



(51) International Patent Classification:

C07D 217/04 (2006.01) A61K 31/472 (2006.01)

SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(21) International Application Number:

PCT/US2024/036369

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

(22) International Filing Date:

01 July 2024 (01.07.2024)

Published:

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

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

63/524,052 29 June 2023 (29.06.2023) US

(71) Applicant: OHIO STATE INNOVATION FOUNDATION [US/US]; Mount Hall, 1st Floor, 1050 Carmack Rd, Columbus, Ohio 43210 (US).

(72) Inventors: DENKO, Nicholas; c/o Ohio State Innovation Foundation, Mount Hall, 1st Floor, 1050 Carmack Rd, Columbus, Ohio 43210 (US). MITTON-FRY, Mark; c/o Ohio State Innovation Foundation, Mount Hall, 1st Floor, 1050 Carmack Rd, Columbus, Ohio 43210 (US). HAINES, Ben; c/o Ohio State Innovation Foundation, Mount Hall, 1st Floor, 1050 Carmack Rd, Columbus, Ohio 43210 (US). BENEJ, Martin; c/o Ohio State Innovation Foundation, Mount Hall, 1st Floor, 1050 Carmack Rd, Columbus, Ohio 43210 (US).

(74) Agent: ANDREANSKY, Eric S. et al.; Meunier Carlin & Curfman LLC, 999 Peachtree St. NE, Suite 1300, Atlanta, Georgia 30309 (US).

(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,

(54) Title: MITOCHONDRIAL COMPLEX I INHIBITORS WITH REDUCED PHOSPHODIESTERASE INHIBITION

(57) Abstract: This disclosure provides compounds for treating medical disorders, and more particularly inhibitors of mitochondrial complex I which are useful in treating cancers, such as by sensitizing cancers to radiation therapy.

WO 2025/007113 A2

MITOCHONDRIAL COMPLEX I INHIBITORS WITH REDUCED PHOSPHODIESTERASE INHIBITION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority to United States Provisional
Application No. 63/524,052 filed June 29, 2023, the disclosure of which is incorporated
herein by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with government support under Grant/Contract Nos.
CA255334 and CA262388 awarded by the National Institutes of Health. The government
has certain rights in the invention.

TECHNICAL FIELD

This disclosure relates to compounds for treating medical disorders, and more
particularly to inhibitors of mitochondrial complex I which are useful in treating cancers,
such as by sensitizing cancers to radiation therapy.

BACKGROUND

Mitochondrial complex I inhibitors such as papaverine and SMV-32 have been
previously shown to sensitive tumors to radiation therapy (see Proc. Natl. Acad. Sci. 2018,
115(49), E11561). However, papaverine also inhibits PDE10a, and this off-target activity is
believed to lead to side effects that limit the dose that can be administered clinically. SMV-
32 partially overcomes this liability, but there is a clear need for additional compounds
which further dissociate mitochondrial complex I inhibition from PDE10a inhibition.

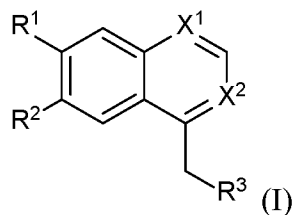
This disclosure addresses these as well as other needs.

SUMMARY

The present disclosure provides compounds which are useful as mitochondrial
complex I inhibitors which also show limited inhibition of phosphodiesterases (particularly

PDE10a). Also provided are methods of using the compounds described herein in the treatment of medical disorders.

In one aspect, a compound is provided of Formula I



or a pharmaceutically acceptable salt thereof;

wherein all variables are as defined herein.

In another aspect, a pharmaceutical composition is provided comprising a compound described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

In another aspect, a method of treating a cancer in a subject in need thereof is provided comprising administering to the subject a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein.

In a further aspect, a method of sensitizing a cancer to radiation therapy in a subject in need thereof is provided, the method comprising administering to the subject a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein prior to or concurrently with the radiation therapy.

The details of one or more embodiments of the disclosure are set forth in the accompanying description below. Other features, objects, and advantages of the disclosure will be apparent from the description and the claims.

DETAILED DESCRIPTION

The following description of the disclosure is provided as an enabling teaching of the disclosure in its best, currently known embodiments. Many modifications and other embodiments disclosed herein will come to mind to one skilled in the art to which the disclosed compositions and methods pertain, benefiting from the teachings presented in the descriptions herein and the associated drawings. Therefore, it is understood that the

disclosures are not limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended claims. The skilled artisan will recognize many variants and adaptations of the aspects described herein. These variants and adaptations are intended to be included in the teachings of this disclosure and to be encompassed by the claims herein.

Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation.

As apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features that may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present disclosure.

Any recited method can be carried out in the order of events recited or any other order that is logically possible. Unless otherwise expressly stated, it is in no way intended that any method or aspect set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not explicitly state in the claims or descriptions that the steps are to be limited to a particular order, it is in no way intended that an order be inferred in any respect. This holds for any possible non-express basis for interpretation, including logic concerning arrangement of steps or operational flow, meaning derived from grammatical organization or punctuation, or the number or type of aspects described in the specification.

All publications mentioned herein are incorporated by reference to disclose and describe the methods or materials in connection with which the publications are cited. The publications discussed herein are provided solely for their disclosure before the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by prior invention. Further, the dates of publication provided herein can be different from the actual publication dates, which can require independent confirmation.

It is also to be understood that the terminology herein describes particular aspects only and is not intended to be limiting. Unless defined otherwise, all technical and scientific terms herein have the same meaning as commonly understood by one of ordinary skill in the art to which the disclosed compositions and methods belong. It can be further

understood that terms, such as those defined in commonly used dictionaries, should be interpreted as having a meaning that is consistent with their meaning in the context of the specification and relevant art and should not be interpreted in an idealized or overly formal sense unless expressly defined herein.

Before describing the various aspects of the present disclosure, the following definitions are provided and should be used unless otherwise indicated. Additional terms may be defined elsewhere in the present disclosure.

Definitions

As used herein, “comprising” is interpreted as specifying the presence of the stated features, integers, steps, or components but does not preclude the presence or addition of one or more features, integers, steps, components, or groups thereof. Moreover, each of the terms “by,” “comprising,” “comprises,” “comprised of,” “including,” “includes,” “included,” “involving,” “involves,” “involved,” and “such as” are used in their open, non-limiting sense and may be used interchangeably. Further, the term “comprising” is intended to include examples and aspects encompassed by the terms “consisting essentially of” and “consisting of.” Similarly, “consisting essentially of” is intended to include examples encompassed by the term “consisting of.”

As used in the specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context dictates otherwise. Thus, for example, reference to “a compound,” “a composition,” or “a cancer” includes, but is not limited to, two or more such compounds, compositions, or cancers, and the like.

As used herein, the terms “about,” “approximate,” “at or about,” and “substantially” mean that the amount or value in question can be the exact value or a value that provides equivalent results or effects as recited in the claims or taught herein. That is, amounts, sizes, formulations, parameters, and other quantities and characteristics are not and need not be exact but may be approximate, larger or smaller, as desired, reflecting tolerances, conversion factors, rounding, measurement error, and the like, and other factors known to those of skill in the art such that equivalent results or effects are obtained. In some circumstances, the value that provides equivalent results or effects cannot be reasonably determined. In such cases, as used herein, “about” and “at or about” mean the nominal value indicated $\pm 10\%$ variation unless otherwise indicated or inferred. In general, an amount, size, formulation, parameter, or other quantity or characteristic is “about,” “approximate,” or “at

or about,” whether or not expressly stated to be such. Where “about,” “approximate,” or “at or about” is used before a quantitative value, the parameter also includes the specific quantitative value itself unless expressly stated otherwise.

As used herein, the term “therapeutically effective amount” refers to an amount sufficient to achieve the desired therapeutic result or to have an effect on undesired symptoms but generally insufficient to cause adverse side effects. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors, including the disorder being treated and the severity of the disorder; the specific composition employed; the age, body weight, general health, sex, and diet of the patient; the time of administration; the route of administration; the rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the particular compound employed and like factors within the knowledge and expertise of the health practitioner and which may be well known in the medical arts. In the case of treating a particular disease or condition, in some instances, the desired response can be inhibiting the progression of the disease or condition. This may involve only slowing the progression of the disease temporarily. However, in other instances, it may be desirable to permanently halt the progression of the disease. This can be monitored by routine diagnostic methods known to one of ordinary skill in the art for any particular disease. The desired response to treatment of the disease or condition can also be delaying the onset or even preventing the onset.

For example, it is well within the skill of the art to start doses of a compound at levels lower than those required to achieve the desired therapeutic effect and to increase the dosage gradually until the desired effect is achieved. If desired, the effective daily dose can be divided into multiple doses for administration. Consequently, single dose compositions can contain such amounts or submultiples thereof to make up the daily dose. The individual physician can adjust the dosage in the event of any contraindications. It is generally preferred that a maximum dose of the pharmacological agents of the invention (alone or in combination with other therapeutic agents) be used, that is, the highest safe dose according to sound medical judgment. However, a patient may insist on a lower or tolerable dose for medical reasons, psychological reasons, or virtually any other reason.

A response to a therapeutically effective dose of a disclosed compound or composition can be measured by determining the physiological effects of the treatment or medication, such as the decrease or lack of disease symptoms following the administration

of the treatment or pharmacological agent. Other assays will be known to one of ordinary skill in the art and can be employed for measuring the level of the response. The amount of a treatment may be varied, for example, by increasing or decreasing the amount of a disclosed compound or pharmaceutical composition, changing the disclosed compound or pharmaceutical composition administered, changing the route of administration, changing the dosage timing, and so on. Dosage can vary and can be administered in one or more dose administrations daily for one or several days. Guidance can be found in the literature for appropriate dosages for given classes of pharmaceutical products.

As used herein, “optional” or “optionally” means that the subsequently described event or circumstance can or cannot occur. The description includes instances where said event or circumstance occurs and those where it does not.

As used interchangeably herein, “subject,” “individual,” or “patient” can refer to a vertebrate organism, such as a mammal (e.g., human). “Subject” can also refer to a cell, a population of cells, a tissue, an organ, or an organism, preferably to a human and constituents thereof.

As used herein, “treating” and “treatment” generally refer to obtaining a desired pharmacological or physiological effect. The effect can be but does not necessarily have to be prophylactic in preventing or partially preventing a disease, symptom, or condition such as a cancer. The effect can be therapeutic regarding a partial or complete cure of a disease, condition, symptom, or adverse effect attributed to the disease, disorder, or condition. The term “treatment” as used herein can include any treatment of a disorder in a subject, particularly a human. It can include any one or more of the following: (a) preventing the disease from occurring in a subject who may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development; and (c) relieving the disease, i.e., mitigating or ameliorating the disease or its symptoms or conditions. The term “treatment,” as used herein, can refer to both therapeutic treatment alone, prophylactic treatment alone, or both therapeutic and prophylactic treatment. Those in need of treatment (i.e., subjects in need thereof) can include those already with the disorder or those in which the disorder is to be prevented. As used herein, the term “treating” can include inhibiting the disease, disorder, or condition, e.g., impeding its progress; and relieving the disease, disorder, or condition, e.g., causing regression of the disease, disorder, or condition. Treating the disease, disorder, or condition can include ameliorating at least one symptom of the particular disease, disorder, or condition, even if

the underlying pathophysiology is not affected, e.g., such as treating the pain of a subject by administration of an analgesic agent even though such agent does not treat the cause of the pain.

As used herein, “dose,” “unit dose,” or “dosage” can refer to physically discrete units suitable for use in a subject, each unit containing a predetermined quantity of a disclosed compound or a pharmaceutical composition thereof calculated to produce the desired response or responses in association with its administration.

As used herein, “therapeutic” can refer to treating, healing, or ameliorating a disease, disorder, condition, or side effect or decreasing the rate of advancement of a disease, disorder, condition, or side effect.

Chemical Definitions

Compounds are described using standard nomenclature. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

The compounds described herein include enantiomers, mixtures of enantiomers, diastereomers, tautomers, racemates and other isomers, such as rotamers, as if each is specifically described, unless otherwise indicated or otherwise excluded by context. It is to be understood that the compounds provided herein may contain chiral centers. Such chiral centers may be of either the (*R*-) or (*S*-) configuration. The compounds provided herein may either be enantiomerically pure, or be diastereomeric or enantiomeric mixtures. It is to be understood that the chiral centers of the compounds provided herein may undergo epimerization *in vivo*. As such, one of skill in the art will recognize that administration of a compound in its (*R*-) form is equivalent, for compounds that undergo epimerization *in vivo*, to administration of the compound in its (*S*-) form. Unless stated to the contrary, a formula with chemical bonds shown only as solid lines and not as wedges or dashed lines contemplates each possible isomer, e.g., each enantiomer, diastereomer, and meso compound, and a mixture of isomers, such as a racemic or scalemic mixture.

Compounds described herein may contain one or more double bonds and, thus, potentially give rise to cis/trans (*E/Z*) isomers, as well as other conformational isomers. Unless states to the contrary, all such possible isomers are contemplated, as well as mixtures of such isomers.

Compounds described herein may also present as an equilibrium of tautomers. For example, ketones with an α -hydrogen can exist in an equilibrium of the keto form and the enol form. Likewise, amides with an N-hydrogen can exist in an equilibrium of the amide form and the imidic acid form. Unless stated to the contrary, all possible tautomers of the compounds described herein are contemplated.

A dash (“-”) that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, $-(C=O)NH_2$ is attached through the carbon of the keto ($C=O$) group.

The term “substituted”, as used herein, means that any one or more hydrogens on the designated atom or group is replaced with a moiety selected from the indicated group, provided that the designated atom’s normal valence is not exceeded and the resulting compound is stable. For example, when the substituent is oxo (i.e., $=O$) then two hydrogens on the atom are replaced. For example, a pyridyl group substituted by oxo is a pyridine. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds or useful synthetic intermediates. A stable active compound refers to a compound that can be isolated and can be formulated into a dosage form with a shelf life of at least one month. A stable manufacturing intermediate or precursor to an active compound is stable if it does not degrade within the period needed for reaction or other use. A stable moiety or substituent group is one that does not degrade, react or fall apart within the period necessary for use. Non-limiting examples of unstable moieties are those that combine heteroatoms in an unstable arrangement, as typically known and identifiable to those of skill in the art.

Any suitable group may be present on a “substituted” or “optionally substituted” position that forms a stable molecule and meets the desired purpose of the invention and includes, but is not limited to: alkyl, haloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycle, aldehyde, amino, carboxylic acid, ester, ether, halo, hydroxy, keto, nitro, cyano, azido, oxo, silyl, sulfo-oxo, sulfonyl, sulfone, sulfoxide, sulfonylamino, or thiol.

As used herein, the symbol “” (which hereinafter can be referred to as “a point of attachment bond”) denotes a bond that is a point of attachment between two chemical entities, one of which is depicted as being attached to the point of attachment bond and the other of which is not depicted as being attached to the point of attachment bond. For

example, “ $\text{XY} \text{---} \text{Z}$ ” indicates that the chemical entity “XY” is bonded to another chemical entity via the point of attachment bond. Furthermore, the specific point of attachment to the non-depicted chemical entity can be specified by inference. For example, the compound $\text{CH}_3\text{-R}^3$, wherein R^3 is H or “ $\text{XY} \text{---} \text{Z}$ ” infers that when R^3 is “XY”, the point of attachment bond is the same bond as the bond by which R^3 is depicted as being bonded to CH_3 .

“Alkyl” is a straight chain or branched saturated aliphatic hydrocarbon group. In certain embodiments, the alkyl is $\text{C}_1\text{-C}_2$, $\text{C}_1\text{-C}_3$, or $\text{C}_1\text{-C}_6$ (i.e., the alkyl chain can be 1, 2, 3, 4, 5, or 6 carbons in length). The specified ranges as used herein indicate an alkyl group with length of each member of the range described as an independent species. For example, $\text{C}_1\text{-C}_6\text{alkyl}$ as used herein indicates an alkyl group having from 1, 2, 3, 4, 5, or 6 carbon atoms and is intended to mean that each of these is described as an independent species and $\text{C}_1\text{-C}_4\text{alkyl}$ as used herein indicates an alkyl group having from 1, 2, 3, or 4 carbon atoms and is intended to mean that each of these is described as an independent species. When $\text{C}_0\text{-C}_n\text{alkyl}$ is used herein in conjunction with another group, for example $(\text{C}_3\text{-C}_7\text{cycloalkyl})\text{C}_0\text{-C}_4\text{alkyl}$, or $\text{-C}_0\text{-C}_4(\text{C}_3\text{-C}_7\text{cycloalkyl})$, the indicated group, in this case cycloalkyl, is either directly bound by a single covalent bond (C_0alkyl), or attached by an alkyl chain, in this case 1, 2, 3, or 4 carbon atoms. Alkyls can also be attached via other groups such as heteroatoms, as in $\text{-O-C}_0\text{-C}_4\text{alkyl}(\text{C}_3\text{-C}_7\text{cycloalkyl})$. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, tert-pentyl, neopentyl, n-hexyl, 2-methylpentane, 3-methylpentane, 2,2-dimethylbutane, and 2,3-dimethylbutane. In some embodiments, the alkyl group is optionally substituted as described herein. The term “alkyl” as used herein is not intended to be limited to monovalent radicals and may include polyvalent radical groups as appropriate, such as divalent, trivalent, tetravalent, pentavalent, and hexavalent alkyl, and the like, based on the position and location of such groups in the compounds described herein as would be readily understood by the skilled person.

“Cycloalkyl” is a saturated mono- or multi-cyclic hydrocarbon ring system. When composed of two or more rings, the rings may be joined together in a fused or bridged fashion. Non-limiting examples of typical cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. In some embodiments, the cycloalkyl group is optionally substituted as described herein. The term “cycloalkyl” as used herein is

not intended to be limited to monovalent radicals and may include polyvalent radical groups as appropriate, such as divalent, trivalent, tetravalent, pentavalent, and hexavalent cycloalkyl, and the like, based on the position and location of such groups in the compounds described herein as would be readily understood by the skilled person.

5 “Alkenyl” is a straight or branched chain aliphatic hydrocarbon group having one or more carbon-carbon double bonds, each of which is independently either cis or trans, that may occur at a stable point along the chain. Non-limiting examples include C₂-C₄alkenyl and C₂-C₆alkenyl (i.e., having 2, 3, 4, 5, or 6 carbons). The specified ranges as used herein indicate an alkenyl group having each member of the range described as an independent
10 species, as described above for the alkyl moiety. Examples of alkenyl include, but are not limited to, ethenyl and propenyl. In one embodiment, the alkenyl group is optionally substituted as described herein. The term “alkenyl” as used herein is not intended to be limited to monovalent radicals and may include polyvalent radical groups as appropriate, such as divalent, trivalent, tetravalent, pentavalent, and hexavalent alkenyl, and the like,
15 based on the position and location of such groups in the compounds described herein as would be readily understood by the skilled person.

 “Alkynyl” is a straight or branched chain aliphatic hydrocarbon group having one or more carbon-carbon triple bonds that may occur at any stable point along the chain, for example, C₂-C₄alkynyl or C₂-C₆alkynyl (i.e., having 2, 3, 4, 5, or 6 carbons). The specified
20 ranges as used herein indicate an alkynyl group having each member of the range described as an independent species, as described above for the alkyl moiety. Examples of alkynyl include, but are not limited to, ethynyl, propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentyne, 2-pentyne, 3-pentyne, 4-pentyne, 1-hexyne, 2-hexyne, 3-hexyne, 4-hexyne, and 5-hexyne. In one embodiment, the alkynyl group is optionally substituted as described
25 herein. The term “alkynyl” as used herein is not intended to be limited to monovalent radicals and may include polyvalent radical groups as appropriate, such as divalent, trivalent, tetravalent, pentavalent, and hexavalent alkynyl, and the like, based on the position and location of such groups in the compounds described herein as would be readily understood by the skilled person.

30 “Alkoxy” is an alkyl group as defined above covalently bound through an oxygen bridge (-O-). Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, 2-butoxy, tert-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, n-hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy. Similarly, an

“alkylthio” or “thioalkyl” group is an alkyl group as defined above with the indicated number of carbon atoms covalently bound through a sulfur bridge (-S-).

“Alkanoyl” is an alkyl group as defined above covalently bound through a carbonyl (C=O) bridge. The carbonyl carbon is included in the number of carbons, for example C₂alkanoyl is a CH₃(C=O)- group. In one embodiment, the alkanoyl group is optionally substituted as described herein.

“Halo” or “halogen” indicates, independently, any of fluoro, chloro, bromo or iodo.

“Aryl” indicates an aromatic group containing only carbon in the aromatic ring or rings. In one embodiment, the aryl group contains 1 to 3 separate or fused rings and is 6 to 14 or 18 ring atoms, without heteroatoms as ring members. When indicated, such aryl groups may be further substituted with carbon or non-carbon atoms or groups. Such substitution may include fusion to a 4- to 7- or 5- to 7-membered saturated or partially unsaturated cyclic group that optionally contains 1, 2, or 3 heteroatoms independently selected from N, O, B, P, Si and S, to form, for example, a 3,4-methylenedioxyphenyl group. Aryl groups include, for example, phenyl and naphthyl, including 1-naphthyl and 2-naphthyl. In one embodiment, aryl groups are pendant. An example of a pendant ring is a phenyl group substituted with a phenyl group. In one embodiment, the aryl group is optionally substituted as described herein. The term “aryl” as used herein is not intended to be limited to monovalent radicals and may include polyvalent radical groups as appropriate, such as divalent, trivalent, tetravalent, pentavalent, and hexavalent aryl, and the like, based on the position and location of such groups in the compounds described herein as would be readily understood by the skilled person.

The term “heterocycle” refers to saturated and partially saturated heteroatom-containing ring radicals, where the heteroatoms may be selected from N, O, and S. The term heterocycle includes monocyclic 3-12 members rings, as well as bicyclic 5-16 membered ring systems (which can include fused, bridged, or spiro bicyclic ring systems). It does not include rings containing -O-O-, -O-S-, and -S-S- portions. Examples of saturated heterocycle groups including saturated 4- to 7-membered monocyclic groups containing 1 to 4 nitrogen atoms [e.g., pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, azetidiny], piperazinyl, and pyrazolidinyl]; saturated 4- to 6-membered monocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g., morpholinyl]; and saturated 3- to 6-membered heteromonocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen

atoms [e.g., thiazolidinyl]. Examples of partially saturated heterocycle radicals include, but are not limited, dihydrothienyl, dihydropyranyl, dihydrofuryl, and dihydrothiazolyl. Examples of partially saturated and saturated heterocycle groups include, but are not limited to, pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, pyrazolidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, thiazolidinyl, dihydrothienyl, 2,3-dihydrobenzo[1,4]dioxanyl, indolinyl, isoindolinyl, dihydrobenzothienyl, dihydrobenzofuryl, isochromanyl, chromanyl, 1,2-dihydroquinolyl, 1,2,3,4-tetrahydro-isoquinolyl, 1,2,3,4-tetrahydro-quinolyl, 2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7-trihydro-1,2,4-triazolo[3,4-a]isoquinolyl, 3,4-dihydro-2H-benzo[1,4]oxazinyl, benzo[1,4]dioxanyl, 2,3-dihydro-1H-benzo[d]isothazol-6-yl, dihydropyranyl, dihydrofuryl, and dihydrothiazolyl. Bicyclic heterocycle includes groups wherein the heterocyclic radical is fused with an aryl radical wherein the point of attachment is the heterocycle ring. Bicyclic heterocycle also includes heterocyclic radicals that are fused with a carbocyclic radical. Representative examples include, but are not limited to, partially unsaturated condensed heterocyclic groups containing 1 to 5 nitrogen atoms, for example indoline and isoindoline, partially unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, partially unsaturated condensed heterocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, and saturated condensed heterocyclic groups containing 1 to 2 oxygen or sulfur atoms. The term “heterocycle” as used herein is not intended to be limited to monovalent radicals and may include polyvalent radical groups as appropriate, such as divalent, trivalent, tetravalent, pentavalent, and hexavalent heterocycle, and the like, based on the position and location of such groups in the compounds described herein as would be readily understood by the skilled person.

“Heteroaryl” refers to a stable monocyclic, bicyclic, or multicyclic aromatic ring which contains from 1 to 4, or in some embodiments 1, 2, or 3 heteroatoms selected from N, O, S, B, and P (and typically selected from N, O, and S) with remaining ring atoms being carbon, or a stable bicyclic or tricyclic system containing at least one 5, 6, or 7 membered aromatic ring which contains from 1 to 4, or in some embodiments from 1 to 3 or from 1 to 2, heteroatoms selected from N, O, S, B, or P, with remaining ring atoms being carbon. In one embodiment, the only heteroatom is nitrogen. In one embodiment, the only heteroatom is oxygen. In one embodiment, the only heteroatom is sulfur. Monocyclic heteroaryl groups typically have from 5 to 6 ring atoms. In some embodiments, bicyclic heteroaryl groups are 8- to 10-membered heteroaryl groups, that is groups containing 8 or 10 ring atoms in which

one 5-, 6-, or 7-membered aromatic ring which contains from 1 to 4 heteroatoms selected from N, O, S, B, or P is fused to a second aromatic or non-aromatic ring, wherein the point of attachment is an aromatic ring. When the total number of S and O atoms in the heteroaryl ring exceeds 1, these heteroatoms are not adjacent to one another within the ring. In one embodiment, the total number of S and O atoms in the heteroaryl ring is not more than 2. In another embodiment, the total number of S and O atoms in the heteroaryl ring is not more than 1. Examples of heteroaryl groups include, but are not limited to, pyridinyl, imidazolyl, imidazopyridinyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, furyl, thienyl, isoxazolyl, thiazolyl, oxadiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indoliziny, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, triazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The term “heteroaryl” as used herein is not intended to be limited to monovalent radicals and may include polyvalent radical groups as appropriate, such as divalent, trivalent, tetravalent, pentavalent, and hexavalent heteroaryl, and the like, based on the position and location of such groups in the compounds described herein as would be readily understood by the skilled person.

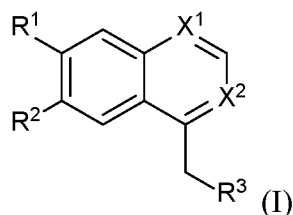
A “pharmaceutically acceptable salt” is a derivative of the disclosed compound in which the parent compound is modified by making inorganic and organic, pharmaceutically acceptable, acid or base addition salts thereof. The salts of the present compounds can be synthesized from a parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate, or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are typical, where practicable. Salts of the present compounds further include solvates of the compounds and of the compound salts. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include salts which are acceptable for human consumption and the quaternary ammonium salts of the parent compound formed, for

example, from inorganic or organic salts. Example of such salts include, but are not limited to, those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, mesylic, esylic, besylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, $\text{HOOC}-(\text{CH}_2)_{1-4}-\text{COOH}$, and the like, or using a different acid that produced the same counterion. Suitable counterions found in pharmaceutically acceptable salts described herein include, but are not limited to, cations such as calcium, chloroprocaine, choline, diethanolamine, ethanolamine, ethylenediamine, meglumine, potassium, procaine, sodium, triethylamine, and zinc, and anions such as acetate, aspartate, benzenesulfonate, besylate, bicarbonate, bitartrate, bromide, camsylate, carbonate, chloride, citrate, decanoate, edetate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolate, hexanoate, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, octanoate, oleate, pamoate, pantothenate, phosphate, polygalacturonate, propionate, salicylate, stearate, succinate, sulfate, tartrate, teoclate, and tosylate. Lists of additional suitable salts may be found, e.g., in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA., p. 1418 (1985).

Compounds

The present disclosure provides compounds which are inhibitors of mitochondrial complex I. Unlike the previously described inhibitor papaverine, the presently disclosed compounds also show limited inhibition of phosphodiesterases (particularly PDE10a), reducing off-target activity which leads to side effects.

In one aspect, a compound is provided of Formula I



or a pharmaceutically acceptable salt thereof;

wherein:

R^1 and R^2 are each independently selected from H or -O-(C₁-C₆ alkyl), wherein at least one of R^1 and R^2 is H;

X^1 and X^2 are each independently selected from N or C(R^4), wherein at least one of X^1 and X^2 is N;

R^3 is 5- to 10-membered monocyclic or bicyclic aryl optionally substituted with one or more groups (for example, 1, 2, 3, or 4 groups) selected from R^5 ;

R^4 is independently selected at each occurrence from H or halo;

R^5 is selected from hydrogen, halo, nitro, cyano, azido, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, (C₃-C₆ cycloalkyl)(C₀-C₃ alkyl)-, (3- to 8-membered monocyclic or bicyclic heterocycle)-(C₀-C₃ alkyl)-, (6- to 10-membered monocyclic or bicyclic aryl)-(C₀-C₃ alkyl)-, (5- to 10-membered monocyclic or bicyclic heteroaryl)-(C₀-C₃ alkyl)-, R^xO -(C₀-C₃ alkyl)-, R^xS -(C₀-C₃ alkyl)-, (R^xR^yN)-(C₀-C₃ alkyl)-, R^xO -C(O)-(C₀-C₃ alkyl)-, R^xS -C(O)-(C₀-C₃ alkyl)-, (R^xR^yN) C(O)-(C₀-C₃ alkyl)-, R^xO -S(O)₂-(C₀-C₃ alkyl)-, (R^xR^yN) S(O)₂-(C₀-C₃ alkyl)-, R^zC (O)-O-(C₀-C₃ alkyl)-, R^zC (O)-(R^xN)-(C₀-C₃ alkyl)-, R^zS (O)₂-O-(C₀-C₃ alkyl)-, R^zS (O)₂-(R^xN)-(C₀-C₃ alkyl)-, R^zC (O)-(C₀-C₆ alkyl)-, R^zS (O)-(C₀-C₃ alkyl)-, and R^zS (O)₂-(C₀-C₃ alkyl)-, each of which may be optionally substituted by one or more groups (for example, 1, 2, 3, or 4 groups) selected from Y as allowed by valency;

R^x and R^y are independently selected at each occurrence from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, (C₃-C₇cycloalkyl)-(C₀-C₃ alkyl)-, (4- to 6-membered heterocycle)-(C₀-C₃ alkyl)-, (5- to 10-membered monocyclic or bicyclic aryl)-(C₀-C₃ alkyl)-, (5- to 10-membered monocyclic or bicyclic heteroaryl)-(C₀-C₃ alkyl)-, each of which may be optionally substituted with one or more Y groups as allowed by valency;

R^z is independently selected at each occurrence from hydrogen, halo, C₁-C₆alkyl, C₁-C₆haloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, (C₃-C₇cycloalkyl)-(C₀-C₃ alkyl)-, (4- to 6-membered heterocycle)-(C₀-C₃ alkyl)-, (5- to 10-membered monocyclic or bicyclic aryl)-(C₀-C₃ alkyl)-, (5- to 10-membered monocyclic or bicyclic heteroaryl)-(C₀-C₃ alkyl)-, -OR^x, -SR^x, and -NR^xR^y, each of which may be optionally substituted with one or more Y groups (for example, 1, 2, 3, or 4 groups) as allowed by valency; and

Y is independently selected at each occurrence from alkyl, haloalkyl, hydroxyalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycle, aldehyde, amino,

carboxylic acid, ester, ether, halo, hydroxy, keto, nitro, cyano, azido, oxo, silyl, sulfo-oxo, sulfonyl, sulfone, sulfoxide, sulfonylamino, phospho, thiol, or combinations thereof.

In some aspects of Formula I, R^1 is H. In some aspects of Formula I, R^1 is $-O(C_1-C_6 \text{ alkyl})$. In some aspects of Formula I, R^1 is $-OCH_3$.

5 In some aspects of Formula I, R^2 is H. In some aspects of Formula I, R^2 is $-O(C_1-C_6 \text{ alkyl})$. In some aspects of Formula I, R^2 is $-OCH_3$.

In some aspects of Formula I, R^1 is $-OCH_3$ and R^2 is H. In some aspects of Formula I, R^1 is H and R^2 is $-OCH_3$. In some aspects of Formula I, R^1 and R^2 are each H.

In some aspects of Formula I, X^1 is N. In some aspects of Formula I, X^1 is $C(R^4)$.

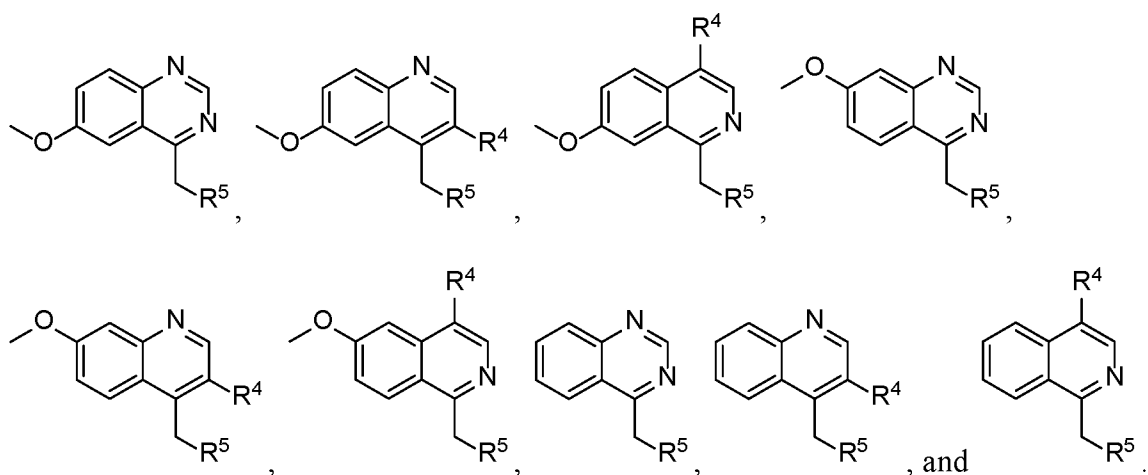
10 In some aspects of Formula I, X^2 is N. In some aspects of Formula I, X^2 is $C(R^4)$.

In some aspects of Formula I, X^1 is N and X^2 is $C(R^4)$. In some aspects of Formula I, X^1 is $C(R^4)$ and X^2 is N.

In some aspects of Formula I, R^4 is H. In some aspects of Formula I, R^4 is halo. In some aspects of Formula I, R^4 is selected from fluoro, chloro, bromo, and iodo. In some aspects of Formula I, R^4 is fluoro.

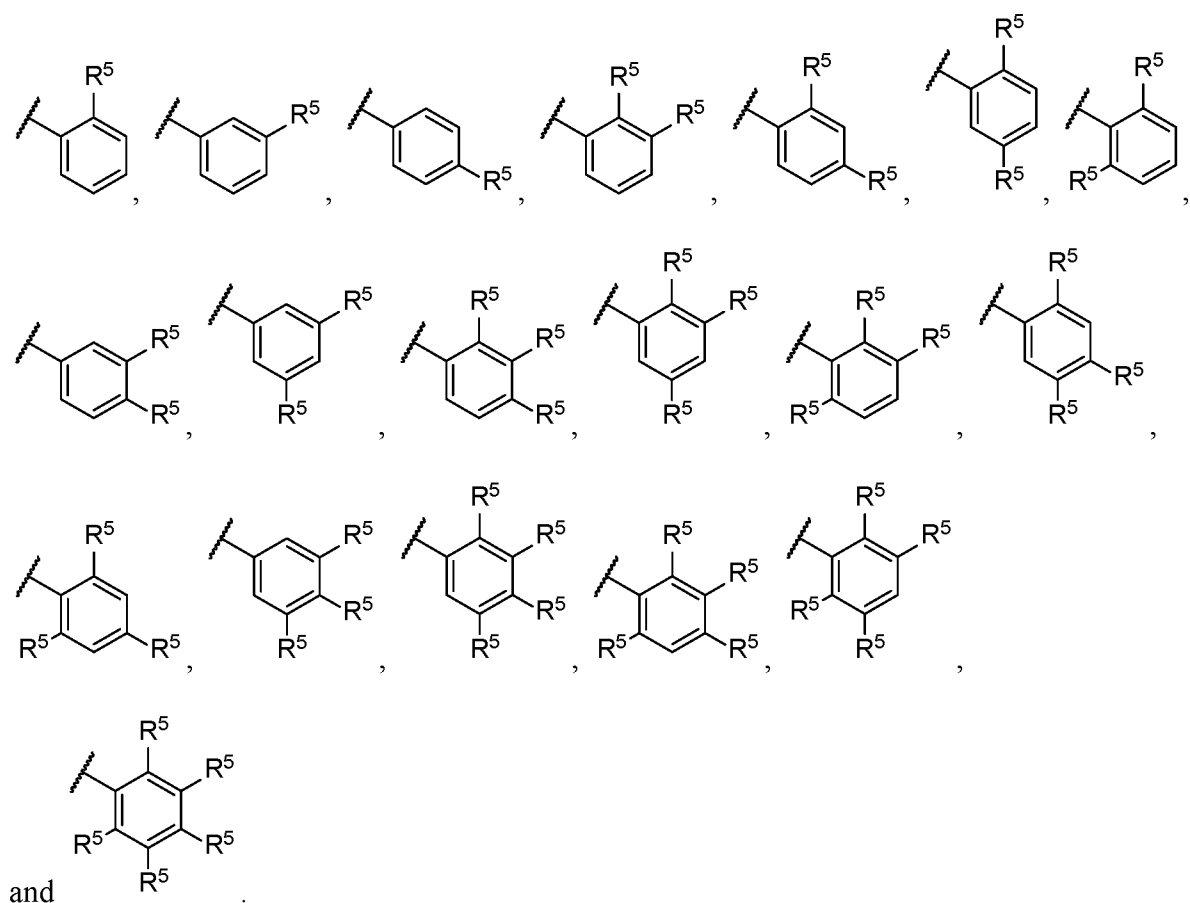
In some aspects of Formula I, X^1 and X^2 are each N.

In some aspects, the compound of Formula I is selected from the group consisting of



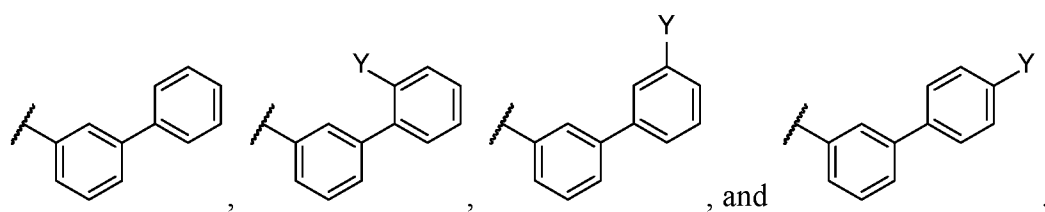
20 In some aspects of Formula I, R^3 is phenyl or 1-naphthyl optionally substituted with one or more groups (for example, 1, 2, 3, or 4 groups) selected from R^5 .

In some aspects of Formula I, R^3 is selected from the group consisting of:

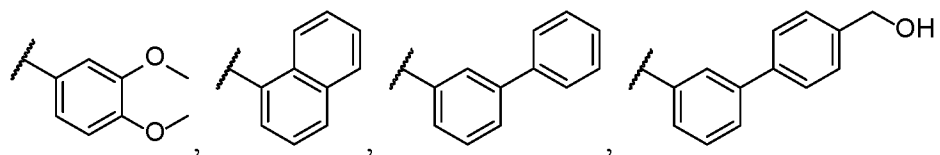


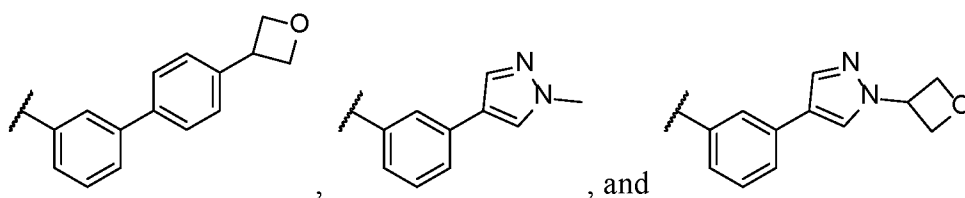
5 In some aspects of Formula I, R³ is phenyl substituted with one group selected from R⁵, wherein R⁵ is phenyl optionally substituted with one or more groups (for example, 1, 2, 3, or 4 groups) selected from Y.

In some aspects of Formula I, R³ is selected from the group consisting of:

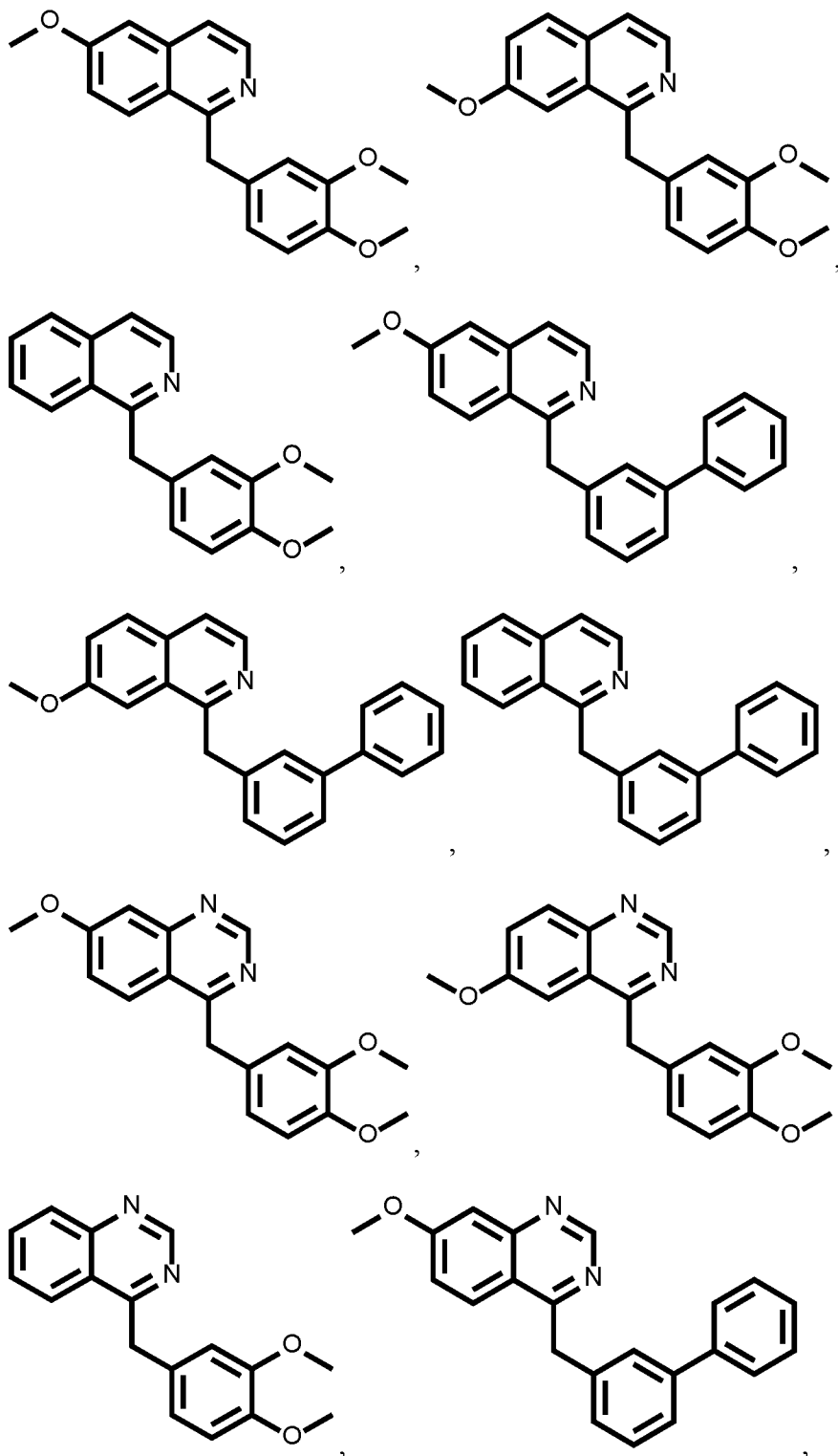


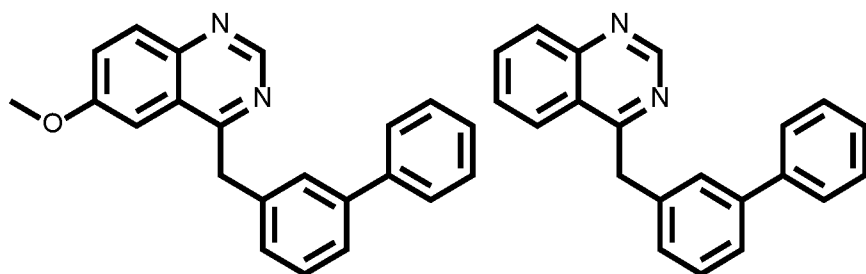
10 In some aspects of Formula I, R³ is selected from the group consisting of:



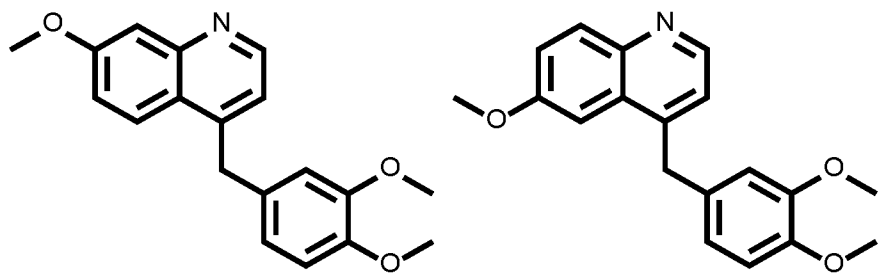


Representative examples of compounds of Formula I include, but are not limited to:

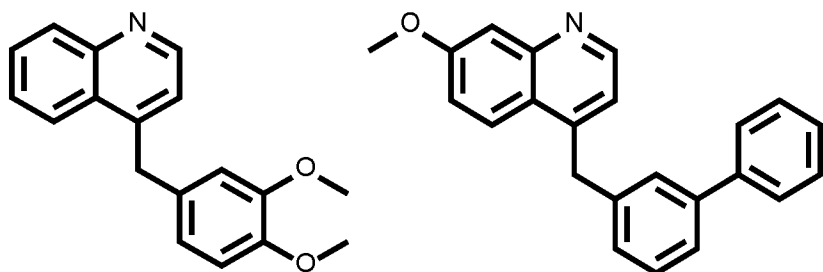




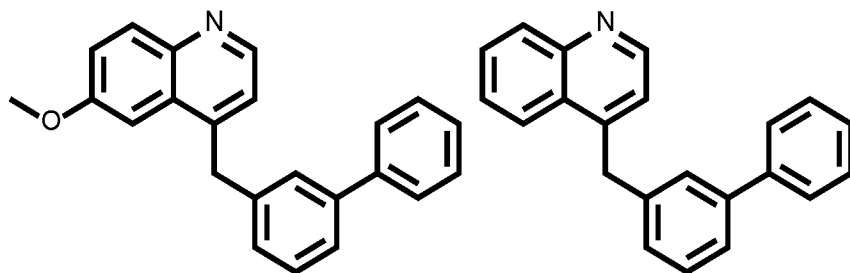
,



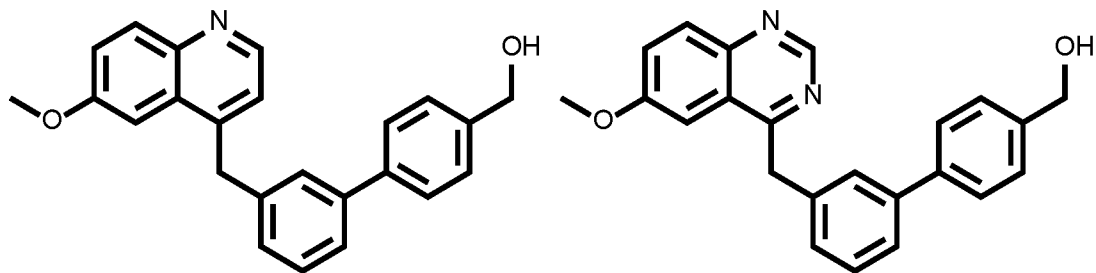
,



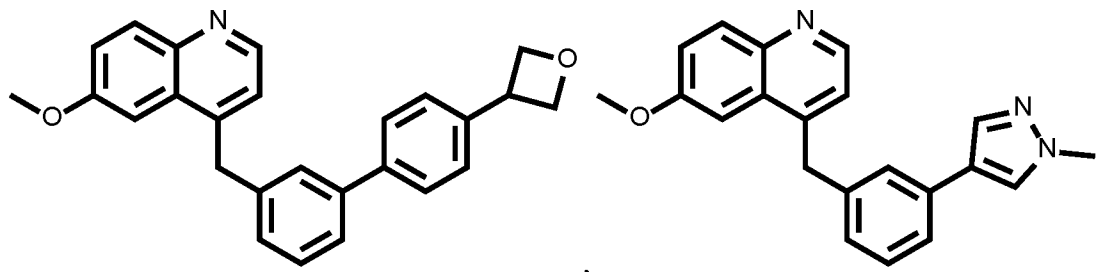
,



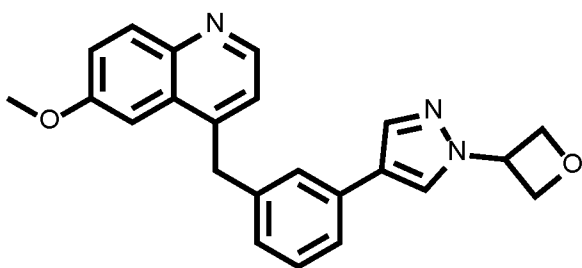
,



,



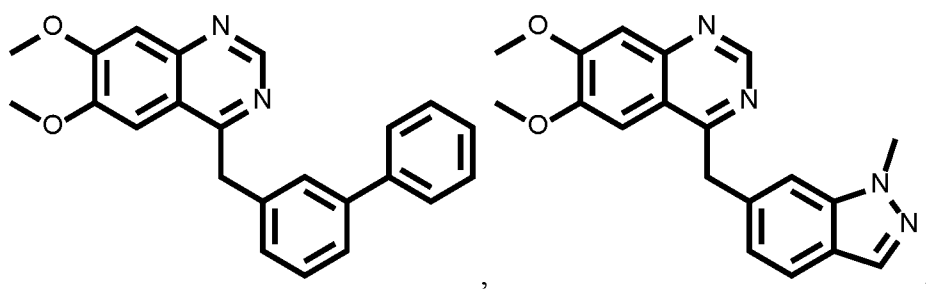
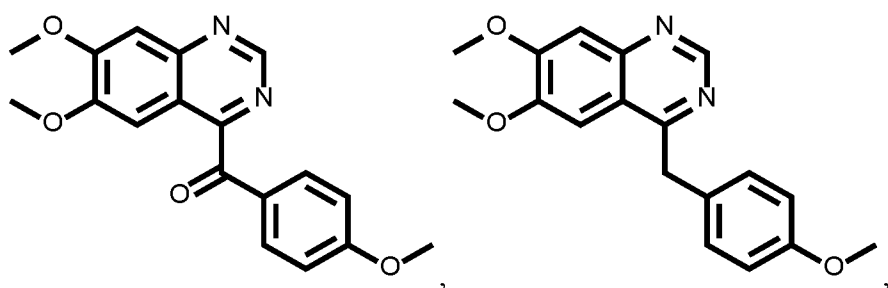
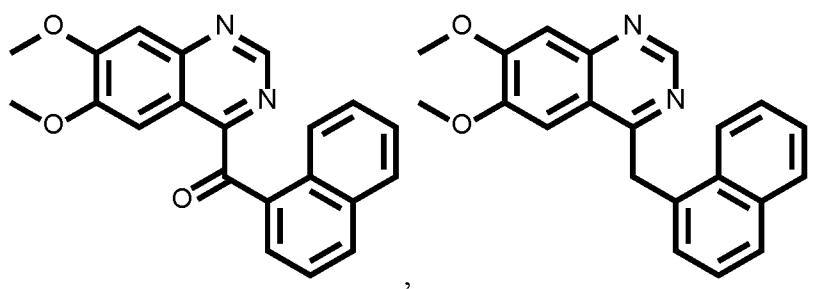
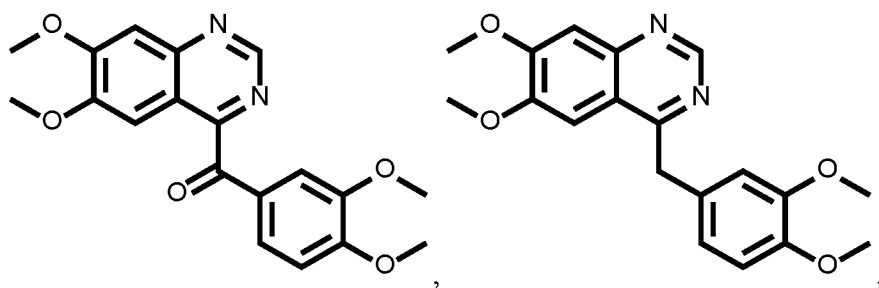
,

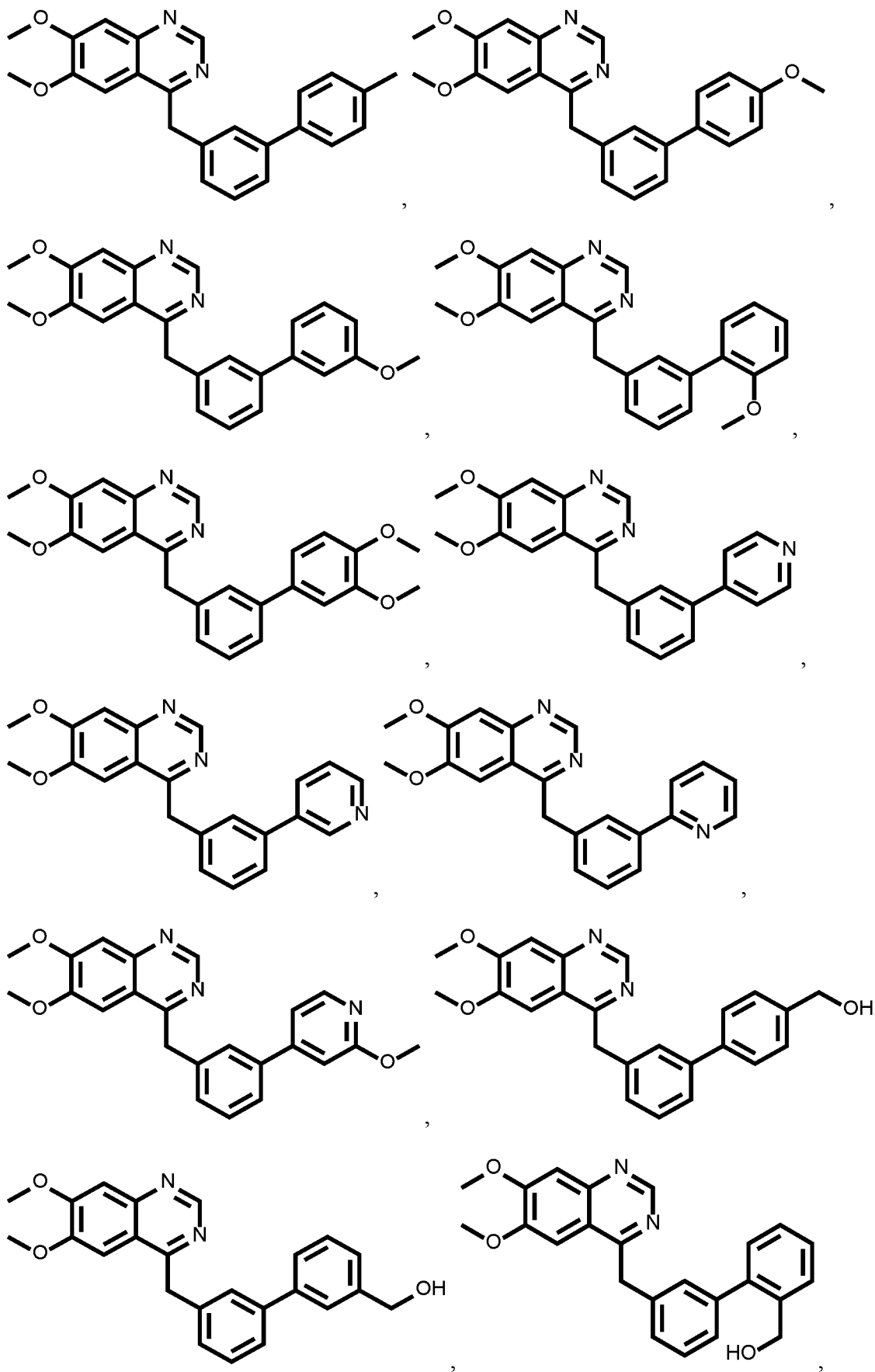


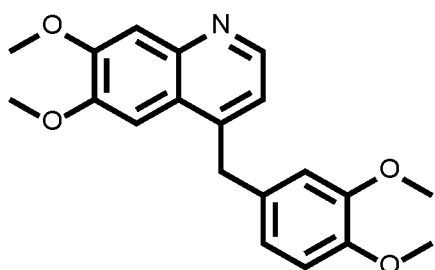
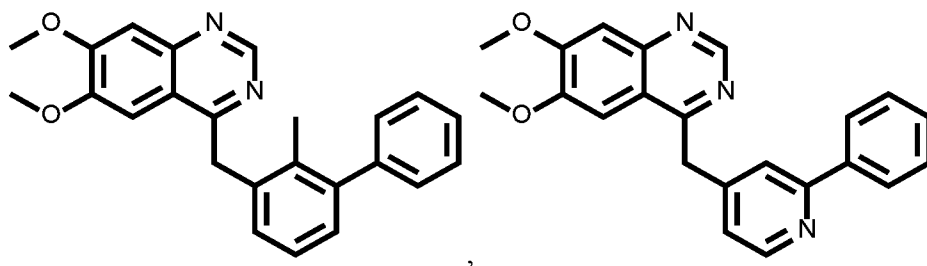
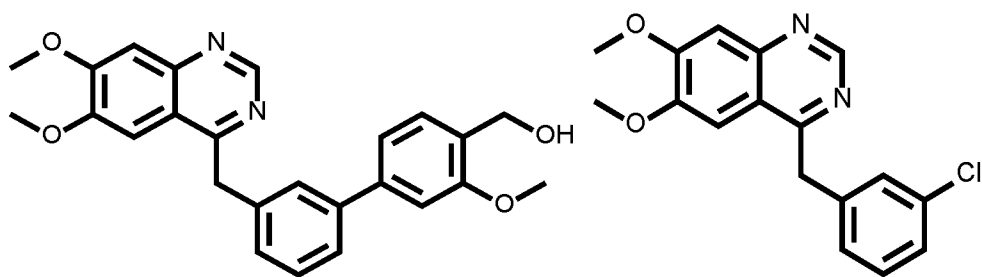
and

or a pharmaceutically acceptable salt thereof.

In another aspect, a compound is provided selected from:



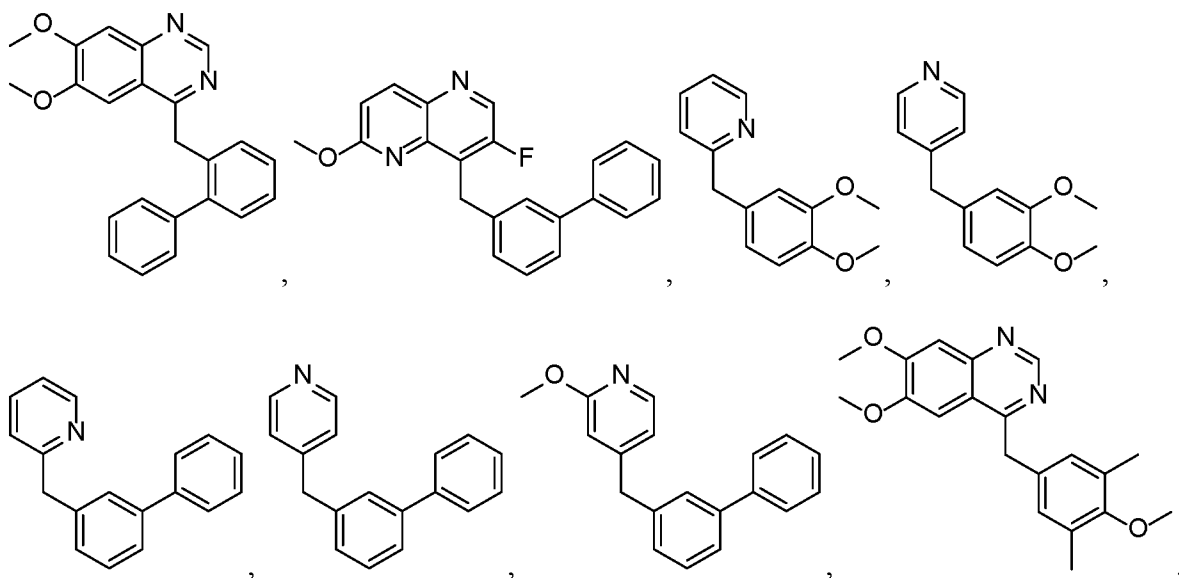


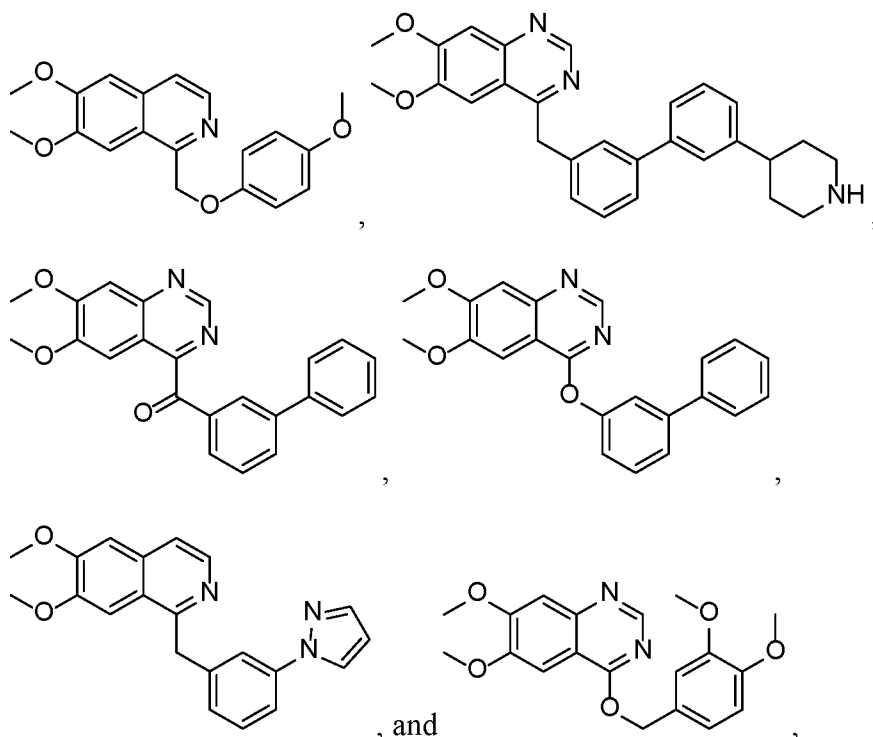


and

or a pharmaceutically acceptable salt thereof.

5 In a further aspect, a compound is provided selected from:





or a pharmaceutically acceptable salt thereof.

The present disclosure also includes compounds described herein with at least one desired isotopic substitution of an atom, at an amount above the natural abundance of the isotope, i.e., enriched.

Examples of isotopes that can be incorporated into compounds of the present disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{15}N , ^{17}O , ^{18}O , ^{18}F , ^{31}P , ^{32}P , ^{35}S , ^{36}Cl , and ^{125}I , respectively. In one embodiment, isotopically labeled compounds can be used in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^2H or ^3H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug and substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F labeled compound may be particularly desirable for PET or SPECT studies. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed herein by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

By way of general example and without limitation, isotopes of hydrogen, for example deuterium (^2H) and tritium (^3H) may optionally be used anywhere in described structures that achieves the desired result. Alternatively, or in addition, isotopes of carbon,

e.g., ^{13}C and ^{14}C , may be used. In one embodiment, the isotopic substitution is replacing hydrogen with a deuterium at one or more locations on the molecule to improve the performance of the molecule as a drug, for example, the pharmacodynamics, pharmacokinetics, biodistribution, half-life, stability, AUC, T_{max} , C_{max} , etc. For example, the deuterium can be bound to carbon in allocation of bond breakage during metabolism (an alpha-deuterium kinetic isotope effect) or next to or near the site of bond breakage (a beta-deuterium kinetic isotope effect).

Isotopic substitutions, for example deuterium substitutions, can be partial or complete. Partial deuterium substitution means that at least one hydrogen is substituted with deuterium. In certain embodiments, the isotope is 80, 85, 90, 95, or 99% or more enriched in an isotope at any location of interest. In some embodiments, deuterium is 80, 85, 90, 95, or 99% enriched at a desired location. Unless otherwise stated, the enrichment at any point is above natural abundance, and in an embodiment is enough to alter a detectable property of the compounds as a drug in a human.

The compounds of the present disclosure may form a solvate with solvents (including water). Therefore, in one embodiment, the invention includes a solvated form of the active compound. The term “solvate” refers to a molecular complex of a compound of the present invention (including a salt thereof) with one or more solvent molecules. Non-limiting examples of solvents are water, ethanol, dimethyl sulfoxide, acetone and other common organic solvents. The term “hydrate” refers to a molecular complex comprising a disclosed compound and water. Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g., D_2O , d_6 -acetone, or d_6 -DMSO. A solvate can be in a liquid or solid form.

A “prodrug” as used herein means a compound which when administered to a host *in vivo* is converted into a parent drug. As used herein, the term “parent drug” means any of the presently described compounds herein. Prodrugs can be used to achieve any desired effect, including to enhance properties of the parent drug or to improve the pharmaceutic or pharmacokinetic properties of the parent, including to increase the half-life of the drug *in vivo*. Prodrug strategies provide choices in modulating the conditions for *in vivo* generation of the parent drug. Non-limiting examples of prodrug strategies include covalent attachment of removable groups, or removable portions of groups, for example, but not limited to, acylating, phosphorylation, phosphonylation, phosphoramidate derivatives, amidation, reduction, oxidation, esterification, alkylation, other carboxy derivatives, sulfoxy or sulfone

derivatives, carbonylation, or anhydrides, among others. In certain embodiments, the prodrug renders the parent compound more lipophilic. In certain embodiments, a prodrug can be provided that has several prodrug moieties in a linear, branched, or cyclic manner. For example, non-limiting embodiments include the use of a divalent linker moiety such as a dicarboxylic acid, amino acid, diamine, hydroxycarboxylic acid, hydroxylamine, dihydroxy compound, or other compound that has at least two functional groups that can link the parent compound with another prodrug moiety and is typically biodegradable *in vivo*. In some embodiments, 2, 3, 4, or 5 prodrug biodegradable moieties are covalently bound in a sequence, branched, or cyclic fashion to the parent compound. Non-limiting examples of prodrugs according to the present disclosure are formed with: a carboxylic acid on the parent drug and a hydroxylated prodrug moiety to form an ester; a carboxylic acid on the parent drug and an amine prodrug to form an amide; an amino on the parent drug and a carboxylic acid prodrug moiety to form an amide; an amino on the parent drug and a sulfonic acid to form a sulfonamide; a sulfonic acid on the parent drug and an amino on the prodrug moiety to form a sulfonamide; a hydroxyl group on the parent drug and a carboxylic acid on the prodrug moiety to form an ester; a hydroxyl on the parent drug and a hydroxylated prodrug moiety to form an ester; a phosphonate on the parent drug and a hydroxylated prodrug moiety to form a phosphonate ester; a phosphoric acid on the parent drug and a hydroxylated prodrug moiety to form a phosphate ester; a hydroxyl on the parent drug and a phosphonate on the prodrug to form a phosphonate ester; a hydroxyl on the parent drug and a phosphoric acid prodrug moiety to form a phosphate ester; a carboxylic acid on the parent drug and a prodrug of the structure $\text{HO}-(\text{CH}_2)_2-\text{O}-(\text{C}_{2-24} \text{ alkyl})$ to form an ester; a carboxylic acid on the parent drug and a prodrug of the structure $\text{HO}-(\text{CH}_2)_2-\text{S}-(\text{C}_{2-24} \text{ alkyl})$ to form a thioester; a hydroxyl on the parent drug and a prodrug of the structure $\text{HO}-(\text{CH}_2)_2-\text{O}-(\text{C}_{2-24} \text{ alkyl})$ to form an ether; a hydroxyl on the parent drug and a prodrug of the structure $\text{HO}-(\text{CH}_2)_2-\text{O}-(\text{C}_{2-24} \text{ alkyl})$ to form a thioether; and a carboxylic acid, oxime, hydrazide, hydrazine, amine or hydroxyl on the parent compound and a prodrug moiety that is a biodegradable polymer or oligomer including but not limited to polylactic acid, polylactide-co-glycolide, polyglycolide, polyethylene glycol, polyanhydride, polyester, polyamide, or a peptide.

In some embodiments, a prodrug is provided by attaching a natural or non-natural amino acid to an appropriate functional moiety on the parent compound, for example, oxygen, nitrogen, or sulfur, and typically oxygen or nitrogen, usually in a manner such that

the amino acid is cleaved *in vivo* to provide the parent drug. The amino acid can be used alone or covalently linked (straight, branched or cyclic) to one or more other prodrug moieties to modify the parent drug to achieve the desired performance, such as increased half-life, lipophilicity, or other drug delivery or pharmacokinetic properties. The amino acid can be any compound with an amino group and a carboxylic acid, which includes an aliphatic amino acid, alkyl amino acid, aromatic amino acid, heteroaliphatic amino acid, heteroalkyl amino acid, heterocyclic amino acid, or heteroaryl amino acid.

Pharmaceutical Compositions

The compounds as used in the methods described herein can be administered by any suitable method and technique presently or prospectively known to those skilled in the art. For example, the active components described herein can be formulated in a physiologically- or pharmaceutically-acceptable form and administered by any suitable route known in the art including, for example, oral and parenteral routes of administering. As used herein, the term "parenteral" includes subcutaneous, intradermal, intravenous, intramuscular, intraperitoneal, and intrasternal administration, such as by injection. Administration of the active components of their compositions can be a single administration, or at continuous and distinct intervals as can be readily determined by a person skilled in the art.

Compositions, as described herein, comprising an active compound and a pharmaceutically acceptable carrier or excipient of some sort may be useful in a variety of medical and non-medical applications. For example, pharmaceutical compositions comprising an active compound and an excipient may be useful for the treatment or prevention of a cancer in a subject in need thereof.

"Pharmaceutically acceptable carrier" (sometimes referred to as a "carrier") means a carrier or excipient that is useful in preparing a pharmaceutical or therapeutic composition that is generally safe and non-toxic and includes a carrier that is acceptable for veterinary and/or human pharmaceutical or therapeutic use. The terms "carrier" or "pharmaceutically acceptable carrier" can include, but are not limited to, phosphate buffered saline solution, water, emulsions (such as an oil/water or water/oil emulsion) and/or various types of wetting agents. As used herein, the term "carrier" encompasses, but is not limited to, any excipient, diluent, filler, salt, buffer, stabilizer, solubilizer, lipid, stabilizer, or other material

well known in the art for use in pharmaceutical formulations and as described further herein.

“Excipients” include any and all solvents, diluents or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. General considerations in formulation and/or manufacture can be found, for example, in Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980), and Remington: The Science and Practice of Pharmacy, 21st Edition (Lippincott Williams & Wilkins, 2005).

Exemplary excipients include, but are not limited to, any non-toxic, inert solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as excipients include, but are not limited to, sugars such as lactose, glucose, and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols such as propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; detergents such as Tween 80; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator. As would be appreciated by one of skill in this art, the excipients may be chosen based on what the composition is useful for. For example, with a pharmaceutical composition or cosmetic composition, the choice of the excipient will depend on the route of administration, the agent being delivered, time course of delivery of the agent, etc., and can be administered to humans and/or to animals, orally, rectally, parenterally, intracisternally, intravaginally, intranasally, intraperitoneally, topically (as by powders, creams, ointments, or drops), buccally, or as an oral or nasal spray. In some embodiments, the active compounds disclosed herein are administered topically.

Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium

phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, etc., and combinations thereof.

Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinyl-pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, etc., and combinations thereof.

Exemplary surface active agents and/or emulsifiers include natural emulsifiers (e.g. acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (e.g. bentonite [aluminum silicate] and Veegum [magnesium aluminum silicate]), long chain amino acid derivatives, high molecular weight alcohols (e.g. stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (e.g. carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxy vinyl polymer), carrageenan, cellulosic derivatives (e.g. carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (e.g. polyoxyethylene sorbitan monolaurate [Tween 20], polyoxyethylene sorbitan [Tween 60], polyoxyethylene sorbitan monooleate [Tween 80], sorbitan monopalmitate [Span 40], sorbitan monostearate [Span 60], sorbitan tristearate [Span 65], glyceryl monooleate, sorbitan monooleate [Span 80]), polyoxyethylene esters (e.g. polyoxyethylene monostearate [Myrj 45], polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol), sucrose fatty acid esters, polyethylene glycol fatty acid esters (e.g. Cremophor), polyoxyethylene ethers, (e.g. polyoxyethylene lauryl ether [Brij 30]), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic F 68, Poloxamer 188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, etc. and/or

combinations thereof. Exemplary binding agents include starch (e.g. cornstarch and starch paste), gelatin, sugars (e.g. sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, etc.), natural and synthetic gums (e.g. acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinylpyrrolidone), magnesium aluminum silicate (Veegum), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, etc., and/or combinations thereof.

Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives.

Exemplary antioxidants include alpha tocopherol, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof (e.g., sodium edetate, disodium edetate, trisodium edetate, calcium disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof (e.g., citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof. Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal.

Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid.

Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid. Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrinide, butylated hydroxyanisol (BHA), butylated hydroxytoluene (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant Plus, Phenonip, methylparaben, Germall 115, Germaben II, Neolone, Kathon, and Euxyl. In certain embodiments, the preservative is an anti-oxidant. In other embodiments, the preservative is a chelating agent.

Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium gluconate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, etc., and combinations thereof.

Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behenate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, etc., and combinations thereof.

Exemplary natural oils include almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, chamomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mint, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean,

sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary synthetic oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and combinations thereof.

5 Additionally, the composition may further comprise a polymer. Exemplary polymers contemplated herein include, but are not limited to, cellulosic polymers and copolymers, for example, cellulose ethers such as methylcellulose (MC), hydroxyethylcellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), methylhydroxyethylcellulose (MHEC), methylhydroxypropylcellulose (MHPC),
 10 carboxymethyl cellulose (CMC) and its various salts, including, e.g., the sodium salt, hydroxyethylcarboxymethylcellulose (HECMC) and its various salts, carboxymethylhydroxyethylcellulose (CMHEC) and its various salts, other polysaccharides and polysaccharide derivatives such as starch, dextran, dextran derivatives, chitosan, and alginic acid and its various salts, carageenan, various gums, including xanthan gum, guar
 15 gum, gum arabic, gum karaya, gum ghatti, konjac and gum tragacanth, glycosaminoglycans and proteoglycans such as hyaluronic acid and its salts, proteins such as gelatin, collagen, albumin, and fibrin, other polymers, for example, polyhydroxyacids such as polylactide, polyglycolide, poly(lactide-co-glycolide) and poly(epsilon-caprolactone-co-glycolide)-, carboxyvinyl polymers and their salts (e.g., carbomer), polyvinylpyrrolidone (PVP),
 20 polyacrylic acid and its salts, polyacrylamide, polyacrylic acid/acrylamide copolymer, polyalkylene oxides such as polyethylene oxide, polypropylene oxide, poly(ethylene oxide-propylene oxide), and a Pluronic polymer, polyoxy ethylene (polyethylene glycol), polyanhydrides, polyvinylalcohol, polyethyleneamine and polypyrrolidone, polyethylene glycol (PEG) polymers, such as PEGylated lipids (e.g., PEG-stearate, 1,2-Distearoyl-sn-glycero-3-
 25 Phosphoethanolamine-N-[Methoxy(Polyethylene glycol)-1000], 1,2-Distearoyl-sn-glycero-3-Phosphoethanolamine-N-[Methoxy(Polyethylene glycol)-2000], and 1,2-Distearoyl-sn-glycero-3-Phosphoethanolamine-N-[Methoxy(Polyethylene glycol)-5000]), copolymers and salts thereof.

 Additionally, the composition may further comprise an emulsifying agent.
 30 Exemplary emulsifying agents include, but are not limited to, a polyethylene glycol (PEG), a polypropylene glycol, a polyvinyl alcohol, a poly-N-vinyl pyrrolidone and copolymers thereof, poloxamer nonionic surfactants, neutral water-soluble polysaccharides (e.g., dextran, Ficoll, celluloses), non-cationic poly(meth)acrylates, non-cationic polyacrylates,

such as poly (meth) acrylic acid, and esters amide and hydroxy alkyl amides thereof, natural emulsifiers (e.g. acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (e.g. bentonite [aluminum silicate] and Veegum [magnesium aluminum silicate]), long chain amino acid derivatives, high molecular weight alcohols (e.g. stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (e.g. carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxy vinyl polymer), carrageenan, cellulosic derivatives (e.g. carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (e.g. polyoxyethylene sorbitan monolaurate [Tween 20], polyoxyethylene sorbitan [Tween 60], polyoxyethylene sorbitan monooleate [Tween 80], sorbitan monopalmitate [Span 40], sorbitan monostearate [Span 60], sorbitan tristearate [Span 65], glyceryl monooleate, sorbitan monooleate [Span 80]), polyoxyethylene esters (e.g. polyoxyethylene monostearate [Myrj 45], polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol), sucrose fatty acid esters, polyethylene glycol fatty acid esters (e.g. Cremophor), polyoxyethylene ethers, (e.g. polyoxyethylene lauryl ether [Brij 30]), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic F 68, Poloxamer 188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, etc. and/or combinations thereof. In certain embodiments, the emulsifying agent is cholesterol.

Liquid compositions include emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compound, the liquid composition may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable compositions, for example, injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a injectable solution, suspension, or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents for pharmaceutical or cosmetic compositions that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. Any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables. In certain embodiments, the particles are suspended in a carrier fluid comprising 1% (w/v) sodium carboxymethyl cellulose and 0.1% (v/v) Tween 80. The injectable composition can be sterilized, for example, by filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

Compositions for rectal or vaginal administration may be in the form of suppositories which can be prepared by mixing the particles with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol, or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the particles.

Solid compositions include capsules, tablets, pills, powders, and granules. In such solid compositions, the particles are mixed with at least one excipient and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets, and pills, the dosage form may also comprise buffering agents. Solid compositions of a similar type may also be

employed as fillers in soft and hard- filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

Tablets, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard- filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

Compositions for topical or transdermal administration include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, or patches. The active compound is admixed with an excipient and any needed preservatives or buffers as may be required.

The ointments, pastes, creams, and gels may contain, in addition to the active compound, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc, and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the active compound, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates, and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the nanoparticles in a proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the particles in a polymer matrix or gel.

Methods of Treatment

The present disclosure also provides methods for treating cancer in a subject, comprising administering to the subject a therapeutically effective amount of a compound or composition disclosed herein. The methods can further comprise administering one or more additional therapeutic agents, for example anti-cancer agents or anti-inflammatory

agents. Additionally, the method can further comprise administering a therapeutically effective amount of ionizing radiation to the subject.

Methods of killing a cancer or tumor cell are also provided comprising contacting the cancer or tumor cell with an effective amount of a compound or composition as described herein. In some embodiments, the compounds can inhibit mitochondrial complex I. The methods can further include administering one or more additional therapeutic agents or administering an effective amount of ionizing radiation.

The disclosed methods can optionally include identifying a patient who is or can be in need of treatment of an oncological disorder. The patient can be a human or other mammal, such as a primate (monkey, chimpanzee, ape, etc.), dog, cat, cow pig, or horse, or other animals having an oncological disorder. In some aspects, the subject can receive the therapeutic compositions prior to, during, or after surgical intervention to remove part or all of a tumor.

In another aspect, a method is provided for sensitizing a cancer to radiation therapy in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof.

The term “neoplasia” or “cancer” is used throughout this disclosure to refer to the pathological process that results in the formation and growth of a cancerous or malignant neoplasm, i.e., abnormal tissue (solid) or cells (non-solid) that grow by cellular proliferation, often more rapidly than normal and continues to grow after the stimuli that initiated the new growth cease. Malignant neoplasms show partial or complete lack of structural organization and functional coordination with the normal tissue and most invade surrounding tissues, can metastasize to several sites, are likely to recur after attempted removal and may cause the death of the patient unless adequately treated. As used herein, the term neoplasia is used to describe all cancerous disease states and embraces or encompasses the pathological process associated with malignant, hematogenous, ascitic and solid tumors. The cancers which may be treated by the compositions disclosed herein may comprise carcinomas, sarcomas, lymphomas, leukemias, germ cell tumors, or blastomas.

Carcinomas which may be treated by the compositions of the present disclosure include, but are not limited to, acinar carcinoma, acinous carcinoma, alveolar adenocarcinoma, carcinoma adenomatosum, adenocarcinoma, carcinoma of adrenal cortex,

alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellular, basaloid carcinoma, basosquamous cell carcinoma, breast carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedocarcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epibulbar carcinoma, epidermoid carcinoma, carcinoma epitheliate adenoids, carcinoma exulcere, carcinoma fibrosum, gelatiniform carcinoma, gelatinous carcinoma, giant cell carcinoma, gigantocellulare, glandular carcinoma, granulose cell carcinoma, hair matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypernephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, lentivular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma mastotoids, carcinoma medullare, medullary carcinoma, carcinoma melanodes, melanotonic carcinoma, mucinous carcinoma, carcinoma muciparum, carcinoma mucocullare, mucoepidermoid carcinoma, mucous carcinoma, carcinoma myxomatodes, masopharyngeal carcinoma, carcinoma nigrum, oat cell carcinoma, carcinoma ossificans, osteroid carcinoma, ovarian carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prostate carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, scheindlerian carcinoma, scirrhous carcinoma, carcinoma scrota, signet-ring cell carcinoma, carcinoma simplex, small cell carcinoma, solandoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tuberous carcinoma, verrucous carcinoma, and carcinoma vilosum.

Representative sarcomas which may be treated by the compositions of the present disclosure include, but are not limited to, liposarcomas (including myxoid liposarcomas and pleomorphic liposarcomas), leiomyosarcomas, rhabdomyosarcomas, neurofibrosarcomas, malignant peripheral nerve sheath tumors, Ewing's tumors (including Ewing's sarcoma of bone, extraskeletal or non-bone) and primitive neuroectodermal tumors (PNET), synovial sarcoma, hemangioendothelioma, fibrosarcoma, desmoids tumors, dermatofibrosarcoma protuberance (DFSP), malignant fibrous histiocytoma (MFH), hemangiopericytoma,

malignant mesenchymoma, alveolar soft-part sarcoma, epithelioid sarcoma, clear cell sarcoma, desmoplastic small cell tumor, gastrointestinal stromal tumor (GIST) and osteosarcoma (also known as osteogenic sarcoma) skeletal and extra-skeletal, and chondrosarcoma.

The compositions of the present disclosure may be used in the treatment of a lymphoma. Lymphomas which may be treated include mature B cell neoplasms, mature T cell and natural killer (NK) cell neoplasms, precursor lymphoid neoplasms, Hodgkin lymphomas, and immunodeficiency-associated lymphoproliferative disorders. Representative mature B cell neoplasms include, but are not limited to, B-cell chronic lymphocytic leukemia/small cell lymphoma, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma (such as Waldenström macroglobulinemia), splenic marginal zone lymphoma, hairy cell leukemia, plasma cell neoplasms (such as plasma cell myeloma/multiple myeloma, plasmacytoma, monoclonal immunoglobulin deposition diseases, and heavy chain diseases), extranodal marginal zone B cell lymphoma (MALT lymphoma), nodal marginal zone B cell lymphoma, follicular lymphoma, primary cutaneous follicular center lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, diffuse large B-cell lymphoma associated with chronic inflammation, Epstein-Barr virus-positive DLBCL of the elderly, lymphomatoid granulomatosis, primary mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, ALK+ large B-cell lymphoma, plasmablastic lymphoma, primary effusion lymphoma, large B-cell lymphoma arising in HHV8-associated multicentric Castleman's disease, and Burkitt lymphoma/leukemia. Representative mature T cell and NK cell neoplasms include, but are not limited to, T-cell prolymphocytic leukemia, T-cell large granular lymphocyte leukemia, aggressive NK cell leukemia, adult T-cell leukemia/lymphoma, extranodal NK/T-cell lymphoma, nasal type, enteropathy-associated T-cell lymphoma, hepatosplenic T-cell lymphoma, blastic NK cell lymphoma, lymphomatoid papulosis/Sezary syndrome, primary cutaneous CD30-positive T cell lymphoproliferative disorders (such as primary cutaneous anaplastic large cell lymphoma and lymphomatoid papulosis), peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T cell lymphoma, and anaplastic large cell lymphoma. Representative precursor lymphoid neoplasms include B-lymphoblastic leukemia/lymphoma not otherwise specified, B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities, or T-lymphoblastic leukemia/lymphoma. Representative Hodgkin lymphomas include classical

Hodgkin lymphomas, mixed cellularity Hodgkin lymphoma, lymphocyte-rich Hodgkin lymphoma, and nodular lymphocyte-predominant Hodgkin lymphoma.

The compositions of the present disclosure may be used in the treatment of a leukemia. Representative examples of leukemias include, but are not limited to, acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), hairy cell leukemia (HCL), T-cell prolymphocytic leukemia, adult T-cell leukemia, clonal eosinophilias, and transient myeloproliferative disease.

The compositions of the present disclosure may be used in the treatment of a germ cell tumor, for example germinomatous (such as germinoma, dysgerminoma, and seminoma), non germinomatous (such as embryonal carcinoma, endodermal sinus tumor, choriocarcinoma, teratoma, polyembryoma, and gonadoblastoma) and mixed tumors.

The compositions of the present disclosure may be used in the treatment of blastomas, for example hepatoblastoma, medulloblastoma, nephroblastoma, neuroblastoma, pancreatoblastoma, pleuropulmonary blastoma, retinoblastoma, and glioblastoma multiforme.

Representative cancers which may be treated include, but are not limited to: bone and muscle sarcomas such as chondrosarcoma, Ewing's sarcoma, malignant fibrous histiocytoma of bone/osteosarcoma, osteosarcoma, rhabdomyosarcoma, and heart cancer; brain and nervous system cancers such as astrocytoma, brainstem glioma, pilocytic astrocytoma, ependymoma, primitive neuroectodermal tumor, cerebellar astrocytoma, cerebral astrocytoma, glioma, medulloblastoma, neuroblastoma, oligodendroglioma, pineal astrocytoma, pituitary adenoma, and visual pathway and hypothalamic glioma; breast cancers including invasive lobular carcinoma, tubular carcinoma, invasive cribriform carcinoma, medullary carcinoma, male breast cancer, Phyllodes tumor, and inflammatory breast cancer; endocrine system cancers such as adrenocortical carcinoma, islet cell carcinoma, multiple endocrine neoplasia syndrome, parathyroid cancer, pheochromocytoma, thyroid cancer, and Merkel cell carcinoma; eye cancers including uveal melanoma and retinoblastoma; gastrointestinal cancers such as anal cancer, appendix cancer, cholangiocarcinoma, gastrointestinal carcinoid tumors, colon cancer, extrahepatic bile duct cancer, gallbladder cancer, gastric cancer, gastrointestinal stromal tumor, hepatocellular cancer, pancreatic cancer, and rectal cancer; genitourinary and gynecologic

cancers such as bladder cancer, cervical cancer, endometrial cancer, extragonadal germ cell tumor, ovarian cancer, ovarian epithelial cancer, ovarian germ cell tumor, penile cancer, renal cell carcinoma, renal pelvis and ureter transitional cell cancer, prostate cancer, testicular cancer, gestational trophoblastic tumor, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, and Wilms tumor; head and neck cancers such as esophageal cancer, head and neck cancer, nasopharyngeal carcinoma, oral cancer, oropharyngeal cancer, paranasal sinus and nasal cavity cancer, pharyngeal cancer, salivary gland cancer, and hypopharyngeal cancer; hematopoietic cancers such as acute biphenotypic leukemia, acute eosinophilic leukemia, acute lymphoblastic leukemia, acute myeloid leukemia, acute myeloid dendritic cell leukemia, AIDS-related lymphoma, anaplastic large cell lymphoma, angioimmunoblastic T-cell lymphoma, B-cell prolymphocytic leukemia, Burkitt's lymphoma, chronic lymphocytic leukemia, chronic myelogenous leukemia, cutaneous T-cell lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, hairy cell leukemia, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, hairy cell leukemia, intravascular large B-cell lymphoma, large granular lymphocytic leukemia, lymphoplasmacytic lymphoma, lymphomatoid granulomatosis, mantle cell lymphoma, marginal zone B-cell lymphoma, Mast cell leukemia, mediastinal large B cell lymphoma, multiple myeloma/plasma cell neoplasm, myelodysplastic syndromes, mucosa-associated lymphoid tissue lymphoma, mycosis fungoides, nodal marginal zone B cell lymphoma, non-Hodgkin lymphoma, precursor B lymphoblastic leukemia, primary central nervous system lymphoma, primary cutaneous follicular lymphoma, primary cutaneous immunocytoma, primary effusion lymphoma, plasmablastic lymphoma, Sezary syndrome, splenic marginal zone lymphoma, and T-cell prolymphocytic leukemia; skin cancers such as basal cell carcinoma, squamous cell carcinoma, skin adnexal tumors (such as sebaceous carcinoma), melanoma, Merkel cell carcinoma, sarcomas of primary cutaneous origin (such as dermatofibrosarcoma protuberans), and lymphomas of primary cutaneous origin (such as mycosis fungoides); thoracic and respiratory cancers such as bronchial adenomas/carcinoids, small cell lung cancer, mesothelioma, non-small cell lung cancer, pleuropulmonary blastoma, laryngeal cancer, and thymoma or thymic carcinoma; HIV/AIDs-related cancers such as Kaposi sarcoma; epithelioid hemangioendothelioma; desmoplastic small round cell tumor; and liposarcoma.

Compounds and compositions disclosed herein can be locally administered at one or more anatomical sites, such as sites of unwanted cell growth (such as a tumor site or benign

skin growth, e.g., injected or topically applied to the tumor or skin growth), optionally in combination with a pharmaceutically acceptable carrier such as an inert diluent. Compounds and compositions disclosed herein can also be systemically administered, such as intravenously or orally, optionally in combination with a pharmaceutically acceptable carrier such as an inert diluent, or an assimilable edible carrier for oral delivery. In addition, the active compound can be incorporated into sustained release preparations and/or devices.

For the treatment of oncological disorder, compounds, agents, and compositions disclosed herein can be administered to a patient in need of treatment prior to, subsequent to, or in combination with other antitumor or anticancer agents or substances (e.g., chemotherapeutic agents, immunotherapeutic agents, radiotherapeutic agents, cytotoxic agents, etc.) and/or with radiation therapy and/or with surgical treatment to remove a tumor. For example, compounds, agents, and compositions disclosed herein can be used in methods of treating cancer wherein the patient is to be treated or is or has been treated with mitotic inhibitors such as taxol or vinblastine, alkylating agents such as cyclophosphamide or ifosfamide, antimetabolites such as 5-fluorouracil or hydroxyurea, DNA intercalators such as adriamycin or bleomycin, topoisomerase inhibitors such as etoposide or camptothecin, antiangiogenic agents such as angiostatin, antiestrogens such as tamoxifen, and/or other anti-cancer drugs or antibodies, such as, for example, imatinid or trastuzumab. These other substances or radiation treatments can be given at the same time as or at different times from the compounds disclosed herein. Examples of other suitable chemotherapeutic agents include, but are not limited to, altretamine, bleomycin, bortezomib, busulphan, calcium folinate, capecitabine, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, crisantaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, docetaxel, doxorubicin, epirubicin, etoposide, fludarabine, fluorouracil, gefitinib, gemcitabine, hydroxyurea, idarubicin, ifosfamide, imatinib, irinotecan, liposomal doxorubicin, lomustine, melphalan, mercaptopurine, methotrexate, mitomycin, mitoxantrone, oxaliplatin, paclitaxel, pentostatin, procarbazine, raltitrexed, streptozocin, tegafur-uraxil, temozolomide, thiotepa, tioguanine/thioguanine, topotecan, treosulfan, vinblastine, vincristine, vindesine, and vinorelbine. Examples of suitable immunotherapeutic agents include, but are not limited to, alemtuzumab, cetuximab, gentuzumab, iodine 131 tositumomab, rituximab, and trastuzumab. Cytotoxic agents include, for example, radioactive isotopes and toxins of bacterial, fungal, plant, or animal origin. Also disclosed are methods of treating an oncological disorder comprising

administering an effective amount of a compound described herein prior to, subsequent to, and/or in combination with administration of a chemotherapeutic agent, an immunotherapeutic agent, a radiotherapeutic agent, or radiotherapy.

5 The active ingredient may be administered in such amounts, time, and route deemed necessary in order to achieve the desired result. The exact amount of the active ingredient will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the medical disorder, the particular active ingredient, its mode of administration, its mode of activity, and the like. The active ingredient, whether the active compound itself, or the active compound in combination with an agent, is preferably
10 formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the active ingredient will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of
15 the active ingredient employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

20 The active ingredient may be administered by any route. In some embodiments, the active ingredient is administered via a variety of routes, including oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, subcutaneous, intraventricular, transdermal, interdermal, rectal, intravaginal, intraperitoneal, topical (as by powders, ointments, creams, and/or drops), mucosal, nasal, bucal, enteral, sublingual; by intratracheal
25 instillation, bronchial instillation, and/or inhalation; and/or as an oral spray, nasal spray, and/or aerosol. In general, the most appropriate route of administration will depend upon a variety of factors including the nature of the active ingredient (e.g., its stability in the environment of the gastrointestinal tract), the condition of the subject (e.g., whether the subject is able to tolerate oral administration), etc.

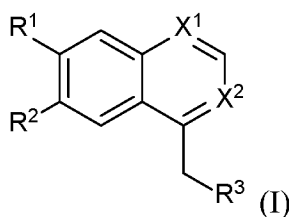
30 The exact amount of an active ingredient required to achieve a therapeutically or prophylactically effective amount will vary from subject to subject, depending on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound(s), mode of administration, and the like. The amount to be

administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

Useful dosages of the active agents and pharmaceutical compositions disclosed herein can be determined by comparing their in vitro activity, and in vivo activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art.

In view of the described compounds, compositions, and methods, hereinbelow are described certain more particular aspects of the disclosure. These particularly recited aspects should not, however, be interpreted to have any limiting effect on any different claims containing different or more general teachings described herein, or that the “particular” aspects are somehow limited in some way other than the inherent meanings of the language and formulae literally used therein.

Aspect 1. A compound of Formula I



or a pharmaceutically acceptable salt thereof;

wherein:

R¹ and R² are each independently selected from H or -O-(C₁-C₆ alkyl), wherein at least one of R¹ and R² is H;

X¹ and X² are each independently selected from N or C(R⁴), wherein at least one of X¹ and X² is N;

R³ is 5- to 10-membered monocyclic or bicyclic aryl optionally substituted with one or more groups selected from R⁵;

R⁴ is independent selected at each occurrence from H or halo;

R⁵ is selected from hydrogen, halo, nitro, cyano, azido, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, (C₃-C₆ cycloalkyl)(C₀-C₃ alkyl)-, (3- to 8-membered monocyclic or bicyclic heterocycle)-(C₀-C₃ alkyl)-, (6- to 10-membered monocyclic or

bicyclic aryl)-(C₀-C₃ alkyl)-, (5- to 10-membered monocyclic or bicyclic heteroaryl)-(C₀-C₃ alkyl)-, R^xO-(C₀-C₃ alkyl)-, R^xS-(C₀-C₃ alkyl)-, (R^xR^yN)-(C₀-C₃ alkyl)-, R^xO-C(O)-(C₀-C₃ alkyl)-, R^xS-C(O)-(C₀-C₃ alkyl)-, (R^xR^yN) C(O)-(C₀-C₃ alkyl)-, R^xO-S(O)₂-(C₀-C₃ alkyl)-, (R^xR^yN) S(O)₂-(C₀-C₃ alkyl)-, R^zC(O)-O-(C₀-C₃ alkyl)-, R^zC(O)-(R^xN)-(C₀-C₃ alkyl)-, R^zS(O)₂-O-(C₀-C₃ alkyl)-, R^zS(O)₂-(R^xN)-(C₀-C₃ alkyl)-, R^zC(O)-(C₀-C₆ alkyl)-, R^zS(O)-(C₀-C₃ alkyl)-, and R^zS(O)₂-(C₀-C₃ alkyl)-, each of which may be optionally substituted by one or more groups selected from Y as allowed by valency;

R^x and R^y are independently selected at each occurrence from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, (C₃-C₇cycloalkyl)-(C₀-C₃ alkyl)-, (4- to 6-membered heterocycle)-(C₀-C₃ alkyl)-, (5- to 10-membered monocyclic or bicyclic aryl)-(C₀-C₃ alkyl)-, (5- to 10-membered monocyclic or bicyclic heteroaryl)-(C₀-C₃ alkyl)-, each of which may be optionally substituted with one or more Y groups as allowed by valency;

R^z is independently selected at each occurrence from hydrogen, halo, C₁-C₆alkyl, C₁-C₆haloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, (C₃-C₇cycloalkyl)-(C₀-C₃ alkyl)-, (4- to 6-membered heterocycle)-(C₀-C₃ alkyl)-, (5- to 10-membered monocyclic or bicyclic aryl)-(C₀-C₃ alkyl)-, (5- to 10-membered monocyclic or bicyclic heteroaryl)-(C₀-C₃ alkyl)-, -OR^x, -SR^x, and -NR^xR^y, each of which may be optionally substituted with one or more Y groups as allowed by valency; and

Y is independently selected at each occurrence from alkyl, haloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycle, aldehyde, amino, carboxylic acid, ester, ether, halo, hydroxy, keto, nitro, cyano, azido, oxo, silyl, sulfo-oxo, sulfonyl, sulfone, sulfoxide, sulfonylamino, phospho, thiol, or combinations thereof.

Aspect 2. The compound of aspect 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is -OCH₃ and R² is H.

Aspect 3. The compound of aspect 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is H and R² is -OCH₃.

Aspect 4. The compound of aspect 1, or a pharmaceutically acceptable salt thereof, wherein R¹ and R² are each H.

Aspect 5. The compound of any one of aspects 1-4, or a pharmaceutically acceptable salt thereof, wherein X¹ is N and X² is C(R⁴).

Aspect 6. The compound of any one of aspects 1-4, or a pharmaceutically acceptable salt thereof, wherein X^1 is $C(R^4)$ and X^2 is N.

Aspect 7. The compound of any one of aspects 1-6, or a pharmaceutically acceptable salt thereof, wherein R^4 is H.

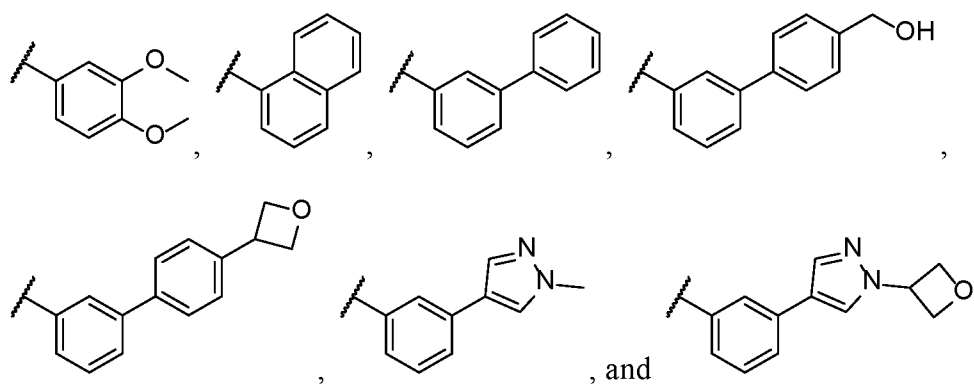
5 Aspect 8. The compound of any one of aspects 1-6, or a pharmaceutically acceptable salt thereof, wherein R^4 is halo.

Aspect 9. The compound of any one of aspects 1-6, or a pharmaceutically acceptable salt thereof, wherein R^4 is fluoro.

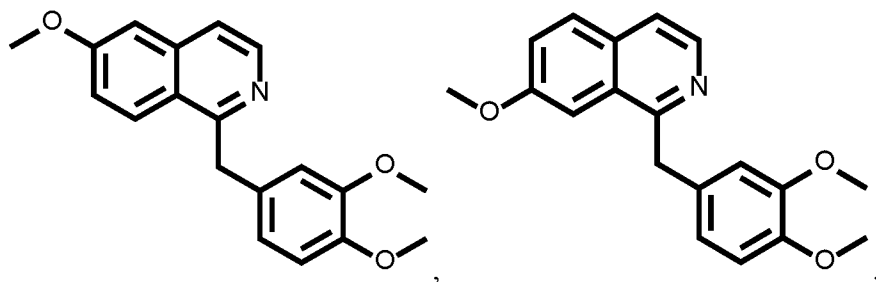
10 Aspect 10. The compound of any one of aspects 1-4, or a pharmaceutically acceptable salt thereof, wherein X^1 and X^2 are each N.

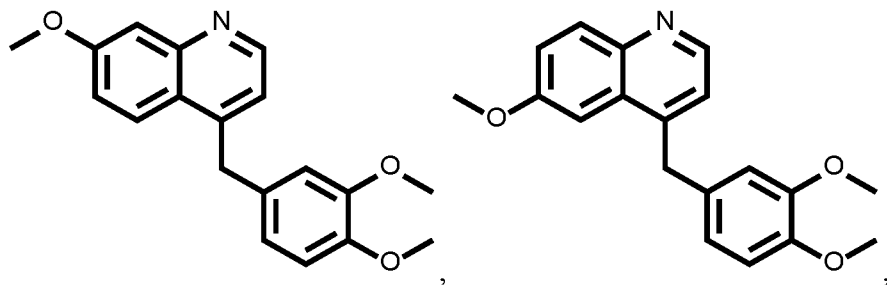
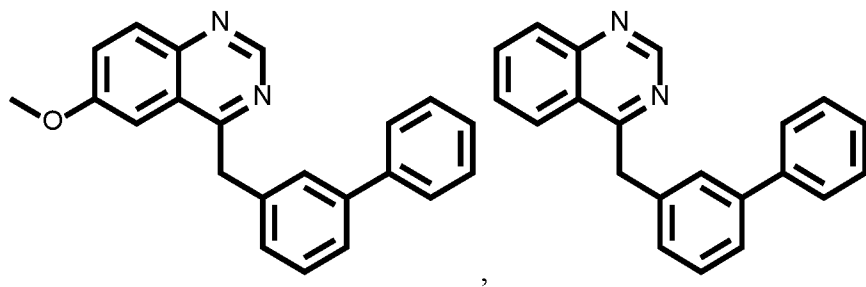
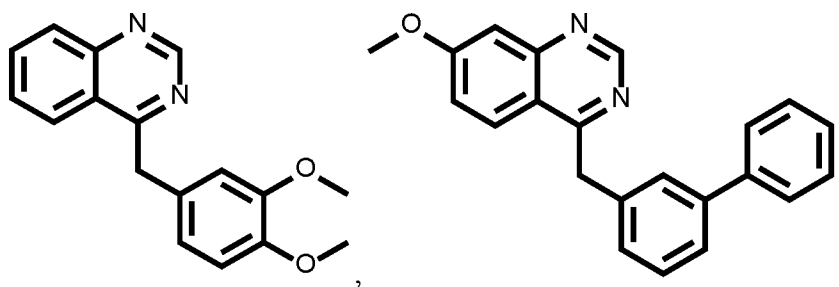
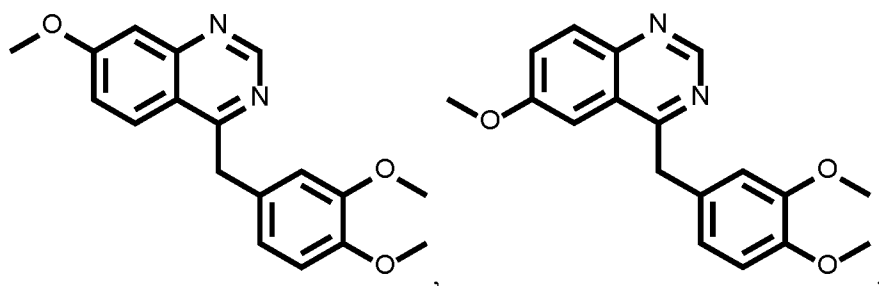
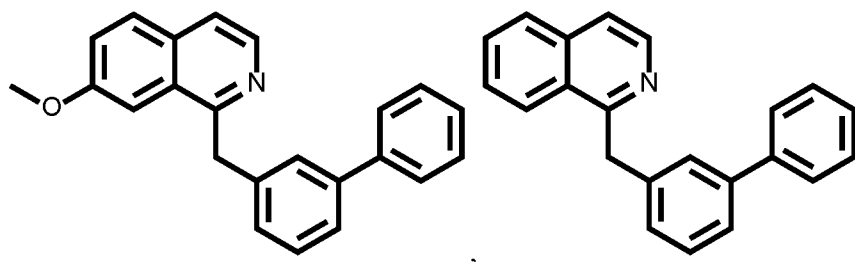
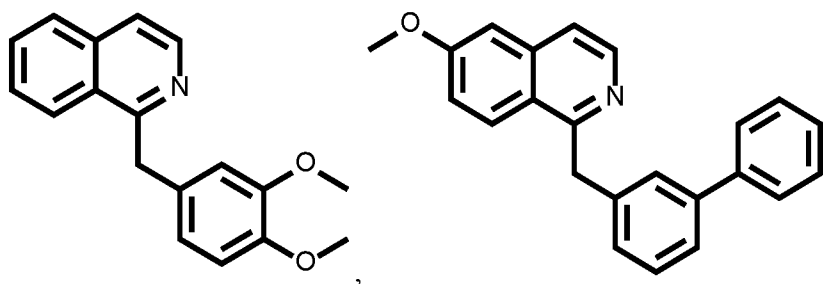
Aspect 11. The compound of any one of aspects 1-10, or a pharmaceutically acceptable salt thereof, wherein R^3 is phenyl or 1-naphthyl optionally substituted with one or more groups selected from R^5 .

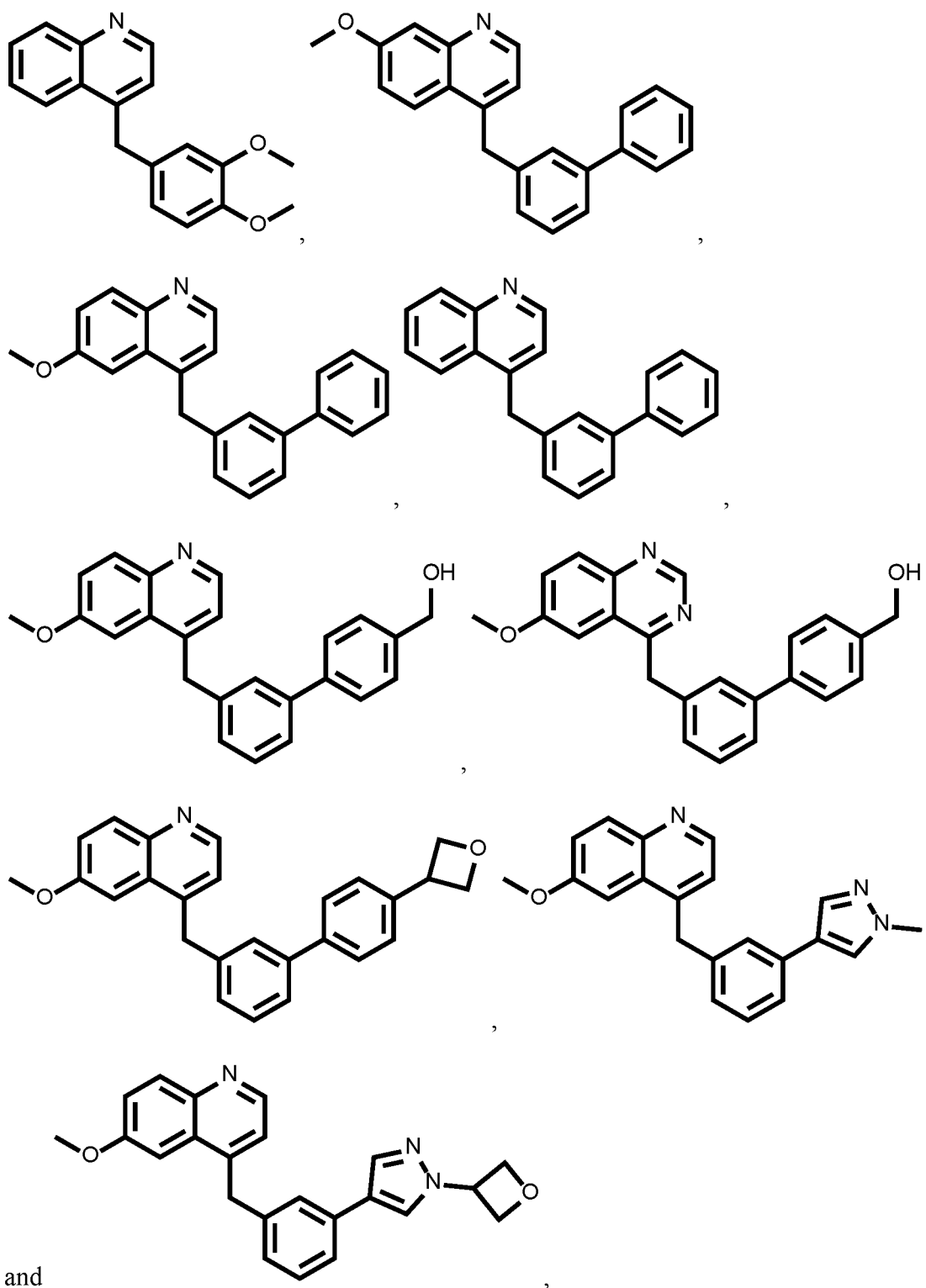
15 Aspect 12. The compound of any one of aspects 1-11, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from the group consisting of:



Aspect 13. The compound of aspect 1 selected from the group consisting of:







5 and

or a pharmaceutically acceptable salt thereof.

Aspect 14. A pharmaceutical composition comprising a compound of any one of aspects 1-13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

Aspect 15. A method of treating a cancer in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of any one of aspects 1-13, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of aspect 14.

5 Aspect 16. A method of sensitizing a cancer to radiation therapy in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of aspects 1-13, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of aspect 14 prior to or concurrently with the radiation therapy.

10 A number of embodiments of the disclosure have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention. Accordingly, other embodiments are within the scope of the following claims.

15 By way of non-limiting illustration, examples of certain embodiments of the present disclosure are given below.

EXAMPLES

20 The following examples are set forth below to illustrate the compounds, compositions, methods claimed herein, along with associated methods and results according to the disclosed subject matter. These examples are not intended to be inclusive of all aspects of the subject matter disclosed herein, but rather to illustrate representative methods and results. These examples are not intended to exclude equivalents and variations of the present disclosure, which are apparent to one skilled in the art.

25 Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.), but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C or is at ambient temperature, and pressure is at or near atmospheric. There are numerous variations and combinations of reaction conditions, e.g., component concentrations, temperatures, pressures, and other reaction ranges and conditions that can be used to optimize the product purity and yield obtained from the described process. Only reasonable and routine experimentation will be
30 required to optimize such process conditions.

General Chemistry. All reactions were conducted in oven-dried glassware under nitrogen protection unless otherwise noted. Flash chromatography was performed with a Teledyne-ISCO CombiFlash Rf+ Lumen. ¹H NMR spectra were obtained at 400 MHz using residual protonated solvent as the internal reference: CDCl₃ (7.26 ppm), CD₃OD (3.31 ppm), DMSO-d₆ (2.50 ppm), D₂O (4.79). ¹³C NMR spectra were obtained at 100 MHz using the solvent as the internal reference: CDCl₃ (77.16 ppm), CD₃OD (49.00 ppm), DMSO-d₆ (39.52 ppm).

General procedure A- NHC-catalyzed arylation: Aryl halide (1 equiv.), aryl aldehyde (1.2 equiv.), and 1,3-Dimethylimidazolium iodide (0.1 equiv.) were added to an appropriately sized flask equipped with a dry stir bar and placed under nitrogen via 3 evacuation/ backfill cycles (note: liquid aldehydes were added via syringe after THF was added under nitrogen). Anhydrous THF (0.075 M) was added to the combined reagents via syringe under nitrogen to typically give a white suspension (as 4-chloro-6,7-dimethoxyquinazoline is poorly THF soluble). Sodium hydride (60% by wt suspension in mineral oil, 1.60 equiv.) was added in one portion to the stirred solution. After sodium hydride addition, the flask was quickly fitted with a reflux condenser and the reaction contents heated under nitrogen in an oil bath set to 66 °C. Upon heating the reaction was monitored by TLC with an appropriate eluent. Often TLC showed complete halide consumption after 30-60 minutes. Some products were very poorly soluble in THF and precipitated from solution. Once TLC demonstrated halide consumption, the flask was cooled in an ice/water bath and the reaction quenched via slow dropwise addition of distilled water (~2 mL per mmol NaH). The reaction contents were then diluted and transferred to a separatory funnel using ethyl acetate and water. Phases were separated, and the aqueous phase was extracted twice with ethyl acetate. The combined organic phases were washed with saturated NaCl, dried over anhydrous sodium sulfate, filtered through cotton, and concentrated *in vacuo* to afford the crude residue. Purification of the crude residue could be carried out by recrystallization from either ethanol or ethyl acetate for these substrates.

General procedure B- Benzoylation of ketones: The appropriate diphenyl ketone (1.0 equiv) was added to an oven-dried round bottom flask equipped with a stir bar and placed under nitrogen via 3 evacuation/ backfill cycles. Anhydrous THF (0.1 M of the limiting reagent) followed by anhydrous MeOH (0.1 M of the limiting reagent, 0.05M combined solutions) were added to the ketone via syringe under nitrogen to typically create a fine

suspension (as the ketones have poor solubility in more polar solvents). NaBH₄ (1.5 equiv.) was added to the reaction quickly in one portion, often rapidly resulting in a clear homogenous solution. Progress was monitored by TLC with an appropriate eluent. After TLC suggested consumption of the limiting reagent, the reaction was quenched with a saturated aqueous NH₄Cl solution. The quenched solution was concentrated *in vacuo* to remove THF and MeOH and the remaining residue was transferred to a separatory funnel using DCM and water. Phases were separated, and the aqueous phase was extracted twice with DCM. The combined organic phases were washed with saturated NaCl, dried over anhydrous sodium sulfate, filtered through cotton, and concentrated *in vacuo* to afford the crude residue. Attempts to purify these resultant alcohols by flash chromatography were unsuccessful as they appeared to oxidize on silica (confirmed by 2D TLC) to the ketone starting material. In addition, if left to sit in CDCl₃ in an NMR tube overnight, considerable oxidation to the ketones was often observed. Considering these data, the alcohols were taken without further purification directly into the next step.

The crude residue (assumed the mass equated to 1.0 equiv. alcohol) was transferred to an oven-dried round bottom flask equipped with a stir bar and dissolved in anhydrous pyridine (0.05 M). Benzoyl chloride (1.60 equiv.) was added to the reaction solution under nitrogen. The reaction solution was left to stir overnight at room temperature under a nitrogen atmosphere. After stirring overnight, TLC commonly demonstrated consumption of the limiting reagent, and the reaction was quenched with distilled water and the reaction contents concentrated *in vacuo* to remove pyridine. The remaining residue was transferred to a separatory funnel using ethyl acetate and water and the phases separated. After separation, the aqueous phase was extracted twice with ethyl acetate; the combined organic phases were washed with saturated NaCl, dried over anhydrous sodium sulfate, filtered through cotton, and concentrated *in vacuo* to afford the crude residue. Crude residues were dissolved in DCM, adsorbed onto silica, and purified through flash chromatography with an appropriate column using the noted eluent gradient to obtain the desired benzoate unless otherwise noted.

General procedure C- Benzoate hydrogenolysis: The appropriate benzoate (1.0 equiv.) and ammonium formate (10.0 equiv.) were added to an oven-dried round bottom flask equipped with a stir bar and placed under nitrogen via 3 evacuation/ backfill cycles. Ethyl acetate (~ 1 M) followed by ethanol (~ 0.05 M) were added to the solids to often create a homogenous solution. Reaction contents heated in an oil bath set to 70 °C and allowed to

stir for 5 minutes. After 5 minutes of heating, 10% palladium on carbon (50 mg per mmol benzoate) was added to the reaction flask and the flask was fitted with a reflux condenser. The contents were allowed to stir overnight; TLC frequently demonstrated complete conversion of starting material after heating overnight. After starting material consumption was shown by TLC, the reaction contents were vacuum filtered through a pad of celite and the filtrate concentrated *in vacuo* to obtain the crude residue. Crude residues were dissolved in DCM, adsorbed onto silica, and purified through flash chromatography with an appropriate column using the noted eluent gradient to obtain the dibenzyl methylene compounds unless otherwise noted.

General procedure E- Deoxygenative arylation: *Preparing the activation vessel:* The appropriate alcohol (1.7-1.8 equiv.) and benzoxazolium salt (1.6 equiv.) were added to an oven-dried vessel equipped with a stir bar and placed under a nitrogen atmosphere via three evacuation/ backfill cycles (note: liquid alcohols were added via syringe after solvent was added under nitrogen). An appropriate solvent was added to the alcohol activation vessel to create a fine white suspension and stirred for at least 5 minutes. Pyridine (1.6 equiv.) was added to the activation vessel as a solution in the chosen solvent under nitrogen over 5 minutes. For most substrates this addition created little to no change in the appearance of the activation vessel. The activation vessel was allowed to stir for a minimum of 10 minutes after pyridine addition before combination with the reaction vessel. Benzoxazolium salts for deoxygenative arylation were synthesized according to established literature precedents.

Preparing the reaction vessel: To an oven-dried vessel equipped with a stir bar was added the halide (1.0 equiv.), phthalimide (0.225 equiv.), the chosen base (either sodium acetate or quinuclidine; most often sodium acetate was chosen for cost-effectiveness, but quinuclidine was frequently used on more expensive substrates where maximum yield was desired), Ir(ppy)₂(dtbbpy)PF₆ (0.015 equiv.), and Ni(dtbbpy)Br₂ (0.075 equiv.) then the combined contents were placed under a nitrogen atmosphere via three evacuation/ backfill cycles. Anhydrous dimethylacetamide (DMA) was added to the contents of the reaction vessel via syringe under nitrogen. After the DMA solution was prepared, the contents of the activation vessel were taken up into an appropriate syringe, the needle was quickly removed, and then it was equipped with a needle attached to a nylon 0.45 μ M syringe filter. The activation vessel contents were then added to the reaction vessel contents in DMA through the filter. The combined reaction vessel contents were sparged with nitrogen for 15 minutes and the sparged solution was tightly sealed with parafilm immediately afterwards.

Irradiation and processing: Irradiation of the combined reaction vessel was performed immediately after sparging using a 456 nm PR160 Kessil light held ~5-7 cm from the wall of the vessel. Following photoirradiation the vessel was open to the air, diluted with ethyl acetate, and transferred to a separatory funnel. The reaction contents were washed with saturated sodium bicarbonate solution and water, then the aqueous phase was extracted twice with ethyl acetate and the combined organic phases were further washed with water and saturated NaCl solution. The washed organic phase was dried over anhydrous sodium sulfate, filtered through cotton, and concentrated *in vacuo* to afford the crude residue. Crude residues were dissolved in DCM, adsorbed onto silica, and purified through flash chromatography with an appropriate column using the specified eluent gradient to obtain the desired product unless otherwise noted.

General procedure E modification (E-IP): Deoxygenative arylation in parallel:

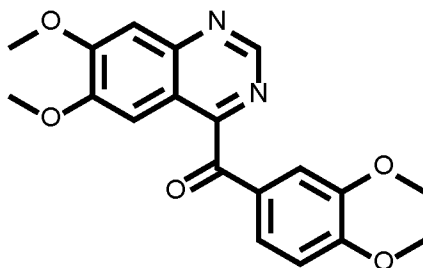
To facilitate more expedient analog synthesis by reacting substrates in parallel, the following changes were made to general procedure E: Three times the calculated amount of alcohol and NHC precursor (for one individual reaction) were weighed into a vessel and placed under a nitrogen atmosphere. Activation with pyridine and the selected solvent were carried out as noted in general procedure E. Upon completed activation and 10 minutes of stirring, the contents of the activation vessel were completely transferred through a nylon 0.45 μ M syringe filter into a separate flask under nitrogen. The filtered contents were then evenly partitioned between the selected substrates under nitrogen.

General procedure F- Suzuki-Miyaura cross coupling:

To an oven-dried vessel equipped with a stir bar was added the appropriate pinacol boronate (1.0 equiv.), aryl halide (2.0 equiv.), Cs_2CO_3 (2.5 equiv.), palladium precatalyst (0.05 equiv.), and ligand (if used, 0.1 equiv.). Then the combined vial contents were placed under nitrogen via 3 evacuation/backfill cycles. Solvent degassed through 15 minutes of nitrogen sparging was added to the combined vial material and the vial contents sealed with parafilm. After solvent addition, the reaction contents were heated to 90 °C overnight. Upon stirring overnight, the reaction progress was assessed by TLC using an appropriate eluent. The vial contents were transferred to a separatory funnel using ethyl acetate and water and the phases separated. After separation the aqueous phase was extracted twice with ethyl acetate; the combined organic phases were washed with saturated NaCl, dried over anhydrous sodium sulfate, filtered through cotton, and concentrated *in vacuo* to afford the crude residue. Crude residues were dissolved in DCM, adsorbed onto silica, and purified through flash

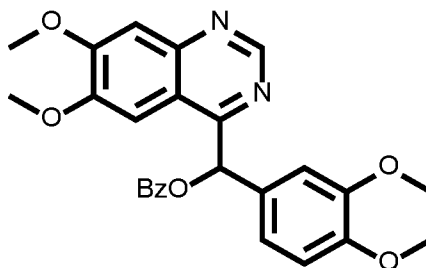
chromatography with an appropriate column using the noted eluent gradient to obtain the cross-coupled product unless otherwise noted.

Analog and Intermediate Synthesis Details



1

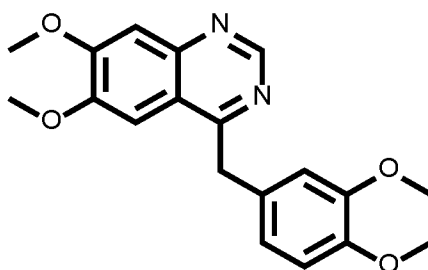
Compound **1** was prepared following general procedure A using 4-chloro-6,7-dimethoxyquinazoline (0.3496 mg, 1.56 mmol, 1.0 equiv.), 3,4-dimethoxybenzaldehyde (0.3109 mg, 1.87 mmol, 1.20 equiv.), 1,3-dimethylimidazolium iodide (38 mg, 0.17 mmol, 0.11 equiv.), and sodium hydride (57-63% mineral oil dispersion) (97.5 mg, 2.44 mmol, 1.56 equiv.) in THF (21 mL, 0.07 M). Reaction completion was suggested by TLC after 30 minutes of heating and was cooled and quenched with water (2 mL) after 45 minutes. Workup was performed using 40 mL of water and ethyl acetate in each phase separation. The crude material was purified by recrystallization from ethyl acetate (~60 mL) to obtain the title compound as a white solid (406.9 mg, 1.15 mmol, 73.7% yield). ¹H NMR (400 MHz, CDCl₃) δ: 9.22 (s, 1H), 7.71 (d, *J* = 2.0 Hz, 1H), 7.44-7.39 (m, 2H), 7.32 (s, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 4.10 (s, 3H), 3.97 (s, 3H), 3.96 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ: 192.3, 160.5, 156.7, 154.6, 152.6, 151.4, 149.9, 149.5, 128.7, 127.3, 118.4, 111.6, 110.2, 107.0, 102.7, 56.6, 56.4, 56.3, 56.2. LCMS (ESI) *m/z* [M+H]⁺: 355.2.



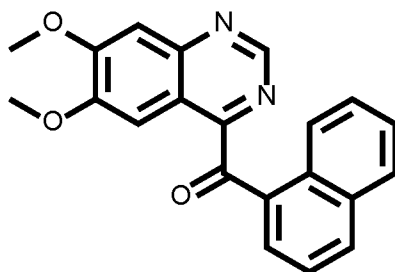
R1

Compound **R1** was prepared following general procedure C using **1** (100.7 mg, 0.28 mmol, 1.0 equiv.), sodium borohydride (16.1 mg, 0.43 mmol, 1.5 equiv.), THF: MeOH (1:1, 6 mL, 0.05 M), benzoyl chloride (45 μL, 0.39 mmol, 1.4 equiv.), and pyridine (4 mL, 0.07

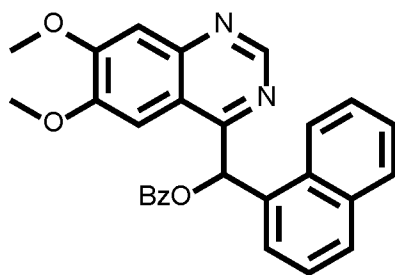
M). Step one (borohydride reduction) was quenched with sat. aqueous NH_4Cl after 30 minutes of stirring, while step two (benzoyl chloride addition to the intermediate alcohol) was allowed to stir 20 hours before being quenched with water. Workup was performed using 20 mL of water and organic phase in each phase separation. The crude residue was purified via flash chromatography on silica eluting with a 55 to 65 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to obtain the title compound as an off-white solid (96.4 mg, 0.21 mmol, 75% yield). ^1H NMR (400 MHz, CDCl_3) δ : 9.16 (s, 1H), 8.16 (d, $J = 7.7$ Hz, 2H), 7.59 (br t, $J = 7.4$ Hz, 1H), 7.54-7.42 (m, 4H), 7.33 (s, 1H), 7.12 (br d, $J = 7.7$ Hz, 1H), 7.10 (s, 1H), 6.86 (br d, $J = 8.2$ Hz, 1H), 4.03 (s, 3H), 3.93 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H).

**2**

Compound **2** was prepared following general procedure C using **R1** (67.5 mg, 0.15 mmol, 1.0 equiv.), ammonium formate (92.2 mg, 1.5 mmol, 10.0 equiv.), and 10% Pd/C (8.9 mg, 59 mg/ 1 mmol **R1**) in ethyl acetate (240 μL) and ethanol (3.2 mL). Reaction completion was suggested by TLC after stirring in an oil bath set to 70 $^\circ\text{C}$ for 18 hours and the reaction contents were filtered through a pad of celite to give the crude residue. Crude residue purified via flash chromatography on silica eluting with a 70 to 90 percent ethyl acetates in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a white solid (41.5 mg, 0.12 mmol, 83% yield). ^1H NMR (400 MHz, CDCl_3) δ : 9.10 (s, 1H), 7.31 (s, 1H), 7.28 (s, 1H), 6.85- 6.76 (m, 3H), 4.48 (s, 2H), 4.04 (s, 3H), 3.94 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ : 166.2, 155.7, 153.7, 150.3, 149.3, 148.6, 148.0, 130.6, 120.9, 119.7, 112.1, 111.4, 107.3, 102.6, 56.5, 56.2, 56.01, 55.99, 41.5. LCMS (ESI) m/z $[\text{M}+\text{H}]^+$: 341.2.

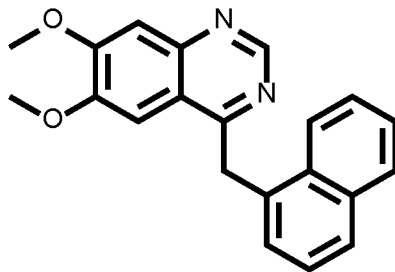
**3**

Compound **3** was prepared following general procedure A using 4-chloro-6,7-dimethoxyquinazoline (299.7 mg, 1.33 mmol, 1.00 equiv.), 1-naphthaldehyde (220 μ L, 1.62 mmol, 1.22 equiv), 1,3-dimethylimidazolium iodide (22.5 mg, 0.10 mmol, 0.08 equiv.), and sodium hydride (57-63% mineral oil dispersion) (85.1 mg, 2.13 mmol, 1.60 equiv.) in THF (18 mL, 0.07 M). Reaction completion was suggested by TLC after 30 minutes of heating and was cooled and quenched with water (2 mL) after 45 minutes. Workup was performed using 40 mL of water and ethyl acetate in each phase separation. The crude residue was purified by recrystallization from ethanol (~ 60 mL) to obtain the title compound as a cotton-like white solid (324.3 mg, 0.94 mmol, 70.8% yield). ^1H NMR (400 MHz, CDCl_3) δ : 9.20 (s, 1H), 8.87 (d, J = 8.51 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.69 (m, 1H), 7.61 (m, 2H), 7.57 (s, 1H), 7.49 (s, 1H), 7.47 (t, J = 7.9 Hz, 1H), 4.12 (s, 3H), 3.96 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ : 196.5, 160.8, 156.8, 152.9, 151.8, 150.2, 134.7, 134.2, 133.4, 133.2, 131.5, 128.8, 126.9, 125.9, 125.4, 124.3, 118.6, 107.0, 102.7, 56.7, 56.5. LCMS (ESI) m/z $[\text{M}+\text{H}]^+$: 345.2.

**R2**

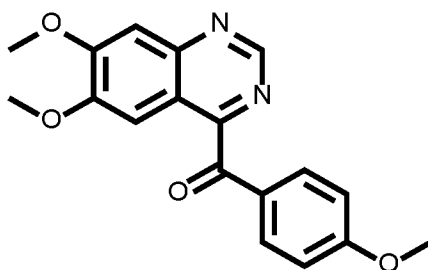
Compound **R2** was prepared following general procedure B using **3** (200.7 mg, 0.58 mmol, 1.0 equiv.), sodium borohydride (32.9 mg, 0.87 mmol, 1.5 equiv.), THF: MeOH (1:1, 12 mL, 0.05 M), benzoyl chloride (100 μ L, 0.86 mmol, 1.5 equiv.), and pyridine (12 mL, 0.05 M). Step one (borohydride reduction) was quenched with sat. aqueous NH_4Cl after 30 minutes of stirring, while step two (benzoyl chloride addition to the intermediate alcohol) was allowed to stir 18 hours before being quenched with water. Workup was performed

using 30 mL of water and organic phase in each phase separation. The crude residue was purified via flash chromatography on silica eluting with 45% ethyl acetate in hexanes. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to obtain the title compound as a white solid (224.9 mg, 0.50 mmol, 86% yield). ¹H NMR (400 MHz, CDCl₃) δ: 9.17 (s, 1H), 8.36 (d, *J* = 8.6 Hz, 2H), 8.16 (dd, *J* = 8.5, 1.27 Hz, 2H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.61-7.50 (m, 4H), 7.48-7.41 (m, 3H), 7.36 (s, 1H), 7.31 (s, 1H), 4.02 (s, 3H), 3.68 (s, 3H).



4

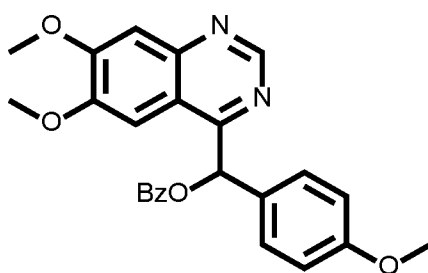
Compound **4** was prepared following general procedure C using **R2** (100 mg, 0.22 mmol, 1.0 equiv.), ammonium formate (143.1 mg, 2.27 mmol, 10.3 equiv.), and 10% Pd/C (10.9 mg, 50mg/ 1 mmol **R2**) in ethyl acetate (240 μL) and ethanol (3.2 mL). Reaction completion was suggested by TLC after stirring for 4 hours in an oil bath set to 70 °C and the reaction solution was filtered through a pad of celite to give the crude material. The crude residue was purified via flash chromatography on silica eluting with a 55 to 60 percent ethyl acetates in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a white solid (60.2 mg, 0.18 mmol, 83% yield). ¹H NMR (400 MHz, CDCl₃) δ: 9.11 (s, 1H), 8.19 (d, *J* = 8.2 Hz, 1H), 7.88 (dd, *J* = 7.2, 2.1 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.55- 7.47 (m, 2H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.33 (s, 1H), 7.24 (d, *J* = 7.1 Hz, 1H), 7.21 (s, 1H), 5.01 (s, 2H), 4.03 (s, 3H), 3.72 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 166.2, 155.7, 153.7, 150.3, 148.4, 134.3, 134.1, 132.1, 129.1, 127.8, 127.2, 126.5, 125.9, 125.6, 123.8, 120.1, 107.3, 102.5, 56.5, 56.2, 39.2. LCMS (ESI) *m/z* [M+H]⁺: 331.2.



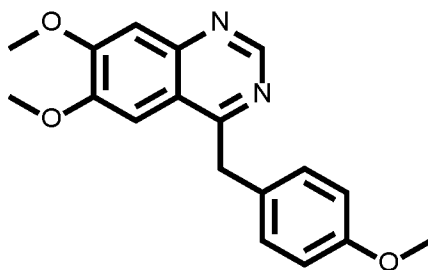
55

5

Compound **3** was prepared following general procedure A using 4-chloro-6,7-dimethoxyquinazoline (500 mg, 2.23 mmol, 1.0 equiv.), p-Anisaldehyde (325 μ L, 2.67 mmol, 1.20 equiv.), 1,3-Dimethylimidazolium iodide (53.9 mg, 0.20 mmol, 0.07 equiv.), and sodium hydride (57-63% mineral oil dispersion) (144.5 mg, 3.61 mmol, 1.35 equiv.) in THF (30 mL, 0.09 M). Reaction completion was suggested by TLC after 1hr of heating and cooled/quenched with water (2 mL) after 90 minutes of heating. Workup was performed using 70 mL of water and DCM in each phase separation. DCM was required as the solid was poorly ethyl acetate soluble. The crude material was purified by recrystallization from 1:1 ethyl acetate: ethanol (~75 mL) to obtain the title compound as a white solid (550.6 mg, 2.22 mmol, 76% yield). ^1H NMR (400 MHz, CDCl_3) δ : 9.23 (s, 1H), 7.97 (d, $J = 8.8$ Hz, 2H), 7.44 (s, 1H), 7.34 (s, 1H), 6.98 (d, $J = 8.8$ Hz, 2H), 4.10 (s, 3H), 3.96 (s, 3H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ : 192.3, 164.7, 160.5, 156.7, 152.6, 151.4, 150.0, 133.4, 128.6, 118.4, 114.1, 107.0, 102.7, 56.6, 56.4, 55.8. LCMS (ESI) m/z $[\text{M}+\text{H}]^+$: 325.2.

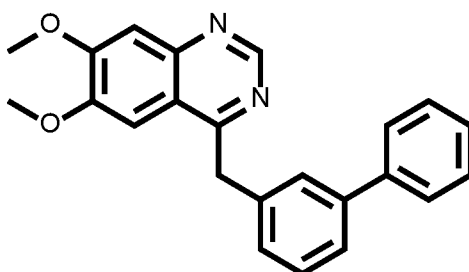
**R3**

Compound **R3** was prepared following general procedure B using **5** (101.4 mg, 0.31 mmol, 1.0 equiv.), sodium borohydride (19.6 mg, 0.52 mmol, 1.7 equiv.), THF: MeOH (1:1, 6 mL, 0.05 M), benzoyl chloride (50 μ L, 0.43 mmol, 1.4 equiv.), and pyridine (6 mL, 0.05 M). Step one (borohydride reduction) was quenched with sat. aqueous NH_4Cl after 30 minutes of stirring, while step two (benzoyl chloride addition to the intermediate alcohol) was allowed to stir 20 hours before being quenched with water. Workup was performed using 30 mL of water and organic phase in each phase separation. The crude residue was purified via flash chromatography on silica eluting with 60 percent ethyl acetate in hexanes. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to obtain the title compound as a white solid (89.3 mg, 0.21 mmol, 67% yield).



6

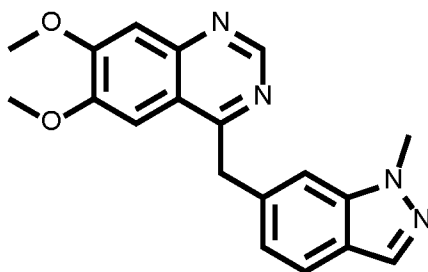
Compound **6** was prepared following general procedure C using **R3** (85.8 mg, 0.20 mmol, 1.0 equiv.), ammonium formate (129.8 mg, 2.1 mmol, 10.3 equiv.), and 10% Pd/C (10.8 mg, 54 mg/ mmol **R3**) in ethyl acetate (240 μ L) and ethanol (3.2 mL). Reaction completion was suggested by TLC after stirring in an oil bath set to 70 $^{\circ}$ C for 16 hours and the reaction contents were filtered through a pad of celite to give the crude residue. The crude residue was purified by flash chromatography on silica eluting with 60 percent ethyl acetates in hexanes. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a white solid (48.2 mg, 0.16 mmol, 78% yield). ^1H NMR (400 MHz, DMSO- d_6) δ : 8.96 (s, 1H), 7.57 (s, 1H), 7.32 (s, 1H), 7.28 (d, J = 8.9 Hz, 2H), 6.84 (d, J = 8.9 Hz, 2H), 4.50 (s, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 3.68 (s, 3H), 3.31 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ : 166.4, 158.5, 155.7, 153.7, 150.2, 148.6, 130.1, 129.8, 119.6, 114.3, 107.3, 102.6, 56.5, 56.2, 55.3, 41.0. LCMS (ESI) m/z $[\text{M}+\text{H}]^+$: 311.2.



7

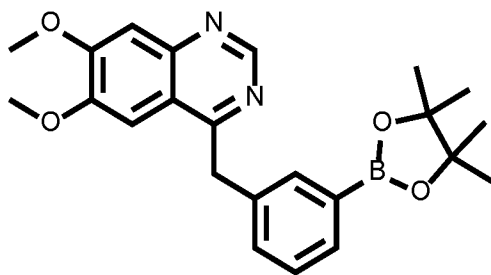
Compound **7** was prepared following general procedure E using 4-chloro-6,7-dimethoxyquinazoline (115.0 mg, 0.51 mmol, 1.0 equiv.), sodium acetate (74.5 mg, 0.91 mmol, 1.78 equiv.), [1,1'-biphenyl]-3-ylmethanol (165.0 mg, 0.89 mmol, 1.75 equiv.), NHC-1 BF_4 (324.0 mg, 0.82 mmol, 1.60 equiv.), pyridine (66 μ L, 0.82 mmol, 1.61 equiv.), phthalimide (19.6 mg, 0.13 mmol, 0.26 equiv.), $\text{Ni}(\text{dtbbpy})\text{Br}_2$ (20.1 mg, 41.3 μ mol, 0.081 equiv.), and $\text{Ir}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$ (7.7 mg, 8.4 μ mol, 0.017 equiv.) in TBME (5 mL, 0.16 M for alcohol activation) and DMA (5 mL, 0.05 M combined with TBME solution for

irradiation). The crude residue was purified via flash chromatography on silica eluting with a 60 to 95 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a light-yellow solid (67.5 mg, 0.19 mmol, 37% yield). ¹H NMR (400 MHz, CDCl₃) δ: 9.11 (s, 1H), 7.54-7.49 (m, 3H), 7.47-7.27 (m, 8H), 4.61 (s, 2H), 4.03 (s, 3H), 3.91 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 165.9, 155.7, 153.8, 150.3, 148.7, 141.9, 141.0, 138.6, 129.3, 128.9, 127.7, 127.6, 127.2, 125.8, 119.7, 107.4, 102.6, 56.5, 56.2, 42.0. LCMS (ESI) m/z [M+H]⁺: 357.3.

**8**

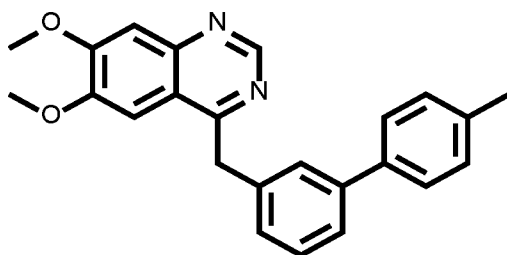
Compound **8** was prepared following general procedure E with the following modifications: The alcohol was used as the limiting reagent with the halide in excess. Alcohol activation was achieved by first combining the alcohol and pyridine under nitrogen and subsequently adding NHC-1 BF₄ in five portions over 10 minutes under a constant stream of nitrogen in a Schlenk flask. The procedure was performed using 4-chloro-6,7-dimethoxyquinazoline (190 mg, 0.85 mmol, 1.50 equiv.), sodium acetate (59.7 mg, 0.73 mmol, 1.29 equiv.), (1-methyl-1H-indazol-6-yl)methanol (91.3 mg, 0.56 mmol, 1.0 equiv.), NHC-1 BF₄ (208 mg, 0.53 mmol, 0.94 equiv.), pyridine (46 μL, 0.57 mmol, 1.01 equiv.), phthalimide (23.4 mg, 0.16 mmol, 0.28 equiv.), Ni(dtbbpy)Br₂ (26.2 mg, 53.8 μmol, 0.10 equiv.), and Ir(ppy)₂(dtbbpy)PF₆ (7.9 mg, 8.64 μmol, 0.015 equiv.) in 1,4 dioxane (5 mL, 0.11 M for activation) and DMA (5 mL, 0.06 M combined with dioxane solution). The crude residue was purified via flash chromatography on silica eluting with 50 percent acetone in hexanes. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a white solid (34.9 mg, 0.10 mmol, 19 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ: 8.98 (s, 1H), 7.95 (d, *J* = 0.7 Hz, 1H), 7.66-7.62 (m, 3H), 7.33 (s, 1H), 7.12 (dd, *J* = 8.1, 1.3 Hz, 1H), 4.72 (s, 2H), 3.98 (s, 3H), 3.95 (s, 3H), 3.94 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 165.9, 155.8, 153.7, 150.4, 148.6, 140.4,

136.5, 132.7, 123.1, 122.1, 121.4, 119.6, 108.7, 107.3, 102.4, 56.5, 56.2, 42.0, 35.6. LCMS (ESI) m/z $[M+H]^+$: 335.2.



R4

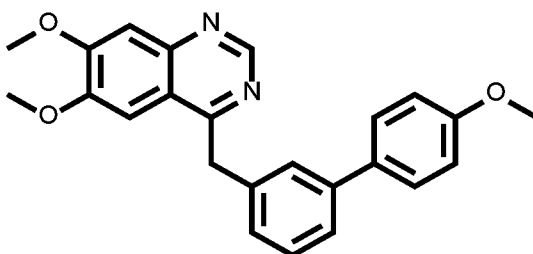
Compound **R4** was prepared following general procedure E using 4-chloro-6,7-dimethoxyquinazoline (230 mg, 1.02 mmol, 1.0 equiv.), sodium acetate (169.0 mg, 2.06 mmol, 2.01 equiv.), [3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (421.0 mg, 1.80 mmol, 1.76 equiv.), NHC-1 BF_4 (647 mg, 1.64 mmol, 1.60 equiv.), pyridine (135 μL , 1.68 mmol, 1.64 equiv.), phthalimide (33.1 mg, 0.23 mmol, 0.22 equiv.), Ni(dtbbpy) Br_2 (36.9 mg, 75.8 μmol , 0.074 equiv.), and Ir(ppy) $_2$ (dtbbpy) PF_6 (14.7 mg, 16.1 μmol , 0.016 equiv.) in TBME (5 mL, 0.33 M for activation) and DMA (mL, 0.10 M combined with TBME solution). The crude residue was purified via liquid loading with DCM onto a Teledyne Isco 12 g gold spherical silica column and eluting with a 60 to 70 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a white solid (145.5 mg, 0.36 mmol, 35% yield). ^1H NMR (400 MHz, CDCl_3) δ : 9.10 (s, 1H), 7.87 (br s, 1H), 7.66 (br d, J = 7.2 Hz, 1H), 7.35 (br d, J = 7.9 Hz, 1H), 7.32 (s, 1H), 7.31 (s, 1H), 7.28 (d, J = 7.4 Hz, 1H), 4.56 (s, 2H), 4.03 (s, 3H), 3.94 (s, 1H), 1.33 (s, 12H).



9

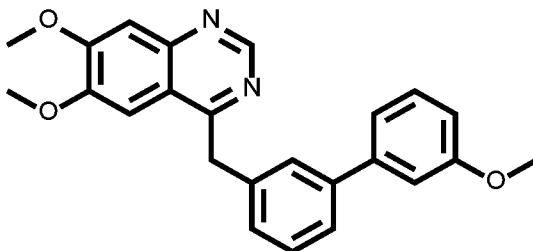
Compound **9** was prepared following general procedure F using **R4** (38.0 mg, 93 μmol , 1.00 equiv.), 4-bromotoluene (23 μL , 0.19 mmol, 2.00 equiv.), Cs_2CO_3 (75.8 mg, 0.23 mmol, 2.49 equiv.), XPhos (4.3 mg, 9 μmol , 0.01 equiv.), and $\text{Pd}(\text{OAc})_2$ (1.2 mg, 5 μmol , 0.06 equiv.) in 9:1 dioxane: water (1.4 mL, 0.07 M). The crude residue was purified

by flash chromatography on silica eluting with a 50 to 65 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as an off-white solid (17.0 mg, 46 μ mol, 49% yield). ^1H NMR (400 MHz, CDCl_3) δ : 9.11 (s, 1H), 7.51 (br s, 1H), 7.45-7.39 (m, 3H), 7.34 (t, $J = 7.6$ Hz, 1H), 7.31 (s, 1H), 7.28 (s, 1H), 7.25-7.19 (m, 3H), 4.60 (s, 2H), 4.03 (s, 3H), 3.90 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ : 166.0, 155.8, 153.7, 150.3, 148.6, 141.8, 138.5, 138.0, 137.4, 129.6, 129.3, 127.53, 127.45, 127.1, 125.6, 119.7, 107.3, 102.6, 56.5, 56.2, 42.0, 21.2. LCMS (ESI) m/z $[\text{M}+\text{H}]^+$: 371.3.



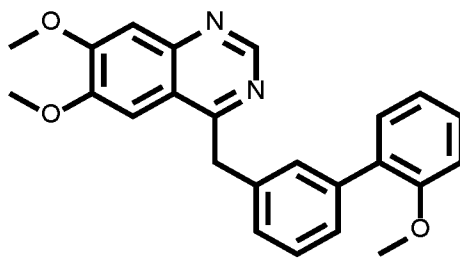
10

Compound **10** was prepared following general procedure F using **R4** (50.0 mg, 0.12 mmol, 1.00 equiv.), 4-bromoanisole (31 μ L, 0.25 mmol, 2.01 equiv.), Cs_2CO_3 (100.0 mg, 0.31 mmol, 2.50 equiv.), and $\text{Pd}(\text{dppf})\text{Cl}_2$ DCM adduct (3.0 mg, 3.7 μ mol, 0.03 equiv.) in 9:1 dioxane: water (1.6 mL, 0.08 M). The crude residue was purified by flash chromatography on silica eluting with a 50 to 60 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a light orange solid (12.9 mg, 33 μ mol, 27% yield). ^1H NMR (400 MHz, CDCl_3) δ : 9.11 (s, 1H), 7.48 (br s, 1H), 7.47-7.43 (m, 2H), 7.40 (br d, $J = 7.6$ Hz, 1H), 7.36-7.30 (m, 2H), 7.29 (s, 1H), 7.22 (br d, $J = 7.6$ Hz, 1H), 6.96-6.91 (m, 2H), 4.60 (s, 2H), 4.03 (s, 3H), 3.90 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ : 166.0, 159.4, 155.8, 153.6, 150.3, 148.6, 141.5, 138.5, 133.5, 129.3, 128.2, 127.3, 127.2, 125.4, 119.8, 114.4, 107.3, 102.6, 56.5, 56.2, 55.5, 42.0. LCMS (ESI) m/z $[\text{M}+\text{H}]^+$: 387.3.

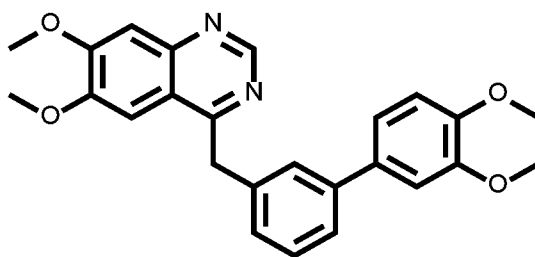


11

Compound **11** was prepared following general procedure F using **R4** (51.0 mg, 0.13 mmol, 1.00 equiv.), 3-bromoanisole (34 μ L, 0.27 mmol, 2.13 equiv.), Cs₂CO₃ (102.0 mg, 0.31 mmol, 2.50 equiv.), and Pd(PPh₃)₄ (4.3 mg, 3.8 μ mol, 0.03 equiv.) in 9:1 dioxane: water (1.7 mL, 0.07 M). The crude residue was purified by flash chromatography on silica eluting with a 70 to 80 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a white solid (21.4 mg, 55.4 μ mol, 44% yield). ¹H NMR (400 MHz, CDCl₃) δ : 9.11 (s, 1H), 7.52 (br s, 1H), 7.44 (br d, *J* = 7.4 Hz, 1H), 7.41-7.27 (m, 5H), 7.10 (br d, *J* = 8.2 Hz, 1H), 7.04 (t, *J* = 2.1 Hz, 1H), 6.88 (ddd, *J* = 8.2, 2.6, 0.8 Hz, 1H), 4.61 (s, 2H), 4.03 (s, 3H), 3.91 (s, 3H), 3.84 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ : 165.9, 160.1, 155.8, 153.7, 150.4, 148.6, 142.5, 141.8, 138.6, 129.9, 129.3, 127.9, 127.8, 125.9, 119.7, 113.1, 112.9, 107.3, 102.6, 56.5, 56.2, 55.4, 41.9. LCMS (ESI) *m/z* [M+H]⁺: 387.3.

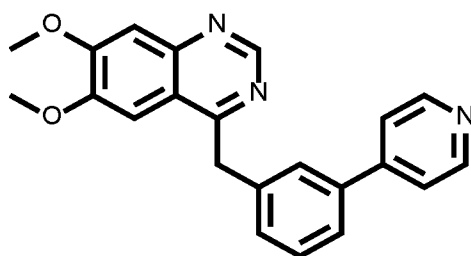
**12**

Compound **12** was prepared following general procedure F using **R4** (60.0 mg, 0.15 mmol, 1.00 equiv.), 2-bromoanisole (37 μ L, 0.30 mmol, 2.01 equiv.), Cs₂CO₃ (120.0 mg, 0.37 mmol, 2.50 equiv.), XPhos (7.0 mg, 14.7 μ mol, 0.01 equiv.), and Pd(OAc)₂ (1.6 mg, 7.1 μ mol, 0.05 equiv.) in 9:1 dioxane: water (2.0 mL, 0.08 M). The crude residue was purified by flash chromatography on silica eluting with a 70 to 100 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as an off-white solid (31.8 mg, 82.3 μ mol, 56% yield). ¹H NMR (400 MHz, CDCl₃) δ : 9.10 (s, 1H), 7.47 (br s, 1H), 7.37 (dt, *J* = 7.5, 1.3 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.31-7.28 (m, 3H), 7.25-7.21 (m, 2H), 6.99 (td, *J* = 7.3, 1.0 Hz, 1H), 6.94 (br d, *J* = 8.3 Hz, 1H), 4.59 (s, 2H), 4.03 (s, 3H), 3.90 (s, 3H), 3.72 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ : 166.2, 156.5, 155.7, 153.7, 150.2, 148.6, 139.2, 137.7, 130.9, 130.4, 130.1, 128.9, 128.5, 128.1, 127.4, 120.9, 119.8, 111.4, 107.3, 102.9, 56.5, 56.2, 55.6, 42.0. LCMS (ESI) *m/z* [M+H]⁺: 387.3.



13

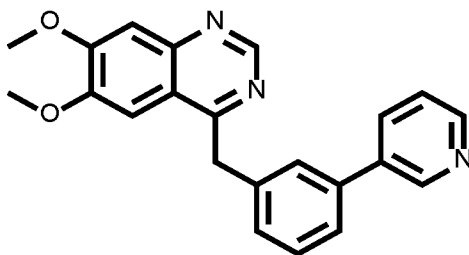
Compound **13** was prepared following general procedure F using **R4** (60.0 mg, 0.15 mmol, 1.00 equiv.), 4-bromoveratrole (43 μ L, 0.30 mmol, 2.02 equiv.), Cs₂CO₃ (122.0 mg, 0.37 mmol, 2.53 equiv.), XPhos (7.1 mg, 14.9 μ mol, 0.10 equiv.), and Pd(OAc)₂ (1.9 mg, 8.5 μ mol, 0.06 equiv.) in 9:1 dioxane: water (2.0 mL, 0.08 M). The crude residue was purified by flash chromatography on silica eluting with a 20 to 40 percent acetone in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as an off-white solid (29.1 mg, 69.9 μ mol, 47% yield). ¹H NMR (400 MHz, CDCl₃) δ : 9.11 (s, 1H), 7.49 (br s, 1H), 7.41 (br d, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.31 (s, 1H), 7.29 (s, 1H), 7.23 (br d, *J* = 7.5 Hz, 1H), 7.06 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.03 (d, *J* = 1.9 Hz, 1H), 6.91 (d, *J* = 8.1 Hz, 1H), 4.60 (s, 2H), 4.03 (s, 3H), 3.914 (s, 6H), 3.907 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ : 165.9, 155.7, 153.7, 150.3, 149.3, 148.9, 148.6, 141.7, 138.5, 134.0, 129.2, 127.4, 127.3, 125.5, 119.7, 119.5, 111.6, 110.6, 107.3, 102.6, 56.5, 56.2, 56.09, 56.06. LCMS (ESI) *m/z* [M+H]⁺: 417.3.



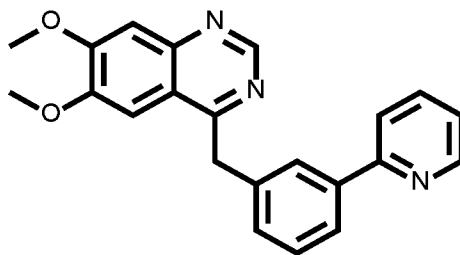
14

Compound **14** was prepared following general procedure F using **R4** (73.7 mg, 0.18 mmol, 1.00 equiv.), 4-bromopyridine hydrochloride (71.3 mg, 0.37 mmol, 2.02 equiv.), Cs₂CO₃ (298.0 mg, 0.91 mmol, 5.03 equiv.), and Pd(PPh₃)₄ (10.5 mg, 9.1 μ mol, 0.05 equiv.) in 9:1 dioxane: water (2.3 mL, 0.07 M). The crude residue was purified by flash chromatography on silica eluting with a 40 to 55 percent acetone in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a white solid (36.9 mg, 0.10 mmol, 57% yield). ¹H NMR (400

MHz, DMSO- d_6) δ : 8.98 (s, 1H), 8.62 (d, J = 5.6 Hz, 2H), 7.86 (s, 1H), 7.68-7.60 (m, 4H), 7.43 (d, J = 4.9 Hz, 2H), 7.34 (s, 1H), 4.69 (s, 2H), 3.96 (s, 3H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ : 165.5, 155.8, 153.7, 150.40, 150.35, 148.6, 148.0, 139.0, 138.8, 129.6, 129.5, 127.5, 125.6, 121.7, 119.6, 107.4, 102.2, 56.5, 56.2, 41.5. LCMS (ESI) m/z [M+H] $^+$: 358.2.

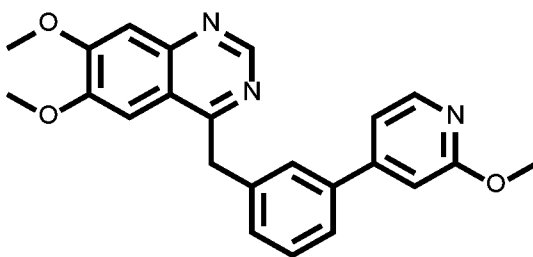
**15**

Compound **15** was prepared following general procedure F using **R4** (66.0 mg, 0.16 mmol, 1.00 equiv.), 3-bromopyridine (24 μL , 0.25 mmol, 1.53 equiv.), Cs_2CO_3 (134.0 mg, 0.41 mmol, 2.53 equiv.), and $\text{Pd}(\text{PPh}_3)_4$ (5.8 mg, 5.0 μmol , 0.03 equiv.) in 9:1 dioxane: water (2 mL, 0.08 M). The crude residue was purified by flash chromatography on silica eluting with a 30 to 60% acetone in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a light-yellow solid (39.2 mg, 0.11 mmol, 68% yield). ^1H NMR (400 MHz, CDCl_3) δ : 9.11 (s, 1H), 8.79 (br s, 1H), 8.58 (d, J = 4.0 Hz, 1H), 7.86 (dt, J = 8.0, 1.9 Hz, 1H), 7.52 (s, 1H), 7.47-7.34 (m, 4H), 7.34 (s, 1H), 7.27 (s, 1H), 4.63 (s, 2H), 4.04 (s, 3H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ : 165.6, 155.8, 153.8, 150.4, 148.67, 148.66, 148.3, 139.0, 138.5, 136.5, 134.6, 129.6, 128.7, 127.7, 125.8, 123.7, 119.7, 107.4, 102.3, 56.5, 56.2, 41.6. LCMS (ESI) m/z [M+H] $^+$: 358.2.

**16**

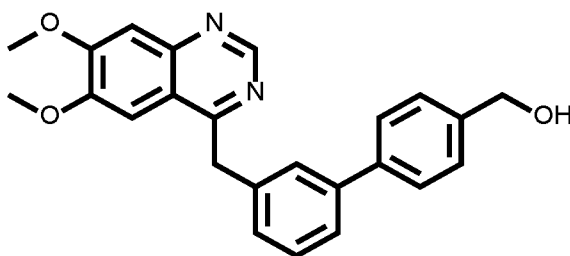
Compound **16** was prepared following general procedure F using **R4** (73.2 mg, 0.18 mmol, 1.00 equiv.), 2-bromopyridine (27 μL , 0.28 mmol, 1.54 equiv.), Cs_2CO_3 (170.0 mg, 0.52 mmol, 2.90 equiv.), XPhos Pd G3 (3.2 mg, 3.8 μmol , 0.02 equiv.) in 9:1 dioxane: water

(2.3 mL, 0.08 M). The crude residue was purified by flash chromatography on silica eluting with a 60 to 90 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a white solid (18.6 mg, 52.0 μ mol, 29% yield). ^1H NMR (400 MHz, DMSO- d_6) δ : 8.99 (s, 1H), 8.63 (br d, J = 4.9 Hz, 1H), 8.17 (br s, 1H), 7.93-7.82 (m, 3H), 7.67 (s, 1H), 7.45-7.37 (m, 2H), 7.36-7.30 (m, 2H), 4.68 (s, 2H), 3.95 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ : 165.9, 157.2, 155.7, 153.8, 150.3, 149.8, 148.6, 134.0, 138.7, 136.9, 129.5, 129.3, 127.6, 125.4, 122.4, 120.7, 119.7, 107.3, 102.7, 56.5, 56.3, 42.0. LCMS (ESI) m/z $[\text{M}+\text{H}]^+$: 358.2.



17

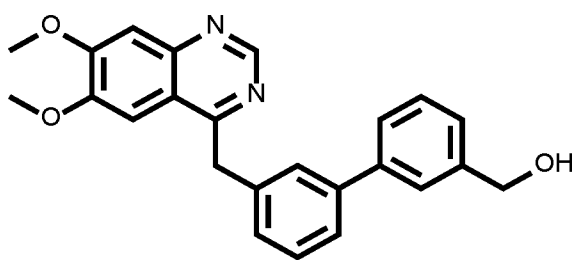
Compound **17** was prepared following general procedure F using **R4** (60.0 mg, 0.15 mmol, 1.00 equiv.), 4-bromo-2-methoxypyridine (55.0 mg, 0.29 mmol, 2.00 equiv.), Cs_2CO_3 (120.0 mg, 3.67 mmol, 2.50 equiv.), and $\text{Pd}(\text{PPh}_3)_4$ (8.4 mg, 0.007 mmol, 0.05 equiv.) in 9:1 dioxane: water (2 mL, 0.08 M). The crude residue was purified by flash chromatography on silica eluting with 40 to 50 percent acetone in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as an off-white solid (22.5 mg, 0.06 mmol, 39% yield). ^1H NMR (400 MHz, CDCl_3) δ : 9.11 (s, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.55 (br s, 1H), 7.47 (br d, J = 7.8 Hz, 1H), 7.39 (t, J = 7.4 Hz, 1H), 7.36-7.31 (m, 2H), 7.25 (br s, 1H), 7.02 (dd, J = 5.4, 1.4 Hz, 1H), 6.88 (br s, 1H), 4.61 (s, 2H), 4.04 (s, 3H), 3.96 (s, 3H), 3.92 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ : 165.6, 165.0, 155.9, 153.6, 151.0, 150.5, 148.6, 147.4, 139.0, 138.9, 129.53, 129.46, 127.6, 125.7, 119.7, 115.4, 108.6, 107.4, 102.3, 56.5, 56.2, 53.7, 41.6. LCMS (ESI) m/z $[\text{M}+\text{H}]$: 388.3.



64

18

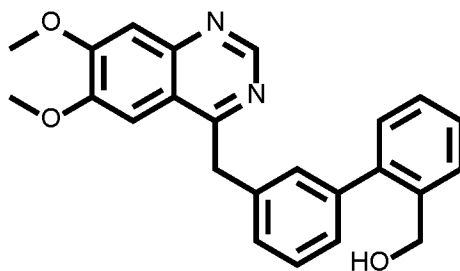
Compound **18** was prepared following general procedure F using **R4** (40.0 mg, 98.5 μ mol, 1.00 equiv.), 4-bromobenzyl alcohol (34.5 mg, 0.18 mmol, 1.87 equiv.), Cs₂CO₃ (77.9 mg, 0.24 mmol, 2.43 equiv.), and Pd(PPh₃)₄ (5.4 mg, 4.7 μ mol, 0.05 equiv.) in 9:1 dioxane: water (1.5 mL, 0.07 M). The crude residue was purified by flash chromatography on silica eluting with a 75 to 95 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a light-yellow solid (22.8 mg, 59.0 μ mol, 60% yield). ¹H NMR (400 MHz, DMSO-d₆) δ : 8.99 (s, 1H), 7.72 (s, 1H), 7.65 (s, 1H), 7.56 (br d, *J* = 8.3 Hz, 2H), 7.48 (dt, *J* = 7.3, 1.4 Hz, 1H), 7.38 (br d, *J* = 8.3 Hz, 2H), 7.36-7.28 (m, 3H), 5.19 (t, *J* = 5.9 Hz, 1H), 4.66 (s, 2H), 4.52 (d, *J* = 5.9 Hz, 2H), 3.95 (s, 3H), 3.93 (s, 3H). ¹³C NMR (100 MHz, DMSO-d₆) δ : 165.1, 155.5, 153.0, 149.9, 147.7, 141.8, 140.2, 139.0, 138.4, 129.0, 127.9, 127.3, 127.0, 126.3, 124.6, 118.7, 106.8, 103.0, 62.6, 56.1, 56.0, 40.0. LCMS (ESI) *m/z* [M+H]⁺: 387.3.



19

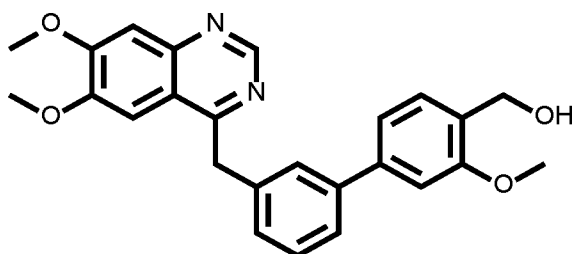
Compound **19** was prepared following general procedure F using **R4** (40.0 mg, 98.5 μ mol, 1.00 equiv.), 3-bromobenzyl alcohol (18 μ L, 0.15 mmol, 1.52 equiv.), Cs₂CO₃ (66.9 mg, 0.21 mmol, 2.09 equiv.), XPhos (3.5 mg, 7.3 μ mol, 0.07 equiv.), and Pd(OAc)₂ (1.1 mg, 4.9 μ mol, 0.05 equiv.) in 9:1 dioxane: water (1.5 mL, 0.07 M). The crude residue was purified by flash chromatography on silica eluting with 75 to 100 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as an off-white solid (17.0 mg, 44.0 μ mol, 45% yield). ¹H NMR (400 MHz, DMSO-d₆) δ : 8.99 (s, 1H), 7.72 (br s, 1H), 7.66 (s, 1H), 7.56 (br s, 1H), 7.51-7.43 (m, 2H), 7.42-7.31 (m, 4H), 7.29 (br d, *J* = 7.6 Hz), 5.21 (t, *J* = 5.9 Hz, 1H), 4.66 (s, 2H), 4.55 (d, *J* = 5.9 Hz, 2H), 3.95 (s, 3H), 3.94 (s, 3H). ¹³C NMR (100 MHz, DMSO-d₆) δ : 165.1, 155.5, 153.0, 150.0, 147.7, 143.2, 140.5, 139.8, 139.0,

129.0, 128.7, 128.0, 127.4, 125.6, 124.9, 124.7, 124.6, 118.7, 106.8, 103.0, 62.7, 56.07, 56.05, 40.0. LCMS (ESI) m/z $[M+H]^+$: 387.3.



20

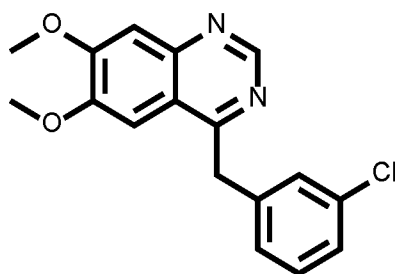
Compound **20** was prepared following general procedure F using **R4** (40.0 mg, 98.5 μ mol, 1.00 equiv.), 2-bromobenzyl alcohol (36.7 mg, 0.20 mmol, 1.99 equiv.), Cs_2CO_3 (76.0 mg, 0.23 mmol, 2.37 equiv.), and $\text{Pd}(\text{PPh}_3)_4$ (6.2 mg, 5.4 μ mol, 0.05 equiv.) in 9:1 dioxane: water (1.5 mL, 0.07 M). The crude residue was purified by flash chromatography on silica eluting with a 75 to 85 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as an off-white solid (16.6 mg, 4.0 μ mol, 44% yield). ^1H NMR (400 MHz, DMSO-d_6) δ : 8.98 (s, 1H), 7.60 (s, 1H), 7.55 (br d, $J = 7.8$ Hz, 1H), 7.39-7.32 (m, 5H), 7.29 (td, $J = 7.4, 1.3$ Hz, 1H), 7.23-7.17 (m, 1H), 7.14 (dd, $J = 7.5, 1.3$ Hz, 1H), 5.06 (t, $J = 5.5$ Hz, 1H), 4.63 (s, 2H), 4.33 (d, $J = 5.6$ Hz, 2H), 3.96 (s, 3H), 3.92 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ : 166.0, 155.5, 153.0, 150.0, 147.7, 140.5, 139.8, 139.3, 138.3, 129.6, 129.1, 128.3, 127.8, 127.6, 127.3, 127.0, 126.7, 118.8, 106.8, 103.0, 60.7, 56.1, 56.0, 39.9. LCMS (ESI) m/z $[M+H]^+$: 387.3.



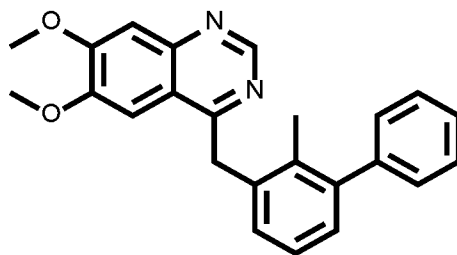
21

Compound **21** was prepared following general procedure F using **R4** (60.0 mg, 0.15 mmol, 1.00 equiv.), (4-bromo-2-methoxyphenyl)methanol (62.7 mg, 0.29 mmol, 1.96 equiv.), Cs_2CO_3 (122.0 mg, 0.38 mmol, 2.54 equiv.), and $\text{Pd}(\text{PPh}_3)_4$ (8.3 mg, 7.2 μ mol, 0.05 equiv.) in 9:1 dioxane: water (2 mL, 0.15 M). The crude residue was purified by flash chromatography on silica eluting with a 30 to 50 percent acetone in hexanes gradient. The

fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a white solid (32.0 mg, 76.8 μ mol, 52% yield). ^1H NMR (400 MHz, DMSO- d_6) δ : 8.98 (s, 1H), 7.76 (br s, 1H), 7.66 (s, 1H), 7.51 (br d, $J = 7.7$ Hz, 1H), 7.42 (d, $J = 7.7$ Hz, 1H), 7.38-7.32 (m, 2H), 7.30 (br d, $J = 7.7$ Hz, 1H), 7.17 (dd, $J = 7.7$, 1.3 Hz, 1H), 7.12 (d, $J = 1.3$ Hz, 1H), 5.00 (br s, 1H), 4.66 (s, 2H), 4.51 (s, 2H), 3.95 (s, 3H), 3.94 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ : 165.9, 157.8, 155.8, 153.5, 150.4, 148.6, 142.0, 141.8, 138.5, 129.3, 129.1, 128.5, 127.9, 127.7, 125.8, 119.7, 119.5, 109.3, 107.3, 102.5, 61.7, 56.5, 56.2, 55.5, 41.8. LCMS (ESI) m/z $[\text{M}+\text{H}]^+$: 417.3.

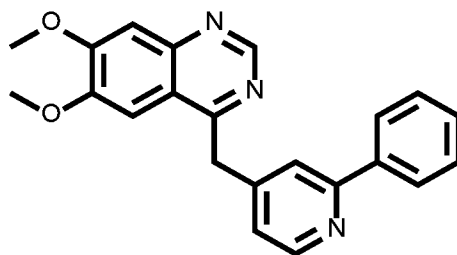
**22**

Compound **22** was prepared following general procedure E using 4-chloro-6,7-dimethoxyquinazoline (110.0 mg, 0.49 mmol, 1.0 equiv.), sodium acetate (74.0 mg, 0.90 mmol, 1.84 equiv.), (3-chlorophenyl)methanol (121.0 mg, 0.85 mmol, 1.73 equiv.), NHC-1 BF_4 (310 mg, 0.78 mmol, 1.60 equiv.), pyridine (64 μL , 0.80 mmol, 1.62 equiv.), phthalimide (16 mg, 0.11 mmol, 0.22 equiv.), $\text{Ni}(\text{dtbbpy})\text{Br}_2$ (18.6 mg, 38.2 μmol , 0.078 equiv.), and $\text{Ir}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$ (6.7 mg, 7.4 μmol , 0.015 equiv.) in TBME (5 mL, 0.16 M for alcohol activation) and DMA (5 mL, 0.05 M combined with TBME solution). The crude residue was purified via flash chromatography on silica eluting with a 60 to 85 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as an off-white solid (69.0 mg, 0.22 mmol, 45% yield). ^1H NMR (400 MHz, CDCl_3) δ : 9.11 (s, 1H), 7.35 (s, 1H), 7.28 (s, 1H), 7.24-7.14 (m, 4H), 4.52 (s, 2H), 4.05 (s, 3H), 3.95 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ : 165.1, 155.8, 153.7, 150.5, 148.6, 139.9, 134.7, 130.1, 129.0, 127.1, 127.0, 119.6, 107.4, 102.2, 56.5, 56.2, 41.2. LCMS (ESI) m/z $[\text{M}+\text{H}]^+$: 314.1.



23

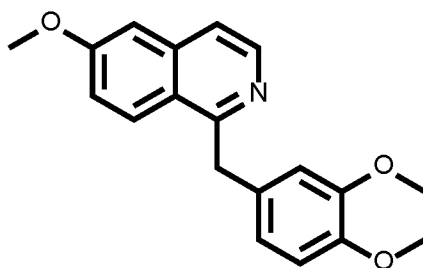
Compound **23** was prepared following general procedure E using 4-chloro-6,7-dimethoxyquinazoline (115.0 mg, 0.51 mmol, 1.00 equiv.), sodium acetate (86.5 mg, 1.05 mmol, 2.06 equiv.), {2-methyl-[1,1'-biphenyl]-3-yl}methanol (173.0 mg, 0.87 mmol, 1.71 equiv.), NHC-1 BF₄ (324.0 mg, 0.82 mmol, 1.61 equiv.), pyridine (66 μ L, 0.82 mmol, 1.60 equiv.), phthalimide (18.4 mg, 0.13 mmol, 0.24 equiv.), Ni(dtbbpy)Br₂ (18.9 mg, 38.8 μ mol, 0.076 equiv.), and Ir(ppy)₂(dtbbpy)PF₆ (7.8 mg, 8.5 μ mol, 0.017 equiv.) in TBME (5 mL, 0.16 M for activation) and DMA (5 mL, 0.05 M combined with TBME solution). The crude residue was purified via flash chromatography on silica eluting with a 50 to 60 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a white solid (38.5 mg, 0.10 mmol, 20% yield). ¹H NMR (400 MHz, CDCl₃) δ : 9.11 (s, 1H), 7.43-7.38 (m, 3H), 7.34 (tt, *J* = 6.1, 1.4 Hz, 1H), 7.30-7.27 (m, 2H), 7.23 (s, 1H), 7.16 (s, 1H), 7.15 (d, *J* = 1.1 Hz, 1H), 7.04-6.99 (m, 1H), 4.63 (s, 2H), 4.07 (s, 3H), 3.92 (s, 3H), 2.23 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ : 166.2, 155.7, 153.8, 150.3, 148.4, 143.1, 142.4, 137.1, 134.2, 129.5, 128.9, 128.7, 128.2, 126.9, 125.8, 120.0, 107.4, 102.4, 56.5, 56.2, 40.0, 17.5. LCMS (ESI) *m/z* [M+H]⁺: 371.3.



24

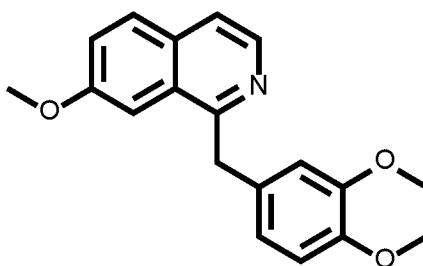
Compound **24** was prepared following general procedure E with the following modifications: The alcohol was activated using the alternative salt NHC-1 OTf and activation was achieved by adding NHC-1 OTf in five even portions over 10 minutes to a solution of the alcohol in THF under nitrogen. The resultant dark orange homogenous

solution required no filtration to transfer. The procedure was performed using 4-chloro-6,7-dimethoxyquinazoline (70.0 mg, 0.31 mmol, 1.00 equiv.), quinuclidine (115.0 mg, 1.03 mmol, 3.32 equiv.), (2-phenylpyridin-4-yl)methanol (99.0 mg, 0.53 mmol, 1.72 equiv.), NHC-1 OTf (230.0 mg, 0.50 mmol, 1.61 equiv.), phthalimide (18.4 mg, 0.13 mmol, 0.40 equiv.), Ni(dtbbpy)Br₂ (14.8 mg, 30.4 μmol, 0.01 equiv.), and Ir(ppy)₂(dtbbpy)PF₆ (4.4 mg, 4.8 μmol, 0.015 equiv.) in THF (3 mL, 0.18 M for activation) and DMA (2 mL, 0.06 M combined with THF solution). The crude residue was purified via flash chromatography with silica, but this required two purifications to achieve appropriate purity. The first purification eluted with 30 to 40 percent acetone in hexanes, while the second purification eluted with 0 to 1% methanol in DCM. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a light-pink solid. (8.2 mg, 22.9 μmol, 7% yield). ¹H NMR (400 MHz, CDCl₃) δ: 9.12 (s, 1H), 8.60 (d, *J* = 5.1 Hz, 1H), 7.92 (m, 2H), 7.65 (br s, 1H), 7.47-7.37 (m, 3H), 7.34 (s, 1H), 7.19 (s, 1H), 7.14 (dd, *J* = 5.1, 1.6 Hz, 1H), 4.60 (s, 2H), 4.05 (s, 3H), 3.94 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 164.2, 158.1, 156.0, 153.8, 150.7, 150.1, 148.8, 147.6, 139.3, 129.2, 128.9, 127.1, 122.6, 121.0, 119.7, 107.6, 101.9, 56.6, 56.3, 41.1. LCMS (ESI) *m/z* [M+H]⁺: 358.2.

**25**

Compound **25** was prepared following general procedure E with the following modifications: Additional activated alcohol and reaction time (20 hours) were used to induce product formation as this reaction returned a very poor yield (~6%) under standard reaction conditions. Reaction performed using 1-chloro-6-methoxyisoquinoline (50.0 mg, 0.26 mmol, 1.00 equiv.), quinuclidine (90.0 mg, 0.81 mmol, 3.13 equiv.), (3,4-dimethoxyphenyl) methanol (149.0 mg, 0.89 mmol, 3.43 equiv.), NHC-1 BF₄ (305.0 mg, 0.77 mmol, 2.99 equiv.), pyridine (62 μL, 78 mmol, 3.00 equiv.), phthalimide (16.0 mg, 0.11 mmol, 0.42 equiv.), Ni(dtbbpy)Br₂ (17.7 mg, 36.4 μmol, 0.14 equiv.), and Ir(ppy)₂(dtbbpy)PF₆ (5.7 mg, 6.2 μmol, 0.024 equiv.) in THF (2 mL, 0.45 M for activation) and DMA (2 mL, 0.07 M combined with THF solution). The reaction solution was

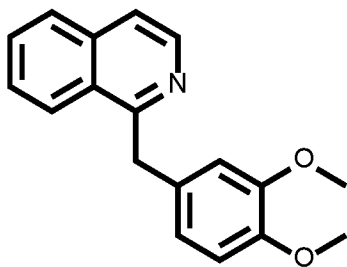
irradiated for 20 hours. The crude residue was purified via flash chromatography on silica eluting with a 5 to 30 percent acetone in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a clear semi-solid (33.4 mg, 42% yield). ¹H NMR (400 MHz, CDCl₃) δ: 8.41 (d, *J* = 5.8 Hz, 1H), 8.06 (d, *J* = 9.2 Hz, 1H) 7.45 (d, *J* = 5.8 Hz, 1H), 7.15 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.06 (d, *J* = 2.5 Hz, 1H), 6.83 (d, *J* = 1.5 Hz, 1H), 6.78 (dd, *J* = 8.2, 1.5 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 4.55 (s, 2H), 3.93 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 160.5, 159.8, 149.1, 147.6, 142.8, 138.8, 132.3, 127.7, 123.0, 120.6, 120.0, 119.3, 112.0, 111.3, 105.0, 55.94, 55.91, 55.5, 41.8. LCMS (ESI) *m/z* [M+H]⁺: 310.2.



26

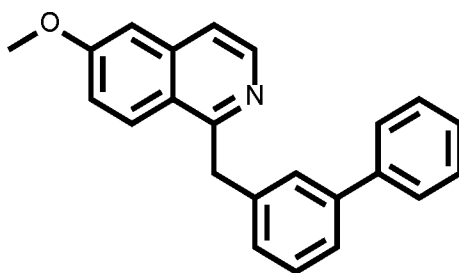
Compound **26** was prepared following general procedure E with the following modifications: Additional activated alcohol and reaction time were used to induce product formation as these conditions were effective for 1-chloro-6-methoxyisoquinoline when standard conditions failed. Reaction performed using 1-chloro-7-methoxyisoquinoline (50.0 mg, 0.26 mmol, 1.0 equiv.), quinuclidine (58.0 mg, 0.52 mmol, 2.02 equiv.), (3,4-dimethoxyphenyl) methanol (87.9 mg, 0.52 mmol, 2.02 equiv.), NHC-1 BF₄ (197.0 mg, 0.50 mmol, 1.93 equiv.), pyridine (41 μL, 51 mmol, 1.97 equiv.), phthalimide (10.7 mg, 72.7 μmol, 0.28 equiv.), Ni(dtbbpy)Br₂ (12.4 mg, 25.5 μmol, 0.099 equiv.), and Ir(ppy)₂(dtbbpy)PF₆ (4.6 mg, 5.0 μmol, 0.020 equiv.) in TBME (2 mL, 0.25 M for activation) and DMA (2 mL, 0.07 M combined with TBME solution). The reaction solution was irradiated for 20 hours. The crude residue was purified via flash chromatography on silica eluting with a 40 to 60 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as an off-white solid (32.8 mg, 0.11 mmol, 41% yield). ¹H NMR (400 MHz, CDCl₃) δ: 8.39 (d, *J* = 5.6 Hz, 1H), 7.73 (d, *J* = 9.0 Hz, 1H), 7.53 (d, *J* = 5.8 Hz, 1H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.32 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.87-6.81 (m, 2H), 6.77 (d, *J* = 8.0 Hz, 1H), 4.59 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ:

158.8, 158.2, 149.1, 147.7, 140.3, 132.2, 129.0, 128.3, 122.7, 120.7, 119.6, 112.1, 111.3, 104.0, 56.0, 55.9, 55.4, 42.3. LCMS (ESI) m/z $[M+H]^+$: 310.2.



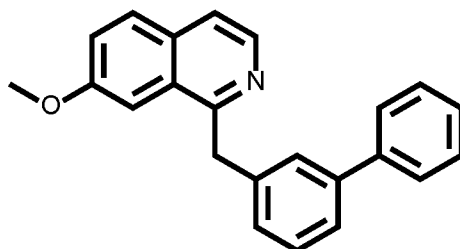
27

Compound **27** was prepared following general procedure E using 1-bromoisoquinoline (100.0 mg, 0.48 mmol, 1.0 equiv.), sodium acetate (80.4 mg, 0.98 mmol, 2.04 equiv.), (3,4-dimethoxyphenyl) methanol (120 μ L, 0.83 mmol, 1.72 equiv.), NHC-1 BF₄ (309.0 mg, 0.78 mmol, 1.63 equiv.), pyridine (65 μ L, 0.81 mmol, 1.68 equiv.), phthalimide (23.8 mg, 0.16 mmol, 0.34 equiv.), Ni(dtbbpy)Br₂ (18.6 mg, 38.2 μ mol, 0.080 equiv.), and Ir(ppy)₂(dtbbpy)PF₆ (7.8 mg, 8.5 μ mol, 0.018 equiv.) in TBME (2.5 mL, 0.31 M for activation) and DMA (2.5 mL, 0.10 M combined with TBME solution). The crude residue was purified via flash chromatography on silica eluting with a 10 to 20 percent acetone in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as an off-white solid (14.8 mg, 53 μ mol, 11% yield). ¹H NMR (400 MHz, CDCl₃) δ : 8.50 (d, J = 5.8 Hz, 1H), 8.18 (dd, J = 8.4, 0.9 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.64 (td, J = 7.3, 1.2 Hz, 1H), 7.57-7.51 (m, 2H), 6.85 (d, J = 1.9 Hz, 1H), 6.80 (dd, J = 8.1, 1.9 Hz, 1H), 6.75 (d, J = 8.1 Hz, 1H), 4.61 (s, 2H), 3.81 (s, 3H), 3.79 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ : 160.5, 149.1, 147.7, 142.2, 136.7, 132.2, 130.0, 127.5, 127.3, 127.3, 125.9, 120.7, 119.9, 112.1, 111.4, 55.97, 55.95, 41.8. LCMS (ESI) m/z $[M+H]^+$: 280.2.



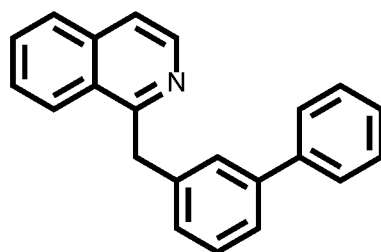
28

Compound **28** was prepared following general procedure E. Reaction performed using 1-chloro-6-methoxyisoquinoline (60.0 mg, 0.31 mmol, 1.0 equiv.), quinuclidine (109.0 mg, 0.98 mmol, 3.16 equiv.), [1,1'-biphenyl]-3-ylmethanol (184.0 mg, 1.00 mmol, 3.21 equiv.), NHC-1 BF₄ (366.0 mg, 0.93 mmol, 3.00 equiv.), pyridine (75 μ L, 0.93 mmol, 3.00 equiv.), phthalimide (14.2 mg, 96.5 μ mol, 0.31 equiv.), Ni(dtbbpy)Br₂ (22.7 mg, 46.6 μ mol, 0.15 equiv.), and Ir(ppy)₂(dtbbpy)PF₆ (7.4 mg, 8.1 μ mol, 0.026 equiv.) in TBME (2 mL, 0.47 M for activation) and DMA (2 mL, 0.08 M combined with TBME solution). The reaction solution was irradiated for 20 hours. The crude residue was purified via flash chromatography on silica eluting with a 10 to 25 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a light-yellow semi-solid (70.0 mg, 0.22 mmol, 69% yield). ¹H NMR (400 MHz, CDCl₃) δ : 8.43 (d, *J* = 5.8 Hz, 1H), 8.08 (d, *J* = 9.3 Hz, 1H), 7.54-7.50 (m, 3H), 7.46 (d, *J* = 5.8 Hz, 1H), 7.43-7.36 (m, 3H), 7.34-7.28 (m, 2H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.15 (dd, *J* = 9.3, 2.6 Hz, 1H), 7.06 (d, *J* = 2.7 Hz, 1H), 4.68 (s, 2H), 3.92 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ : 158.5, 158.3, 141.6, 141.2, 140.4, 140.1, 132.2, 129.1, 129.0, 128.8, 128.4, 127.7, 127.6, 127.4, 127.2, 125.3, 122.8, 119.7, 103.9, 55.4, 42.8. LCMS (ESI) *m/z* [M+H]⁺: 326.2.

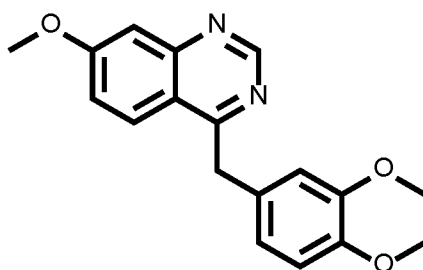
**29**

Compound **29** was prepared following general procedure E with the following modifications: Additional activated alcohol and reaction time were used to induce product formation as these conditions were effective for 1-chloro-6-methoxyisoquinoline when standard conditions failed. Reaction performed using 1-chloro-7-methoxyisoquinoline (48.5 mg, 0.25 mmol, 1.0 equiv.), quinuclidine (87.0 mg, 0.78 mmol, 3.12 equiv.), [1,1'-biphenyl]-3-ylmethanol (152.0 mg, 0.82 mmol, 3.29 equiv.), NHC-1 BF₄ (304.0 mg, 0.77 mmol, 3.07 equiv.), pyridine (61 μ L, 0.76 mmol, 3.02 equiv.), phthalimide (14.0 mg, 95.2 μ mol, 0.38 equiv.), Ni(dtbbpy)Br₂ (17.9 mg, 36.8 μ mol, 0.15 equiv.), and Ir(ppy)₂(dtbbpy)PF₆ (5.5 mg, 6.0 μ mol, 0.024 equiv.) in THF (2 mL, 0.39 M for activation) and DMA (2 mL, 0.06 M combined with THF solution). The reaction solution was

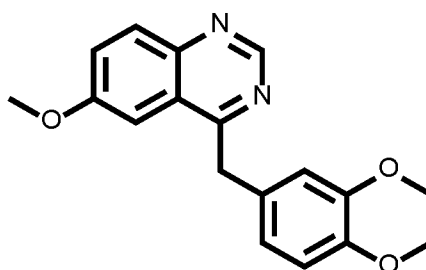
irradiated for 20 hours. The crude residue was purified via flash chromatography on silica eluting with a 0 to 20 percent acetone in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a light-yellow solid (43.7 mg, 0.13 mmol, 54% yield). ¹H NMR (400 MHz, DMSO-d₆) δ: 8.33 (d, *J* = 5.5 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 1H), 7.69 (br s, 1H), 7.65 (d, *J* = 5.5 Hz, 1H), 7.62 (d, *J* = 2.2 Hz, 1H), 7.60-7.55 (m, 2H), 7.48-7.41 (m, 3H), 7.39 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.37-7.28 (m, 3H), 4.69 (s, 2H), 3.87 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 158.5, 158.3, 141.6, 141.2, 140.4, 140.1, 132.2, 129.1, 129.0, 128.8, 128.4, 127.7, 127.6, 127.4, 127.2, 125.3, 122.8, 119.7, 103.9, 55.4, 42.8. LCMS (ESI) *m/z* [M+H]⁺: 326.2.

**30**

Compound **30** was prepared following general procedure E-IP using 1-bromoisoquinoline (75.8 mg, 0.37 mmol, 1.00 equiv.), sodium acetate (47.8 mg, 0.58 mmol, 1.60 equiv.), [1,1'-biphenyl]-3-ylmethanol (97.4 mg, 0.53 mmol, 1.45 equiv.), NHC-1 BF₄ (202.0 mg, 0.51 mmol, 1.40 equiv.), pyridine (43 μL, 0.54 mmol, 1.48 equiv.), phthalimide (24.3 mg, 0.17 mmol, 0.45 equiv.), Ni(dtbbpy)Br₂ (13.0 mg, 26.7 μmol, 0.073 equiv.), and Ir(ppy)₂(dtbbpy)PF₆ (5.0 mg, 5.5 μmol, 0.015 equiv.) in THF (3 mL (9 mL /3), 0.17 M for activation) and DMA (3 mL, 0.06 M combined with THF solution). The crude residue was purified via flash chromatography on silica eluting with a 0 to 20 percent ethyl acetate in hexanes gradient. A second purification was required using a 5 to 15% ethyl acetate in hexanes gradient to achieve sufficient purity. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a clear semi-solid (24.9 mg, 84.3 μmol, 23% yield). ¹H NMR (400 MHz, CDCl₃) δ: 8.46 (d, *J* = 5.6 Hz, 1H), 8.40 (br d, *J* = 8.6 Hz, 1H), 7.96 (br d, *J* = 8.2 Hz, 1H), 7.77-7.70 (m, 2H), 7.68-7.62 (m, 2H), 7.60-7.55 (m, 2H), 7.47-7.41 (m, 3H), 7.37-7.31 (m, 2H), 7.27 (br d, 7.6 Hz, 1H), 4.71 (s, 2H). ¹³C NMR (100 MHz, CDCl₃) δ: 160.2, 142.2, 141.6, 141.3, 140.1, 136.7, 130.0, 129.0, 128.8, 127.71, 127.65, 127.5, 127.4, 127.3, 125.9, 125.4, 120.0, 42.3. LCMS (ESI) *m/z* [M+H]⁺: 296.2.

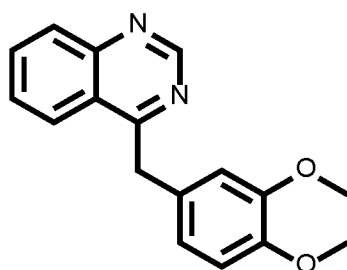
**31**

Compound **31** was prepared following general procedure E using 4-chloro-7-methoxyquinazoline (60.0 mg, 0.31 mmol, 1.0 equiv.), sodium acetate (53.0 mg, 0.65 mmol, 2.10 equiv.), (3,4-dimethoxyphenyl)methanol (77 μ L, 0.53 mmol, 1.72 equiv.), NHC-1 BF₄ (195.0 mg, 0.50 mmol, 1.60 equiv.), pyridine (40 μ L, 0.50 mmol, 1.61 equiv.), phthalimide (10.5 mg, 0.23 mmol, 0.23 equiv.), Ni(dtbbpy)Br₂ (11.0 mg, 22.6 μ mol, 0.073 equiv.), and Ir(ppy)₂(dtbbpy)PF₆ (4.0 mg, 4.38 μ mol, 0.014 equiv.) in 1,4-dioxane (2 mL, 0.25 M for activation) and DMA (mL, 0.08 M combined with dioxane solution). The crude residue was purified via flash chromatography on silica eluting with a 25 to 40 percent acetone in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a white solid (22.3 mg, 71.9 μ mol, 23% yield). ¹H NMR (400 MHz, DMSO-d₆) δ : 9.08 (s, 1H), 8.33 (br d, *J* = 8.9 Hz, 1H), 7.35-7.30 (m, 2H), 6.99 (d, *J* = 1.8 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.77 (dd, *J* = 8.2, 1.9 Hz, 1H), 4.49 (s, 2H), 3.95 (s, 3H), 3.69 (s, 3H), 3.67 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ : 168.4, 163.9, 155.4, 153.0, 149.2, 148.0, 130.4, 126.7, 121.2, 120.9, 119.5, 112.1, 111.5, 106.8, 56.01, 56.00, 55.9, 40.9. LCMS (ESI) *m/z* [M+H]⁺: 311.2.

**32**

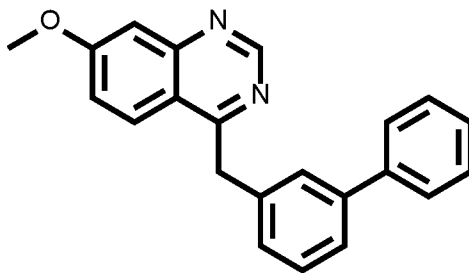
Compound **32** was prepared following general procedure E using 4-chloro-6-methoxyquinazoline (60.0 mg, 0.31 mmol, 1.0 equiv.), sodium acetate (50.5 mg, 0.62 mmol, 2.0 equiv.), (3,4-dimethoxyphenyl)methanol (78 μ L, 0.54 mmol, 1.74 equiv.), NHC-1 BF₄ (196.0 mg, 0.50 mmol, 1.61 equiv.), pyridine (40 μ L, 0.50 mmol, 1.61 equiv.), phthalimide (12.1 mg, 82.2 μ mol, 0.27 equiv.), Ni(dtbbpy)Br₂ (11.3 mg, 23.1 μ mol, 0.075

equiv.), and Ir(ppy)₂(dtbbpy)PF₆ (4.1 mg, 4.5 μmol, 0.015 equiv.) in TBME (2 mL, 0.25 M for activation) and DMA (2 mL, 0.08 M combined with TBME solution). The crude residue was purified via flash chromatography on silica eluting with a 65 to 80 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as an off-white solid (26.4 mg, 85.1 μmol, 28% yield). ¹H NMR (400 MHz, CDCl₃) δ: 9.17 (s, 1H), 7.98 (d, *J* = 9.0 Hz, 1H), 7.53 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.36 (d, *J* = 2.7 Hz, 1H), 6.87-6.83 (m, 2H), 6.79 (d, *J* = 8.0 Hz, 1H), 4.55 (s, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 167.7, 158.4, 152.9, 149.4, 148.1, 146.6, 130.7, 130.3, 126.4, 125.0, 121.0, 112.3, 111.5, 102.8, 56.0, 55.7, 41.4. LCMS (ESI) *m/z* [M+H]⁺: 311.2.

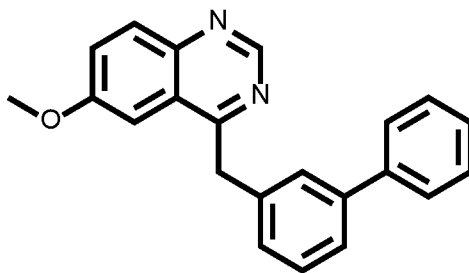
**33**

Compound **33** was prepared following general procedure E-IP using 4-chloroquinazoline (60.0 mg, 0.37 mmol, 1.00 equiv.), quinuclidine (64.2 mg, 0.58 mmol, 1.58 equiv.), (3,4-dimethoxyphenyl)methanol (96 μL, 0.66 mmol, 1.81 equiv.), NHC-1 BF₄ (245.0 mg, 0.62 mmol, 1.70 equiv.), pyridine (50 μL, 0.62 mmol, 1.70 equiv.), phthalimide (24.2 mg, 0.16 mmol, 0.45 equiv.), Ni(dtbbpy)Br₂ (22.1 mg, 45.4 μmol, 0.13 equiv.), and Ir(ppy)₂(dtbbpy)PF₆ (5.5 mg, 6.0 μmol, 0.017 equiv.) in THF (3 mL (9 mL /3), 0.21 M for activation) and DMA (3 mL, 0.06 M combined with THF solution). The crude residue was purified via flash chromatography on silica eluting with a 25 to 50 percent ethyl acetate in hexanes gradient. A second purification was required using flash chromatography on silica eluting with a 10 to 15 percent acetone in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a white solid (11.9 mg, 42.5 μmol, 12% yield). ¹H NMR (400 MHz, CDCl₃) δ: 9.28 (s, 1H), 8.19 (br d, *J* = 8.2 Hz, 1H), 8.05 (br d, *J* = 8.2 Hz, 1H), 7.87 (td, *J* = 6.9, 1.3 Hz, 1H), 7.61 (td, *J* = 6.9, 1.2 Hz, 1H), 6.87-6.81 (m, 2H), 6.78 (d, *J* = 8.3 Hz, 1H), 4.57 (s, 2H), 3.83 (s, 3H), 3.81 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 169.7, 154.9, 150.5, 149.3, 148.1, 133.7,

130.2, 129.4, 127.8, 125.2, 124.1, 121.0, 112.2, 111.5, 56.01, 55.99, 41.0. LCMS (ESI) m/z $[M+H]^+$: 281.2.

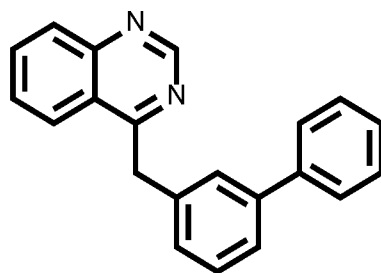
**34**

Compound **34** was prepared following general procedure E-IP using 4-chloro-7-methoxyquinazoline (60 mg, 0.31 mmol, 1.0 equiv.), sodium acetate (52.0 mg, 0.63 mmol, 2.06 equiv.), [1,1'-biphenyl]-3-ylmethanol (108 mg, 0.59 mmol, 1.90 equiv.), NHC-1 BF_4 (219 mg, 0.56 mmol, 1.80 equiv.), pyridine (45 μL , 0.56 mmol, 1.81 equiv.), phthalimide (14.0 mg, 95.2 μmol , 0.31 equiv.), $\text{Ni}(\text{dtbbpy})\text{Br}_2$ (14.4 mg, 29.6 μmol , 0.096 equiv.), and $\text{Ir}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$ (4.8 mg, 5.25 μmol , 0.017 equiv.) in TBME (2 mL (6 mL /3), 0.3 M for activation) and DMA (2 mL, 0.078 M combined with TBME solution). The crude residue was purified via flash chromatography on silica eluting with a 30 to 55 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as an off-white solid (45.4 mg, 0.14 mmol, 45% yield). ^1H NMR (400 MHz, CDCl_3) δ : 9.18 (s, 1H), 8.09 (d, $J = 9.2$ Hz, 1H), 7.54-7.51 (m, 3H), 7.46-7.27 (m, 7H), 7.23 (dd, $J = 9.2, 2.70$ Hz, 1H), 4.64 (s, 2H), 3.97 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ : 168.1, 163.8, 155.5, 153.1, 141.8, 141.0, 138.5, 129.4, 128.8, 127.8, 127.7, 127.5, 127.3, 126.6, 125.8, 121.1, 119.5, 106.8, 55.9, 41.4. LCMS (ESI) m/z $[M+H]^+$: 327.2.

**35**

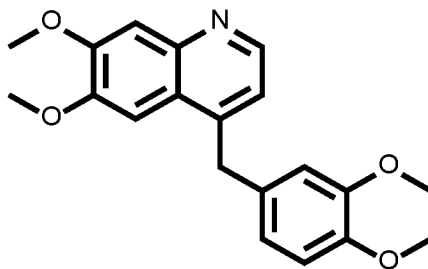
Compound **35** was prepared following general procedure E using 4-chloro-6-methoxyquinazoline (47 mg, 0.24 mmol, 1.0 equiv.), sodium acetate (36.5 mg, 0.45 mmol,

1.84 equiv.), [1,1'-biphenyl]-3-ylmethanol (69.4 mg, 0.38 mmol, 1.56 equiv.), NHC-1 BF₄ (141 mg, 0.36 mmol, 1.48 equiv.), pyridine (29 μ L, 0.36 mmol, 1.49 equiv.), phthalimide (8.4 mg, 57.1 μ mol, 0.24 equiv.), Ni(dtbbpy)Br₂ (10 mg, 20.5 μ mol, 0.085 equiv.), and Ir(ppy)₂(dtbbpy)PF₆ (3.2 mg, 3.5 μ mol, 0.015 equiv.) in 1,4-dioxane (2 mL, 0.18 M for activation) and DMA (2 mL, 0.06 M combined with dioxane solution). The crude residue was purified via flash chromatography on silica eluting with a 30 to 40 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a light-yellow semi-solid (27.4 mg, 83.9 μ mol, 35% yield). ¹H NMR (400 MHz, CDCl₃) δ : 9.18 (s, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.56-7.50 (m, 4H), 7.48-7.38 (m, 3H), 7.37 (d, *J* = 4.6 Hz, 1H), 7.36-7.30 (m, 2H), 7.29 (br d, *J* = 7.7 Hz, 1H), 4.68 (s, 2H), 3.86 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ : 167.5, 158.4, 152.9, 146.7, 141.9, 141.0, 138.3, 130.8, 129.3, 128.9, 127.82, 127.80, 127.6, 127.3, 126.5, 125.9, 125.0, 102.7, 55.7, 41.9. LCMS (ESI) *m/z* [M+H]⁺: 327.2.

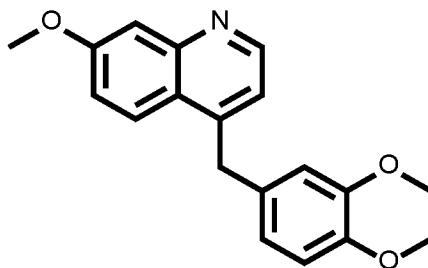
**36**

Compound **36** was prepared following general procedure E-IP using 4-chloroquinazoline (60.0 mg, 0.37 mmol, 1.0 equiv.), quinuclidine (68.4 mg, 0.62 mmol, 1.69 equiv.), [1,1'-biphenyl]-3-ylmethanol (121 mg, 0.66 mmol, 1.80 equiv.), NHC-1 BF₄ (245.0 mg, 0.62 mmol, 1.70 equiv.), pyridine (50 μ L, 0.62 mmol, 1.70 equiv.), phthalimide (11.9 mg, 80.9 μ mol, 0.22 equiv.), Ni(dtbbpy)Br₂ (14.5 mg, 29.8 μ mol, 0.082 equiv.), and Ir(ppy)₂(dtbbpy)PF₆ (5.2 mg, 5.7 μ mol, 0.016 equiv.) in THF (2 mL (6 mL /3), 0.31 M for activation) and DMA (2 mL, 0.09 M combined with THF solution). The crude residue was purified via flash chromatography on silica eluting with a 20 to 35 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a light yellow semi-solid (23.9 mg, 80.6 μ mol, 22% yield). ¹H NMR (400 MHz, CDCl₃) δ : 9.29 (s, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.87 (td, *J* = 7.0, 1.3 Hz, 1H), 7.61 (td, *J* = 7.0, 1.1 Hz, 1H), 7.56-7.51 (m, 3H), 7.47-7.27 (m, 6H), 4.70 (s, 2H). ¹³C NMR (100 MHz, CDCl₃) δ : 169.4, 154.9,

150.5, 141.9, 141.0, 138.2, 133.8, 129.4, 129.3, 128.9, 127.9, 127.85, 127.82, 127.5, 127.3, 125.9, 125.2, 124.2, 41.5. LCMS (ESI) m/z $[M+H]^+$: 297.2.

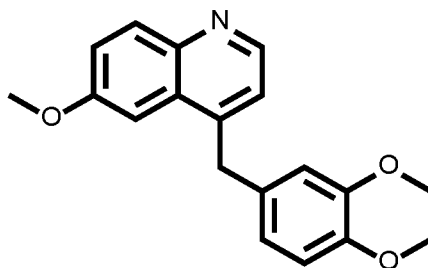
**37**

Compound **37** was prepared following general procedure E using 4-bromo-6,7-dimethoxyquinoline (75.0 mg, 0.28 mmol, 1.0 equiv.), quinuclidine (56.1 mg, 0.51 mmol, 1.80 equiv.), (3,4-dimethoxyphenyl)methanol (71 μ L, 0.49 mmol, 1.73 equiv.), NHC-1 BF_4 (177.0 mg, 0.45 mmol, 1.60 equiv.), pyridine (36 μ L, 0.45 mmol, 1.60 equiv.), phthalimide (9.5 mg, 64.6 μ mol, 0.23 equiv.), $\text{Ni}(\text{dtbbpy})\text{Br}_2$ (10.2 mg, 21.0 μ mol, 0.075 equiv.), and $\text{Ir}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$ (4.2 mg, 4.6 μ mol, 0.016 equiv.) in TBME (2 mL, 0.23 M for activation) and DMA (mL, 0.07 M combined with TBME solution). The crude residue was purified via flash chromatography on silica eluting with a 20 to 40 percent acetone in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as an off-white solid (53.7 mg, 0.16 mmol, 57% yield). ^1H NMR (400 MHz, CDCl_3) δ : 8.63 (d, J = 4.6 Hz, 1H), 7.48 (s, 1H), 7.21 (s, 1H), 7.04 (d, J = 4.6 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 6.76-6.70 (m, 2H), 4.32 (s, 2H), 4.04 (s, 3H), 3.93 (s, 3H), 3.88 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ : 152.1, 149.7, 149.3, 148.2, 147.9, 145.6, 145.1, 131.3, 123.0, 121.1, 120.3, 112.2, 111.5, 108.7, 101.9, 56.2, 56.03, 55.96, 38.4. LCMS (ESI) m/z $[M+H]^+$: 340.2.

**38**

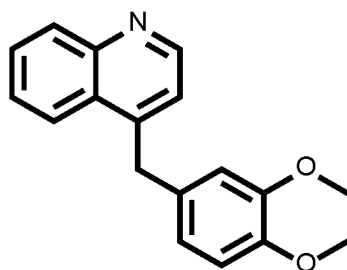
Compound **38** was prepared following general procedure E-IP using 4-bromo-7-methoxyquinoline (86.8 mg, 0.37 mmol, 1.00 equiv.), sodium acetate (59.6 mg, 0.73 mmol,

1.99 equiv.), (3,4-dimethoxyphenyl)methanol (96 μ L, 0.66 mmol, 1.81 equiv.), NHC-1 BF₄ (245.0 mg, 0.62 mmol, 1.70 equiv.), pyridine (50 μ L, 0.62 mmol, 1.70 equiv.), phthalimide (20.2 mg, 0.14 mmol, 0.38 equiv.), Ni(dtbbpy)Br₂ (16.3 mg, 33.5 μ mol, 0.092 equiv.), and Ir(ppy)₂(dtbbpy)PF₆ (5.7 mg, 6.2 μ mol, 0.017 equiv.) in THF (3 mL (9 mL /3), 0.21 M for activation) and DMA (3 mL, 0.06 M combined with THF solution). The crude residue was purified via flash chromatography on silica eluting with a 30 to 60 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a white solid (58.1 mg, 1.88 mmol, 52% yield). ¹H NMR (400 MHz, CDCl₃) δ : 8.74 (d, *J* = 4.5 Hz, 1H), 7.93 (d, *J* = 9.2 Hz, 1H), 7.45 (d, *J* = 2.6 Hz, 1H), 7.18 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.01 (d, *J* = 4.5 Hz, 1H), 6.82-6.78 (m, 1H), 6.73-6.83 (m, 2H), 4.35 (s, 2H), 3.96 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ : 160.4, 150.8, 150.3, 149.2, 147.9, 146.8, 131.3, 125.1, 122.8, 121.1, 120.0, 119.6, 112.2, 111.5, 108.2, 556.02, 55.96, 55.6, 37.9, 37.9. LCMS (ESI) *m/z* [M+H]⁺: 310.2.

**39**

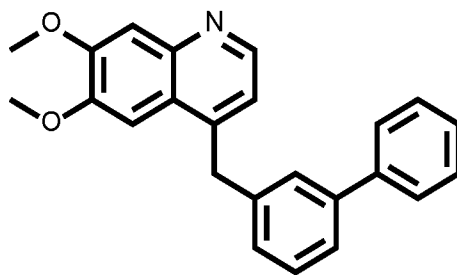
Compound **39** was prepared following general procedure E using 4-bromo-6-methoxyquinoline (119.0 mg, 0.50 mmol, 1.0 equiv.), sodium acetate (82.8 mg, 1.01 mmol, 2.02 equiv.), (3,4-dimethoxyphenyl)methanol (127 μ L, 0.88 mmol, 1.75 equiv.), NHC-1 BF₄ (316.0 mg, 0.80 mmol, 1.60 equiv.), pyridine (65 μ L, 0.81 mmol, 1.61 equiv.), phthalimide (17.4 mg, 0.12 mmol, 0.24 equiv.), Ni(dtbbpy)Br₂ (18.1 mg, 37.2 μ mol, 0.074 equiv.), and Ir(ppy)₂(dtbbpy)PF₆ (7.4 mg, 8.1 μ mol, 0.016 equiv.) in TBME (5 mL, 0.16 M for activation) and DMA (5 mL, 0.05 M combined with TBME solution). The crude residue was purified via flash chromatography on silica eluting with a 30 to 50 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a white solid (85.6 mg, 0.277 mmol, 55% yield). ¹H NMR (400 MHz, DMSO-d₆) δ : 8.64 (d, *J* = 4.4 Hz, 1H), 7.92 (d, *J* = 9.3 Hz, 1H), 7.46 (d, *J* = 2.8 Hz, 1H), 7.38 (dd, *J* = 9.3, 2.8 Hz, 1H), 7.25 (d, *J* = 4.6 Hz, 1H), 6.98

(d, $J = 1.9$ Hz, 1H), 6.87 (d, $J = 8.2$ Hz, 1H), 6.77 (dd, $J = 8.2, 2.0$ Hz, 1H), 4.36 (s, 2H), 3.88 (s, 3H), 3.702 (s, 3H), 3.699 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ : 157.8, 149.3, 147.95, 147.91, 145.5, 144.5, 131.7, 131.1, 128.6, 122.0, 121.6, 121.2, 112.3, 111.5, 102.2, 56.04, 55.98, 55.6, 38.3. LCMS (ESI) m/z $[\text{M}+\text{H}]^+$: 310.2.



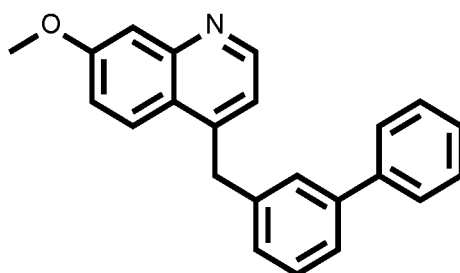
40

Compound **40** was prepared following general procedure E-IP using 4-bromoquinoline (75.8 mg, 0.37 mmol, 1.00 equiv.), sodium acetate (60.5 mg, 0.74 mmol, 2.02 equiv.), (3,4-dimethoxyphenyl)methanol (96 μL , 0.66 mmol, 1.81 equiv.), NHC-1 BF_4 (245.0 mg, 0.62 mmol, 1.70 equiv.), pyridine (50 μL , 0.62 mmol, 1.70 equiv.), phthalimide (23.5 mg, 0.16 mmol, 0.44 equiv.), $\text{Ni}(\text{dtbbpy})\text{Br}_2$ (16.6 mg, 34.1 μmol , 0.094 equiv.), and $\text{Ir}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$ (4.9 mg, 5.4 μmol , 0.015 equiv.) in THF (3 mL (9 mL /3), 0.21 M for activation) and DMA (3 mL, 0.06 M combined with THF solution). The crude residue was purified via flash chromatography on silica eluting with a 25 to 40% ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a cloudy white semi-solid (68.6 mg, 0.25 mmol, 67% yield). ^1H NMR (400 MHz, CDCl_3) δ : 8.83 (d, $J = 4.4$ Hz, 1H), 8.13 (br d, $J = 8.4$ Hz, 1H), 8.05 (br d, $J = 8.5$ Hz, 1H), 7.71 (td, $J = 6.9, 1.3$ Hz, 1H), 7.54 (td, $J = 6.9, 1.2$ Hz, 1H), 7.13 (d, $J = 4.5$ Hz, 1H), 6.83-6.73 (m, 1H), 6.75-6.70 (m, 2H), 4.40 (s, 2H), 3.86 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ : 150.5, 149.3, 148.5, 148.0, 147.0, 131.2, 130.4, 129.3, 127.8, 127.0, 123.9, 121.8, 121.2, 112.3, 111.5, 56.05, 55.99, 37.9. LCMS (ESI) m/z $[\text{M}+\text{H}]^+$: 280.2.



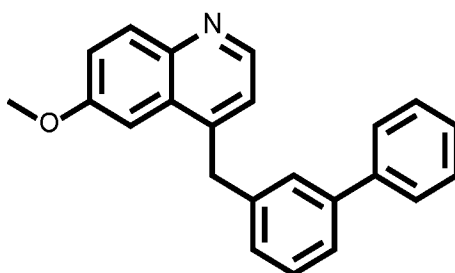
41

Compound **41** was prepared following general procedure E-IP using 4-bromo-6,7-dimethoxyquinoline (82.6 mg, 0.31 mmol, 1.0 equiv.), quinuclidine (65.3 mg, 0.59 mmol, 1.91 equiv.), [1,1'-biphenyl]-3-ylmethanol (108 mg, 0.59 mmol, 1.90 equiv.), NHC-1 BF₄ (219.0 mg, 0.55 mmol, 1.80 equiv.), pyridine (45 μ L, 0.56 mmol, 1.81 equiv.), phthalimide (10.1 mg, 68.7 μ mol, 0.22 equiv.), Ni(dtbbpy)Br₂ (11.2 mg, 23.1 μ mol, 0.075 equiv.), and Ir(ppy)₂(dtbbpy)PF₆ (4.2 mg, 4.6 μ mol, 0.015 equiv.) in TBME (2 mL (6 mL /3), 0.28 M for activation) and DMA (2 mL, 0.08 M combined with TBME solution). The crude residue was purified via flash chromatography on silica eluting with a 30 to 50 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a white solid (83.0 mg, 0.23 mmol, 76% yield). ¹H NMR (400 MHz, CDCl₃) δ : 8.64 (d, *J* = 4.7 Hz, 1H), 7.59 (br s, 1H), 7.54-7.47 (m, 3H), 7.45-7.38 (m, 4H), 7.34 (tt, *J* = 1.4, 6.2 Hz, 1H), 7.24 (s, 1H), 7.18 (d, *J* = 7.7 Hz, 1H), 7.15 (d, *J* = 4.8 Hz, 1H), 4.47 (s, 2H), 4.05 (s, 3H), 3.92 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ : 152.1, 149.7, 148.2, 145.7, 144.7, 141.9, 141.0, 139.4, 129.3, 128.9, 127.9, 127.8, 127.5, 127.2, 125.6, 123.0, 120.6, 108.8, 102.0, 56.2, 56.0, 38.9. LCMS (ESI) *m/z* [M+H]⁺: 356.3.

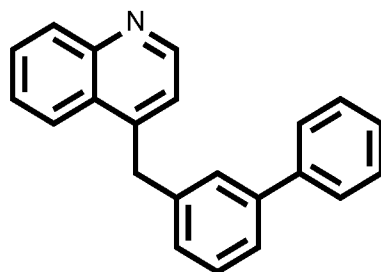
**42**

Compound **42** was prepared following general procedure E-IP using 4-bromo-7-methoxyquinoline (86.8 mg, 0.37 mmol, 1.00 equiv.), sodium acetate (48.2 mg, 0.59 mmol, 1.61 equiv.), [1,1'-biphenyl]-3-ylmethanol (97.4 mg, 0.53 mmol, 1.45 equiv.), NHC-1 BF₄ (202.0 mg, 0.51 mmol, 1.40 equiv.), pyridine (43 μ L, 0.54 mmol, 1.48 equiv.), phthalimide (12.3 mg, 83.8 μ mol, 0.23 equiv.), Ni(dtbbpy)Br₂ (12.2 mg, 25.1 μ mol, 0.069 equiv.), and Ir(ppy)₂(dtbbpy)PF₆ (6.1 mg, 6.7 μ mol, 0.018 equiv.) in THF (3 mL (9 mL /3), 0.17 M for activation) and DMA (3 mL, 0.06 M combined with THF solution). The crude residue was purified via flash chromatography on silica eluting with a 15 to 40 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a clear semi-solid (84.5 mg, 0.26 mmol,

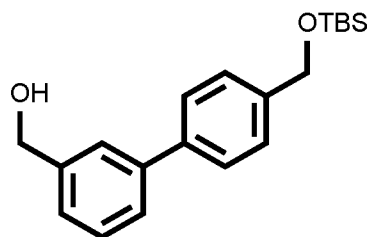
71% yield). ^1H NMR (400 MHz, CDCl_3) δ : 8.75 (d, $J = 4.6$ Hz, 1H), 7.97 (d, $J = 9.1$ Hz, 1H), 7.57-7.50 (m, 3H), 7.47 br d, $J = 7.9$ Hz, 1H), 7.44-7.31 (m, 5H), 7.21 (dd, $J = 9.4$, 2.5 Hz, 1H), 7.16 (br d, $J = 8.1$ Hz, 1H), 7.09 (d, $J = 5.1$ Hz, 1H), 4.48 (s, 2H), 3.96 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ : 160.5, 150.7, 150.4, 146.5, 141.9, 141.0, 139.4, 129.3, 128.9, 127.9, 127.8, 127.5, 127.3, 125.6, 125.1, 122.8, 120.2, 119.8, 108.2, 55.6, 38.4. LCMS (ESI) m/z $[\text{M}+\text{H}]^+$: 326.2.

**43**

Compound **43** was prepared following general procedure E-IP using 4-bromo-6-methoxyquinoline (73.3 mg, 0.31 mmol, 1.0 equiv.), quinuclidine (63.2 mg, 0.57 mmol, 1.85 equiv.), [1,1'-biphenyl]-3-ylmethanol (108.0 mg, 0.59 mmol, 1.90 equiv.), NHC-1 BF_4 (219.0 mg, 0.55 mmol, 1.80 equiv.), pyridine (45 μL , 0.56 mmol, 1.81 equiv.), phthalimide (9.8 mg, 66.6 μmol , 0.22 equiv.), $\text{Ni}(\text{dtbbpy})\text{Br}_2$ (11.3 mg, 23.2 μmol , 0.075 equiv.), and $\text{Ir}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$ (4.1 mg, 4.5 μmol , 0.015 equiv.) in TBME (2 mL (6 mL /3), 0.28 M for activation) and DMA (2 mL, 0.08 M combined with TBME solution). The crude residue was purified via flash chromatography on silica eluting with 10 to 30 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a white solid (70.3 mg, 0.22 mmol, 70% yield). ^1H NMR (400 MHz, CDCl_3) δ : 8.70 (d, $J = 4.4$ Hz, 1H), 8.03 (d, $J = 9.2$ Hz, 1H), 7.56-7.51 (m, 2H), 7.50-7.45 (m, 2H), 7.44-7.31 (m, 5H), 7.27 (d, $J = 2.73$ Hz, 1H), 7.19 (br d, $J = 7.6$ Hz, 1H), 7.15 (d, $J = 4.4$ Hz, 1H), 4.45 (s, 2H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ : 157.9, 148.0, 145.0, 144.6, 141.9, 141.0, 139.2, 131.8, 129.3, 128.9, 128.6, 128.0, 127.9, 127.6, 127.2, 125.7, 122.2, 121.6, 102.2, 55.6, 38.8. LCMS (ESI) m/z $[\text{M}+\text{H}]^+$: 326.2.

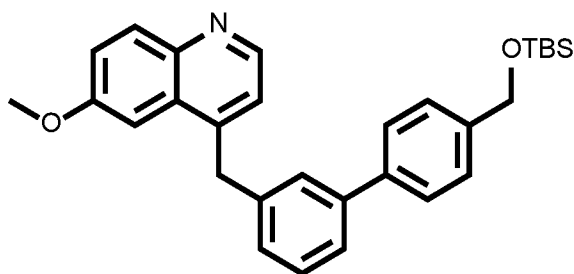
**44**

Compound **44** was prepared following general procedure E-IP using 4-bromoquinoline (75.8 mg, 0.37 mmol, 1.00 equiv.), sodium acetate (49.8 mg, 0.61 mmol, 1.67 equiv.), [1,1'-biphenyl]-3-ylmethanol (97.4 mg, 0.53 mmol, 1.45 equiv.), NHC-1 BF₄ (202.0 mg, 0.51 mmol, 1.40 equiv.), pyridine (43 μ L, 0.54 mmol, 1.48 equiv.), phthalimide (9.8 mg, 66.6 μ mol, 0.18 equiv.), Ni(dtbbpy)Br₂ (11.7 mg, 24.0 μ mol, 0.066 equiv.), and Ir(ppy)₂(dtbbpy)PF₆ (5.3 mg, 5.8 μ mol, 0.016 equiv.) in THF (3 mL (9 mL /3), 0.17 M for activation) and DMA (3 mL, 0.06 M combined with THF solution). The crude residue was purified via flash chromatography on silica eluting with a 10 to 20 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a clear semi-solid (78.6 mg, 0.27 mmol, 73% yield). ¹H NMR (400 MHz, CDCl₃) δ : 8.84 (d, *J* = 4.7 Hz, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 8.10 (d, *J* = 8.3 Hz, 1H), 7.73 (td, 7.7, 1.3 Hz, 1H), 7.60-7.51 (m, 3H), 7.49 (br d, *J* = 7.9 Hz, 1H), 7.46-7.36 (m, 4H), 7.33 (tt, *J* = 7.3, 1.3 Hz, 1H), 7.21 (br d, *J* = 4.4 Hz, 1H), 7.18 (br d, *J* = 7.6 Hz, 1H), 4.53 (s, 2H). ¹³C NMR (100 MHz, CDCl₃) δ : 150.5, 148.5, 146.6, 141.9, 141.0, 139.2, 130.4, 129.33, 129.30, 128.9, 128.0, 127.9, 127.8, 127.6, 127.3, 126.8, 125.7, 124.0, 122.0, 38.4. LCMS (ESI) *m/z* [M+H]⁺: 296.2.

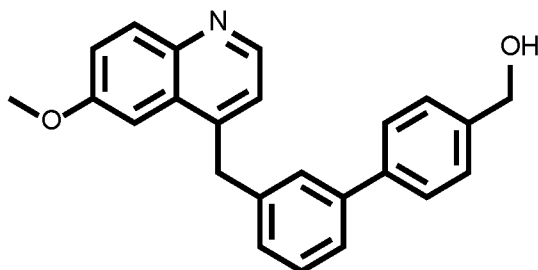
**R5**

Compound **R5** was prepared following general procedure F using (4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (6.50 g, 27.8 mmol, 1.00 equiv.), ((4-Bromobenzyl)oxy)(tert-butyl)dimethylsilane (9.2 g, 30.5 mmol, 1.10 equiv.), K₂CO₃ (7.71 g, 55.8 mmol, 2.01 equiv.), XPhos (527 mg, 1.11 mmol, 0.04 equiv.), and Pd(OAc)₂ (128

mg, 0.57 mmol, 0.02 equiv.) in 9:1 iPOH: water (80 mL, 0.35 M). The reaction mixture was worked up by filtering through a short pad of celite and concentrating. The crude residue was purified by flash chromatography on silica eluting with 10 to 15 percent ethyl acetate in hexanes. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a light brown oil (7.2355 g, 22.0 mmol, 79% yield). ¹H NMR (400 MHz, CDCl₃) δ: 7.62-7.55 (m, 3H), 7.53 (br d, *J* = 7.7 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.34 (br d, *J* = 7.7 Hz, 1H), 4.79 (s, 2H), 4.77 (d, *J* = 5.9 Hz, 2H), 1.68 (t, *J* = 5.9 Hz, 1H), 0.96 (s, 9H), 0.12 (s, 6H).

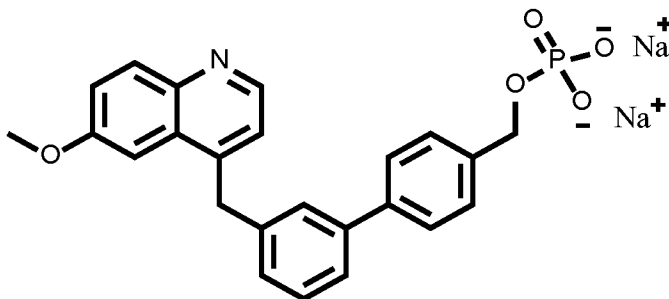
**R6**

Compound **R6** was prepared following general procedure E using 4-bromo-6-methoxyquinoline (1.0 g, 4.20 mmol, 1.00 equiv.), sodium acetate (613.0 mg, 7.47 mmol, 1.78 equiv.), **R5** (2.14 g, 6.51 mmol, 1.55 equiv.), NHC-1 BF₄ (2.41 g, 6.09 mmol, 1.45 equiv.), pyridine (500 μL, 6.21 mmol, 1.48 equiv.), phthalimide (139.0 mg, 0.95 mmol, 0.23 equiv.), Ni(dtbbpy)Br₂ (149.0 mg, 0.31 mmol, 0.073 equiv.), and Ir(ppy)₂(dtbbpy)PF₆ (59.9 mg, 65 μmol, 0.016 equiv.) in THF (24 mL, 0.25 M for activation) and DMA (24 mL, 0.09 M combined with THF solution). The crude residue was purified via flash chromatography on silica, eluting with a 10 to 35 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a light brown semi-solid (1.36 g, 2.90 mmol, 69% yield). ¹H NMR (400 MHz, CDCl₃) δ: 8.70 (d, *J* = 4.4 Hz, 1H), 8.03 (d, *J* = 9.1 Hz, 1H), 7.53-7.44 (m, 3H), 7.40-7.33 (m, 4H), 7.27 (d, *J* = 2.8 Hz, 1H), 7.19-7.14 (m, 2H), 4.77 (s, 2H), 4.45 (s, 2H), 3.85 (s, 3H), 0.95 (s, 9H), 0.11 (s, 6H).



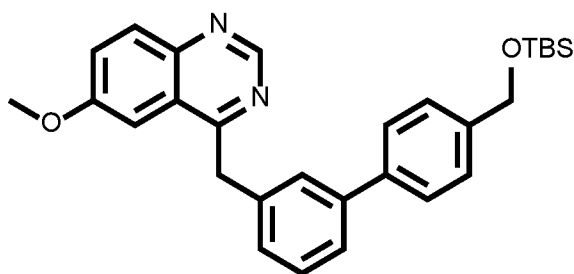
45

Compound **45** (1.35 g, 2.87 mmol, 1.00 equiv.) was added to a 100 mL round bottom flask and placed under nitrogen before being dissolved in THF (29 mL, 0.1 M) to create a clear, colorless solution. TBAF (1M in THF, 3.8 mL, 3.8 mmol, 1.32 equiv.) was added dropwise at room temperature over two minutes to give a light-yellow solution. After stirring for 30 minutes the reaction contents were quenched with water (60 mL) and extracted with DCM (3 x 60 mL). The combined organic phases were washed with brine, dried over sodium sulfate, filtered through cotton, and concentrated *in vacuo* to give an off-white solid. The crude product was purified via flash chromatography on silica, eluting with a 50 to 90 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a white solid (839 mg, 2.36 mmol, 82% yield). ¹H NMR (400 MHz, CDCl₃) δ: 8.69 (d, *J* = 4.4 Hz, 1H), 8.03 (d, *J* = 9.2 Hz, 1H), 7.54 (br d, *J* = 8.2 Hz, 2H), 7.50-7.44 (m, 2H), 7.44-7.33 (m, 4H), 7.27 (d, *J* = 2.8 Hz, 1H), 7.19 (br d, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 4.4 Hz, 1H), 4.74 (d, *J* = 5.7 Hz, 2H), 4.45 (s, 2H), 3.85 (s, 3H), 1.69 (t, *J* = 5.7 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ: 157.9, 147.9, 145.1, 144.5, 141.5, 140.5, 140.2, 139.2, 131.7, 129.3, 128.6, 128.0, 127.8, 127.5, 127.3, 125.6, 122.2, 121.6, 102.2, 65.0, 55.6, 38.7. LCMS (ESI) *m/z* [M+H]⁺: 356.3.

**45-Phosphate**

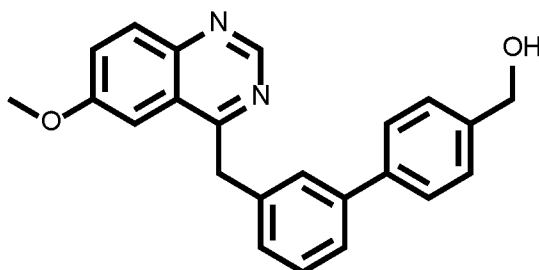
Compound **45-Phosphate** was prepared from **45** (200.0 mg, 0.56 mmol, 1.00 equiv.) and psi^o (334.0 mg, 0.79 mmol, 1.41 equiv.) added to an oven dried vial and placed under nitrogen via three evacuation and backfill cycles. Anhydrous DCM (5.6 mL, 0.10 M) was added to the solids via syringe under nitrogen to give a light orange suspension. After 1 minute of stirring, DBU (0.12 mL, 0.80 mmol, 1.43 equiv.) was added in one portion via syringe to give a clear, homogenous orange solution. The resultant solution was stirred for 1 hour before being quenched by addition of pre-mixed ACN (5.7 mL) and distilled water (0.3 mL) followed by DBU (0.25 mL, 1.67 mmol, 2.98 equiv.). After stirring for 15 minutes, the

reaction contents were transferred with ethanol to a 100 mL round bottom flask and concentrated to give a dark orange residue. The crude residue was purified via flash chromatography using a Teledyne ISCO 12 g gold spherical silica column, eluting with a 10 to 60 percent ammonia 1N methanol in DCM gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the ammonium salt product as a white solid (99.0 mg, 0.23 mmol). The isolated ammonium salt was placed under nitrogen and suspended in anhydrous THF (4.4 mL, 0.05 M) to create a cloudy white suspension. To the stirring suspension was added NaOtBu (2 M in THF, 0.22 mL, 0.44 mmol, 2.00 equiv.) dropwise over five minutes to create additional suspended solid. After addition, the suspension was stirred for an additional 30 minutes before hexanes (4.4 mL) was added in one portion and the suspension was allowed to stir an additional 5 minutes. The suspension was filtered and the precipitate collected and dried give the title compound as a white solid (104.0 mg, 0.22 mmol, 40% yield). ¹H NMR (400 MHz, MeOH-d₄) δ: 8.61 (d, *J* = 4.8 Hz, 1H), 7.93 (d, *J* = 9.3 Hz, 1H), 7.61 (br s, 1H), 7.57-7.52 (m, 2H), 7.52-7.43 (m, 4H), 7.41-7.32 (m, 3H), 7.19 (br d, *J* = 7.7 Hz, 1H), 4.95 (d, *J* = 6.1 Hz, 2H), 4.56 (s, 2H), 3.85 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 159.5, 148.6, 148.2, 144.6, 142.8, 141.2, 140.8, 139.6, 139.5, 130.9, 130.3, 130.1, 128.9, 128.8, 128.7, 127.8, 126.3, 123.4, 103.6, 67.5 (d, *J* = 5.5 Hz), 56.1, 39.4. LCMS (ESI) *m/z* [M+H]⁺: 434.1.

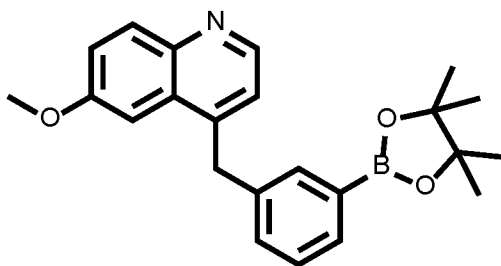
**R7**

Compound **R7** was prepared following general procedure E using 4-chloro-6-methoxyquinazoline (650 mg, 3.34 mmol, 1.00 equiv.), sodium acetate (438.0 mg, 5.34 mmol, 1.60 equiv.), **R5** (1.40 g, 4.26 mmol, 1.28 equiv.), NHC-1 BF₄ (1.58 g, 4.01 mmol, 1.20 equiv.), pyridine (340 μL, 4.22 mmol, 1.26 equiv.), phthalimide (111.0 mg, 0.75 mmol, 0.23 equiv.), Ni(dtbppy)Br₂ (123.0 mg, 0.25 mmol, 0.076 equiv.), and Ir(ppy)₂(dtbbpy)PF₆ (45.3 mg, 50 μmol, 0.015 equiv.) in THF (24 mL, 0.17 M for activation) and DMA (24 mL, 0.07 M combined with THF solution). The crude residue was purified via flash chromatography on silica, eluting with a 10 to 35 percent ethyl acetate in hexanes gradient.

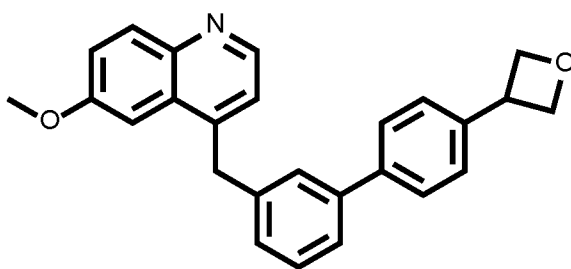
The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a light yellow semi-solid (660 mg, 1.40 mmol, 42% yield). ¹H NMR (400 MHz, CDCl₃) δ: 9.18 (s, 1H), 7.94 (d, *J* = 9.7 Hz, 1H), 7.54 (br s, 1H), 7.51-7.43 (m, 4H), 7.38-7.32 (m, 4H), 7.27 (br s, 1H), 4.77 (s, 2H), 4.65 (s, 2H), 3.85 (s, 3H), 0.95 (s, 9H), 0.11 (s, 6H).

**46**

Compound **46** (650.0 mg, 1.38 mmol, 1.00 equiv.) was added to a 100 mL round bottom flask and placed under nitrogen before being dissolved in THF (14 mL, 0.1 M) to create a light yellow solution. TBAF (1M in THF, 1.8 mL, 1.80 mmol, 1.30 equiv.) was added dropwise at room temperature over two minutes to give a bright red solution. After stirring for 30 minutes the reaction contents were quenched with water (60 mL) (adding water results in a color change back to light yellow) and extracted with DCM (3 x 60 mL). The combined organic phases were washed with brine, dried over sodium sulfate, filtered, and concentrated to give a yellow semi-solid. The crude product was purified via flash chromatography on silica, eluting with a 50 to 90 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a light-yellow solid (363.7 mg, 1.02 mmol, 74% yield). ¹H NMR (400 MHz, CDCl₃) δ: 9.17 (s, 1H), 7.95 (d, *J* = 9.2 Hz, 1H), 7.55-7.48 (m, 4H), 7.45 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.41 (br d, *J* = 8.0 Hz, 2H), 7.39-7.33 (m, 2H), 7.28 (br d, *J* = 7.7 Hz, 1H), 4.73 (d, *J* = 6.0 Hz, 2H), 4.65 (s, 2H), 3.86 (s, 3H), 1.67 (t, 6.0 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ: 167.5, 158.4, 152.9, 146.7, 141.5, 140.34, 140.28, 138.3, 130.8, 129.3, 127.9, 127.7, 127.5, 127.4, 126.5, 125.8, 125.0, 102.7, 65.1, 55.7, 41.8. LCMS (ESI) *m/z* [M+H]⁺: 357.3.

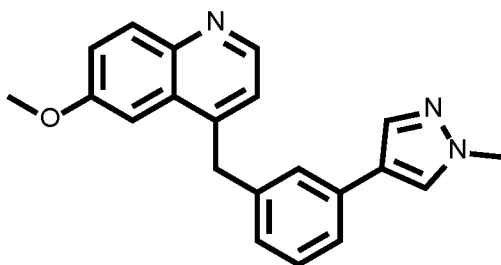
**R8**

Compound **R8** was prepared following general procedure E using 4-bromo-6-methoxyquinoline (250.0 mg, 1.05 mmol, 1.00 equiv.), quinuclidine (179.0 mg, 1.61 mmol, 1.53 equiv.), [3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (402.0 mg, 1.64 mmol, 1.64 equiv.), NHC-1 BF₄ (621 mg, 1.57 mmol, 1.50 equiv.), pyridine (130 μ L, 1.61 mmol, 1.54 equiv.), phthalimide (40.0 mg, 0.27 mmol, 0.26 equiv.), Ni(dtbbpy)Br₂ (41.0 mg, 84.2 μ mol, 0.08 equiv.), and Ir(ppy)₂(dtbbpy)PF₆ (13.0 mg, 14.2 μ mol, 0.014 equiv.) in THF (6 mL, 0.33 M for activation) and DMA (6 mL, 0.10 M combined with TBME solution). The crude residue was purified via liquid loading with DCM onto a Teledyne Isco 12 g gold spherical silica column and eluting with a 60 to 70 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a light brown solid (186.0 mg, 0.50 mmol, 47% yield). ¹H NMR (400 MHz, CDCl₃) δ : 8.67 (d, *J* = 4.5 Hz, 1H), 8.00 (d, *J* = 9.3 Hz, 1H), 7.78 (br s, 1H), 7.69 (br d, *J* = 7.2 Hz, 1H), 7.34 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.29 (d, *J* = 7.25 Hz, 1H), 7.27 (s, 1H, partially obscured by CHCl₃), 7.26-7.23 (m, 1H, partially obscured by CHCl₃), 7.11 (d, *J* = 4.4 Hz, 1H), 4.38 (s, 2H), 3.86 (s, 3H), 1.34 (s, 12H).

**47**

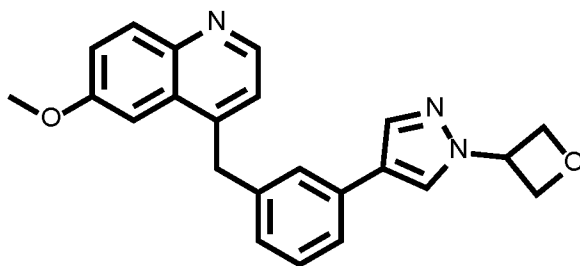
Compound **47** was prepared following general procedure F using **R8** (100.0 mg, 0.27 mmol, 1.00 equiv.), 3-(4-Chlorophenyl)oxetane (50.0 mg, 0.30 mmol, 1.11 equiv.), Cs₂CO₃ (163.0 mg, 0.50 mmol, 1.88 equiv.), XPhos (14.2 mg, 30 μ mol, 0.11 equiv.), and Pd(OAc)₂ (3.1 mg, 14 μ mol, 0.05 equiv.) in 9:1 dioxane: water (2.5 mL, 0.1 M). The crude residue was

purified by flash chromatography on silica eluting with a 40 to 60 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a white solid (46.3 mg, 0.12 mmol, 46% yield). ¹H NMR (400 MHz, CDCl₃) δ: 8.70 (d, *J* = 4.5 Hz, 1H), 8.03 (d, *J* = 9.3 Hz, 1H), 7.56-7.52 (m, 2H), 7.48 (br d, *J* = 7.7 Hz, 1H), 7.46-7.43 (m, 3H), 7.42-7.33 (m, 2H), 7.27 (d, *J* = 3.0 Hz, 1H), 7.20 (br d, *J* = 7.5 Hz, 1H), 7.15 (d, *J* = 4.5 Hz, 1H), 5.09 (dd, *J* = 8.4, 6.2 Hz, 2H), 4.79 (t, *J* = 6.5 Hz, 2H), 4.45 (s, 2H), 4.26 (quintet, *J* = 7.2 Hz, 1H), 3.86 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 157.1, 147.8, 145.3, 140.9, 140.0, 139.9, 138.5, 131.2, 129.2, 127.93, 127.90, 127.3, 127.2, 126.8, 124.6, 122.0, 121.2, 102.8, 77.4, 55.5, 38.9, 37.4. LCMS (ESI) *m/z* [M+H]⁺: 382.3.



48

Compound **48** was prepared following general procedure F using **R8** (106.0 mg, 0.28 mmol, 1.00 equiv.), 4-bromo-1-methylpyrazole (43 μL, 0.43 mmol, 1.51 equiv.), Cs₂CO₃ (199.0 mg, 0.61 mmol, 2.16 equiv.), XPhos (11.4 mg, 24 μmol, 0.08 equiv.), and Pd(OAc)₂ (2.9 mg, 13 μmol, 0.05 equiv.) in 9:1 dioxane: water (3 mL, 0.1 M). The crude residue was purified by flash chromatography on silica eluting with a 15 to 45 percent acetone in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as a light-yellow solid (59.8 mg, 0.18 mmol, 64% yield). ¹H NMR (400 MHz, CDCl₃) δ: 8.69 (d, *J* = 4.5 Hz, 1H), 8.03 (d, *J* = 8.9 Hz, 1H), 7.71 (br s, 1H), 7.54 (br s, 1H), 7.38-7.33 (m, 2H), 7.33-7.28 (m, 2H), 7.25 (br d, *J* = 4.5 Hz, 1H), 7.13 (br d, *J* = 4.5 Hz, 1H), 7.07 (br d, *J* = 7.7 Hz, 1H), 4.40 (s, 2H), 3.92, (s, 3H), 3.85 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 157.1, 147.7, 145.3, 143.9, 139.6, 135.9, 132.8, 131.1, 129.0, 127.9, 127.7, 126.5, 125.6, 123.0, 121.9, 121.7, 121.2, 102.7, 55.5, 38.6, 37.5. LCMS (ESI) *m/z* [M+H]⁺: 330.3.

**49**

Compound **49** was prepared following general procedure F using **R8** (85.0 mg, 0.23 mmol, 1.00 equiv.), 4-bromo-1-(3-oxetanyl)pyrazole (71.1 mg, 0.35 mmol, 1.55 equiv.), Cs₂CO₃ (157.0 mg, 0.48 mmol, 2.13 equiv.), XPhos (11.0 mg, 23 μmol, 0.10 equiv.), and Pd(OAc)₂ (2.6 mg, 12 μmol, 0.05 equiv.) in 9:1 dioxane: water (2.5 mL, 0.1 M). The crude residue was purified by flash chromatography on silica eluting with a 50 to 90 percent ethyl acetate in hexanes gradient. The fractions corresponding to the desired product were combined and concentrated *in vacuo* to give the title compound as an off-white solid (41.0 mg, 0.11 mmol, 49% yield). ¹H NMR (400 MHz, CDCl₃) δ: 8.69 (d, *J* = 4.6 Hz, 1H), 8.14 (br d, *J* = 9.1 Hz, 1H), 7.81 (br s, 1H), 7.78 (br s, 1H), 7.42-7.37 (m, 2H), 7.36-7.31 (m, 2H), 7.27 (br d, *J* = 2.6 Hz, 1H), 7.18 (br d, *J* = 4.4 Hz, 1H), 7.10 (br d, *J* = 7.5 Hz, 1H), 5.46 (quintet, *J* = 6.8 Hz, 1H), 5.07 (d, *J* = 6.8 Hz, 4H), 4.43 (s, 2H), 3.87 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 157.8, 147.9, 145.0, 144.5, 139.4, 137.7, 132.8, 131.7, 129.4, 128.6, 127.5, 126.2, 124.9, 124.1, 123.6, 122.1, 121.5, 102.2, 77.8, 55.8, 55.5, 38.6. LCMS (ESI) *m/z* [M+H]⁺: 372.3.

Biological Data

OCR inhibition: Inhibition of the oxygen consumption rate of live EO771 cells at 10 μM.

PDE10a inhibition: Inhibition of isolated PDE10a at 0.1 μM.

Compound	OCR Inhibition (%)	PDE10a Inhibition (%)
Papaverine	48.6	47.0
1	14.0	64.0
2	22.0	48.2
3	22.0	52.0
4	41.0	56.3
5	11.0	39.0
6	22.7	33.0
7	45.0	63.2

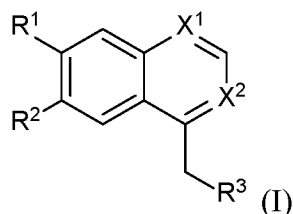
Compound	OCR Inhibition (%)	PDE10a Inhibition (%)
8	24.0	48.2
9	63.5	77.9
10	53.5	79.0
11	58.0	65.4
12	45.0	30.9
13	59.0	85.3
14	8.0	56.8
15	8.0	75.0
16	10.0	50.0
17	17.0	74.1
18	30.0	66.0
19	20.0	70.7
20	20.0	44.4
21	40.0	49.1
22	16.0	68.0
23	32.0	54.0
24	0.0	57.5
25	81.0	25.4
26	48.0	11.2
27	64.0	0.0
28	0.0	2.7
29	0.0	5.0
30	0.0	0.0
31	29.0	21.9
32	12.0	25.3
33	16.0	21.0
34	32.0	22.4
35	62.5	0.0
36	65.0	0.0
37	0.0	25.6
38	13.0	33.0

Compound	OCR Inhibition (%)	PDE10a Inhibition (%)
39	13.5	3.4
40	43.0	11.0
41	76.0	33.1
42	61.0	22.0
43	81.0	4.6
44	93.0	0.0
45	93.5	0.0
46	85.0	0.0
47	95.0	14.0
48	81.0	5.2
49	96.0	2.7

The compositions and methods of the appended claims are not limited in scope by the specific compositions and methods described herein, which are intended as illustrations of a few aspects of the claims and any compositions and methods that are functionally equivalent are intended to fall within the scope of the claims. Various modifications of the compositions and methods in addition to those shown and described herein are intended to fall within the scope of the appended claims. Further, while only certain representative compositions and method steps disclosed herein are specifically described, other combinations of the compositions and method steps also are intended to fall within the scope of the appended claims, even if not specifically recited. Thus, a combination of steps, elements, components, or constituents may be explicitly mentioned herein; however, other combinations of steps, elements, components, and constituents are included, even though not explicitly stated.

WHAT IS CLAIMED IS:

1. A compound of Formula I



or a pharmaceutically acceptable salt thereof;

wherein:

R^1 and R^2 are each independently selected from H or -O-(C₁-C₆ alkyl), wherein at least one of R^1 and R^2 is H;

X^1 and X^2 are each independently selected from N or C(R^4), wherein at least one of X^1 and X^2 is N;

R^3 is 5- to 10-membered monocyclic or bicyclic aryl optionally substituted with one or more groups selected from R^5 ;

R^4 is independent selected at each occurrence from H or halo;

R^5 is selected from hydrogen, halo, nitro, cyano, azido, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, (C₃-C₆ cycloalkyl)(C₀-C₃ alkyl)-, (3- to 8-membered monocyclic or bicyclic heterocycle)-(C₀-C₃ alkyl)-, (6- to 10-membered monocyclic or bicyclic aryl)-(C₀-C₃ alkyl)-, (5- to 10-membered monocyclic or bicyclic heteroaryl)-(C₀-C₃ alkyl)-, R^xO -(C₀-C₃ alkyl)-, R^xS -(C₀-C₃ alkyl)-, (R^xR^yN)-(C₀-C₃ alkyl)-, $R^xO-C(O)$ -(C₀-C₃ alkyl)-, $R^xS-C(O)$ -(C₀-C₃ alkyl)-, (R^xR^yN) C(O)-(C₀-C₃ alkyl)-, $R^xO-S(O)_2$ -(C₀-C₃ alkyl)-, (R^xR^yN) S(O)₂-(C₀-C₃ alkyl)-, $R^zC(O)-O$ -(C₀-C₃ alkyl)-, $R^zC(O)-(R^xN)$ -(C₀-C₃ alkyl)-, $R^zS(O)_2-O$ -(C₀-C₃ alkyl)-, $R^zS(O)_2-(R^xN)$ -(C₀-C₃ alkyl)-, $R^zC(O)-(C_0-C_6$ alkyl)-, $R^zS(O)-(C_0-C_3$ alkyl)-, and $R^zS(O)_2-(C_0-C_3$ alkyl)-, each of which may be optionally substituted by one or more groups selected from Y as allowed by valency;

R^x and R^y are independently selected at each occurrence from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, (C₃-C₇cycloalkyl)-(C₀-C₃ alkyl)-, (4- to 6-membered heterocycle)-(C₀-C₃ alkyl)-, (5- to 10-membered monocyclic or bicyclic aryl)-(C₀-C₃ alkyl)-, (5- to 10-membered monocyclic or bicyclic heteroaryl)-(C₀-C₃ alkyl)-, each of which may be optionally substituted with one or more Y groups as allowed by valency;

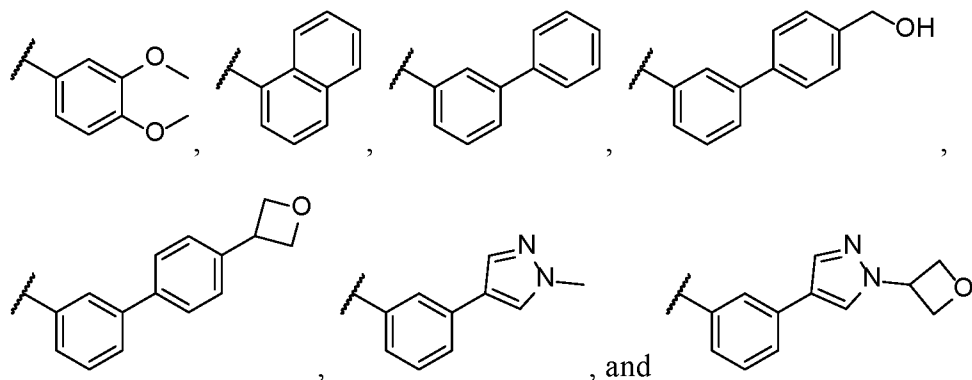
R^Z is independently selected at each occurrence from hydrogen, halo, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, (C_3 - C_7 cycloalkyl)-(C_0 - C_3 alkyl)-, (4- to 6-membered heterocycle)-(C_0 - C_3 alkyl)-, (5- to 10-membered monocyclic or bicyclic aryl)-(C_0 - C_3 alkyl)-, (5- to 10-membered monocyclic or bicyclic heteroaryl)-(C_0 - C_3 alkyl)-, $-OR^x$, $-SR^x$, and $-NR^xR^y$, each of which may be optionally substituted with one or more Y groups as allowed by valency; and

Y is independently selected at each occurrence from alkyl, haloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycle, aldehyde, amino, carboxylic acid, ester, ether, halo, hydroxy, keto, nitro, cyano, azido, oxo, silyl, sulfo-oxo, sulfonyl, sulfone, sulfoxide, sulfonylamino, phospho, thiol, or combinations thereof.

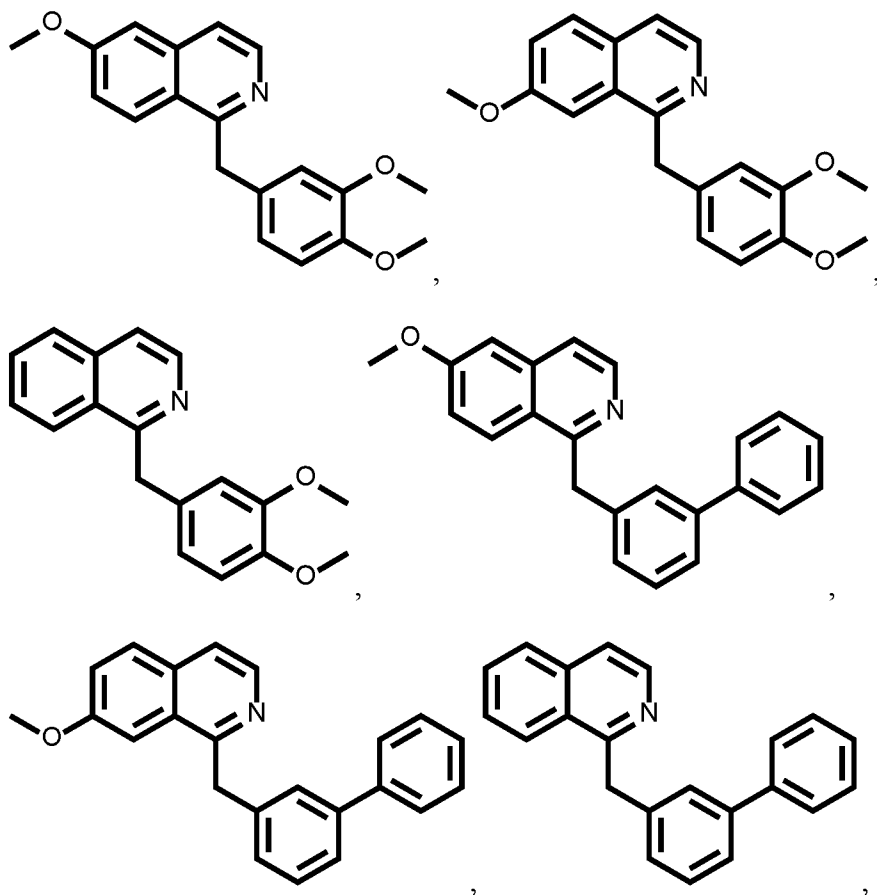
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is $-OCH_3$ and R^2 is H.
3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is H and R^2 is $-OCH_3$.
4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are each H.
5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein X^1 is N and X^2 is $C(R^4)$.
6. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein X^1 is $C(R^4)$ and X^2 is N.
7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^4 is H.
8. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^4 is halo.
9. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^4 is fluoro.
10. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein X^1 and X^2 are each N.

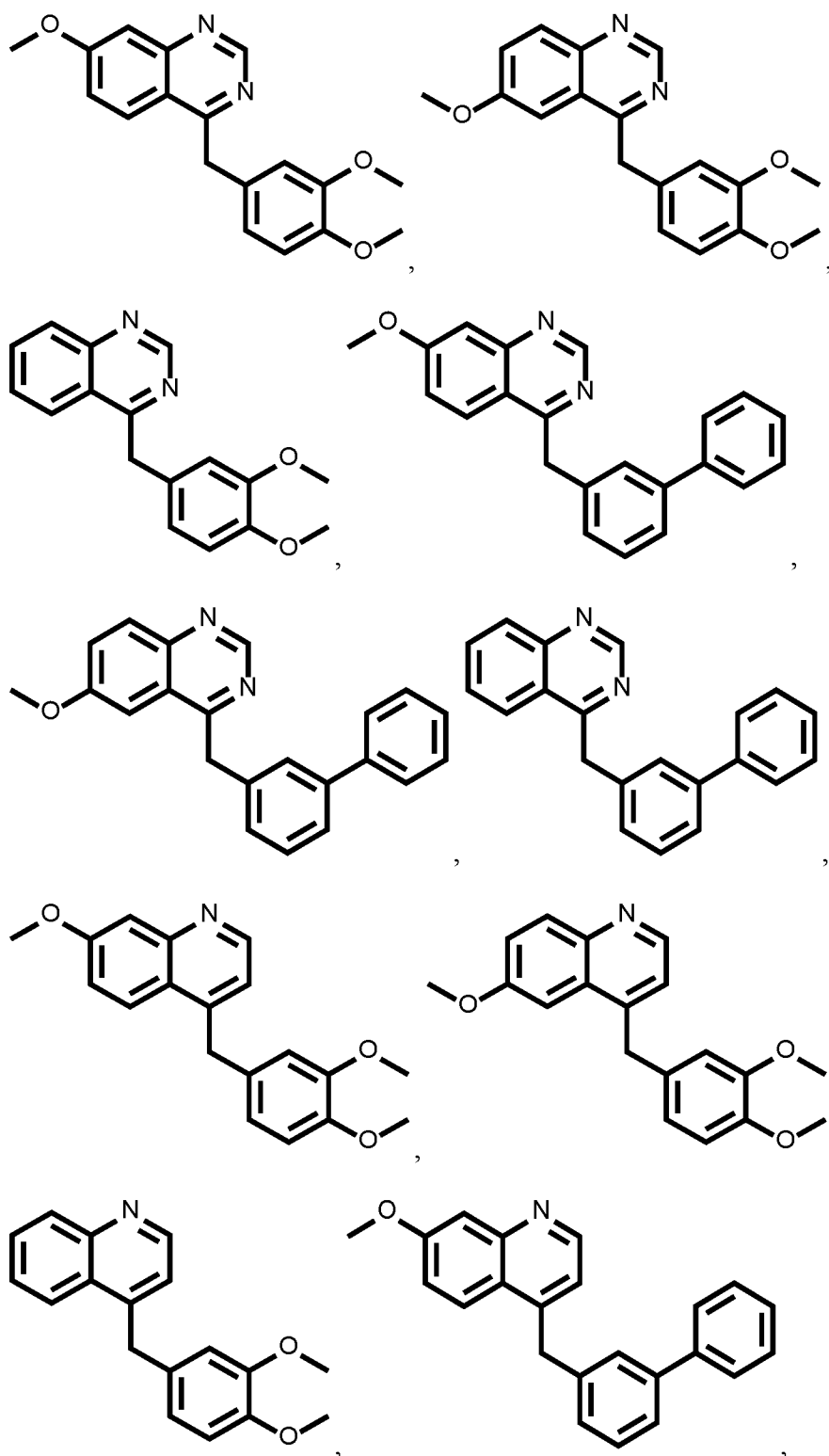
11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R^3 is phenyl or 1-naphthyl optionally substituted with one or more groups selected from R^5 .

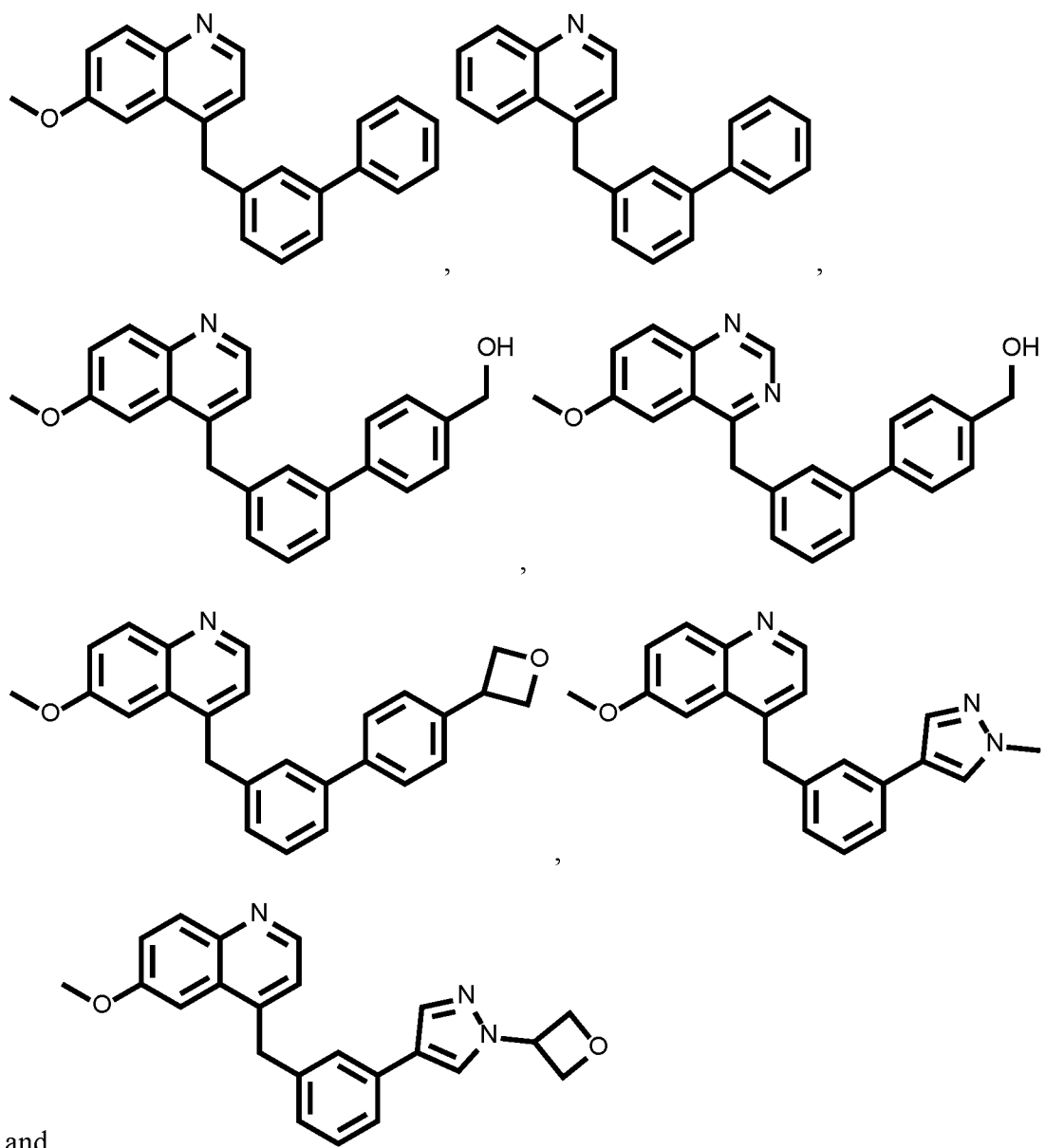
12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from the group consisting of:



13. The compound of claim 1 selected from the group consisting of:







or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition comprising a compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

15. A method of treating a cancer in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 14.

16. A method of sensitizing a cancer to radiation therapy in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a

compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 14 prior to or concurrently with the radiation therapy.