6 Hz, 5H).

Step 3: Synthesis of 3,8-bis(benzyloxy)-9-ethyl-2-methylspiro[benzo[c]chromene-6,1'-cyclobutane]



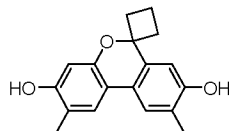
Sodium hydride (46 mg, 60% Wt, 5 Eq, 1.16 mmol) was added to a solution of 1-(4,4'-bis(benzyloxy)-5-ethyl-2'-fluoro-5'-methyl-[1,1'-biphenyl]-2-yl) cyclobutan-1-ol (115 mg, 1 Eq, 232 μ mol) in DMF (3 mL) at 120°C and stirring continued for 15min at 120°C. The mixture was cooled down to room temperature, NH₄Cl saturated solution was added and the aqueous phase was extracted with EtOAc twice. The combined organic phases were dried over sodium sulfate and evaporated under vacuum. The crude was purified by FC eluent EtOAc/cyclohexane 0% to 10% to give 3,8-bis(benzyloxy)-9-ethyl-2-methylspiro[benzo[c]chromene-6,1'-cyclobutane] (90 mg, 0.19 mmol, 82 %) as colorless oil. *R_f* 0.5(EA/cyclohexane 10%). ¹H NMR (400 MHz, CDCl₃) δ 7.53 – 7.27 (m, 12H), 6.94 (s, 1H), 6.60 (s, 1H), 5.17 (s, 2H), 5.08 (s, 2H), 2.76 (q, *J* = 7.5 Hz, 2H), 2.53 (ddd, *J* = 13.0, 10.0, 8.5 Hz, 2H), 2.36 (ddd, *J* = 13.1, 8.8, 4.2 Hz, 1H), 2.28 (s, 3H), 2.01 (dt, *J* = 15.6, 5.2 Hz, 1H), 1.74 (dt, *J* = 11.3, 8.7 Hz, 1H), 1.28 (t, *J* = 7.5 Hz, 3H).

Step 4: Synthesis of 9-ethyl-2-methylspiro[benzo[c]chromene-6,1'-cyclobutane]-3,8-diol (**10**)



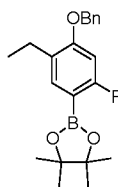
3,8-bis(benzyloxy)-9-ethyl-2-methylspiro[benzo[c]chromene-6,1'-cyclobutane] (80.00 mg, 1.00 Eq, 167.8 μ mol) was dissolved in MeOH (4 mL). Nickelous chloride hexahydrate (199.5 mg, 5 Eq, 839.2 μ mol) was added. SodiumTetrahydroborate (63.50 mg, 59.40 μ L, 10 Eq, 1.678 mmol) were added portionwise (gas evolution) until consumption of all starting material. TLC showed no more starting material. The mixture was filtered off and the crude was loaded on silica gel and purified by FC eluent MeOH/DCM 0% to 4% to give 9-ethyl-2-methylspiro[benzo[c]chromene-6,1'-cyclobutane]-3,8-diol (40 mg, 0.13 mmol, 80 %) as a white solid. *R_f* 0.4 (MeOH/DCM 4%). ¹H NMR (400 MHz, DMSO) δ 9.35 (s, 1H), 9.32 (s, 1H), 7.40 (s, 1H), 7.37 (s, 1H), 6.87 (s, 1H), 6.38 (s, 1H), 2.58 (t, *J* = 7.5 Hz, 2H), 2.39 (ddd, *J* = 12.7, 10.0, 8.6 Hz, 2H), 2.23 (ddd, *J* = 12.7, 8.7, 4.0 Hz, 2H), 2.09 (s, 3H), 1.95 (ddd, *J* = 20.6, 9.7, 4.4 Hz, 1H), 1.74 (dt, *J* = 11.0, 8.6 Hz, 1H), 1.16 (t, *J* = 7.5 Hz, 3H). MS: *m/z*: 297 [M+H]⁺.

17. Synthesis of 2-ethyl-9-methylspiro[benzo[c]chromene-6,1'-cyclobutane]-3,8-diol (**11**)

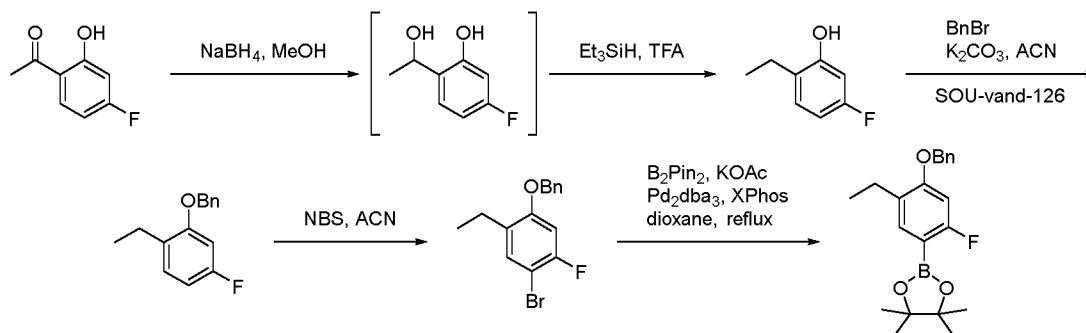


11 was prepared from 1-(benzyloxy)-5-bromo-4-iodo-2-methylbenzene and 2-(4-(benzyloxy)-5-ethyl-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in 4 steps.

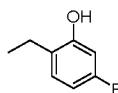
Synthesis of 2-(4-(benzyloxy)-5-ethyl-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Scheme 16.



Step 1: Synthesis of 2-ethyl-5-fluorophenol

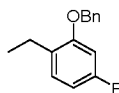


Step a - NaBH₄ (245 mg, 1 Eq, 6.49 mmol) was added portion wise to a stirred solution of 1-(4-fluoro-2-hydroxyphenyl)ethan-1-one (1.00 g, 1 Eq, 6.49 mmol) in methanol (24 g, 30 mL, 1.1e+2 Eq, 0.74 mol) at 0 °C over 30 minutes. The reaction mixture was stirred at room temperature for 15 hours. Then the reaction mixture was quenched with NH₄Cl. The residue was diluted with ethyl acetate. The organic extracts were washed with water, brine, dried over anhydrous sodium sulphate

and evaporated to afford crude 5-fluoro-2-(1-hydroxyethyl)phenol was taken for next step without any purification.

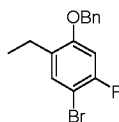
Step b - TFA (7.40 g, 5.00 mL, 10 Eq, 64.9 mmol) was added dropwise to a solution of 5-fluoro-2-(1-hydroxyethyl)phenol(intermediate) (4 g, 11.98 mmol), triethylsilane (1.51 g, 2.07 mL, 2 Eq, 13.0 mmol) in 15 mL of dichloromethane at 0 °C. The reaction mixture was stirred at room temperature for 15 hour. Then the reaction mixture was evaporated under vacuum and the crude was extracted with Na₂CO₃ sat sol and EtOAc twice. The organic solvent was dried over sodium sulfate and evaporated under vacuum. The crude was purified by FC eluent EtOAc/cyclohexane 0% to 7% to give 5-bromo-2-ethylphenol (2.2g, 11mmol, 55%) as yellowish oil which crystallizes at r.t. ¹H NMR (400 MHz, CDCl₃) δ 7.11 – 6.99 (m, 1H), 6.59 (td, *J* = 8.4, 2.5 Hz, 1H), 6.52 (dd, *J* = 9.9, 2.5 Hz, 1H), 4.09 (s, 1H), 2.59 (q, *J* = 7.5 Hz, 2H), 1.22 (t, *J* = 7.5 Hz, 3H).

Step 2: Synthesis of 2-(benzyloxy)-1-ethyl-4-fluorobenzene



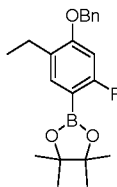
In a 50 mL round bottom flask, 2-ethyl-5-fluorophenol (2000 mg, 14.27 mmol) was dissolved in dry acetonitrile (585.8 mg, 71.35 mL, 0.200 molar, 1 Eq, 14.27 mmol) at room temperature. potassium carbonate (3.944 g, 2.00 Eq, 28.54 mmol) was added then benzyl bromide (2.197 g, 1.528 mL, 0.9 Eq, 12.84 mmol) was added dropwise at room temperature. The suspension was stirred overnight at room temperature. Water was added and the aqueous phase was extracted with EA twice, washed with water and dried over sodium sulfate. The solvent was concentrated under vacuum to give 2-(benzyloxy)-1-ethyl-4-fluorobenzene (3.5 g, 15 mmol, 110 %) as yellowish oil. ¹H NMR (400 MHz, CDCl₃) δ 7.47 – 7.30 (m, 7H), 7.10 (dd, *J* = 8.2, 6.9 Hz, 1H), 6.71 – 6.56 (m, 2H), 5.06 (s, 2H), 2.71 – 2.60 (m, 2H), 1.20 (t, *J* = 7.5 Hz, 3H).

Step 3: Synthesis of 1-(benzyloxy)-4-bromo-2-ethyl-5-fluorobenzene



NBS (1.333 g, 1.15 Eq, 7.491 mmol) was added to a solution of 2-(benzyloxy)-1-ethyl-4-fluorobenzene (1.500 g, 1.00 Eq, 6.514 mmol) in MeCN (267.4 mg, 21.71 mL, 0.300 molar, 1 Eq, 6.514 mmol) at r.t. and the reaction mixture was stirred o.n. NaOH 1M 30ml was added at room temperature and the aqueous phase was extracted with EA twice. The combined organic phases were washed successively with water and brine and dried over sodium sulfate then concentrated under vacuum to give 1-(benzyloxy)-4-bromo-2-ethyl-5-fluorobenzene (1.70 g, 5.50 mmol, 84.4 %) as yellowish oil. ¹H NMR (400 MHz, CDCl₃) δ 7.45 – 7.39 (m, 5H), 7.32 – 7.27 (m, 1H), 6.70 (d, *J* = 10.4 Hz, 1H), 5.04 (s, 2H), 2.75 – 2.59 (m, 2H), 1.20 (t, *J* = 7.5 Hz, 3H).

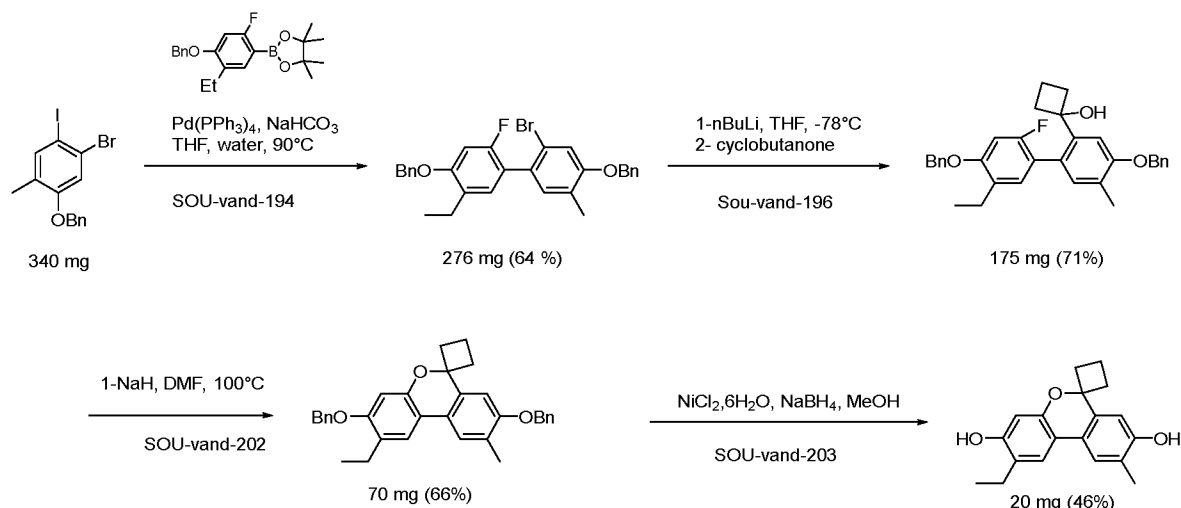
Step 4: Synthesis of 2-(4-(benzyloxy)-5-ethyl-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



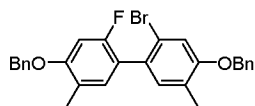
1-(benzyloxy)-4-bromo-2-ethyl-5-fluorobenzene (1.70 g, 1 Eq, 5.50 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.51 g, 1.8 Eq, 9.90 mmol), potassium acetate (2.16 g, 4 Eq, 22.0 mmol) were added followed by dioxane 60ml. The mixture was stirred at 100 °C for 12 hours under N₂. After cooling to 30 °C, the reaction mixture was filtered through Celite. The filtrate was concentrated under reduced pressure. Water (300 mL) was added and the aqueous layer was extracted with EtOAc (300 mL x 3). The combined organic layer was washed with brine (300 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to give the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc in petroleum ether = 0-10%) to give the 2-(4-(benzyloxy)-5-ethyl-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.1 g, 3.1 mmol, 56 %) as yellowish oil. ¹H NMR (400 MHz, CDCl₃) δ 7.49 (d, *J* = 7.1 Hz, 1H), 7.43 – 7.32 (m, 5H), 6.59 (d, *J* = 11.2 Hz, 1H), 5.08 (s, 2H), 2.65 (q, *J* = 7.5 Hz, 2H), 1.35 (s, 12H), 1.20 (t, *J* = 7.5 Hz, 3H).

18. Synthesis of 2-ethyl-9-methylspiro[benzo[*c*]chromene-6,1'-cyclobutane]-3,8-diol (11)

Scheme 17.

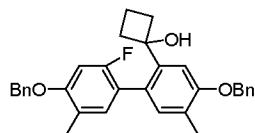


Step 1: Synthesis of 4,4'-bis(benzyloxy)-2-bromo-5'-ethyl-2'-fluoro-5-methyl-1,1'-biphenyl



1-(benzyloxy)-5-bromo-4-iodo-2-methylbenzene (340 mg, 1 Eq, 844 μmol) and 2-(4-(benzyloxy)-5-ethyl-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (421 mg, 1.4 Eq, 1.18 mmol) were dissolved in dioxane (10 mL). Bis-(triphenylphosphino)-palladous chloride (59.2 mg, 0.1 Eq, 84.4 μmol) was added and the solution was degassed for 5 min. then sodium bicarbonate (213 mg, 2.53 mL, 1 molar, 3 Eq, 2.53 mmol) was added dropwise and the mixture was heated at 90°C overnight. Water was added and the mixture was extracted with EtOAc twice. The combined organic phases were dried over sodium sulfate and concentrated under vacuum. The crude was purified by FC biotage EtOAc/cyclohexane 0% to 1% to 2% to 3% to 4% 5% to give 4,4'-bis(benzyloxy)-2-bromo-5'-ethyl-2'-fluoro-5-methyl-1,1'-biphenyl (276 mg, 546 μmol , 64.7 %) as colorless oil. R_f 0.3 (EA/cyclohexane 2%). ^1H NMR (400 MHz, CDCl_3) δ 7.54 – 7.39 (m, 10H), 7.18 (s, 1H), 7.11 (t, $J = 0.8$ Hz, 1H), 7.05 (d, $J = 8.6$ Hz, 1H), 6.71 (d, $J = 11.5$ Hz, 1H), 5.09 (s, 4H), 2.70 (qd, $J = 7.5, 2.1$ Hz, 2H), 2.25 (d, $J = 0.8$ Hz, 3H), 1.27 – 1.18 (m, 3H).

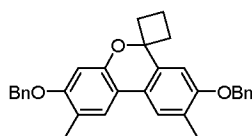
Step 2: Synthesis of 4,4'-bis(benzyloxy)-2-bromo-5'-ethyl-2'-fluoro-5-methyl-1,1'-biphenyl



nBuLi (94.3 mg, 920 μ L, 1.6 molar, 3 Eq, 1.47 mmol) was added to a solution of 4,4'-bis(benzyloxy)-2-bromo-5'-ethyl-2'-fluoro-5-methyl-1,1'-biphenyl (248 mg, 1 Eq, 491 μ mol) in THF (7ml) at -78°C . The mixture was stirred for 30 min at -78°C then 1-Oxocyclobutane (344 mg, 367 μ L, 10 Eq, 4.91 mmol) was added dropwise and the mixture was allowed to warm to rt. over 6h. NH_4Cl saturated solution was added and the mixture was extracted with EtOAc twice. The combined organic phases were dried over sodium sulfate and concentrated under vacuum. The crude was purified by FC eluent EtOAc/cyclohexane 0% to 20% to give 1-(4,4'-bis(benzyloxy)-5'-ethyl-2'-fluoro-5-methyl-[1,1'-biphenyl]-2-yl)cyclobutan-1-ol (175 mg, 352 μ mol, 71.8 %).

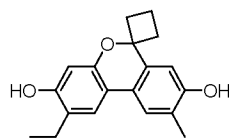
R_f 0.3 EtOAc/cyclohexane 20%. ^1H NMR (400 MHz, CDCl_3) δ 7.58 – 7.31 (m, 10H), 7.06 (d, J = 8.9 Hz, 1H), 6.96 (d, J = 0.9 Hz, 1H), 6.88 (s, 1H), 6.67 (d, J = 11.7 Hz, 1H), 5.13 (s, 2H), 5.10 – 4.97 (m, 2H), 2.68 (q, J = 7.5 Hz, 2H), 2.28 (d, J = 0.7 Hz, 3H), 2.04 – 1.92 (m, 2H), 1.60 (d, J = 3.6 Hz, 1H), 1.39 – 1.32 (m, 1H), 1.21 (t, J = 7.5 Hz, 3H). ^{19}F NMR (400 MHz, CDCl_3) δ -115.97.

Step 3: Synthesis of 3,8-bis(benzyloxy)-2-ethyl-9-methylspiro[benzo[c]chromene-6,1'-cyclobutane]



Sodium hydride (0.18 g, 60% Wt, 20 Eq, 4.43 mmol) was added to a solution of 1-(4,4'-bis(benzyloxy)-5'-ethyl-2'-fluoro-5-methyl-[1,1'-biphenyl]-2-yl)cyclobutan-1-ol (110 mg, 1 Eq, 221 μ mol) in DMF (3 mL) at 120°C and stirring continued for 15 min at 120°C . The mixture was cooled down to room temperature, NH_4Cl saturated solution was added and the aqueous phase was extracted with EtOAc twice. The combined organic phases were dried over sodium sulfate and evaporated under vacuum. The crude was purified by FC eluent EtOAc/cyclohexane 0% to 10% to give 3,8-bis(benzyloxy)-2-ethyl-9-methylspiro[benzo[c]chromene-6,1'-cyclobutane] (70 mg, 0.15 mmol, 66 %) as a white solid. R_f 0.5. (EA/cyclohexane 10%). ^1H NMR (400 MHz, CDCl_3) δ 7.56 – 7.27 (m, 12H), 6.93 (s, 1H), 6.60 (s, 1H), 5.17 (s, 2H), 5.07 (s, 2H), 2.70 (q, J = 7.5 Hz, 2H), 2.60 – 2.45 (m, 2H), 2.39 – 2.35 (m, 2H), 2.35 (d, J = 0.7 Hz, 3H), 2.09 – 1.90 (m, 1H), 1.74 (dp, J = 11.4, 8.7 Hz, 1H), 1.26 (t, J = 7.5 Hz, 3H).

Step 4: Synthesis of 2-ethyl-9-methylspiro[benzo[c]chromene-6,1'-cyclobutane]-3,8-diol (**11**)

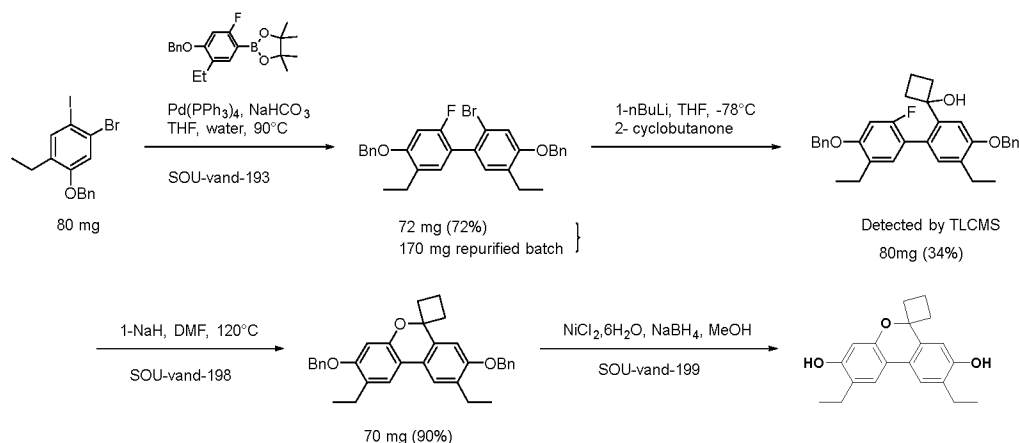


3,8-bis(benzyloxy)-2-ethyl-9-methylspiro[benzo[c]chromene-6,1'-cyclobutane] (70.00 mg, 1.00 Eq, 146.9 μ mol) was dissolved in MeOH (4 mL). Nickelous chloride hexahydrate (174.5 mg, 5 Eq, 734.3 μ mol) was added. SodiumTetrahydroborate (55.56 mg, 51.97 μ L, 10 Eq, 1.469 mmol) were added portionwise (gaz evolution). TLC showed no more starting material. The mixture was filtered off and the crude was loaded on silica gel and purified by FC eluent MeOH/DCM 0% to 4% to give 2-ethyl-9-methylspiro[benzo[c]chromene-6,1'-cyclobutane]-3,8-diol (20 mg, 67 μ mol, 46 %) as a white solid. R_f 0.4 MeOH/DCM 4%. ^1H NMR (400 MHz, DMSO) δ 9.33 (s, 2H), 7.41 (s, 1H), 7.37 (s, 1H), 6.87 (s, 1H), 6.38 (s, 1H), 2.39 (q, J = 10.0 Hz, 2H), 2.27 – 2.19 (m, 2H), 2.19 – 2.12 (m, 3H), 2.02 – 1.90 (m, 1H), 1.83 – 1.67 (m, 1H), 1.14 (t, J = 7.5 Hz, 3H). MS: m/z : 297 [M+H].

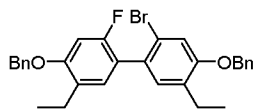
19. Synthesis of 2,9-diethylspiro[benzo[c]chromene-6,1'-cyclobutane]-3,8-diol (13)

13 was prepared from 1-(benzyloxy)-5-bromo-2-ethyl-4-iodobenzene and 2-(4-(benzyloxy)-5-ethyl-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in 4 steps.

Scheme 18.

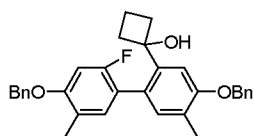


Step 1: Synthesis of 4,4'-bis(benzyloxy)-2-bromo-5,5'-diethyl-2'-fluoro-1,1'-biphenyl



1-(benzyloxy)-5-bromo-2-ethyl-4-iodobenzene (380 mg, 1 Eq, 911 μmol) and 2-(4-(benzyloxy)-5-ethyl-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (454 mg, 1.4 Eq, 1.28 mmol) were dissolved in dioxane (10 mL). Bis-(triphenylphosphino)-palladous chloride (63.9 mg, 0.1 Eq, 91.1 μmol) was added and the solution was degassed for 5 min. then sodium bicarbonate (230 mg, 2.73 mL, 1 molar, 3 Eq, 2.73 mmol) was added dropwise and the mixture was heated at 90°C overnight. Water was added and the mixture was extracted with EtOAc twice. The combined organic phases were dried over sodium sulfate and concentrated under vacuum. The crude was purified by FC biotage EtOAc/cyclohexane 0% to 1% to 2% to 5% to give 4,4'-bis(benzyloxy)-2-bromo-5,5'-diethyl-2'-fluoro-1,1'-biphenyl (375 mg, 722 μmol , 79.2 %) as colorless oil. R_f 0.3 (EA/cyclohexane 2%). ^1H NMR (400 MHz, CDCl_3) δ 7.57 – 7.31 (m, 10H), 7.19 (s, 1H), 7.11 (d, $J = 0.7$ Hz, 1H), 7.06 (d, $J = 8.7$ Hz, 1H), 6.71 (d, $J = 11.5$ Hz, 1H), 5.09 (s, 4H), 2.74 – 2.63 (m, 4H), 1.31 – 1.18 (m, 6H).

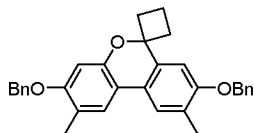
Step 2: Synthesis of 1-(4,4'-bis(benzyloxy)-5,5'-diethyl-2'-fluoro-[1,1'-biphenyl]-2-yl)cyclobutan-1-ol



nBuLi (53.28 mg, 519.78 μL , 1.6 molar, 1.8 Eq, 831.65 μmol) was added to a solution of 4,4'-bis(benzyloxy)-2-bromo-5,5'-diethyl-2'-fluoro-1,1'-biphenyl (240.00 mg, 1 Eq, 462.03 μmol) in THF (7ml) at -78°C. The mixture was stirred for 30 min at -78°C then 1-Oxocyclobutane (161.9 mg, 173 μL , 5 Eq, 2.3101 mmol) was added dropwise and the mixture was allowed to warm to rt. over 6h. NH_4Cl saturated solution was added and the mixture was extracted with EtOAc twice. The combined organic phases were dried over sodium sulfate and concentrated under vacuum. The crude was purified by FC eluent EtOAc/cyclohexane 0% to 20% to give 1-(4,4'-bis(benzyloxy)-5,5'-diethyl-2'-fluoro-[1,1'-biphenyl]-2-yl)cyclobutan-1-ol (80 mg, 0.16 mmol, 34 %). As a yellowish oil. R_f 0.3 (EA/cyclohexane 20%). ^1H NMR (400 MHz, CDCl_3) δ 7.58 – 7.28 (m, 10H),

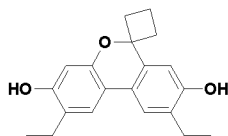
7.08 (d, $J = 8.9$ Hz, 1H), 6.97 (s, 1H), 6.89 (s, 1H), 6.68 (d, $J = 11.7$ Hz, 1H), 5.13 (s, 2H), 5.08 (d, $J = 2.1$ Hz, 2H), 2.70 (dq, $J = 9.9, 7.5$ Hz, 4H), 2.26 (m, 2H), 2.06 (m, 3H), 1.85 – 1.71 (m, 1H), 1.22 (td, $J = 7.5, 5.6$ Hz, 5H).

Step 3: Synthesis of 3,8-bis(benzyloxy)-2,9-diethylspiro[benzo[c]chromene-6,1'-cyclobutane]



Sodium hydride (0.13 g, 60% Wt, 20 Eq, 3.1 mmol) was added to a solution of 1-(4,4'-bis(benzyloxy)-5,5'-diethyl-2'-fluoro-[1,1'-biphenyl]-2-yl)cyclobutan-1-ol (80 mg, 1 Eq, 0.16 mmol) in DMF (3 mL) at 120°C and stirring continued for 15 min at 120°C. The mixture was cooled down to room temperature, NH₄Cl saturated solution was added and the aqueous phase was extracted with EtOAc twice. The combined organic phases were dried over sodium sulfate and evaporated under vacuum. The crude was purified by FC eluent EtOAc/cyclohexane 0% to 10% to give 3,8-bis(benzyloxy)-2,9-diethylspiro[benzo[c]chromene-6,1'-cyclobutane] (70 mg, 0.14 mmol, 91 %) as a white solid. R_f 0.5(EA/cyclohexane 10%). ¹H NMR (400 MHz, CDCl₃) δ 7.53 – 7.30 (m, 12H), 6.94 (s, 1H), 6.60 (s, 1H), 5.18 (s, 2H), 5.08 (s, 2H), 2.76 (q, $J = 7.6$ Hz, 2H), 2.70 (q, $J = 7.6$ Hz, 2H), 2.60 – 2.48 (m, 2H), 2.37 (dddd, $J = 13.1, 8.8, 4.2, 2.4$ Hz, 2H), 2.05 – 1.94 (m, 1H), 1.75 (dt, $J = 11.4, 8.7$ Hz, 1H), 1.36 – 1.16 (m, 6H).

Step 4: Synthesis of 2,9-diethylspiro[benzo[c]chromene-6,1'-cyclobutane]-3,8-diol (**13**)



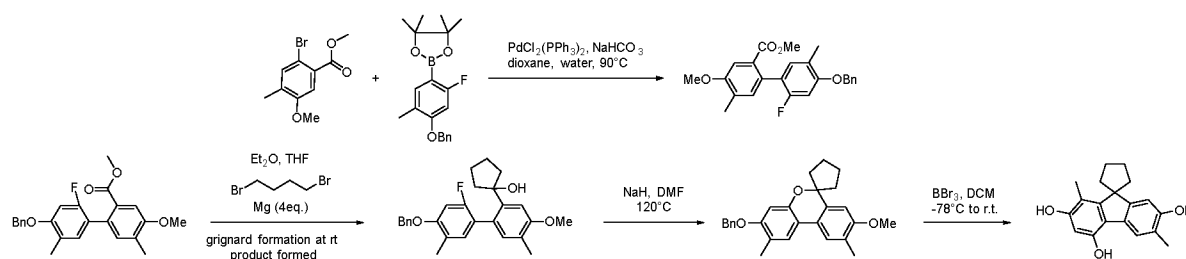
3,8-bis(benzyloxy)-2,9-diethylspiro[benzo[c]chromene-6,1'-cyclobutane] (70.00 mg, 1.00 Eq, 142.7 μ mol) was dissolved in MeOH (4 mL). Nickelous chloride hexahydrate (169.5 mg, 5 Eq, 713.4 μ mol) was added. Sodium Tetrahydroborate (53.97 mg, 50.49 μ L, 10 Eq, 1.427 mmol) were added portion wise (gas evolution). TLC showed no more starting material. The mixture was filtered off and the crude was loaded on silica gel and purified by FC eluent MeOH/DCM 0% to 4% to give 2,9-diethylspiro[benzo[c]chromene-6,1'-cyclobutane]-3,8-diol (29 mg, 93 μ mol, 65 %) as a white solid. R_f 0.4 (MeOH/DCM 4%). ¹H NMR (400 MHz, DMSO) δ 9.33 (s, 2H), 7.39 (d, J

= 1.7 Hz, 2H), 6.87 (s, 1H), 6.38 (s, 1H), 2.62 – 2.51 (m, 4H), 2.45 – 2.35 (m, 2H), 2.28 – 2.18 (m, 2H), 1.95 (ddt, $J = 15.3, 9.9, 4.7$ Hz, 1H), 1.74 (dt, $J = 11.0, 8.6$ Hz, 1H), 1.15 (q, $J = 7.4$ Hz, 6H). MS: m/z : 311 $[M+H]^+$.

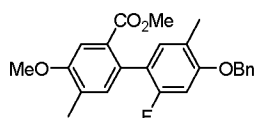
20. Synthesis of 1',6'-dimethylspiro[cyclopentane-1,9'-fluorene]-2',4',7'-triol (16)

16 was prepared from methyl 2-bromo-5-methoxy-4-methylbenzoate and 2-(4-(benzyloxy)-2-fluoro-5-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in 4 steps.

Scheme 19.



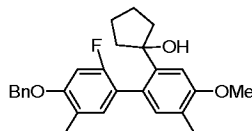
Step 1: synthesis of methyl 4'-(benzyloxy)-2'-fluoro-4-methoxy-5,5'-dimethyl-[1,1'-biphenyl]-2-carboxylate



Methyl 2-bromo-5-methoxy-4-methylbenzoate (370 mg, 1 Eq, 1.43 mmol), 2-(4-(benzyloxy)-2-fluoro-5-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (635 mg, 1.3 Eq, 1.86 mmol) and Bis-(triphenylphosphino)-palladous chloride (100 mg, 0.1 Eq, 143 μ mol) were suspended in THF (103 mg, 14.3 mL, 0.1 molar, 1 Eq, 1.43 mmol) and degassed with Nitrogen for 5 minutes. A solution of sodium bicarbonate (264 mg, 2.2 Eq, 3.14 mmol) in water (25.7 mg, 4.76 mL, 0.3 molar, 1 Eq, 1.43 mmol) was added at r.t. and the mixture was refluxed o.n. After cooling to room temperature, NH_4Cl saturated solution was added and the aqueous phase was extracted with EA twice. The combined organic phases were dried over sodium sulfate, concentrated under vacuum and the organic residue was subjected to column chromatography biotage FC

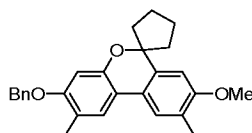
EA/cyclohexane 0% to 10% to give methyl 4'-(benzyloxy)-2'-fluoro-4-methoxy-5,5'-dimethyl-[1,1'-biphenyl]-2-carboxylate (480 mg, 1.22 mmol, 85.2 %) as colourless oil. R_f 0.3 (EA/cyclohexane 10%). MS (APCI+): m/z = 395.

Step 2: synthesis of 1-(4'-(benzyloxy)-4-methoxy-3',5-dimethyl-[1,1'-biphenyl]-2-yl)cyclopentan-1-ol



To a dry magnesium (22.18 mg, 3 Eq, 912.69 μ mol) in dry diethyl ether (1.127 g, 1.58 mL, 50 Eq, 15.211 mmol) was added 1,4-dibromobutane (394.13 mg, 216.6 μ L, 6 Eq, 1.8254 mmol) at rt and the reaction mixture was stirred for 2h. to this turbid solution was added a solution of methyl 4'-(benzyloxy)-2'-fluoro-4-methoxy-5,5'-dimethyl-[1,1'-biphenyl]-2-carboxylate (120.00 mg, 1 Eq, 304.23 μ mol) in dry THF 1ml and the reaction stirred for 5h. tlc showed still some sm (a polar product was formed, TLC MS showed M-18). The reaction was quenched with NH_4Cl and extracted with EtOAc. The combined organic phases were dried over sodium sulfate and evaporated under vacuum to give 1-(4'-(benzyloxy)-4-methoxy-3',5-dimethyl-[1,1'-biphenyl]-2-yl)cyclopentan-1-ol (120 mg, 298 μ mol, 98.0 %) crude used to the next step without further purification.

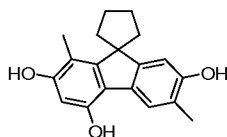
Step 3: Synthesis of 3-(benzyloxy)-8-methoxy-2,9-dimethylspiro[benzo[c]chromene-6,1'-cyclopentane]



1-(4'-(benzyloxy)-2'-fluoro-4-methoxy-5,5'-dimethyl-[1,1'-biphenyl]-2-yl)cyclopentan-1-ol (120 mg, 1 Eq, 285 μ mol) was dissolved in DMF (3 mL) and heated at 120°C. NaH (57 mg, 60% Wt, 5 Eq, 1.43 mmol) was added portion wise at 120°C and stirring continued for 15 min at 120°C. The mixture was cooled down to room temperature, NH_4Cl saturated solution was added and the

aqueous phase was extracted with EtOAc twice. The combined organic phases were dried over sodium sulfate and evaporated under vacuum. The crude was purified by FC eluent EtOAc/cyclohexane 0% to 10% to give 3-(benzyloxy)-8-methoxy-2,9-dimethylspiro[benzo[c]chromene-6,1'-cyclopentane] (40 mg, 0.10 mmol, 35 %) as a white solid. R_f 0.5. (EA/cyclohexane 10%). MS (APCI+): m/z = 401. ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.28 (m, 7H), 6.67 (s, 1H), 6.52 (s, 1H), 5.06 (s, 2H), 3.86 (d, J = 1.4 Hz, 3H), 2.26 (s, 6H), 2.22 (m, 2H), 2.03 – 1.88 (m, 4H), 1.82 (d, J = 7.6 Hz, 2H).

Step 4: Synthesis of 1',6'-dimethylspiro[cyclopentane-1,9'-fluorene]-2',4',7'-triol (**16**)



BBr_3 (65.68 mg, 262.2 μ L, 1 molar, 3 Eq, 262.2 μ mol) was added to a suspension of 3-(benzyloxy)-8-methoxy-2,9-dimethylspiro[benzo[c]chromene-6,1'-cyclopentane] (35.00 mg, 1 Eq, 87.39 μ mol) in DCM (4.305 g, 3.261 mL, 580 Eq, 50.68 mmol) at $-78^\circ C$ over 2 min and the mixture was allowed to warm to r.t. o.n. The reaction mixture was quenched with $NaHCO_3$ saturated solution, and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over sodium sulfate and the organic residue was subjected to column chromatography biotage FC MeOH/DCM 0% to 20% to give 1',6'-dimethylspiro[cyclopentane-1,9'-fluorene]-2',4',7'-triol (15 mg, 51 μ mol, 58 %) as a white solid. R_f 0.5 MeOH/DCM 10 %. ^1H NMR (400 MHz, DMSO) δ 9.22 (s, 1H), 8.98 (s, 1H), 8.88 (s, 1H), 7.47 (s, 1H), 6.80 (s, 1H), 6.33 (d, J = 1.8 Hz, 1H), 2.34 – 2.23 (m, 2H), 2.11 (s, 3H), 2.10 (s, 3H), 2.07 (m, 4H), 1.75 – 1.56 (m, 2H). MS: m/z : 297 $[M+H]^+$.

Example 4. Effects of test compounds in zebrafish model of C9orf72 amyotrophic lateral sclerosis

Generation of a C9orf72 zebrafish model

To generate a C9orf72 ALS model, zebrafish embryos were injected with constructs designed to knock-down C9orf72 gene and overexpress the dipeptide Glycine-Proline repeat (GP100). Injections were performed in 1–4 cell stage blastulae. Embryos were maintained at $28^\circ C$ and

manually dechorionated using fine forceps at 24 hours post-fertilization (hpf). Zebrafish embryos at 48 hpf were analyzed to identify any major morphological abnormalities (body/head malformations and size).

Treatment with test compounds

Embryos are treated with either DMSO or compounds disclosed at several concentrations.

Motor function assessment

Embryos that did not display any developmental abnormalities are touched lightly at the level of the tail with a pipette tip in order to evaluate their locomotor behavior. Touch-Evoked Escape Response (TEER) episodes are performed only in zebrafish that appeared morphologically normal and are recorded with a Grasshopper 2 Camera (Point Grey Research, Richmond, British Columbia, Canada) at 30 Hz. The videos are then analyzed using the manual tracking plugin of ImageJ 1.45r software.

Results

Results show that the compound is able to increase motor function in a dose-dependent manner in C9orf72 zebrafish models, as evidenced by the increase in distance swam during the TEER test.

INCORPORATION BY REFERENCE

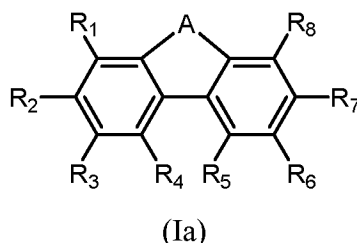
All of the U.S. patents and U.S. and PCT patent application publications cited herein are hereby incorporated by reference.

EQUIVALENTS

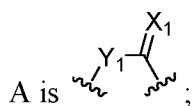
Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

We claim:

1. A method of treating amyotrophic lateral sclerosis (ALS), comprising administering to a subject in need thereof an effective amount of a compound of Formula (Ia),



wherein



X₁ is selected from O and S;

Y₁ is O;

R₁, R₄, R₅ and R₈ are independently selected from H and halogen;

R₃ and R₆ are independently selected from H, CN, OH, CF₃, halogen, and alkyl;

one of R₂ and R₇ is H, OH, or OAc and the other of R₂ and R₇ is halogen, CN, CF₃, CO₂H, NO₂, NHAc, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkylamino, alkyl-R₉, alkenyl-R₉, alkynyl-R₉, OR₁₀, NHR₁₀, NR₁₁C(O)R₁₂, C(O)NR₁₁R₁₂, and NR₁₁SO₂R₁₂;

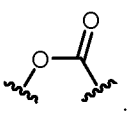
each occurrence of R₉ is independently selected from OH, NH₂, O-alkyl, O-alkyl-O-alkyl, alkylamino, NHC(O)-alkyl, N(CH₃)C(O)-alkyl, NHSO₂-alkyl, N(CH₃)SO₂-alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

R₁₀ is selected from C₂-C₁₂ alkyl, C(O)-alkyl, hydroxyalkyl, aminoalkyl, alkyl-O-alkyl, alkyl-O-alkyl-OH, alkyl-O-alkyl-O-alkyl, alkenyl, alkynyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, alkyl-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, SO₃H, SO₂-alkyl, and SO₂-haloalkyl;

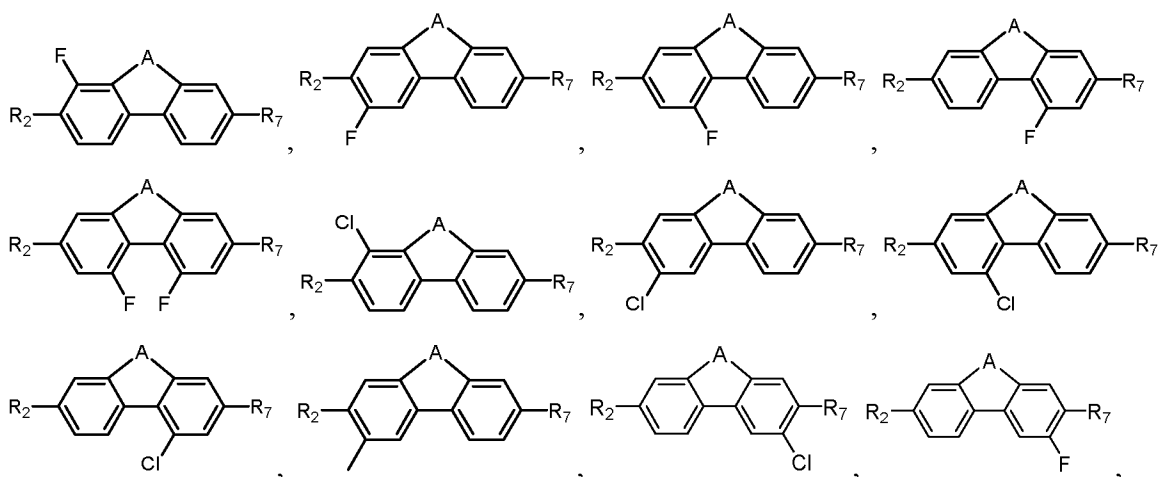
each occurrence of R₁₁ is selected from H and alkyl; and

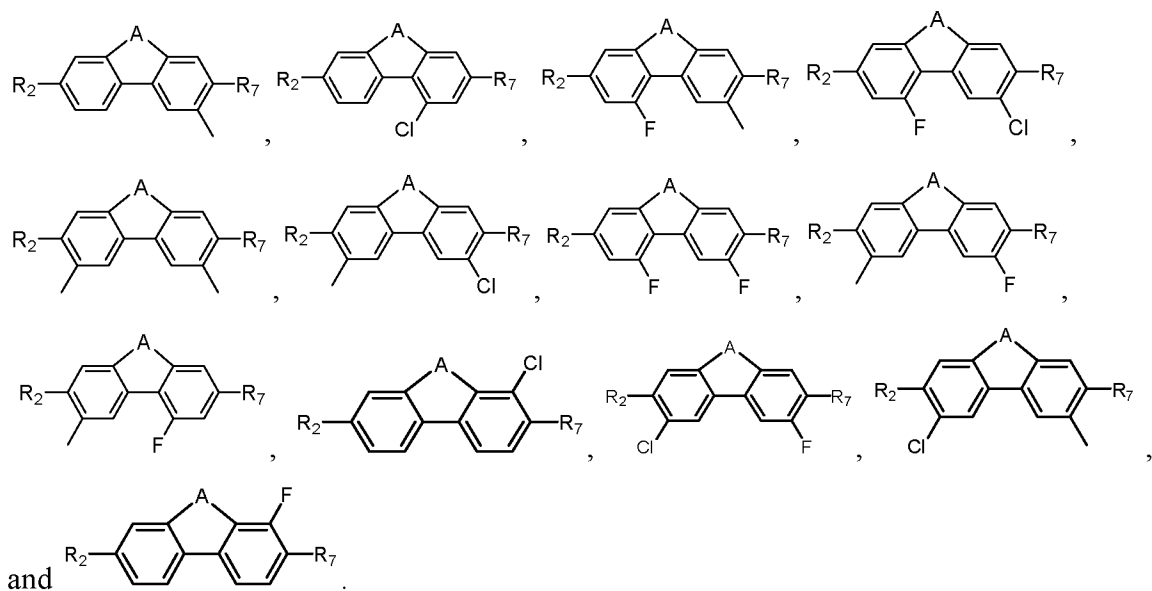
each occurrence of R₁₂ is selected from alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, O-alkyl, aminoalkyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, and alkyl-heterocycloalkyl;

or a pharmaceutically acceptable salt thereof.

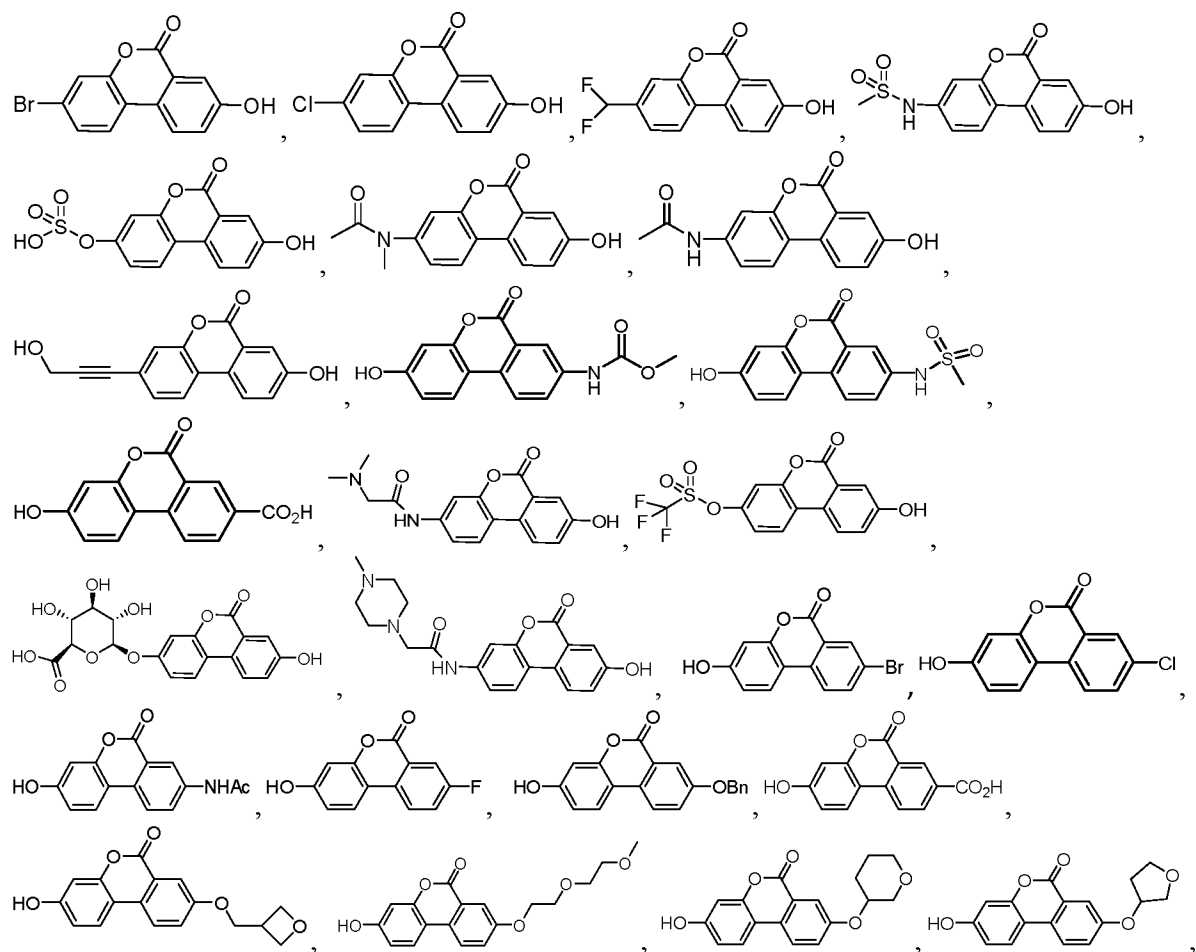
2. The compound of claim 1, wherein A is .
3. The method of claim 1 or 2, wherein R₂ is H.
4. The method of claim 1 or 2, wherein R₂ is OH.
5. The method of claim 1 or 2, wherein R₂ is OAc.
6. The method of claim 1 or 2, wherein
R₂ is selected from haloalkyl, substituted cycloalkyl, alkynyl-R₉, OR₁₀, and C(O)NR₁₁R₁₂;
R₉ is selected from OH, substituted cycloalkyl and heterocycloalkyl;
R₁₀ is selected from alkyl, substituted cycloalkyl, heterocycloalkyl and alkyl heterocycloalkyl; and
R₁₁ is H and R₁₂ is alkyl-heterocycloalkyl.
7. The method of any one of claims 1-6, wherein R₇ is H.
8. The method of any one of claims 1-6, wherein R₇ is OH.
9. The method of any one of claims 1-6, wherein R₇ is OAc.
10. The method of any one of claims 1-5, wherein
R₇ is selected from haloalkyl, substituted cycloalkyl, alkynyl-R₉, OR₁₀, and C(O)NR₁₁R₁₂;
R₉ is selected from OH, substituted cycloalkyl and heterocycloalkyl;
R₁₀ is selected from alkyl, substituted cycloalkyl, heterocycloalkyl and alkyl heterocycloalkyl; and
R₁₁ is H and R₁₂ is alkyl-heterocycloalkyl.

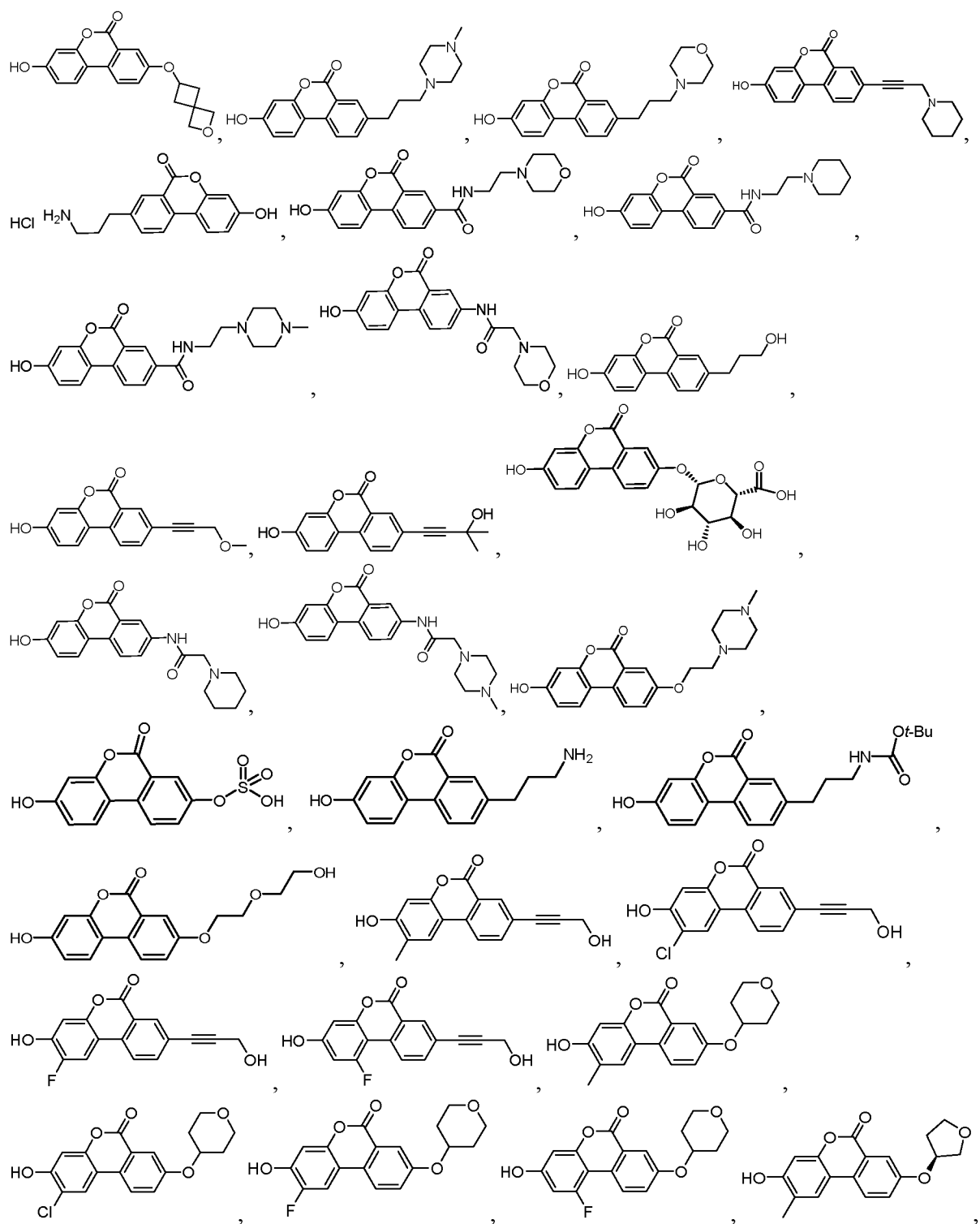
11. The method of claim 6 or 10, wherein each occurrence of substituted cycloalkyl is independently substituted with OH, halogen, or hydroxyalkyl.
12. The method of any one of claims 1-11, wherein R₁, R₃, R₄, R₅, R₆, and R₈ are each H.
13. The method of any one of claims 1-11, wherein one of R₁, R₃, R₄, R₅, R₆, and R₈ is not H.
14. The method of any one of claims 1-11, wherein two of R₁, R₃, R₄, R₅, R₆, and R₈ are not H.
15. The method of claim 13, wherein one of R₁, R₃, R₄, R₅, R₆, and R₈ is alkyl or halogen.
16. The method of claim 14, wherein two of R₁, R₃, R₄, R₅, R₆, and R₈ are independently alkyl or halogen.
17. The method of claim 15 or 16, wherein the compound is selected from:

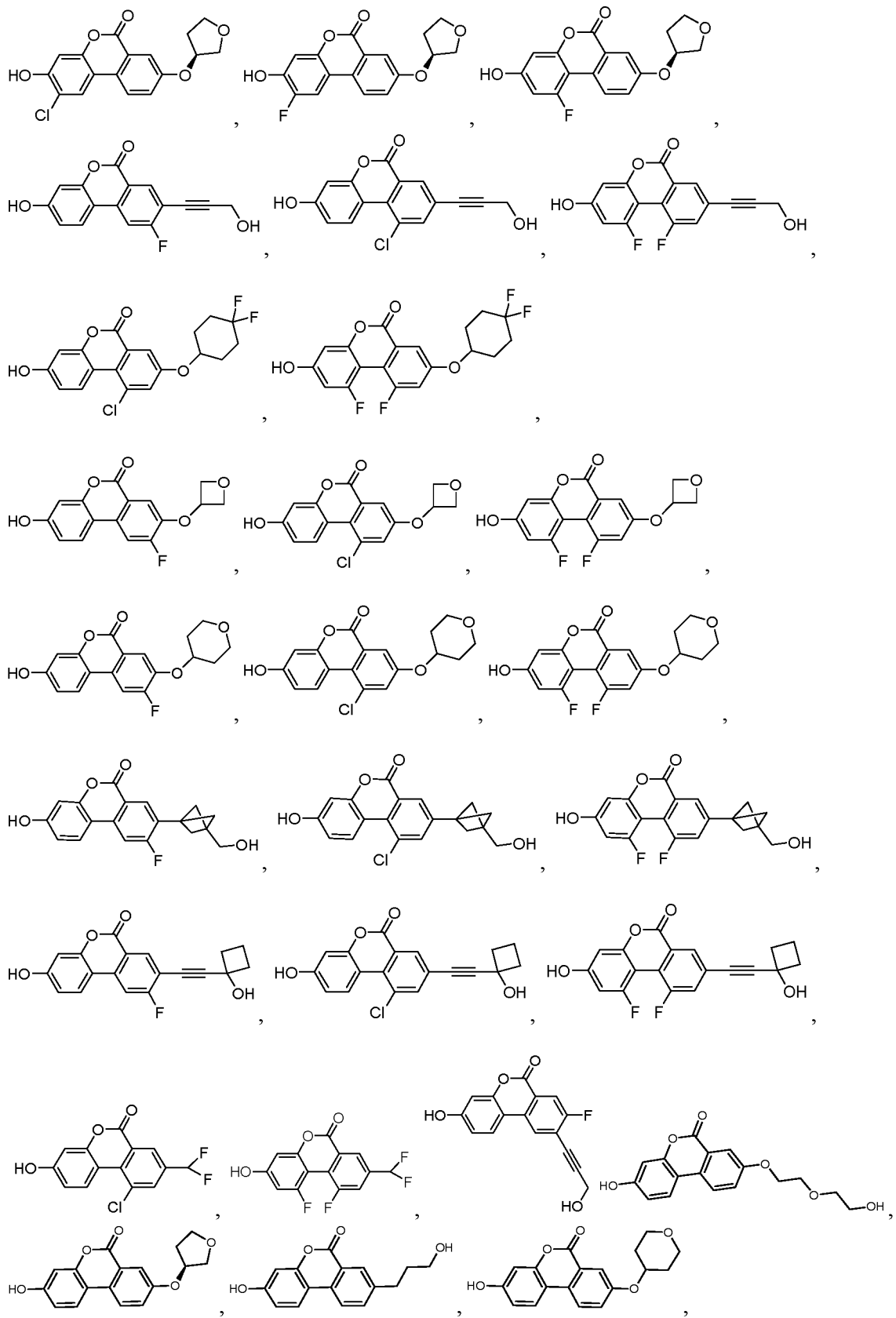


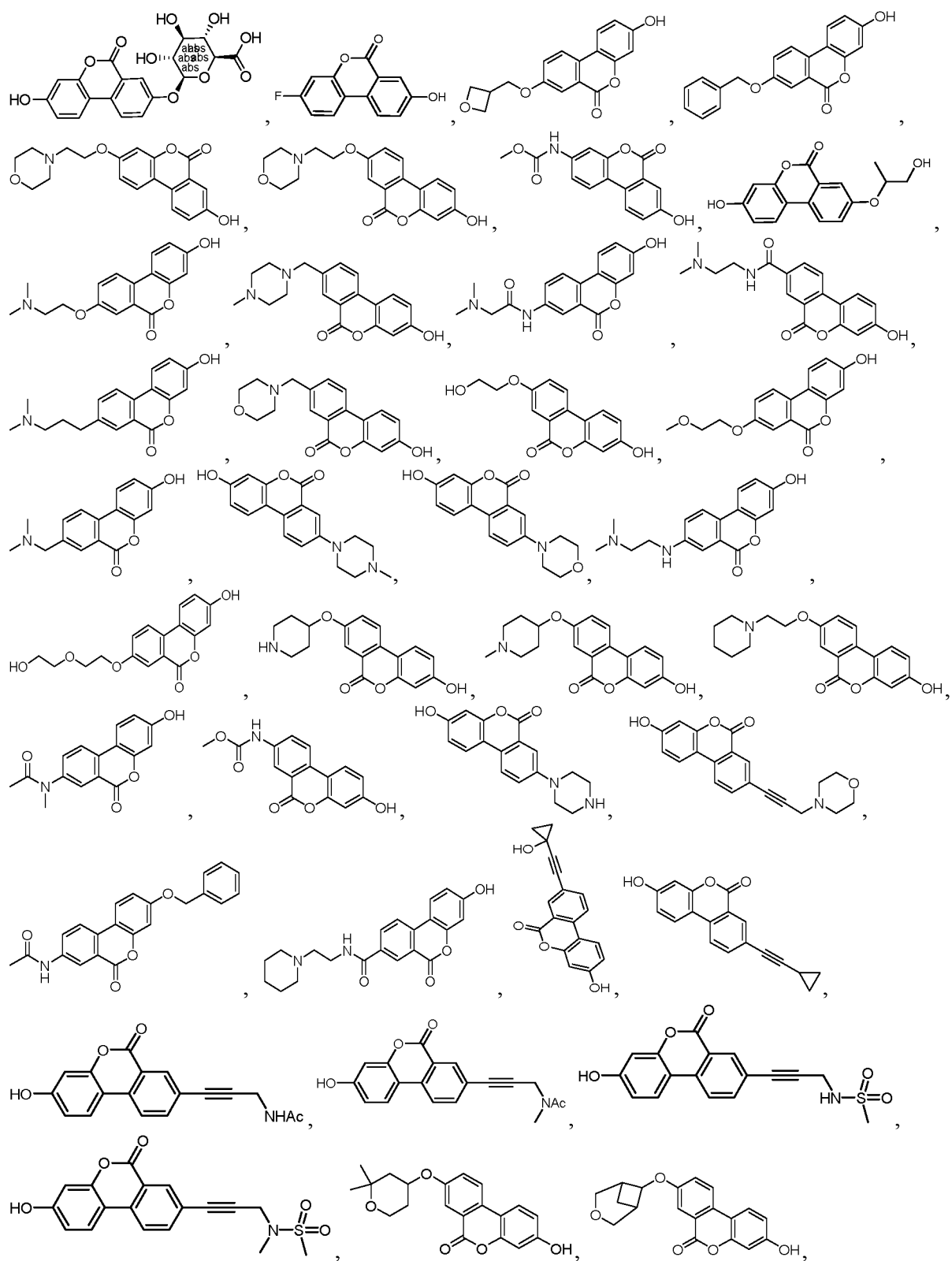


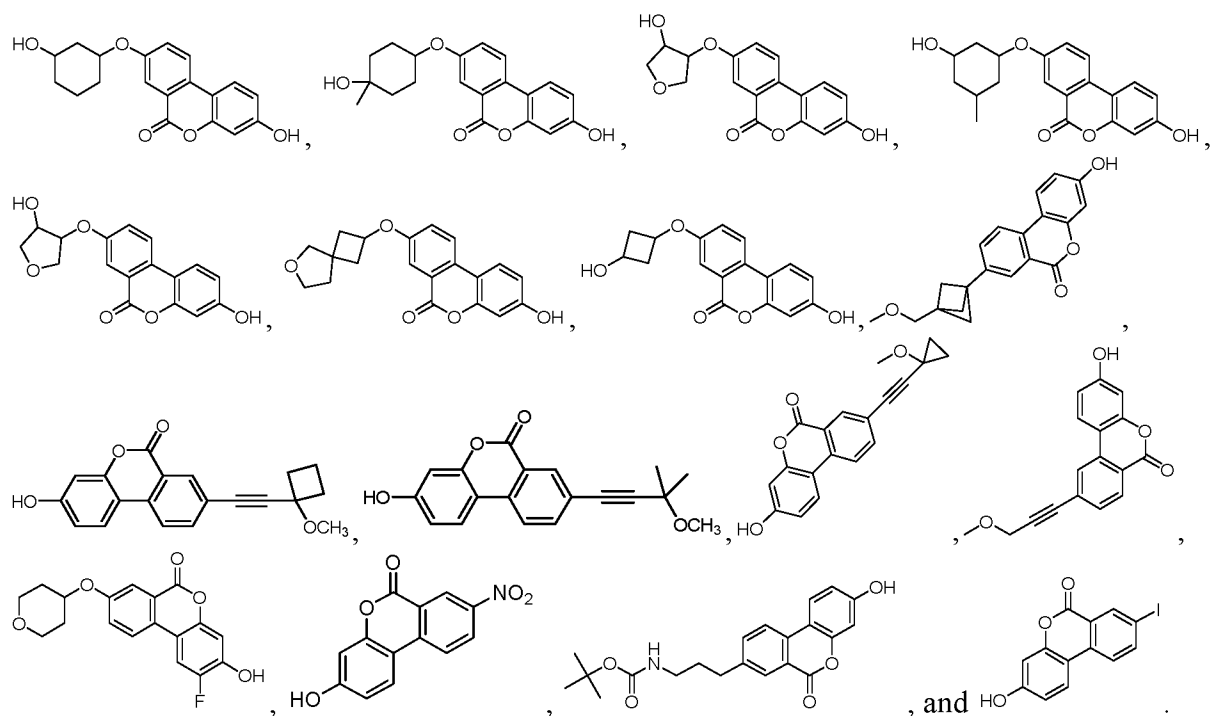
18. The method of claim 1, wherein the compound is selected from:



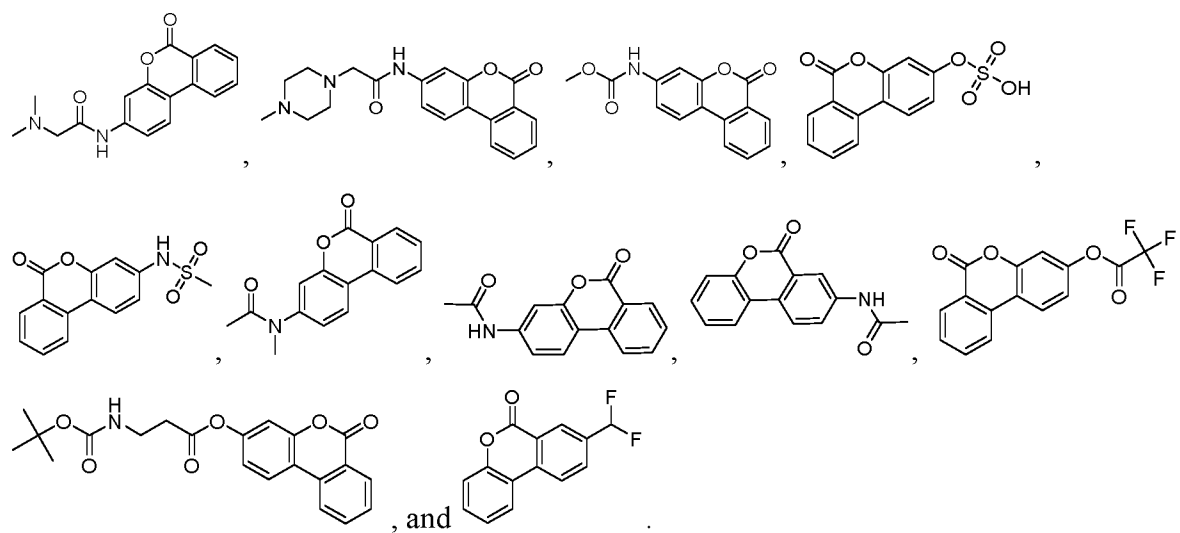




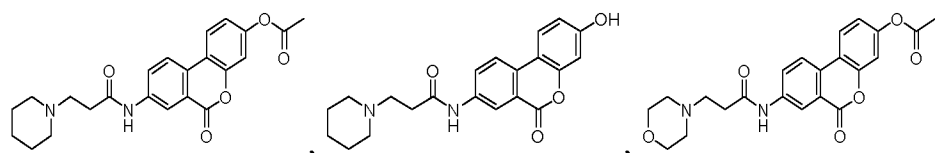


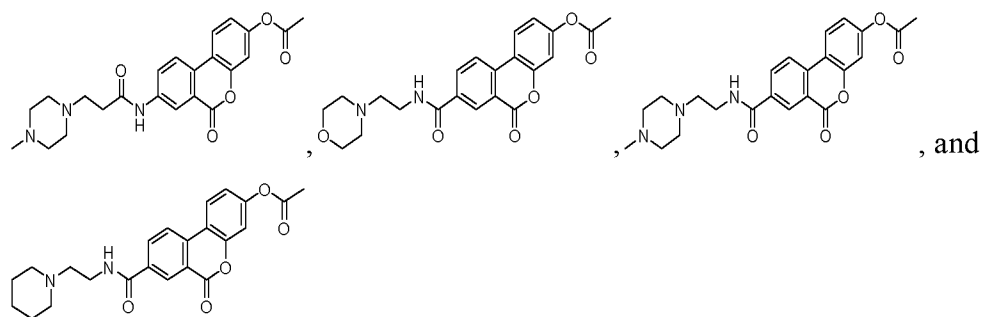


19. The method of claim 1, wherein the compound is selected from:

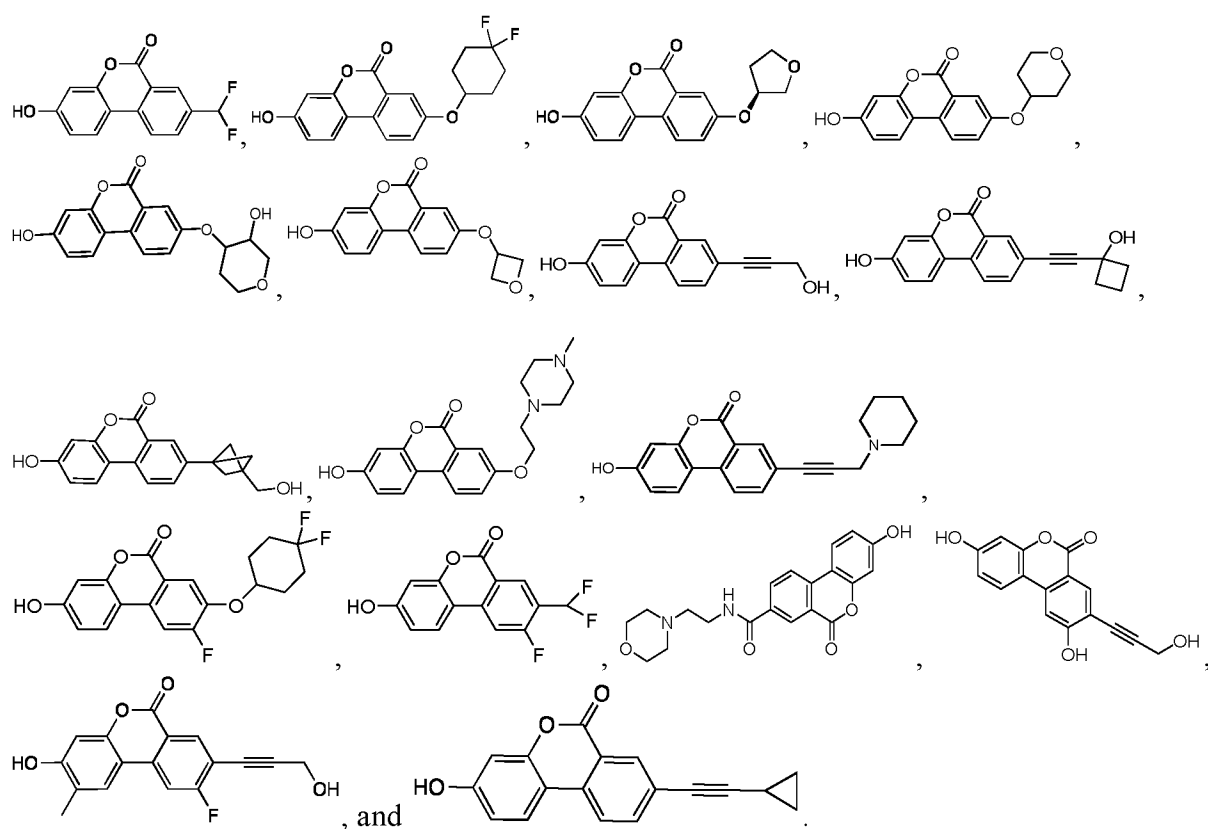


20. The method of claim 1, wherein the compound is selected from:

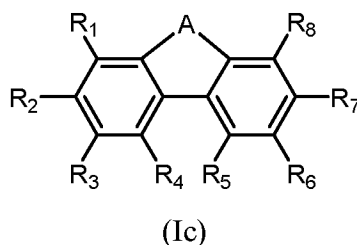




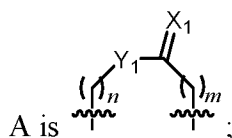
21. The method of claim 1, wherein the compound is selected from:



22. A method of treating amyotrophic lateral sclerosis (ALS), comprising administering to a subject in need thereof an effective amount of a compound of Formula (Ic),



wherein



one of n and m is 0; and the other of n and m is 1;

X_1 and Y_1 are each O;

R_1 , R_2 , R_3 , R_6 , R_7 , and R_8 are independently selected from H, OH, OCH₃, OAc, NH₂, halogen, CN, CF₃, CO₂H, NO₂, NHAc, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkylamino, alkyl-R₉, alkenyl-R₉, alkynyl-R₉, OR₁₀, NHR₁₀, NR₁₁C(O)R₁₂, C(O)NR₁₁R₁₂, and NR₁₁SO₂R₁₂;

R_4 and R_5 are independently selected from H, halogen and alkyl;

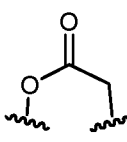
each occurrence of R₉ is independently selected from OH, NH₂, O-alkyl, O-alkyl-O-alkyl, alkylamino, NHC(O)-alkyl, N(CH₃)C(O)-alkyl, NHSO₂-alkyl, N(CH₃)SO₂-alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

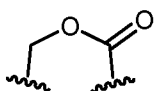
R₁₀ is selected from C₂-C₁₂ alkyl, hydroxyalkyl, aminoalkyl, alkyl-O-alkyl, alkyl-O-alkyl-OH, alkyl-O-alkyl-O-alkyl, alkenyl, alkynyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, alkyl-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, SO₃H, SO₂-alkyl, and SO₂-haloalkyl;

each occurrence of R₁₁ is selected from H and alkyl; and

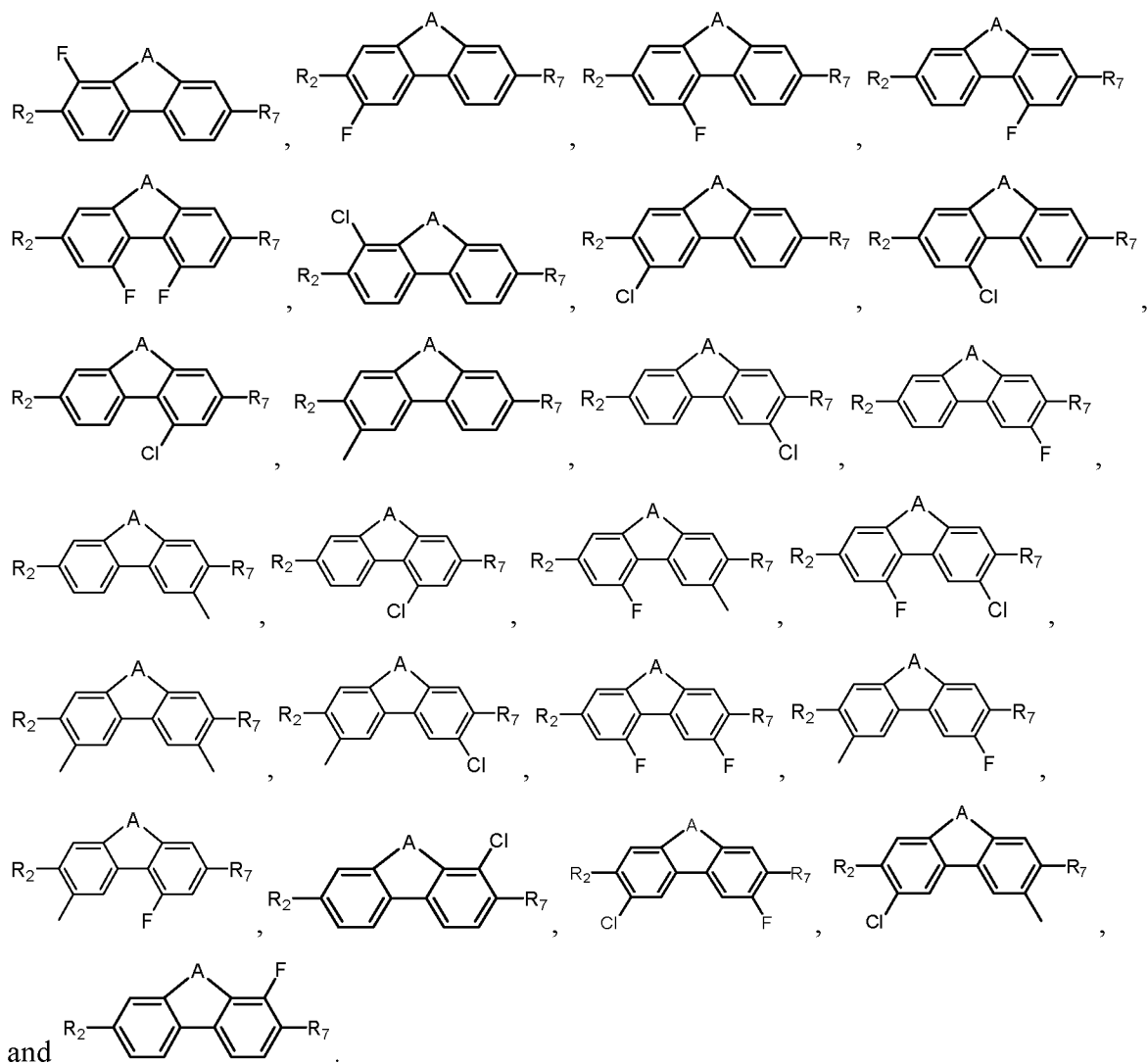
each occurrence of R₁₂ is selected from alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, O-alkyl, aminoalkyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, and alkyl-heterocycloalkyl,

or a pharmaceutically acceptable salt thereof.

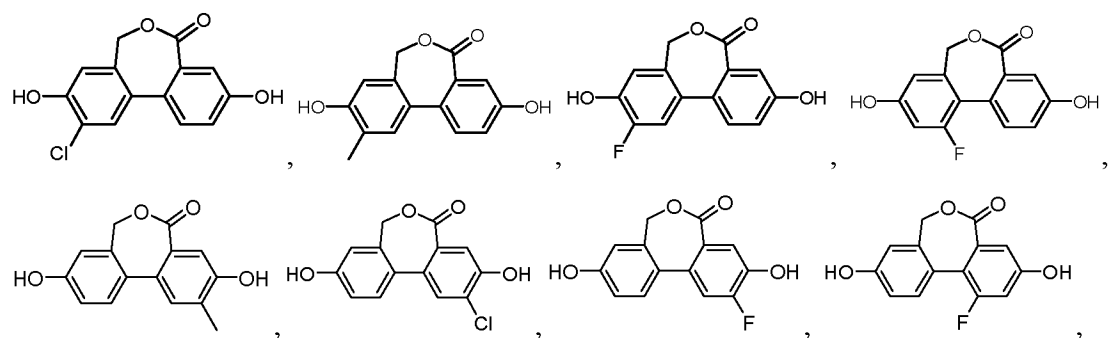
23. The compound of claim 39, wherein A is selected from  and

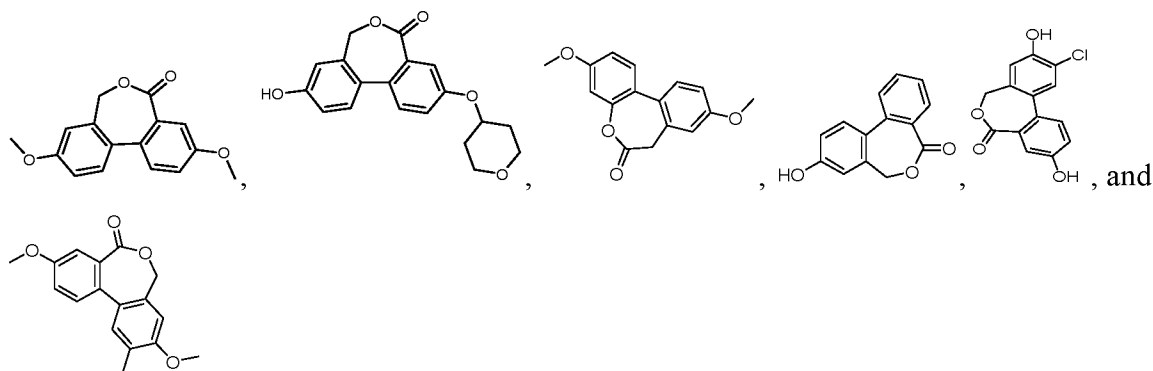


24. The compound of claim 22 or 23, wherein R_2 and R_7 are each OH.
25. The compound of claim 22 or 23, wherein R_2 and R_7 are each O-alkyl.
26. The compound of claim 22 or 23, wherein R_2 is OH; and R_7 is H or O-alkyl.
27. The compound of claim 22 or 23, wherein R_2 is H or O-alkyl; and R_7 is OH.
28. The compound of any one of claims 22-27, wherein R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 are each H.
29. The compound of any one of claims 22-27, wherein one of R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 is not H.
30. The compound of any one of claims 22-27, wherein two of R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 are not H.
31. The compound of claim 29, wherein one of R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 is alkyl or halogen.
32. The compound of claim 30, wherein two of R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 are alkyl or halogen.
33. The compound of claim 31 or 32, wherein the compound is selected from:

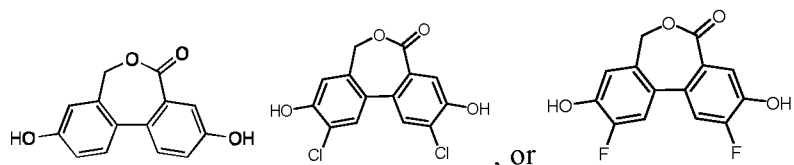


34. The compound of claim 22, wherein the compound is selected from:

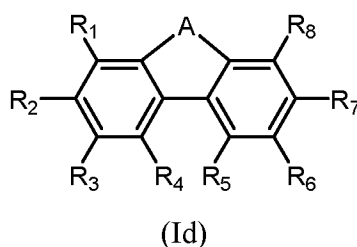




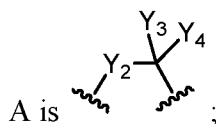
35. The compound of claim 22, wherein the compound is:



36. A method of treating amyotrophic lateral sclerosis (ALS), comprising administering to a subject in need thereof an effective amount of a compound of Formula (Id),



wherein



Y_2 is O;

Y_3 and Y_4 are independently selected from H, halogen and alkyl; or together with the carbon to which they are bonded combine to form a cycloalkyl or heterocycloalkyl;

R_1 , R_4 , R_5 , and R_8 are independently selected from H and halogen;

R_2 , R_3 , R_6 , and R_7 are independently selected from H, OH, OCH₃, OAc, NH₂, halogen, CN, CF₃, CO₂H, NO₂, NHAc, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl,

alkylamino, alkyl-R₉, alkenyl-R₉, alkynyl-R₉, OR₁₀, NHR₁₀, NR₁₁C(O)R₁₂, C(O)NR₁₁R₁₂, and NR₁₁SO₂R₁₂;

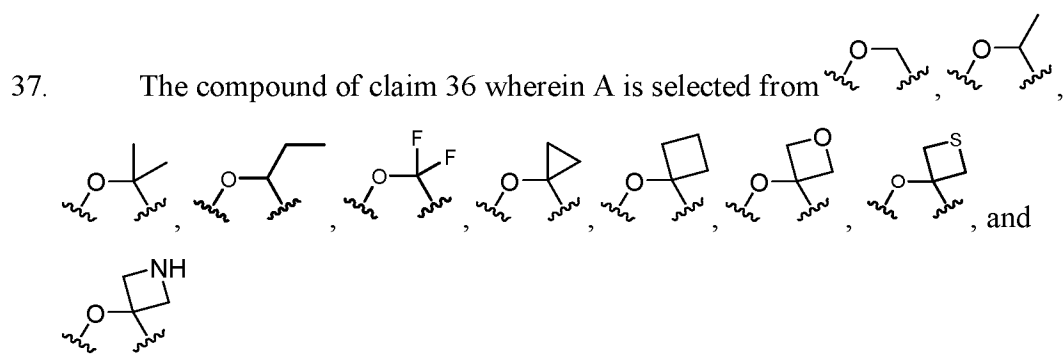
each occurrence of R₉ is independently selected from OH, NH₂, O-alkyl, O-alkyl-O-alkyl, alkylamino, NHC(O)-alkyl, N(CH₃)C(O)-alkyl, NHSO₂-alkyl, N(CH₃)SO₂-alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

R₁₀ is selected from C₂-C₁₂ alkyl, hydroxyalkyl, aminoalkyl, alkyl-O-alkyl, alkyl-O-alkyl-OH, alkyl-O-alkyl-O-alkyl, alkenyl, alkynyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, alkyl-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, SO₃H, SO₂-alkyl, and SO₂-haloalkyl;

each occurrence of R₁₁ is selected from H and alkyl; and

each occurrence of R₁₂ is selected from alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, O-alkyl, aminoalkyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, and alkyl-heterocycloalkyl;

or a pharmaceutically acceptable salt thereof.



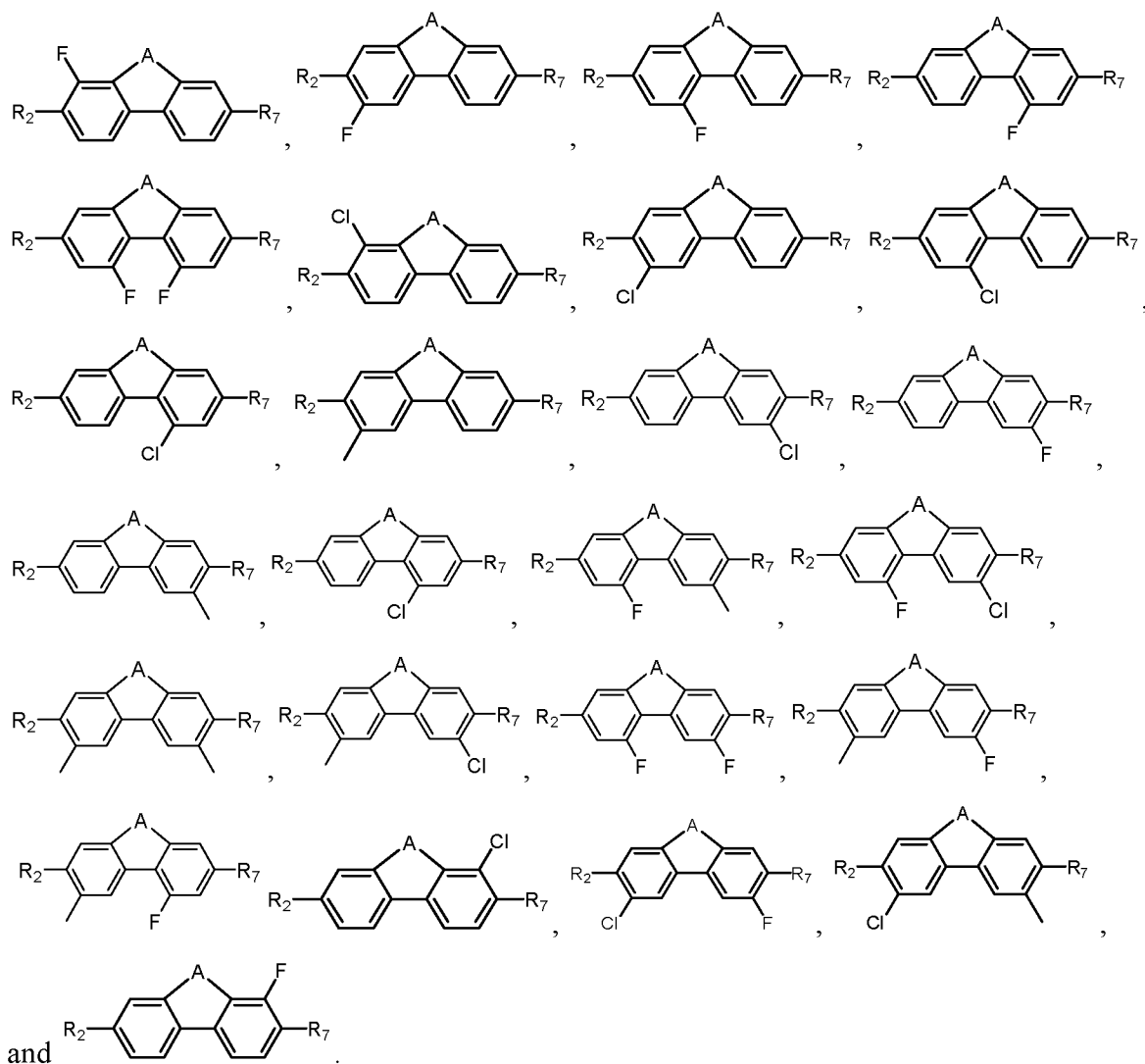
38. The compound of claim 36 or 37, wherein R₂ and R₇ are each OH.

39. The compound of claim 36 or 37, wherein one of R₂ and R₇ is OH and the other of R₂ and R₇ is O-alkyl.

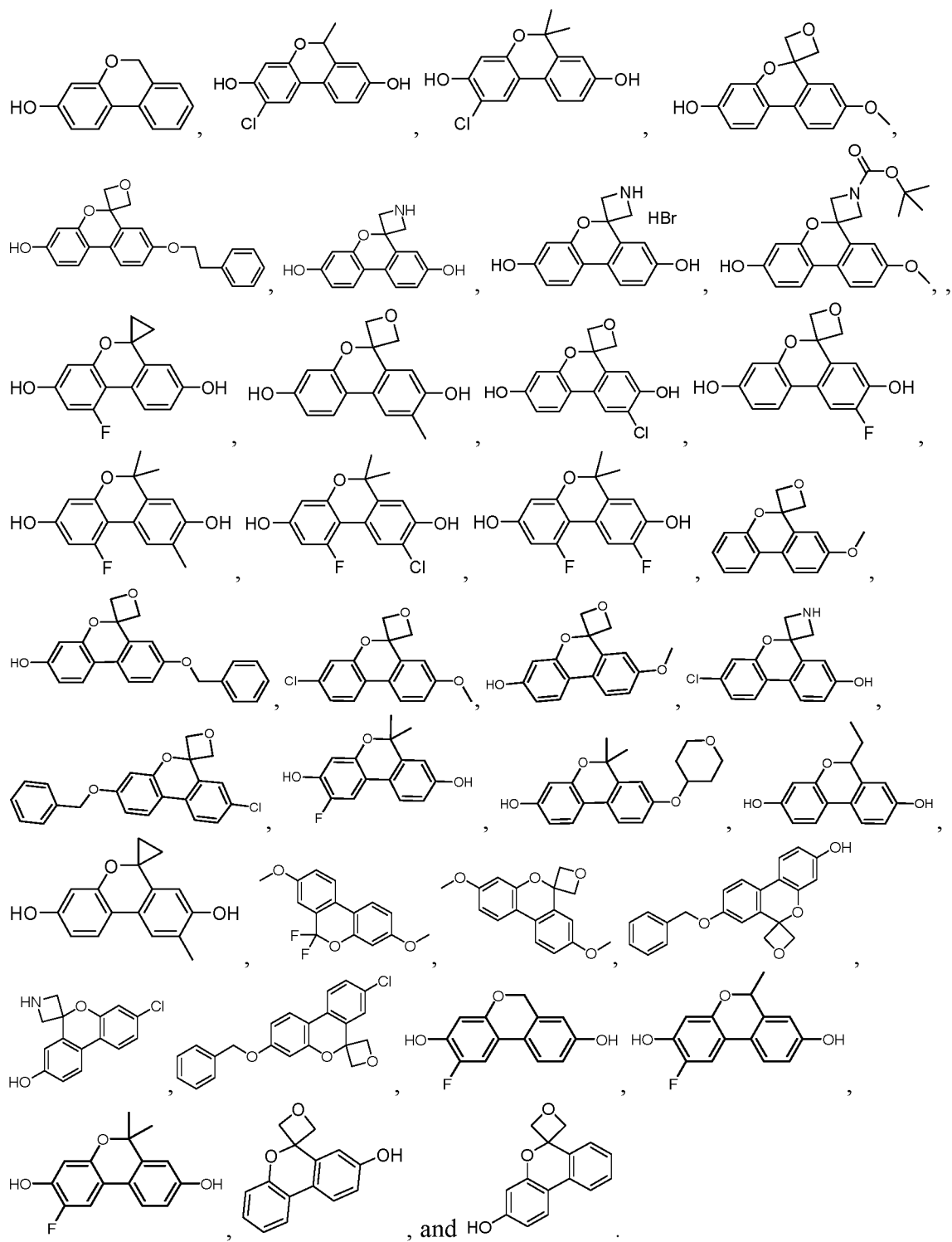
40. The compound of any one of claims 36-39, wherein one of R₁, R₃, R₄, R₅, R₆, and R₈ is alkyl or halogen.

41. The compound of any one of claims 36-39, wherein two of R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 are alkyl or halogen.

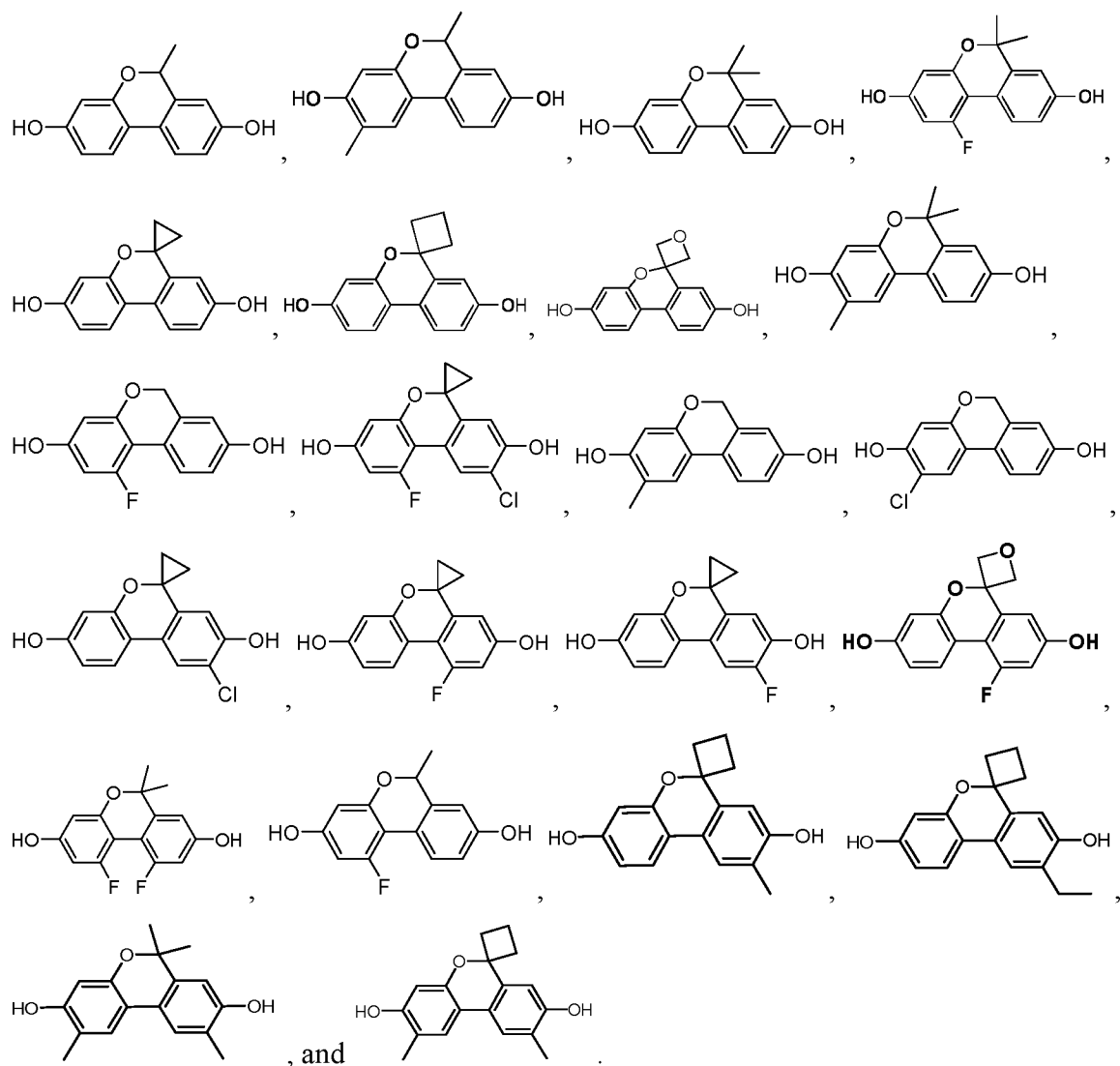
42. The compound of claim 40 or 41, wherein the compound is selected from:



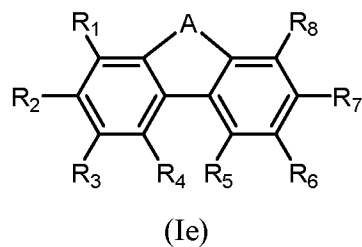
43. The compound of claim 36, wherein the compound is selected from:



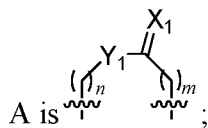
44. The compound of claim 36, wherein the compound is selected from:



45. A method of treating amyotrophic lateral sclerosis (ALS), comprising administering to a subject in need thereof an effective amount of a compound of Formula (Ie),



wherein



n and m are both 0; or one of n and m is 0, and the other of n and m is 1;

X_1 is O;

Y_1 is selected from NH, N-CH₃, N-*t*-Bu, N-cycloalkyl, and N-heterocycloalkyl;

R_1 , R_2 , R_3 , R_6 , R_7 , and R_8 are independently selected from H, OH, OCH₃, OAc, NH₂, halogen, CN, CF₃, CO₂H, NO₂, NHAc, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkylamino, alkyl-R₉, alkenyl-R₉, alkynyl-R₉, OR₁₀, NHR₁₀, NR₁₁C(O)R₁₂, C(O)NR₁₁R₁₂, and NR₁₁SO₂R₁₂;

R_4 and R_5 are independently selected from H, alkyl, and halogen;

each occurrence of R_9 is independently selected from OH, NH₂, O-alkyl, O-alkyl-O-alkyl, alkylamino, NHC(O)-alkyl, N(CH₃)C(O)-alkyl, NHSO₂-alkyl, N(CH₃)SO₂-alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

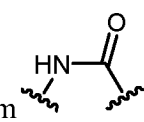
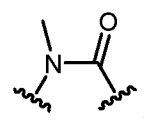
R_{10} is selected from C₂-C₁₂ alkyl, hydroxyalkyl, aminoalkyl, alkyl-O-alkyl, alkyl-O-alkyl-OH, alkyl-O-alkyl-O-alkyl, alkenyl, alkynyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, alkyl-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, SO₃H, SO₂-alkyl, and SO₂-haloalkyl;

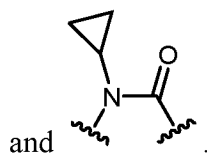
each occurrence of R_{11} is selected from H and alkyl; and

each occurrence of R_{12} is selected from alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, O-alkyl, aminoalkyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, and alkyl-heterocycloalkyl;

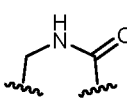
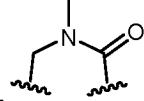
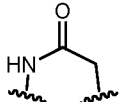
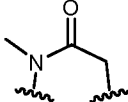
or a pharmaceutically acceptable salt thereof.

46. The compound of claim 45, wherein n and m are both 0.

47. The compound of claim 46, wherein A is selected from , ,



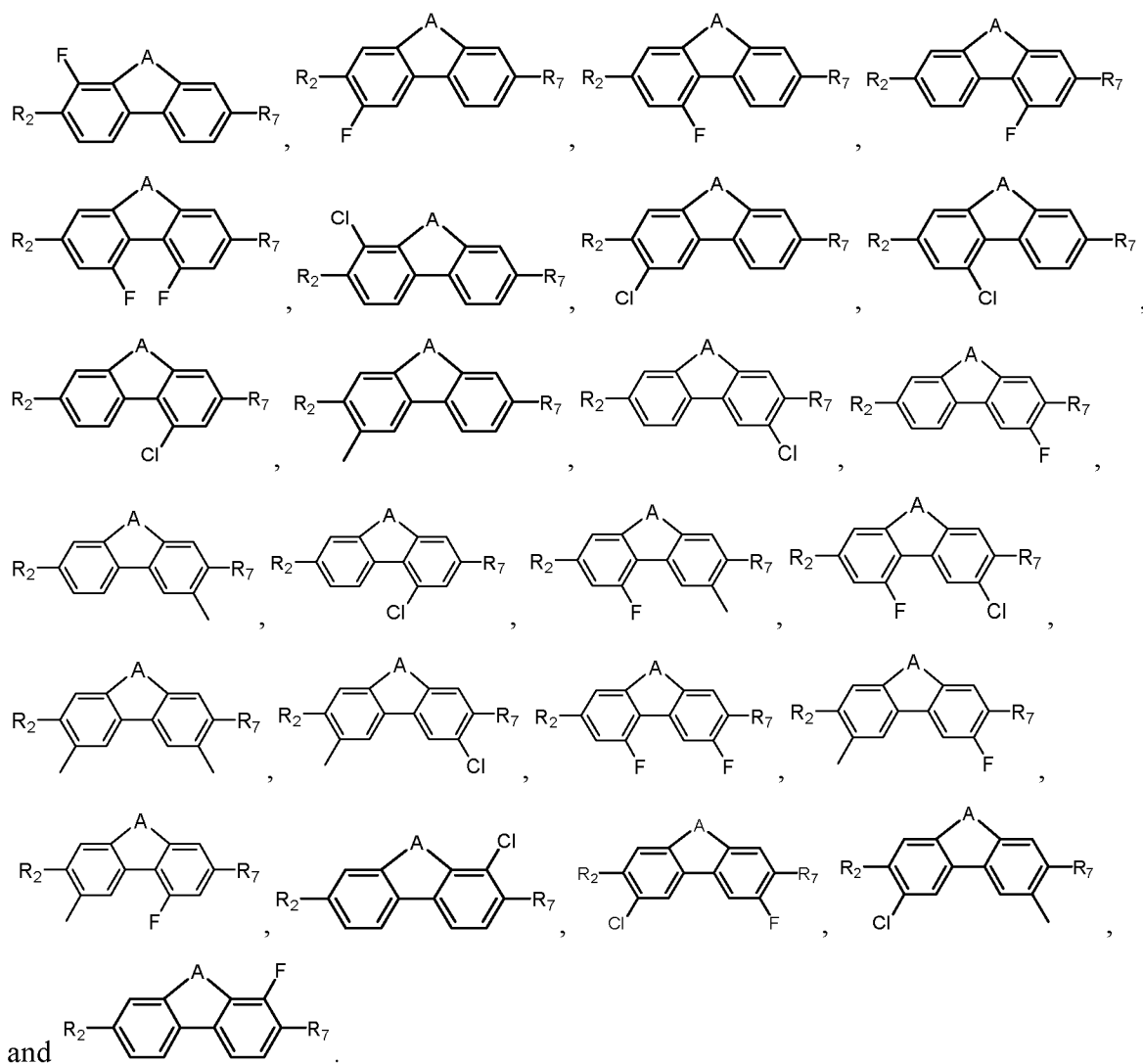
48. The compound of claim 45, wherein one of n and m is 0, and the other of n and m is 1.

49. The compound of claim 48, wherein A is selected from , , , and .

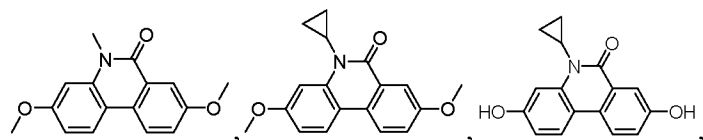
50. The compound of any one of claims 45-49, wherein R_2 and R_7 are each OH.
51. The compound of any one of claims 45-49, wherein one of R_2 and R_7 is OH and the other of R_2 and R_7 is not OH.
52. The compound of any one of claims 45-49, wherein R_2 and R_7 are each O-alkyl.
53. The compound of any one of claims 45-49, wherein R_2 is OH and R_7 is O-alkyl; or R_2 is O-alkyl and R_7 is OH.
54. The compound of any one of claims 45-53, wherein R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 are each H.
55. The compound of any one of claims 45-53, wherein one of R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 is not H.
56. The compound of any one of claims 45-53, wherein two of R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 are not H.
57. The compound of any one of claims 45-53, wherein one of R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 is alkyl or halogen.

58. The compound of any one of claims 45-53, wherein two of R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 are alkyl or halogen.

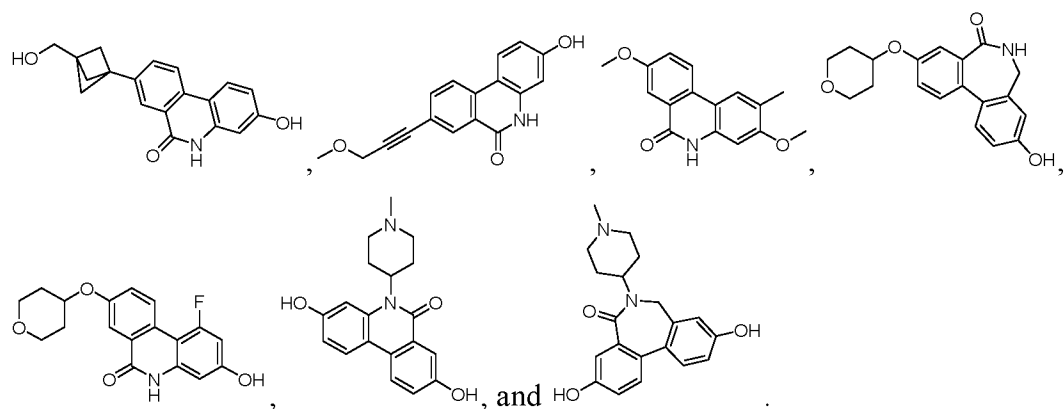
59. The compound of claim 57 or 58, wherein the compound is selected from:



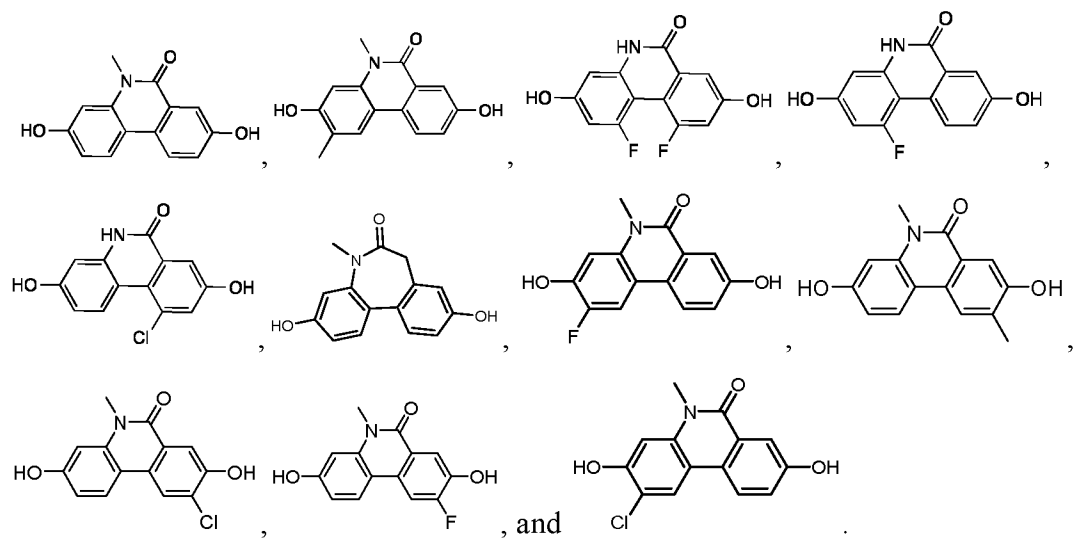
60. The compound of claim 45, wherein the compound is selected from:



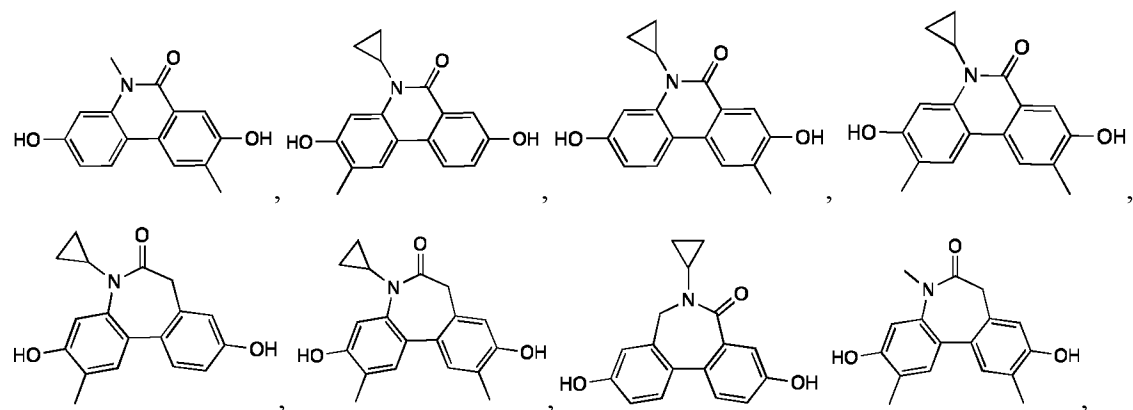


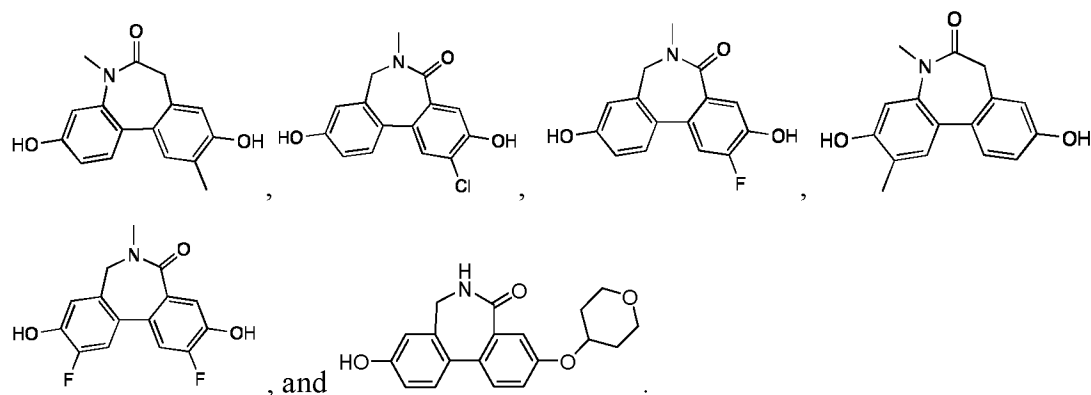


61. The compound of claim 45, wherein the compound is selected from:

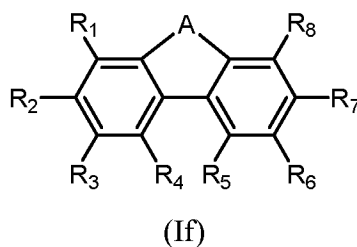


62. The compound of claim 45, wherein the compound is selected from:

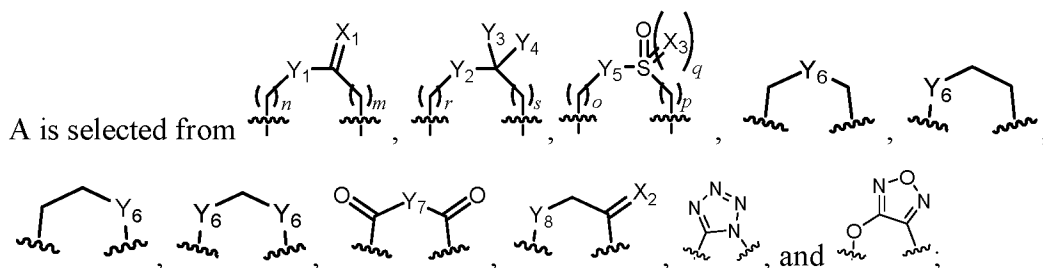




63. A method of treating amyotrophic lateral sclerosis (ALS), comprising administering to a subject in need thereof an effective amount of a compound of Formula (If),



wherein



n and m are both 0; or one of n and m is 0 and the other of n and m is 1;

o and p are both 0; or one of o and p is 0 and the other of o and p is 1;

q is 0 or 1;

r and s are both 0; or one of r and s is 0 and the other of r and s is 1;

X_1 and X_2 are each O;

X_3 is O or N(alkyl);

Y_1 is S;

Y_2 is selected from O, CH₂, NH, N-alkyl, S, S(O), and SO₂;

Y_3 and Y_4 are independently selected from H, halogen, OH, and alkyl, or together with the carbon to which they are bonded combine to form a cycloalkyl or cycloheteroalkyl;

Y_5 is selected from CH_2 , NH, N-alkyl, N-arylalkyl, N-cycloalkyl, and N-heterocycloalkyl;

Each occurrence of Y_6 is independently selected from O, S, S(O), SO_2 , NH, N-alkyl, N-alkylaryl, and N-cycloalkyl;

Y_7 is selected from O, NH and N-alkyl;

Y_8 is selected from O and S;

R_1 , R_2 , R_3 , R_6 , R_7 , and R_8 are independently selected from H, OH, OCH_3 , OAc, NH_2 , halogen, CN, CF_3 , CO_2H , NO_2 , NHAc, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkylamino, alkyl- R_9 , alkenyl- R_9 , alkynyl- R_9 , OR_{10} , NHR_{10} , $NR_{11}C(O)R_{12}$, $C(O)NR_{11}R_{12}$, and $NR_{11}SO_2R_{12}$,

R_4 and R_5 are independently selected from H, alkyl, and halogen;

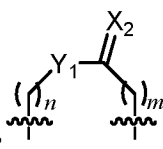
each occurrence of R_9 is independently selected from OH, NH_2 , O-alkyl, O-alkyl-O-alkyl, alkylamino, $NHC(O)$ -alkyl, $N(CH_3)C(O)$ -alkyl, $NHSO_2$ -alkyl, $N(CH_3)SO_2$ -alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

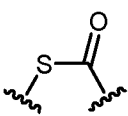
R_{10} is selected from C_2 - C_{12} alkyl, hydroxyalkyl, aminoalkyl, alkyl-O-alkyl, alkyl-O-alkyl-OH, alkyl-O-alkyl-O-alkyl, alkenyl, alkynyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, alkyl-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, SO_3H , SO_2 -alkyl, and SO_2 -haloalkyl;

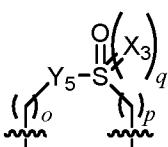
each occurrence of R_{11} is selected from H and alkyl; and

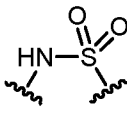
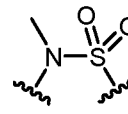
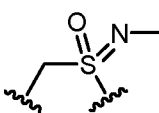
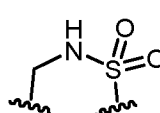
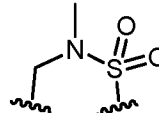
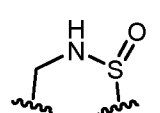
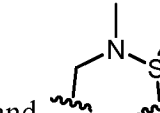
each occurrence of R_{12} is selected from alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, O-alkyl, aminoalkyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, and alkyl-heterocycloalkyl;

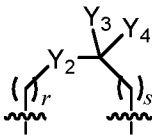
or a pharmaceutically acceptable salt thereof.

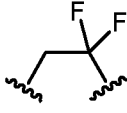
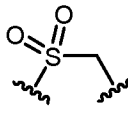
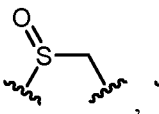
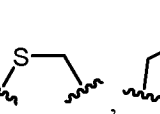
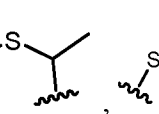
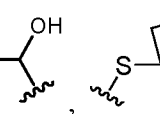
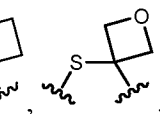
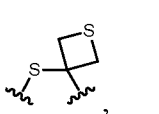
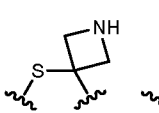
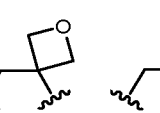
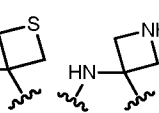
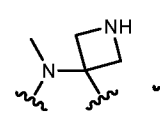
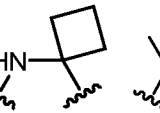
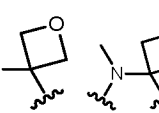
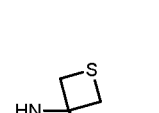
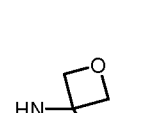
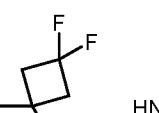
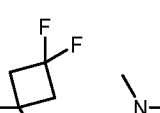
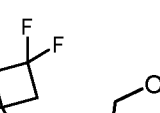
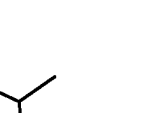
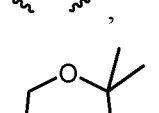
64. The compound of claim 63, wherein A is ; and n and m are both 0.

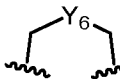
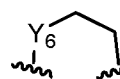
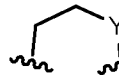
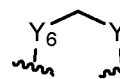
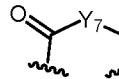
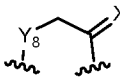
65. The compound of claim 64, wherein A is .

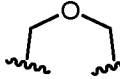
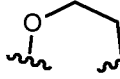
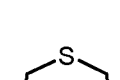
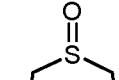
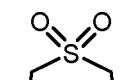
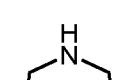
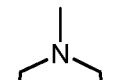
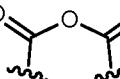
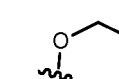
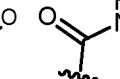
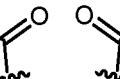
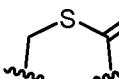
66. The compound of claim 63, wherein A is .

67. The compound of claim 66, wherein A is selected from , , , , , , and .

68. The compound of claim 63, wherein A is .

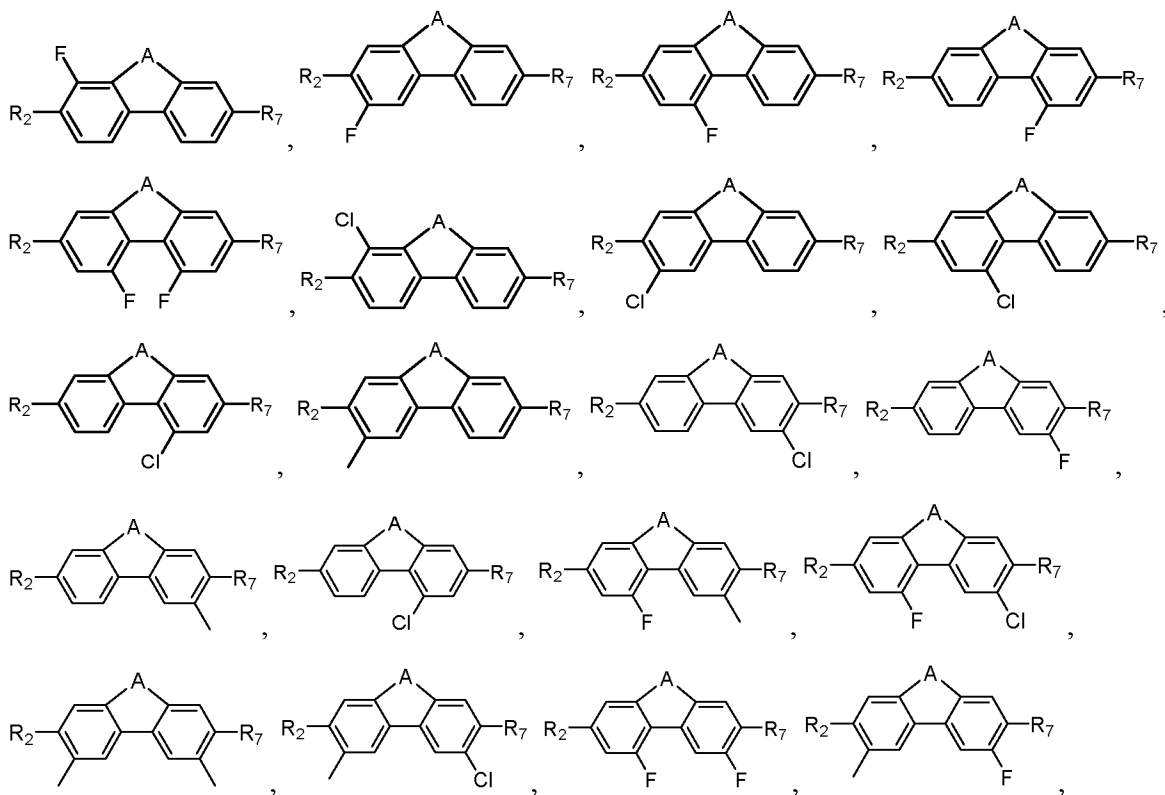
69. The compound of claim 68, wherein A is selected from , , , , , , , , , , , , , , , , , , , , and .

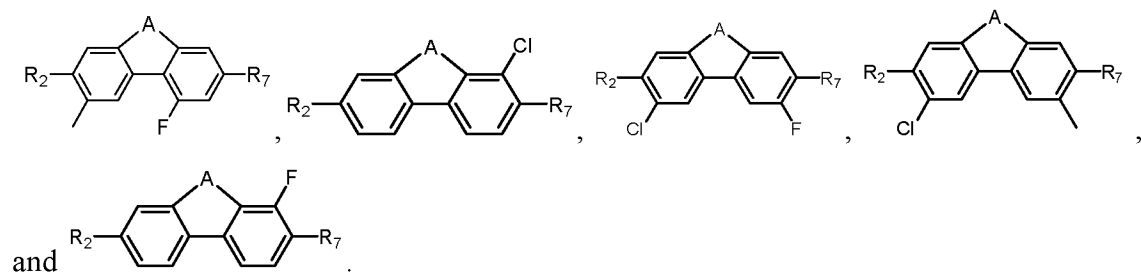
70. The compound of claim 63, wherein A is selected from , , , , , and .

71. The compound of claim 70, wherein A is selected from , , , , , , , , , , , , , and .

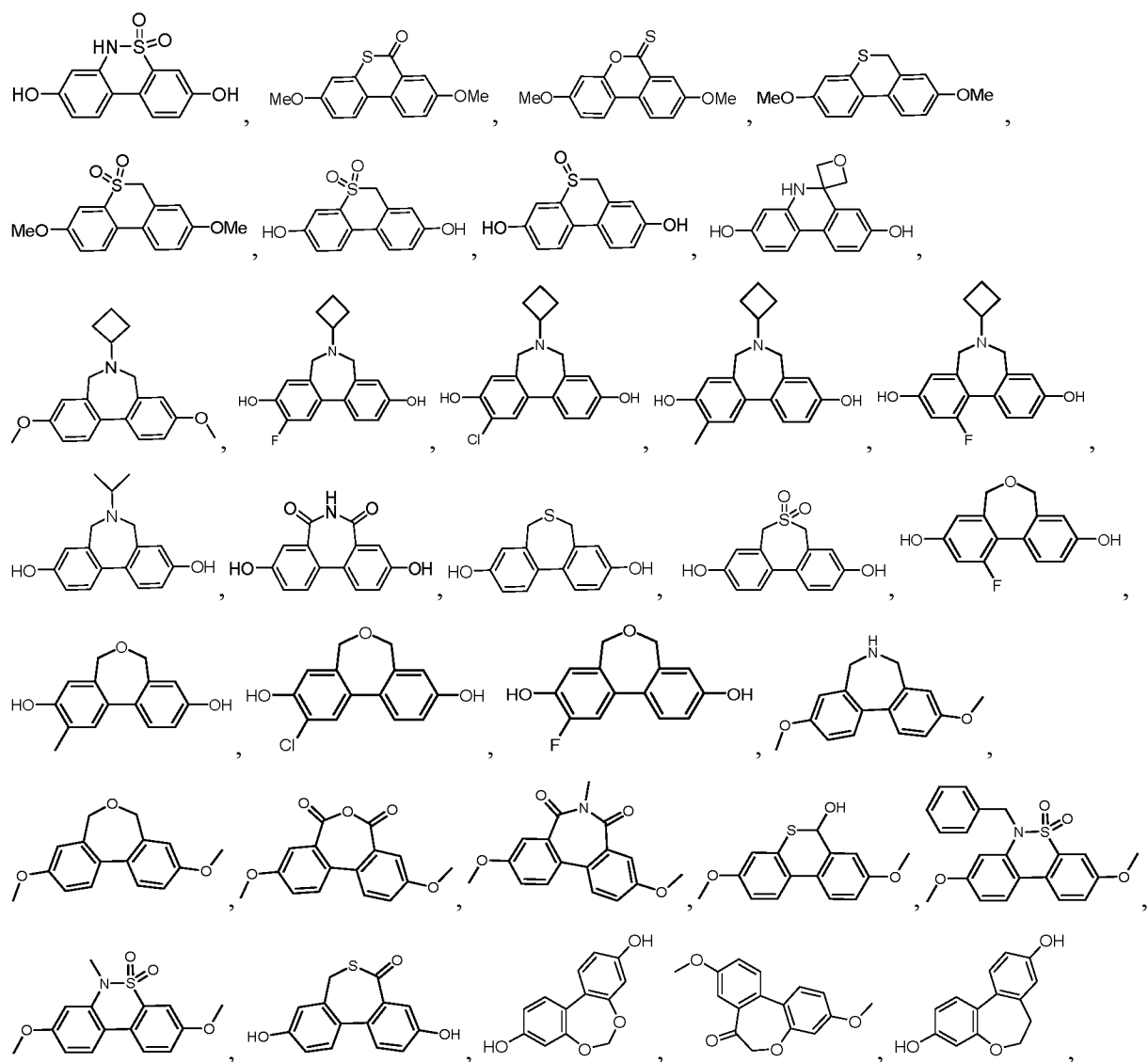
72. The compound of any one of claims 63-71, wherein R_2 and R_7 are each OH.
73. The compound of any one of claims 63-71, wherein one of R_2 and R_7 is OH and the other of R_2 and R_7 is OH is not OH.
74. The compound of any one of claims 63-71, wherein R_2 and R_7 are each O-alkyl.
75. The compound of any one of claims 63-71, wherein R_2 is OH and R_7 is O-alkyl; or R_2 is O-alkyl and R_7 is OH.
76. The compound of any one of claims 63-71, wherein R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 are each H.

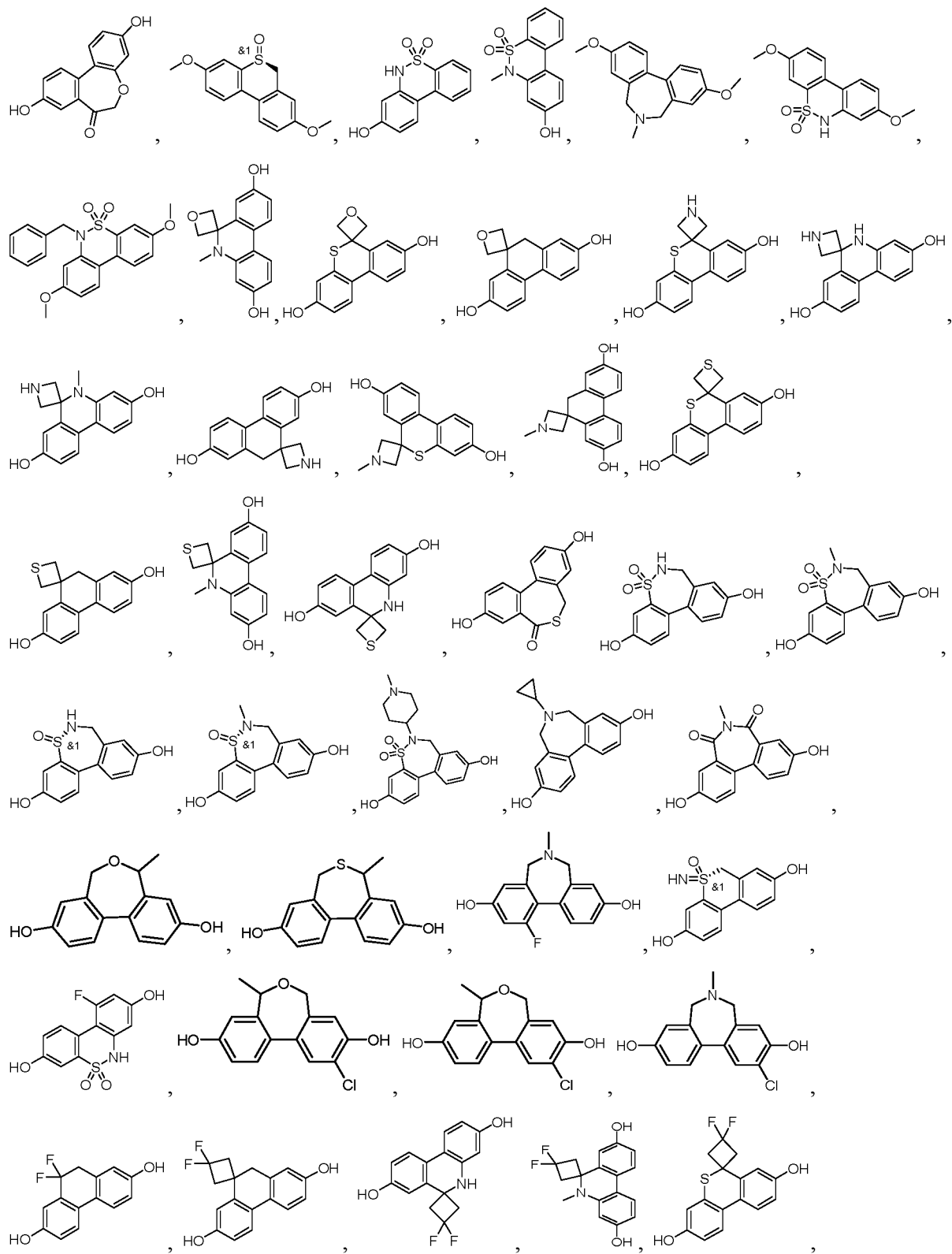
77. The compound of any one of claims 63-71, wherein one of R₁, R₃, R₄, R₅, R₆, and R₈ is not H.
78. The compound of any one of claims 63-71, wherein two of R₁, R₃, R₄, R₅, R₆, and R₈ are not H.
79. The compound of any one of claims 63-71, wherein one of R₁, R₃, R₄, R₅, R₆, and R₈ is alkyl or halogen.
80. The compound of any one of claims 63-71, wherein two of R₁, R₃, R₄, R₅, R₆, and R₈ are alkyl or halogen.
81. The compound of claim 79 or 80, wherein the compound is selected from:

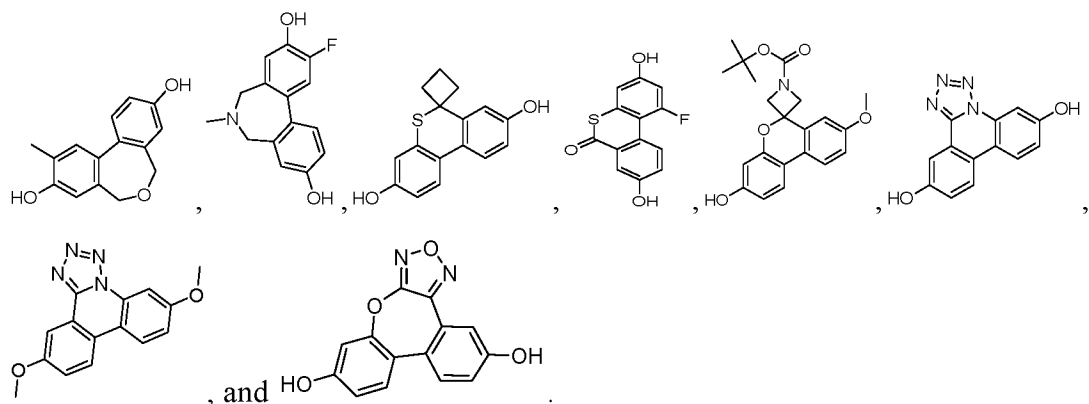




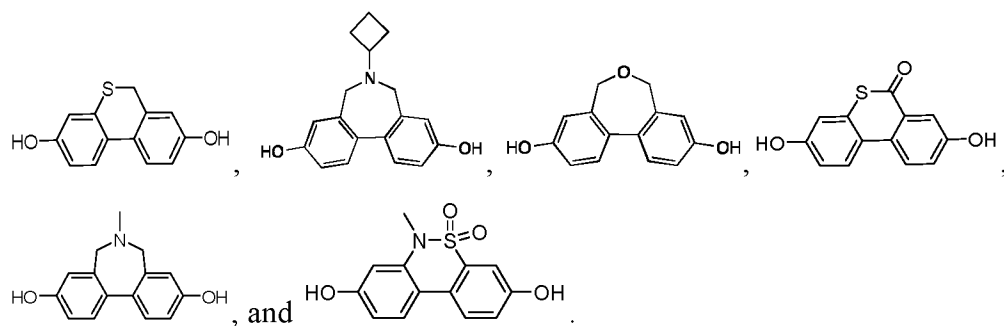
82. The compound of claim 63, wherein the compound is selected from:



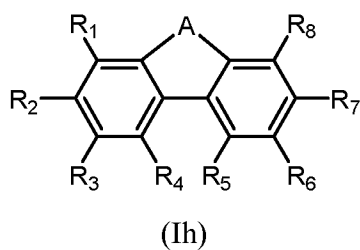




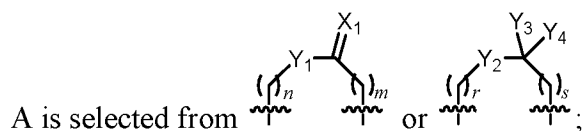
83. The compound of claim 63, wherein the compound is selected from:



84. A method of treating amyotrophic lateral sclerosis (ALS), comprising administering to a subject in need thereof an effective amount of a compound of Formula (Ih),



wherein



n and m are both 0; or one of n and m is 0 and the other of n and m is 1;

r and s are both 0; or one of r and s is 0 and the other of r and s is 1;

X_1 is O;

Y_1 is selected from O, NH, N-alkyl, and N-cycloalkyl;

Y_2 is O;

Y_3 and Y_4 are independently selected from H, halogen, and alkyl, or together with the carbon to which they are bonded combine to form a cycloalkyl or cycloheteroalkyl;

R_1 , R_4 , R_5 and R_8 are independently selected from H and halogen;

R_3 and R_6 are independently selected from H, CN, OH, CF_3 , halogen, and alkyl;

one of R_2 and R_7 is selected NH_2 , $NHCH_3$, and $N(CH_3)_2$ and the other of R_2 and R_7 is selected from H, halogen, OCH_3 , CN, CF_3 , CO_2H , NO_2 , $NHAc$, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkylamino, alkyl- R_9 , alkenyl- R_9 , alkynyl- R_9 , OR_{10} , NHR_{10} , $NR_{11}C(O)R_{12}$, $C(O)NR_{11}R_{12}$, and $NR_{11}SO_2R_{12}$;

each occurrence of R_9 is independently selected from OH, NH_2 , O-alkyl, O-alkyl-O-alkyl, alkylamino, $NHC(O)$ -alkyl, $N(CH_3)C(O)$ -alkyl, $NHSO_2$ -alkyl, $N(CH_3)SO_2$ -alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

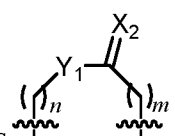
R_{10} is selected from H, C_2 - C_{12} alkyl, hydroxyalkyl, aminoalkyl, alkyl-O-alkyl, alkyl-O-alkyl-OH, alkyl-O-alkyl-O-alkyl, alkenyl, alkynyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, alkyl-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, SO_3H , SO_2 -alkyl, and SO_2 -haloalkyl;

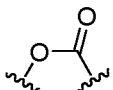
each occurrence of R_{11} is selected from H and alkyl; and

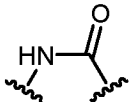
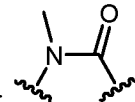
each occurrence of R_{12} is selected from alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, O-alkyl, aminoalkyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, and alkyl-heterocycloalkyl;

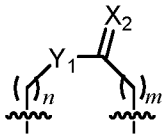
or a pharmaceutically acceptable salt thereof.

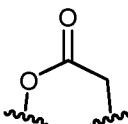
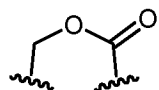
85. The compound of claim 84, wherein Y_1 is selected from O, NH, and N-alkyl.

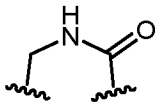
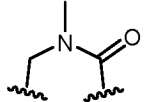
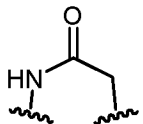
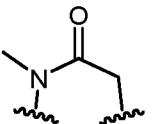
86. The compound of claim 84 or 85, wherein A is ; and n and m are both 0.

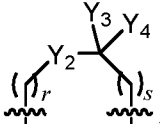
87. The compound of claim 84 or 85, wherein A is .

88. The compound of claim 84 or 85, wherein A is , or .

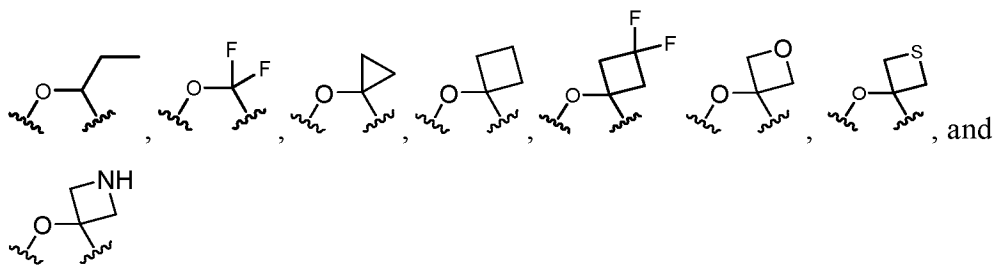
89. The compound of claim 84 or 85, wherein A is ; and one of n or m is 0 and the other of n or m is 1.

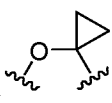
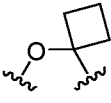
90. The compound of claim 89, wherein A is  or .

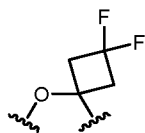
91. The compound of claim 89, wherein A is selected from , , , and .

92. The compound of claim 84, wherein A is ; and r and s are both 0.

93. The compound of claim 92, wherein A is selected from ,  ,  ,



94. The compound of claim 93, wherein A is selected from  ,  , and



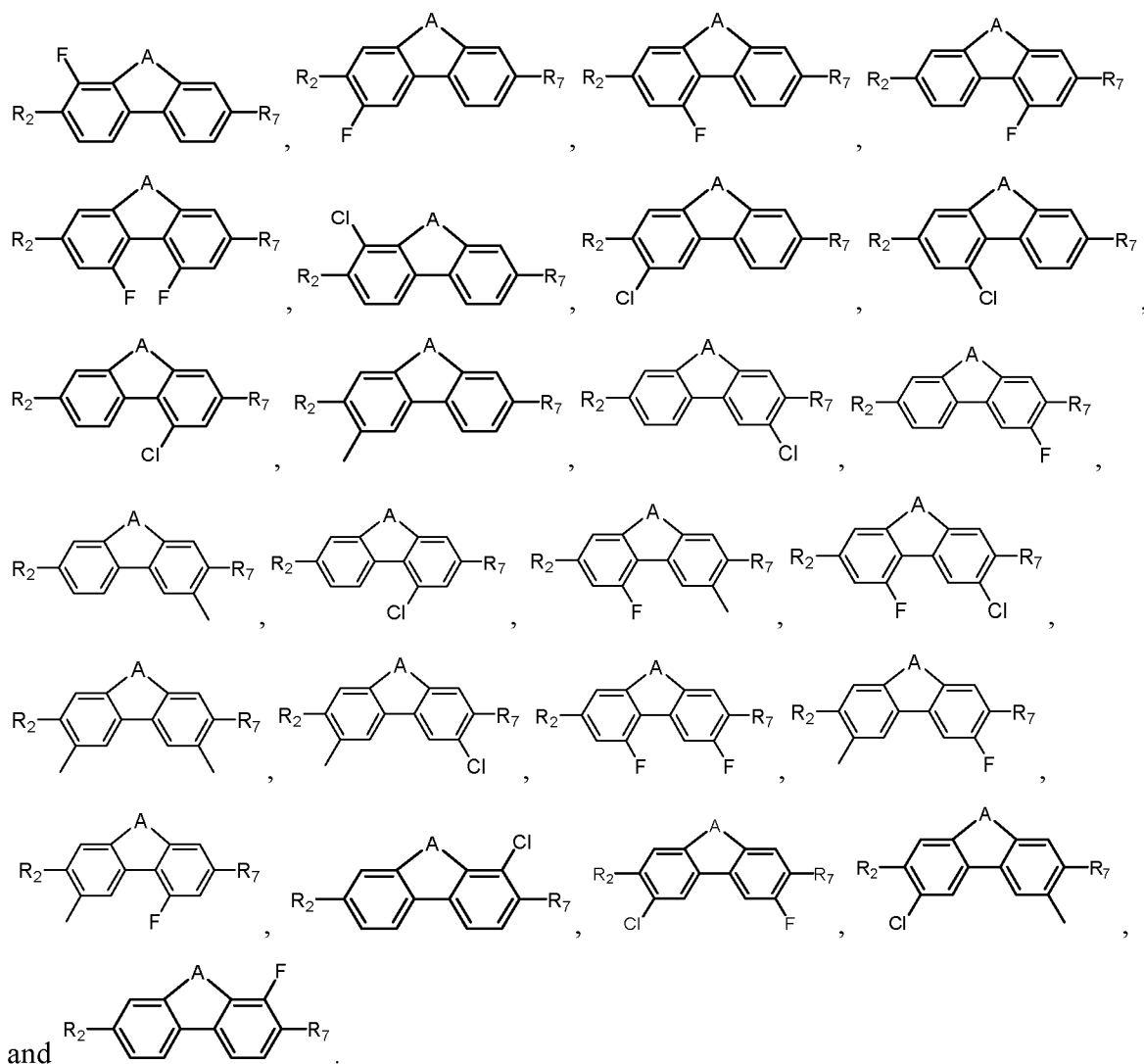
95. The compound of any one of claims 84-94, wherein R_2 is selected from NH_2 , $NHCH_3$, and $N(CH_3)_2$.
96. The compound of any one of claims 84-94, wherein R_7 is selected from H, OH, halogen, O-alkyl, and haloalkyl.
97. The compound of any one of claims 84-94, wherein
 R_7 is selected from alkynyl- R_9 and OR_{10} ;
 R_9 is OH; and
 R_{10} is alkyl-heterocycloalkyl.
98. The compound of any one of claims 84-97, wherein R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 are each H.
99. The compound of any one of claims 84-97, wherein one of R_1 , R_3 , R_4 , R_5 , R_6 , and R_8 is not H.

100. The compound of any one of claims 84-97, wherein two of R₁, R₃, R₄, R₅, R₆, and R₈ are not H.

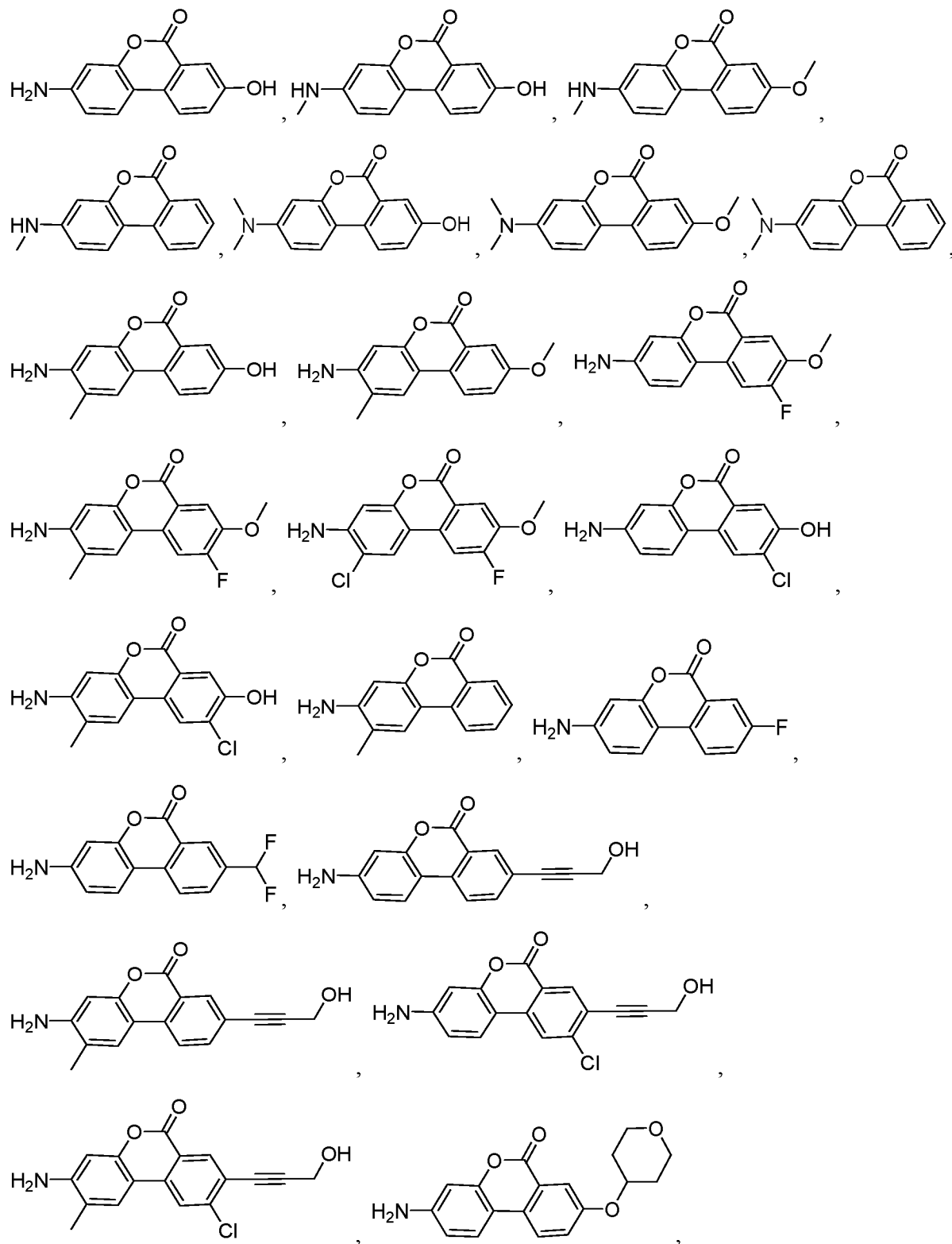
101. The compound of any one of claims 84-97, wherein one of R₁, R₃, R₄, R₅, R₆, and R₈ is alkyl or halogen.

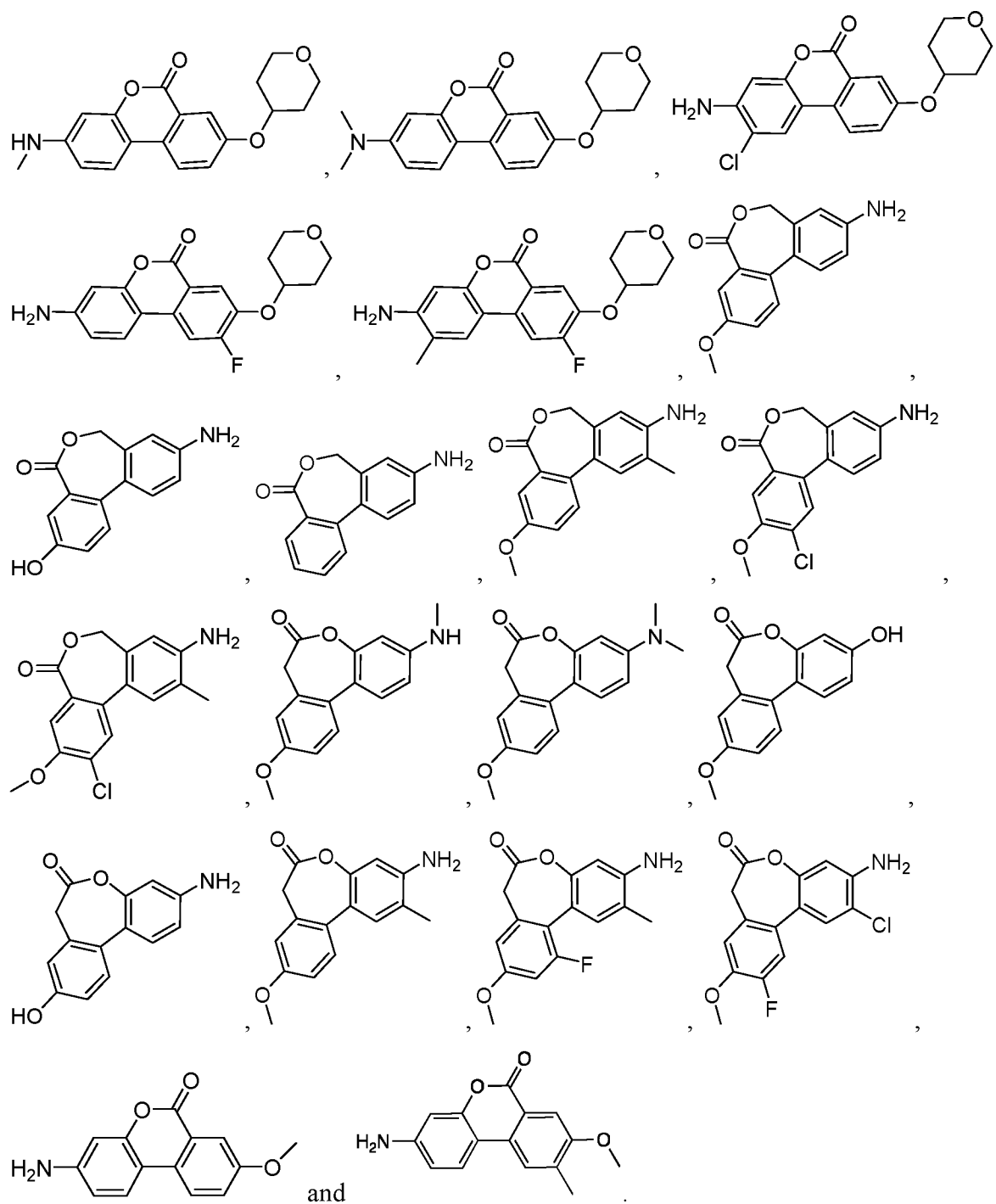
102. The compound of any one of claims 84-97, wherein two of R₁, R₃, R₄, R₅, R₆, and R₈ are independently alkyl or halogen.

103. The compound of claim 101 or 102, wherein the compound is selected from:

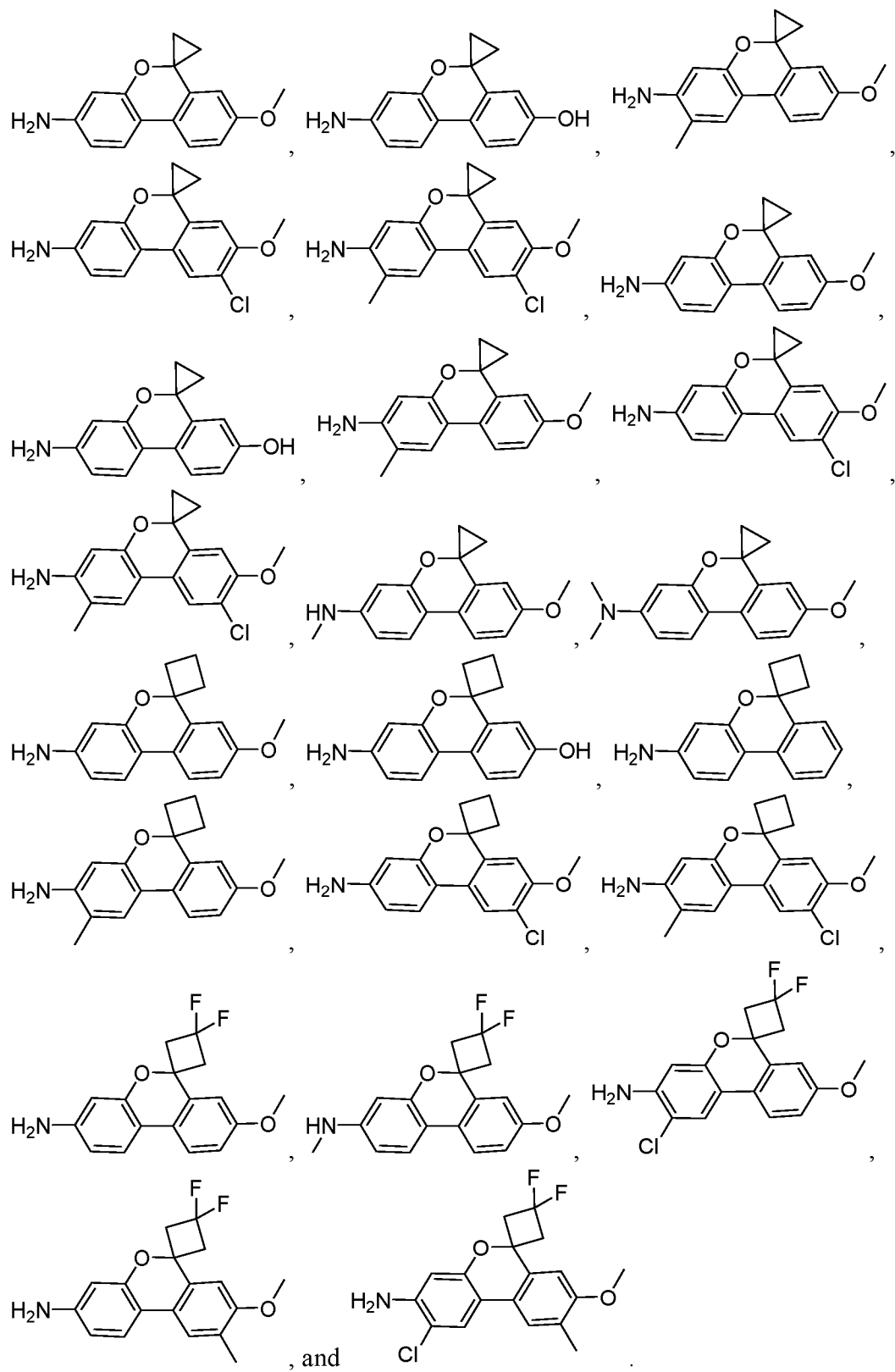


104. The compound of claim 84, wherein the compound is selected from:

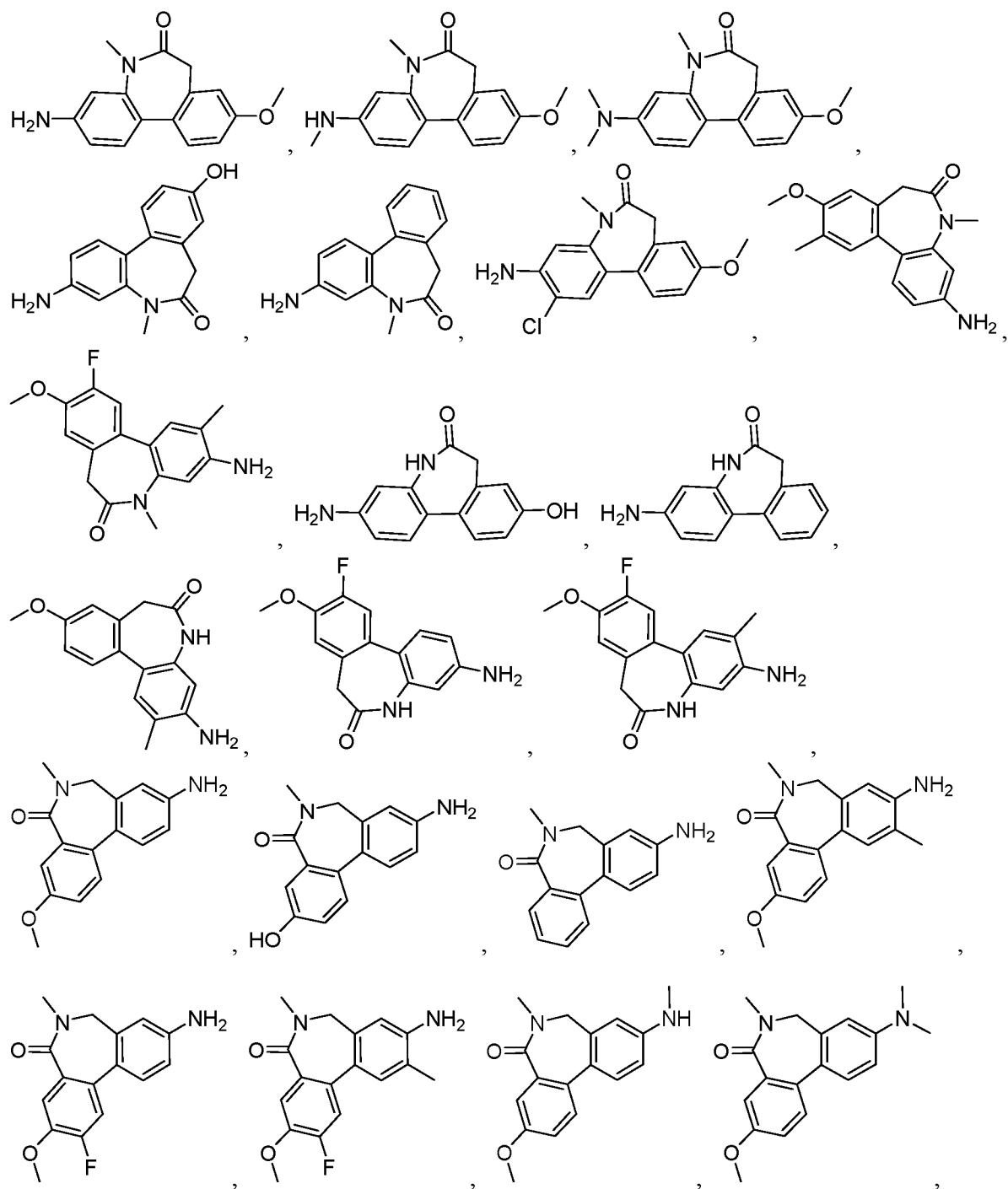


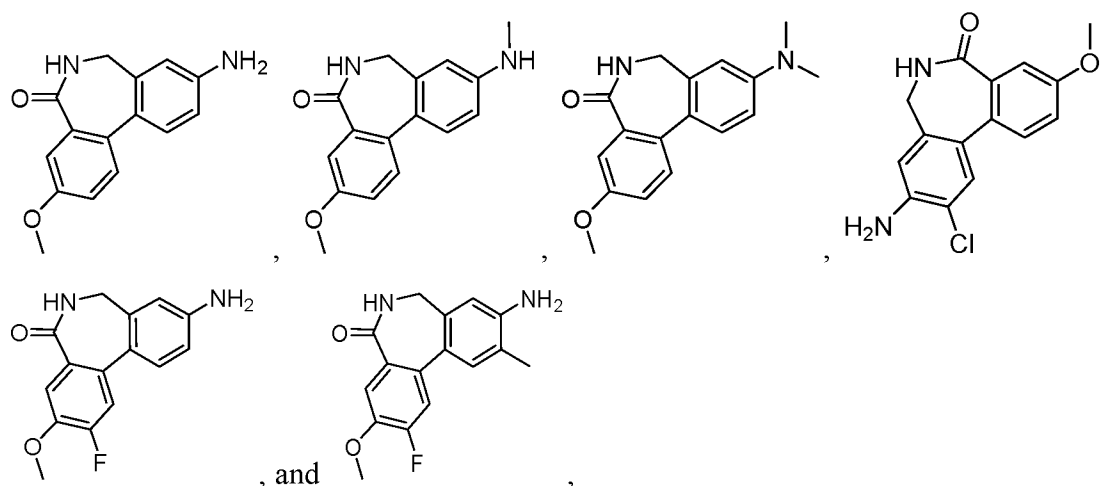


105. The compound of claim 84, wherein the compound is selected from:



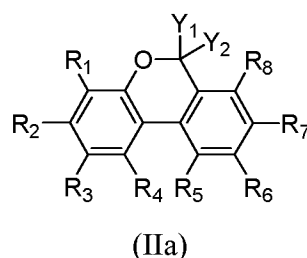
106. The compound of claim 84, wherein the compound is selected from:





or a pharmaceutically acceptable salt thereof.

107. A method of treating amyotrophic lateral sclerosis (ALS), comprising administering to a subject in need thereof an effective amount of a compound of Formula (IIa),



wherein

Y₁ and Y₂ are each alkyl; or taken together with the carbon to which they are bonded combine to form an unsubstituted or substituted spiro cycloalkyl;

R₁, R₄, R₅, and R₈ are independently selected from -H and halogen;

R₂ and R₇ are independently selected from -H, -OH, -OAc, -NH₂, halogen, -CN, -CF₃, -CO₂H, -NO₂, -NHAc, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkylamino, alkyl-R₉, alkenyl-R₉, alkynyl-R₉, -OR₁₀, -NHR₁₀, -NR₁₁C(O)R₁₂, -C(O)NR₁₁R₁₂, and -NR₁₁SO₂R₁₂;

R₃ and R₆ are alkyl;

each occurrence of R₉ is independently selected from OH, NH₂, O-alkyl, O-alkyl-O-alkyl, alkylamino, NHC(O)-alkyl, N(CH₃)C(O)-alkyl, NHSO₂-alkyl, N(CH₃)SO₂-alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

R₁₀ is selected from alkyl, hydroxyalkyl, aminoalkyl, alkyl-O-alkyl, alkyl-O-alkyl-OH, alkyl-O-alkyl-O-alkyl, alkenyl, alkynyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, alkyl-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, SO₃H, SO₂-alkyl, and SO₂-haloalkyl;

each occurrence of R₁₁ is selected from H and alkyl; and

each occurrence of R₁₂ is selected from alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, O-alkyl, aminoalkyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, and alkyl-heterocycloalkyl;

provided that when R₁, R₄, R₅, and R₈ are each -H, R₂ and R₇ are each -OH, and R₃ and R₆ are each CH₃, then Y₁ and Y₂ are not each -Me or are not taken together with the carbon to which they are bonded to form an unsubstituted spiro cyclobutyl;

or a pharmaceutically acceptable salt thereof.

108. The method of claim 107, wherein Y₁ and Y₂ are each independently C₁-C₄ alkyl.

109. The method of claim 107, wherein Y₁ and Y₂ are each -CH₃.

110. The method of claim 107, wherein Y₁ and Y₂ taken together with the carbon to which they are bonded combine to form an unsubstituted spiro cycloalkyl.

111. The method of claim 110, wherein Y₁ and Y₂ taken together with the carbon to which they are bonded combine to form an unsubstituted spiro cyclopropyl, cyclobutyl, or cyclopentyl.

112. The method of any one of claims 107-111, wherein R₃ and R₆ are each independently C₁-C₄ alkyl.

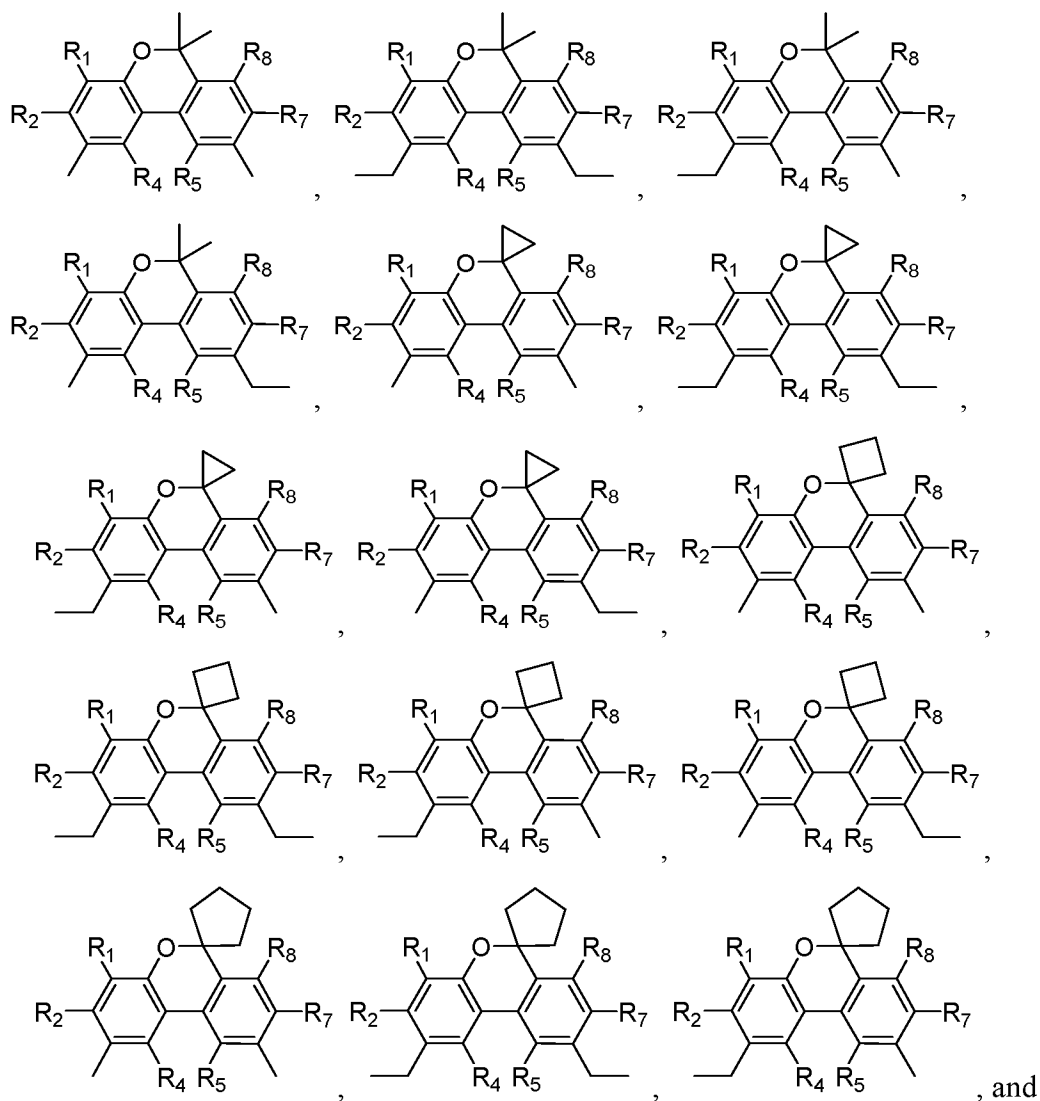
113. The method of any one of claims 107-112, wherein R₃ and R₆ are each independently selected from -CH₃ and -CH₂CH₃.

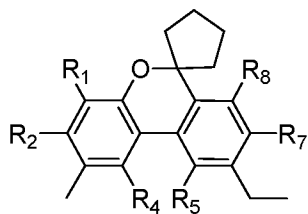
114. The method of any one of claims 107-112, wherein R₃ and R₆ are each -CH₃.

115. The method of any one of claims 107-112, wherein R_3 and R_6 are each $-\text{CH}_2\text{CH}_3$.

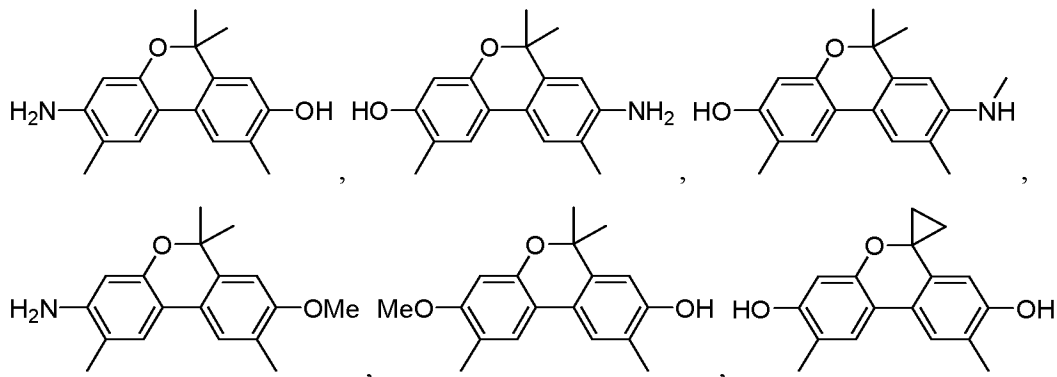
116. The method of any one of claims 107-112, wherein one of R_3 and R_6 is $-\text{CH}_3$ and the other of R_3 and R_6 is $-\text{CH}_2\text{CH}_3$.

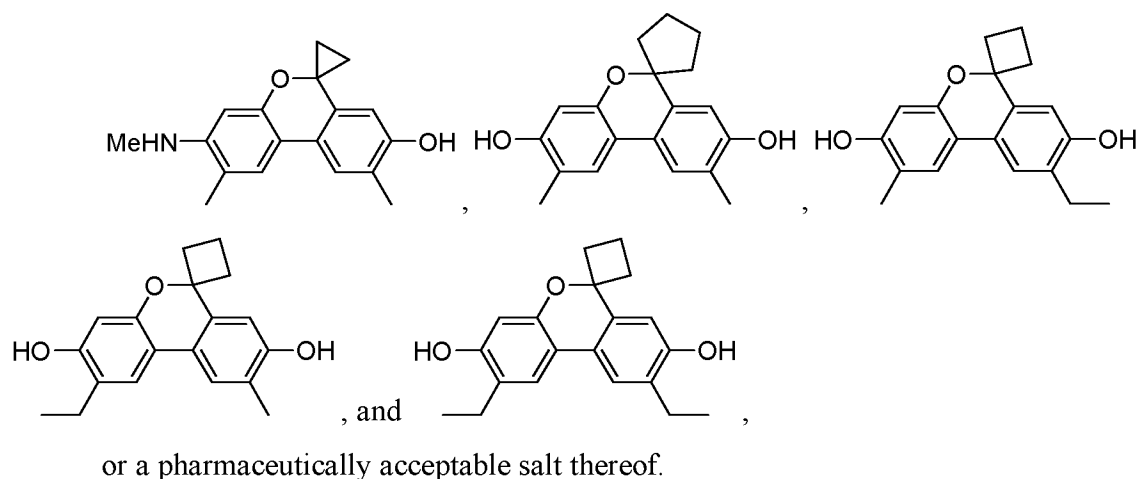
117. The method of any one of claims 107-116, having the structure selected from:



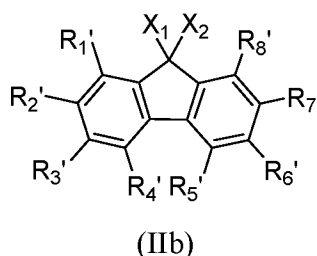


118. The method of any one of claims 107-117, wherein R_2 and R_7 are independently selected from $-OH$, $-NH_2$, alkylamino, and $-OR_{10}$.
119. The method of any one of claims 107-117, wherein R_2 and R_7 are each OH .
120. The method of any one of claims 107-117, wherein R_2 is $-OH$; and R_7 is $-OCH_3$.
121. The method of any one of claims 107-117, wherein R_7 is $-OH$; and R_2 is $-OCH_3$.
122. The method of any one of claims 107-117, wherein R_2 is selected from $-NH_2$, $-NHCH_3$, and $-NH(CH_3)_2$; and R_7 is OH .
123. The method of any one of claims 107-117, wherein R_7 is selected from $-NH_2$, $-NHCH_3$, and $-NH(CH_3)_2$; and R_2 is OH .
124. The method of any one of claims 118-123, wherein R_1 , R_4 , R_5 , and R_8 are each $-H$.
125. The method of claim 107, wherein the compound is selected from:





126. A method of treating amyotrophic lateral sclerosis (ALS), comprising administering to a subject in need thereof an effective amount of a compound of Formula (IIb),



wherein

X_1 and X_2 are each alkyl; or taken together with the carbon to which they are bonded combine to form an unsubstituted or substituted spiro cycloalkyl;

R_1' , R_4' , R_5' , and R_8' are independently selected from -H, -OH, -NH₂, alkyl, and halogen;

R_2' , R_3' , R_6' , and R_7' are independently selected from -H, -OH, -OAc, -NH₂, halogen, -CN, -CF₃, -CO₂H, -NO₂, -NHAc, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkylamino, and -OR_{8'}; and

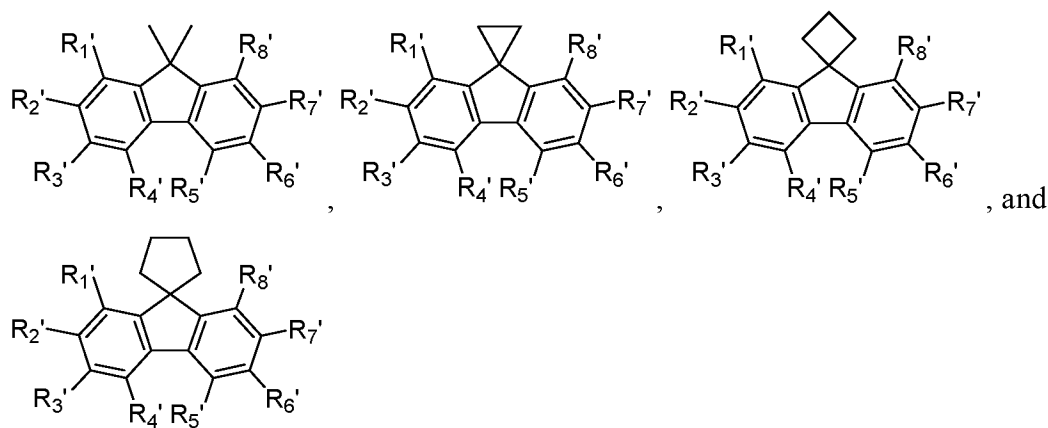
R_8' is selected from alkyl, hydroxyalkyl, aminoalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

or a pharmaceutically acceptable salt thereof.

127. The method of claim 126, wherein X_1 and X_2 are each independently C₁-C₄ alkyl.

128. The method of claim 126, wherein X_1 and X_2 are each -CH₃.

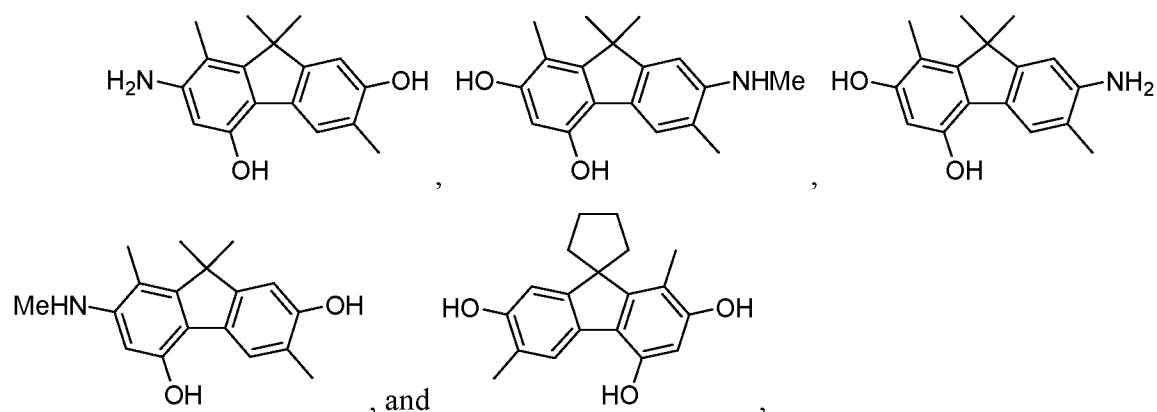
129. The method of claim 126, wherein X_1 and X_2 taken together with the carbon to which they are bonded combine to form an unsubstituted spiro cycloalkyl.
130. The method of claim 129, wherein X_1 and X_2 taken together with the carbon to which they are bonded combine to form an unsubstituted spiro cyclopropyl, cyclobutyl, or cyclopentyl.
131. The method of any one of claims 126-130, having the structure selected from:



132. The method of any one of claims 126-131, wherein R_2' and R_7' are independently selected from $-\text{OH}$, $-\text{NH}_2$, alkylamino, and $-\text{OR}_{10}$.
133. The method of any one of claims 126-131, wherein R_2' and R_7' are each OH .
134. The method of any one of claims 126-131, wherein R_2' is $-\text{OH}$; and R_7' is $-\text{OCH}_3$.
135. The method of any one of claims 126-131, wherein R_7' is $-\text{OH}$; and R_2' is $-\text{OCH}_3$.
136. The method of any one of claims 126-131, wherein R_2' is selected from $-\text{NH}_2$, $-\text{NHCH}_3$, and $-\text{NH}(\text{CH}_3)_2$; and R_7' is OH .

137. The method of any one of claims 126-131, wherein R_7' is selected from $-NH_2$, $-NHCH_3$, and $-NH(CH_3)_2$; and R_2' is OH.
138. The method of any one of claims 126-137, wherein R_3' and R_6' are each independently $-H$ or C_1 - C_4 alkyl.
139. The method of claim 138, wherein R_3' and R_6' are each independently $-H$ or $-CH_3$.
140. The method of any one of claims 126-137, wherein R_1' and R_8' are each independently $-H$ or C_1 - C_4 alkyl.
141. The method of claim 140, wherein R_1' and R_8' are each independently $-H$ or $-CH_3$.
142. The method of any one of claims 126-137, wherein R_4' and R_5' are each independently $-H$ or $-OH$.

143. The method of claim 126, wherein the compound is selected from:



or a pharmaceutically acceptable salt thereof.

144. The method of any one of claims 1, 22, 36, 45, 63, and 83, wherein the compound is a compound selected from Table A.

145. The method of any one of claims 1-144, wherein amyotrophic lateral sclerosis (ALS) is C9orf72 amyotrophic lateral sclerosis (C9-ALS).