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(71) Applicant: **SYMBERIX, INC.** [US/US]; 4819 Emperor Boulevard, Suite 400, Durham, NC 27703 (US).

(72) Inventors: **TAVARES, Francis, X.**; 923 Bluestone Road, Durham, NC 27713 (US). **WALLACE, Bret, D.**; 107 Starling Lane, Durham, NC 27713 (US). **PETERSON, Ward**; 202 Chandler Chase Court, Morrisville, NC 27560 (US).

(74) Agent: **HASAN, Aisha, R.** et al.; Barnes & Thornburg LLP, 4819 Emperor Boulevard, Suite 400, Durham, NC 27703 (US).

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(54) Title: COMPOUNDS, COMPOSITIONS, AND METHODS FOR SELECTIVELY INHIBITING β-GLUCURONIDASES AND ALLEVIATING SIDE EFFECTS ASSOCIATED WITH DRUG TREATMENT INDUCED DIARRHEA

(57) Abstract: The present disclosure describes compounds and compositions that inhibit β- glucuronidase activity, and methods for attenuating the side effects of one or more drugs and improving the efficacy of drugs by administration of selective β- glucuronidase inhibitors.

COMPOUNDS, COMPOSITIONS, AND METHODS FOR SELECTIVELY INHIBITING β-GLUCURONIDASES AND ALLEVIATING SIDE EFFECTS ASSOCIATED WITH DRUG TREATMENT INDUCED DIARRHEA

This invention was made with government support under grant number 1R43CA180270 awarded by the National Institute of Health, National Cancer Institute. The government has certain rights to the invention.

FIELD OF THE INVENTION

The present disclosure describes compounds and compositions that inhibit β-glucuronidase activity, and methods for attenuating the side effects of one or more drugs and improving the efficacy of drugs by administration of selective β-glucuronidase inhibitors.

BACKGROUND

Diarrhea is a common adverse effect associated with drug therapy. Hundreds of drugs have been implicated in causing diarrhea or gastrointestinal distress, including antibiotics, laxatives, magensium-containing antacids, lactose- or sorbitol-containing products, nonsteroidal anti-inflammatory drugs, prostaglandins, colchicine, antineoplastic agents, antiarrhythmic drugs and cholinergic agents. The administration of all these drugs involves the delicate balance between efficacious therapy and patient discomfort and or severe gastrointestinal distress. Drug induced diarrhea can occur without warning and escalate within hours to become severe. Even mild-to-moderate grade diarrhea can be life-threatening when complicated by comorbid vomiting, dehydration, or neutropenia. In the early 2000's, chemotherapy regimens containing irinotecan (IRI) and 5-fluorouracil/leucovorin (5-FU/LV) revolutionized treatment for patients with advanced colorectal cancer, but their therapeutic benefit was compromised by diarrhea that occurred in up to 88% of patients. Clinical trials of IRI plus highdose 5-FU/LV reported early death rates of 2.2% to 4.8%, primarily due to gastrointestinal toxicity.

Drug induced diarrhea (DID) is a burden on multiple levels and can have psychosocial effects on sufferers, who may harbor feelings of embarrassment, isolation and distress. Patients avoid social contact and may not reach out to seek medical help until it escalates. Multiple studies suggest that DID is under-reported in clinical trials and in the real-world setting. In a recent survey of breast cancer patients, diarrhea was second only to nausea/vomiting as a feared toxicity of

chemotherapy. When given the choice of certain death from stopping chemotherapy or chronic diarrhea from continuing chemotherapy, 42% surveyed chose death. For patients who cannot tolerate it, the oncologist's last, often used recourse is to reduce or stop chemotherapy before it kills the patient. Furthermore, DID can often become a dose-limiting side effect of the drug therapy that can impair treatment outcome.

One of the underlying mechanisms of DID is caused by enteric bacteria expressing the β-glucuronidase (bGUS) enzyme classified as a hydrolase. "Glucuronidation" is a common metabolic process involved in drug metabolism whereby glucuronide acts as a conjugation molecule and binds to a substrate via the catalysis of glucuronosyltransferase (UGT) enzymes. The human body uses glucuronidation to make a variety of substances more water-soluble, which allows easy elimination from the body through urine and/or feces. The β-glucuronidase enzyme is involved in the cleaving of glucuronide conjugates. However, drugs or their metabolites which are substrates for glucuronidases can have their respective properties altered by glucuronidase hydrolysis. For example, if the drug, agent, compound or metabolite thereof has been metabolized to a glucuronide, the hydrolysis of the glucuronide can reactivate the drug, agent, compound or metabolite thereof. In many cases, this reactivation can cause adverse reactions, including but not limited to, gastrointestinal distress, leading to diarrhea.

For example, IRI (also called CPT-11) is an i.v.-infused pro-drug that is systemically metabolized by carboxylesterases into the active moiety SN-38, a potent topoisomerase-1 inhibitor. SN-38 is cytotoxic to rapidly dividing cancer cells, as well as enterocytes and neutrophils. It is metabolized by liver UGT enzymes into an inactive glucuronide metabolite SN-38G, which is then excreted along with bile secretions into the small intestine. As SN-38G is transported down the lower GI tract, enteric bacteria expressing the β-glucuronidase (bGUS) enzyme cleave SN-38G back into SN-38, which accumulates to toxic levels in the intestinal lumen. The local reactivation of SN-38 in the intestinal lumen by gut bacteria is considered to be the upstream triggering event that leads to delayed diarrhea.

While broad-spectrum antibiotics have been used to eliminate enteric bacteria from the gastrointestinal tract prior to chemotherapy treatment to reduce reactivation, this approach has several drawbacks. First, enteric bacteria (i.e., normal flora) play essential roles in carbohydrate metabolism, vitamin production and the processing of bile acids, sterols and xenobiotics. Thus, a partial or complete removal of enteric bacteria is not ideal for subjects already challenged by cancer and chemotherapy. Second, the elimination of the symbiotic enteric bacteria from even healthy subjects

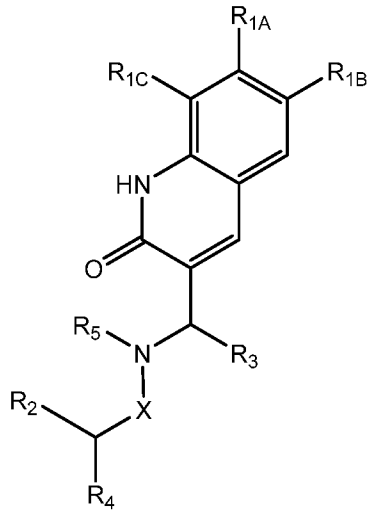
significantly increases risk of infection by pathogenic bacteria, including enterohemorrhagic *Escherichia coli* and *Clostridium difficile*. Third, bacterial antibiotic resistance is a human health crisis, and the unnecessary use of antibiotics is a significant contributor to this crisis.

Thus there remains a need to attenuate the side effects from drugs such as DID and also improve the efficacy drugs that cause DID through the administration of selective β- glucuronidase inhibitors.

International application PCT/US2018/48891, herein incorporated by reference in its entirety, describes novel compunds useful for attenuating the side effects of one or more drug through selective inhibition of β-glucuronidase.

SUMMARY

One embodiment of the present disclosure includes a compound of formula (I):



(I)

wherein

each of R_{1A}, R_{1B}, R_{1C} independently is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkylthio, substituted or unsubstituted C_{1-6} haloalkoxy, substituted or unsubstituted C_{1-6} haloalkylthio, substituted or unsubstituted C_{1-6} alkylamino, substituted or unsubstituted C_{1-6} alkylaminoalkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} haloalkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{2-6} haloalkynyl, halogen, cyano, nitro, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S,

and optionally having one or more degrees of unsaturation;

R_2 is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkylthio, substituted or unsubstituted C_{1-6} haloalkoxy, substituted or unsubstituted C_{1-6} haloalkylthio, substituted or unsubstituted C_{1-6} alkylamino, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} haloalkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{2-6} haloalkynyl, halogen, cyano, nitro, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

R_3 is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkylthio, substituted or unsubstituted C_{1-6} haloalkoxy, substituted or unsubstituted C_{1-6} haloalkylthio, substituted or unsubstituted C_{1-6} alkylamino, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} haloalkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{2-6} haloalkynyl, halogen, cyano, nitro, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

X is CO or SO_2;

Y is CH or N;

R_4 is selected from the group consisting of a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

R_5 is $(L_1)_nR_a$, wherein L_1 is a C_{1-6} alkylene chain, n is 0 or 1, and R_a is OR_b, C_{1-6} alkylamino, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

R_b is hydrogen, $C(O)NHR_c$, or $C(O)R_d$;

R_c is aryl; and

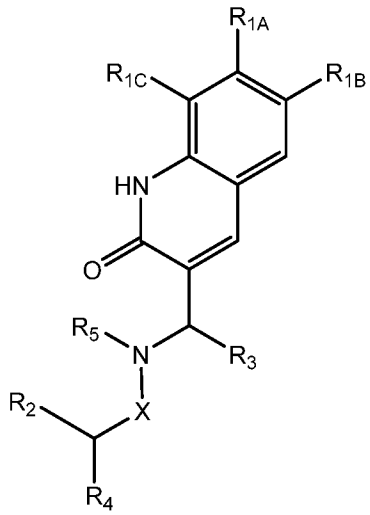
R_d is substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkylthio, substituted or unsubstituted C_{1-6} haloalkoxy, substituted or unsubstituted C_{1-6} haloalkylthio, substituted or unsubstituted C_{1-6} alkylamino, substituted or unsubstituted C_{1-6} alkylaminoalkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} haloalkenyl, substituted or unsubstituted C_{2-6} alkynyl,

substituted or unsubstituted C_{2-6} haloalkynyl, halogen, cyano, nitro, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation,

or a glucuronide thereof,

or a pharmaceutically acceptable salt thereof.

One embodiment of the present disclosure includes a compound of formula (IG):



(IG)

wherein

each of R_{1A}, R_{1B}, R_{1C} independently is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkylthio, substituted or unsubstituted C_{1-6} haloalkoxy, substituted or unsubstituted C_{1-6} haloalkylthio, substituted or unsubstituted C_{1-6} alkylamino, substituted or unsubstituted C_{1-6} alkylaminoalkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} haloalkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{2-6} haloalkynyl, halogen, cyano, nitro, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

R_2 is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkylthio, substituted or unsubstituted C_{1-6} haloalkoxy, substituted or unsubstituted C_{1-6} haloalkylthio, substituted or unsubstituted C_{1-6} alkylamino, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} haloalkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{2-6} haloalkynyl, halogen, cyano, nitro, or a substituted or unsubstituted 3- to 10-

membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

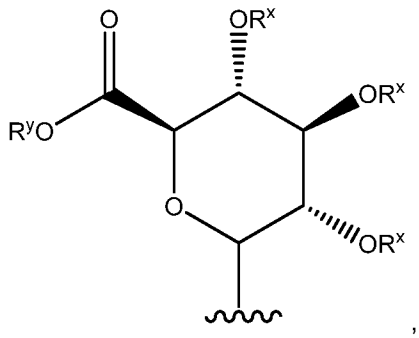
R_3 is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkylthio, substituted or unsubstituted C_{1-6} haloalkoxy, substituted or unsubstituted C_{1-6} haloalkylthio, substituted or unsubstituted C_{1-6} alkylamino, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} haloalkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{2-6} haloalkynyl, halogen, cyano, nitro, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

X is CO or SO_2;

Y is CH or N;

R_4 is selected from the group consisting of a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

R_5 is $(L_1)_nR_a$, wherein L_1 is a C_{1-6} alkylene chain, n is 0 or 1, and R_a is OR_b, C_{1-6} alkylamino, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;



R_b is hydrogen, $C(O)NHR_c$, $C(O)R_d$, or ,

where each R^x independently is hydrogen or $C(O)R^z$,

R^y is H or R^z, and

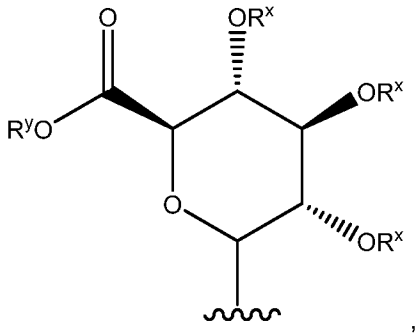
each R^z independently is C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{9-20} alkyl, C_{9-20} alkenyl, or C_{9-20} alkynyl;

R_c is aryl; and

R_d is substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkylthio, substituted or unsubstituted C_{1-6} haloalkoxy, substituted or unsubstituted C_{1-}

$_6$ haloalkylthio, substituted or unsubstituted C_{1-6} alkylamino, substituted or unsubstituted C_{1-6} alkylaminoalkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} haloalkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{2-6} haloalkynyl, halogen, cyano, nitro, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation, or a pharmaceutically acceptable salt thereof.

One aspect of the present disclosure includes wherein R_{1A} is hydrogen. One aspect of the present disclosure includes wherein R_{1B} is substituted or unsubstituted C_{1-6} alkyl. One aspect of the present disclosure includes wherein R_{1C} is substituted or unsubstituted C_{1-6} alkyl. One aspect of the present disclosure includes wherein R_2 is hydrogen or C_{1-6} alkyl. One aspect of the present disclosure includes wherein R_3 is hydrogen. One aspect of the present disclosure includes wherein R_4 is substituted or unsubstituted phenyl. One aspect of the present disclosure includes wherein R_4 is substituted phenyl. One aspect of the present disclosure includes wherein R_4 is phenyl substituted with one or more C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, halogen, or SO_2R_e, where R_e is hydrogen or C_{1-6} alkyl. One aspect of the present disclosure includes wherein R_4 is phenyl and is monosubstituted. One aspect of the present disclosure includes wherein R_4 is phenyl and is disubstituted. One aspect of the present disclosure includes wherein R_5 is $(L_1)_nR_a$, wherein L_1 is a C_2 alkylene, n is 1, and R_a is OR_b, wherein R_b is hydrogen. One aspect of the present disclosure includes wherein R_b



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where each R^x is hydrogen, and R^y is hydrogen. One aspect of the present disclosure includes wherein each R^x is $C(O)R^z$, and R^y is R^z. One aspect of the present disclosure include wherein each R^z is C_{1-6} alkyl.

One embodiment of the present disclosure includes a compound selected from: N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)-2-(o-tolyl)acetamide;

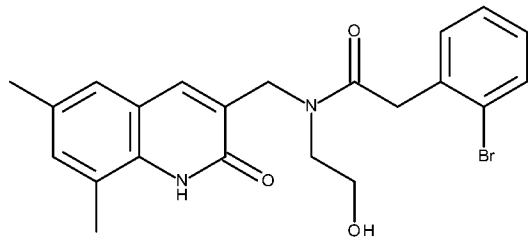
N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)-2-(2-iodophenyl)acetamide;
N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)-2-phenyl-acetamide;
2-(2-bromophenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)acetamide;
2-(2-bromophenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)propanamide;
2-(3-bromophenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)acetamide;
N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)-2-(3-methylsulfonylphenyl)acetamide;
2-(2-chlorophenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)acetamide;
N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)-2-(3-methoxyphenyl)acetamide;
2-(2-chloro-5-methoxy-phenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)acetamide;
2-(2-chloro-4-methoxy-phenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)acetamide; 2-(2-bromo-5-methoxy-phenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)acetamide;
1-(3-bromophenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)methanesulfonamide;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-3-(4-ethoxyphenyl)-1-(2-hydroxyethyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(4-(trifluoromethyl)phenyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(4-(trifluoromethoxy)phenyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(4-methoxyphenyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(3-(trifluoromethyl)phenyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(o-tolyl)urea;
3-(4-bromophenyl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-

hydroxyethyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(2-(trifluoromethyl)phenyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-3-(2,6-dimethylphenyl)-1-(2-hydroxyethyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(2-methoxyphenyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(2-isopropylphenyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(4-isopropylphenyl)urea;
3-(2-bromophenyl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea;
6,8-dibromo-3-(hydroxymethyl)quinolin-2(1H)-one;
6,8-dibromo-2-oxo-1,2-dihydroquinoline-3-carbaldehyde;
3-(2-cyclopropylphenyl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea;
3-([1,1'-biphenyl]-2-yl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(pyridin-3-yl)urea; 1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(2-iodophenyl)urea; 1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-3-(4-fluoro-2-iodophenyl)-1-(2-hydroxyethyl)urea;
1-(1-(2-chloro-6,8-dimethylquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(2-isopropylphenyl)urea;
1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(2-isopropylphenyl)urea;
1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-3-(4-fluoro-2-iodophenyl)-1-(2-hydroxyethyl)urea;
1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(o-tolyl)urea;
1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(4-methoxyphenyl)urea;
1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(3-methoxyphenyl)urea;
1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(m-

tolyl)urea;
1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(3-isopropylphenyl)urea;
1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-3-(3-ethynyl-4-fluorophenyl)-1-(2-hydroxyethyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-3-(4-fluoro-2-((trimethylsilyl)ethynyl)phenyl)-1-(2-hydroxyethyl)urea;
3-([1,1'-biphenyl]-2-yl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea;
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-(o-tolyl)acetamide;
2-bromo-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)benzamide; N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-(2-iodophenyl)acetamide;
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-phenylacetamide;
2-(2-bromophenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)acetamide;
3-bromo-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)benzamide;
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-3-iodobenzamide;
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-iodobenzamide;
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-3-iodobenzamide;
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-iodobenzamide;
2-(2-bromophenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)propanamide;
1-(3-bromophenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)methanesulfonamide;
2-(2-bromo-5-methoxyphenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)acetamide;
3-(2-bromo-5-methoxyphenyl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea;

N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-(3-(methylsulfonyl)phenyl)acetamide;
2-(2-chlorophenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)acetamide;
2-(2-(tert-butyl)phenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)acetamide;
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-(3-methoxyphenyl)acetamide;
3-(2-chloro-5-methoxyphenyl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(3-(trifluoromethoxy)phenyl)urea;
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-(3-methoxyphenyl)acetamide;
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-(3-methoxyphenyl)acetamide;
2-(2-chloro-4-methoxyphenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)acetamide;
6-(2-(1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-3-(4-ethoxyphenyl)ureido)ethoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid;
6-(2-(1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-3-(2-isopropylphenyl)ureido)ethoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid;
6-(2-(2-(2-(tert-butyl)phenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)acetamido)ethoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid;
6-(2-(2-(2-chlorophenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)acetamido)ethoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid;
or a glucuronide thereof, or a pharmaceutically acceptable salt thereof.

One embodiment of the present disclosure includes a compound selected from:



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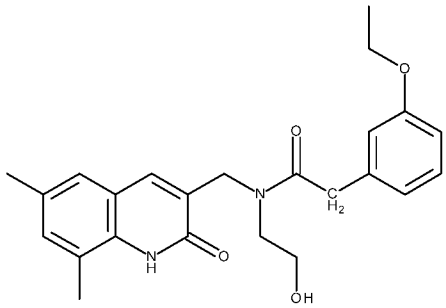

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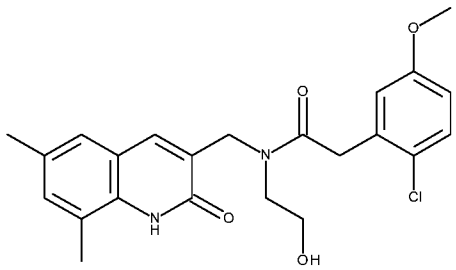

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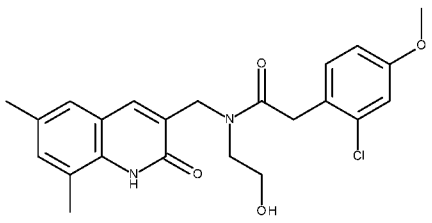

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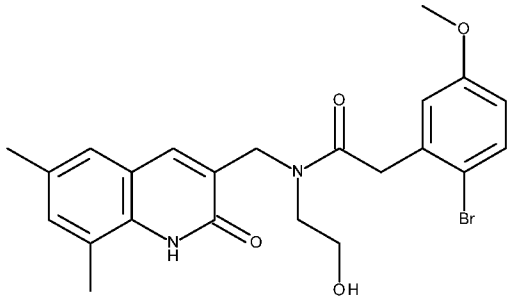

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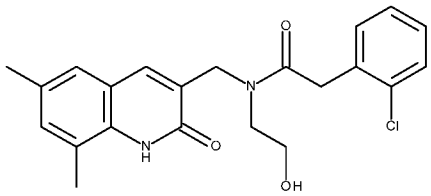
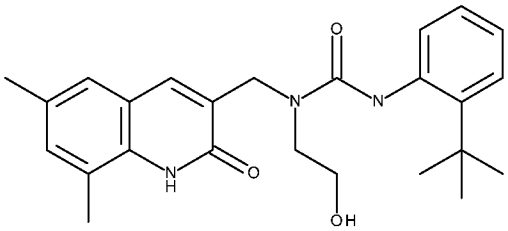


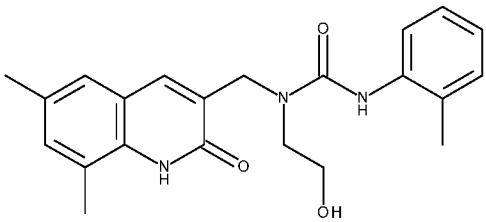
,

or a glucuronide thereof, or pharmaceutically acceptable salt thereof.

One embodiment of the present disclosure includes a compound selected from:



; and



,

or a glucuronide thereof, or pharmaceutically acceptable salt thereof.

One embodiment of the present disclosure includes a composition comprising or more compound or compounds of the present disclosure and one or more pharmaceutically acceptable carriers.

One embodiment of the present disclosure includes a method for attenuating the side effects of one or more drug, by administering to a subject in need thereof an effective amount of one or more compounds of the present disclosure. In one aspect of an embodiment, the one or more compounds selectively inhibit β-glucuronidase. In one aspect of an embodiment, the one or more compounds can be co-administered with the one or more therapeutic compound or product.

One embodiment of the present disclosure includes a compound of the present disclosure for use in medicine. In one aspect of an embodiment, the one or more compounds selectively inhibit β-glucuronidase. In one aspect of an embodiment, the one or more compounds can be co-administered with the one or more therapeutic compound or product.

One embodiment of the present disclosure includes a compound of the present disclosure for the manufacture of a medicament for attenuating side effects of one or more drug. In one aspect of an embodiment, the one or more compounds selectively inhibit β-glucuronidase. In one aspect of an embodiment, the one or more compounds can be co-administered with the one or more therapeutic compound or product.

One embodiment of the present disclosure includes use of a compound of the present disclosure for attenuating the side effects of one or more drug. In one aspect of an embodiment, the one or more compounds selectively inhibit β-glucuronidase. In one aspect of an embodiment, the one or more compounds can be co-administered with the one or more therapeutic compound or product.

One or more aspects and embodiments may be incorporated in a different embodiment although not specifically described. That is, all aspects and embodiments can be combined in any way or combination.

DETAILED DESCRIPTION

Definitions

When referring to the compounds disclosed herein, the following terms have the following meanings unless indicated otherwise. The following definitions are meant to clarify, but not limit, the terms defined. If a particular term used herein is not specifically defined, such term should not be considered indefinite. Rather, terms are used within their accepted meanings.

As used herein, the term “alkoxy” refers to the group -OR where R is alkyl. Illustrative alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, *tert*-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy.

As used herein, “alkyl” refers to monovalent saturated aliphatic hydrocarbyl groups having from 1 to 20 carbon atoms, preferably 1-8 carbon atoms, preferably 1-6 carbon atoms. The hydrocarbon chain can be either straight-chained or branched. Illustrative alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, and *tert*-butyl. Similarly, an “alkenyl” group refers to an alkyl group having one or more double bonds present in the chain. An “alkynyl” group refers to an alkyl group having one or more triple bonds present in the chain.

As used herein, “alkylamino” refers to monovalent saturated aliphatic hydrocarbyl groups having from 1 to 20 carbon atoms, preferably 1-8 carbon atoms, preferably 1-6 carbon atoms, wherein at least one hydrogen atom is substituted by an amine. Similarly, “alkylaminoalkyl” refers to dialkyl “alkylamino”, or alkylamino groups with more than one alkyl chain.

As used herein “aryl” refers to an aromatic ring system containing from 5 to 10 ring atoms. Illustrative aryl groups include phenyl and naphthyl.

As used herein “β-glucuronidase” refers to the bacterial or mammalian enzyme capable of hydrolyzing β-glucuronides. As used herein, “glucuronide” refers to a substance produced by linking glucuronic acid to another substance. An illustrative example of glucuronides are those derived from neoplastic agents such as 7-ethyl-10-hydroxycamptothecin glucouronide derived from camptothecin antineoplastic agents.

As used herein “co-administration” refers to prior to, the same time as, or following administration of a glucuronidase-substrate agent(s)” or compounds, as defined below.

As used herein, “cycloalkyl” refers to an unsaturated or partially saturated hydrocarbon ring, containing from 3 to 6 ring atoms. Illustrative cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, as well as partially saturated versions thereof, such as cyclohexenyl, and cyclohexadienyl.

As used herein, “dose-limiting” refers to a side effect from administration of a drug or glucuronidase-substrate agent or compound that prevents a subject in need thereof from receiving a therapeutically effective amount.

As used herein, “effective amount” refers to the amount sufficient to achieve a therapeutic effect when administered to a patient in need of treatment.

As used herein “halogen” or “halo” refers to a halogen. In some embodiments, the halogen is preferably Br, Cl, or F.

As used herein, “haloalkyl” refers to monovalent saturated aliphatic hydrocarbyl groups having from 1 to 20 carbon atoms, preferably 1-8 carbon atoms,

preferably 1-6 carbon atoms, wherein at least one hydrogen atom is substituted by a halogen, including but not limited to perhalo groups where all hydrogen atoms are replaced with halogen atoms. The haloalkyl chain can be either straight-chained or branched. Illustrative alkyl groups include trifluoromethyl, trifluoroethyl, trifluoropropyl, trifluorobutyl, and pentafluoroethyl. Similarly, a "haloalkenyl" group refers to a haloalkyl group having one or more double bonds present in the chain. A "haloalkynyl" group refers to a haloalkyl group having one or more triple bonds present in the chain.

As used herein, "haloalkylthio" refers to monovalent saturated aliphatic hydrocarbyl groups having from 1 to 20 carbon atoms, preferably 1-8 carbon atoms, preferably 1-6 carbon atoms, wherein at least one hydrogen atom is substituted by a halogen, including but not limited to perhalo groups where all hydrogen atoms are replaced with halogen atoms, and a second hydrogen atom is substituted by sulfur. The haloalkylthio chain can be either straight-chained or branched.

As used herein "glucuronidase-substrate agent(s)" or compounds" refers to any drug, agent, compound, or metabolite thereof that can be a substrate for glucuronidase. In some instances, a drug, compound or agent that is not itself a substrate, but is metabolized to a substrate is encompassed by the term above as used herein. Any drug, compound, agent or metabolite thereof that is glucuronidated, also referred to as glucuuronides, can be a substrate for glucuronidase and is also described herein as glucuronidase-substrate agent(s) or compound(s). Many drugs, agents or compounds undergo glucuronidation at some point in their metabolism. Alternatively, the drug, agent, or compound may be a glucuronide pro-drug. These glucuronides may have different properties than the parent drug, agent or compound.

As used herein "optionally having one or more heteroatoms" refers to the substitution of a ring carbon atom with a nitrogen, oxygen, or sulfur atom. Similarly, "optionally having one or more degrees of unsaturation" refers to varying the number of bonds between atoms of a ring due any substitutions in the ring atoms that results in changes the number of valence electrons available for bonding.

As used herein "pharmaceutically acceptable salt" refers to any salt of a compound disclosed herein which retains its biological properties and which is not toxic or otherwise undesirable for pesticidal, veterinary, or pharmaceutical use. Such salts may be derived from a variety of organic and inorganic counter-ions known in the art. Such salts include: (1) acid addition salts formed with organic or inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, sulfamic, acetic,

trifluoroacetic, trichloroacetic, propionic, hexanoic, cyclopentylpropionic, glycolic, glutaric, pyruvic, lactic, malonic, succinic, sorbic, ascorbic, malic, maleic, fumaric, tartaric, citric, benzoic, 3-(4-hydroxybenzoyl)benzoic, picric, cinnamic, mandelic, phthalic, lauric, methanesulfonic, ethanesulfonic, 1,2-ethane-disulfonic, 2-hydroxyethanesulfonic, benzenesulfonic, 4-chlorobenzenesulfonic, 2-naphthalenesulfonic, 4-toluenesulfonic, camphoric, camphorsulfonic, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic, glucoheptonic, 3-phenylpropionic, trimethylacetic, *tert*-butylacetic, lauryl sulfuric, gluconic, benzoic, glutamic, hydroxynaphthoic, salicylic, stearic, cyclohexylsulfamic, quinic, muconic acid, and like acids.

Salts further include, by way of example only, salts of non-toxic organic or inorganic acids, such as halides, such as , chloride and bromide, sulfate, phosphate, sulfamate, nitrate, acetate, trifluoroacetate, trichloroacetate, propionate, hexanoate, cyclopentylpropionate, glycolate, glutarate, pyruvate, lactate, malonate, succinate, sorbate, ascorbate, malate, maleate, fumarate, tartarate, citrate, benzoate, 3-(4-hydroxybenzoyl)benzoate, picrate, cinnamate, mandelate, phthalate, laurate, methanesulfonate (mesylate), ethanesulfonate, 1,2-ethane-disulfonate, 2-hydroxyethanesulfonate, benzenesulfonate (besylate), 4-chlorobenzenesulfonate, 2-naphthalenesulfonate, 4-toluenesulfonate, camphorate, camphorsulfonate, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylate, glucoheptonate, 3-phenylpropionate, trimethylacetate, *tert*-butylacetate, lauryl sulfate, gluconate, benzoate, glutamate, hydroxynaphthoate, salicylate, stearate, cyclohexylsulfamate, quinate, muconate, and the like.

As used herein, the term “selectively inhibits” and the like means that the β-glucuronidase inhibitor reduces either bacterial or mammalian β-glucuronidase activity.

As used herein, the terms “subject” and “patient” are used interchangeably herein. The terms “subject” and “subjects” refer to a primate such as a monkey such as a cynomolgous monkey, a chimpanzee, and a human or non-primate animal. In one embodiment, the subject is a human. In another embodiment, the subject is a companion animal such as a dog or cat. In a further embodiment the subject is an animal of agricultural importance such as a sheep, cow, horse, goat, fish, pig, or domestic fowl (such as a chicken, turkey, duck, or goose).

As used herein “substituted” refers to a substitution of a hydrogen atom, which would otherwise be present on the substituent. When discussing ring systems, the optional substitution is typically with 1, 2, or 3 substituents replacing the normally-

present hydrogen. When referencing straight and branched moieties, however, the number of substitutions can be more, occurring wherever hydrogen is usually present. The substitutions can be the same or different. Illustrative substitutions include nitro, -NR'R'', cyano, -NR'COR''', alkyl, alkenyl, alkynyl, alkylsilylalkynyl (namely, -C≡C-Si-alkyl), C(O), SO_2R''', $NR'SO_2R'''$, $SO_2NR'R''$, $CONR'R''$, $CONHC_6H_5$, hydroxy, alkoxy, alkylsulfonyl, haloalkyl, haloalkenyl, haloalkoxy, mercapto (namely, -SH), thioalkyl, halogen, cycloalkyl, heterocyclyl, aryl, or heteroaryl, where R' and R'' are the same or different and each represents hydrogen or alkyl; or when R' and R'' are each attached to a nitrogen atom, they may form a saturated or unsaturated heterocyclic ring containing from 4 to 6 ring atoms, and wherein R''' is alkyl or haloalkyl.

In certain cases, the depicted substituents can contribute to optical and/or stereoisomerism. Compounds having the same molecular formula but differing in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space are termed “isomers.” Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers.” Stereoisomers that are not mirror images of one another are termed “diastereomers” and those that are non-superimposable mirror images of each other are termed “enantiomers”. When a compound has an asymmetric center, for example when it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is designated (*R*) or (*S*) according to the rules of Cahn and Prelog (Cahn *et al.*, 1966, *Angew. Chem*. 78: 413-447, *Angew. Chem., Int. Ed. Engl*. 5: 385-414 (errata: *Angew. Chem., Int. Ed. Engl*. 5:511); Prelog and Helmchen, 1982, *Angew. Chem*. 94: 614-631, *Angew. Chem. Internat. Ed. Eng*. 21: 567-583; Mata and Lobo, 1993, *Tetrahedron: Asymmetry* 4: 657-668) or can be characterized by the manner in which the molecule rotates the plane of polarized light and is designated dextrorotatory or levorotatory (namely, as (+)- or (-)-isomers, respectively). A chiral compound can exist as either an individual enantiomer or as a mixture thereof. A mixture containing equal proportions of enantiomers is called a “racemic mixture”.

In certain embodiments, the compounds disclosed herein can possess one or more asymmetric centers; and such compounds can therefore be produced as the individual (*R*)- or (*S*)-enantiomer or as a mixture thereof. Unless indicated otherwise, for example by designation of stereochemistry at any position of a formula, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise,

thereof. Methods for determination of stereochemistry and separation of stereoisomers are well-known in the art. In particular embodiments, stereoisomers of the compounds provided herein are depicted upon treatment with base.

In certain embodiments, the compounds disclosed herein are "stereochemically pure". A stereochemically pure compound has a level of stereochemical purity that would be recognized as "pure" by those of skill in the art. Of course, this level of purity may be less than 100%. In certain embodiments, "stereochemically pure" designates a compound that is substantially free, i.e. at least about 85% or more, of alternate isomers. In particular embodiments, the compound is at least about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5% or about 99.9% free of other isomers.

The present disclosure includes all pharmaceutically acceptable isotopically-labelled compounds of the invention wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulfur, such as ^{35}S. Certain isotopically-labelled compounds of the invention, such as those incorporating a radioactive isotope, may be useful in drug or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^{3}H, and carbon-14, i.e. ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with heavier isotopes such as deuterium, i.e. ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some circumstances. Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

Compounds that inhibit β-glucuronidase activity

The present disclosure provides compounds and methods of inhibiting β-glucuronidase activity. Also described herein are methods of attenuating the side effects of one or more drugs comprising administration of the compounds described herein.

Drugs, agents, compounds or metabolites thereof which are substrates for β-glucuronidase (glucuronidase-substrate agents) can have their respective properties altered by glucuronidase hydrolysis. For example, if the drug, agent, compound or metabolite thereof has been metabolized to a glucuronide, the hydrolysis of the glucuronide can reactivate the drug, agent, compound or metabolite thereof. In many cases, this reactivation can cause adverse reactions, including but not limited to, gastrointestinal distress, leading to diarrhea.

For example, camptothecin-derived antineoplastic agents are useful for treating solid malignancies of the brain, colon and lung, as well as refractory forms of leukemia and lymphoma. Irinotecan is a prodrug that must be converted to its active form, SN-38 (7-ethyl-10-hydroxycamptohtecin), to have antineoplastic activity. During its excretion, SN-38 is glucuronidated to SN-38 glucuronide (SN-380) by drug metabolizing UDP-glucuronosyltranserases. As increasing amounts of the drug are administered to a subject, increased amounts of metabolites are therefore available as a substrate for β-glucuronidases. The resulting reactivated metabolites not only adversely affect a subject's well-being by causing serious side effects, particularly gastrointestinal distress, but also impair treatment outcome by limiting the amount of the glucuronidase-substrate agents that can be administered to the subject.

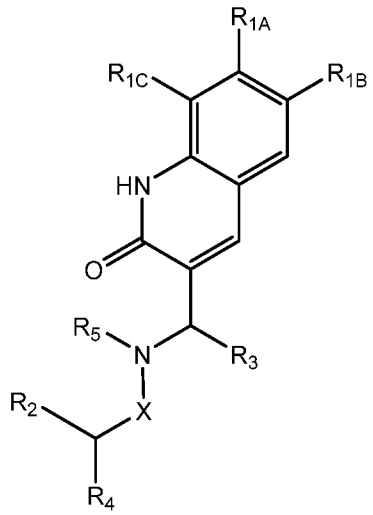
Another example of commonly used glucuronidase-substrate agents are non-steroidal anti-inflammatory agents (NSAIDs). Gastrointestinal Injury (GI) is one of the major adverse NSAIDs. This iatrogenic disease is manifested as ulceration and bleeding of the mucosa, inflammation, and even perforation (Allison et al., New Engl. J. Med, 327:749-754 (1992); Bjarnason et al., Gastroenterology, 104:1832-1847 (1993); Wolfe et al., New Engl. J. Med., 340:1888-1899 (1999)). A portion of the carboxylic acid-containing NSAIDs are conjugated with glucuronic acid in vivo and form acyl glucuronides. Although not wanting to be bound by this, it is believed that inhibition of carboxylic acid NSAID/glucuronic acid deconjugation by inhibition of β-glucuronidase activity results in a reduced exposure of the intestinal mucosa to the NSAID and thereby reduces NSAID toxicity.

Thus, without intending to be bound by any particular theory, the compounds provided herein are thought to inhibit the interaction between β-glucuronidase and its

substrate. Compounds contemplated by the disclosure include, but are not limited to, the exemplary compounds provided herein and salts thereof.

Compounds

One embodiment of the present disclosure includes a compound of formula (I):



(I)

wherein

each of R_{1A}, R_{1B}, R_{1C} independently is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkylthio, substituted or unsubstituted C_{1-6} haloalkoxy, substituted or unsubstituted C_{1-6} haloalkylthio, substituted or unsubstituted C_{1-6} alkylamino, substituted or unsubstituted C_{1-6} alkylaminoalkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} haloalkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{2-6} haloalkynyl, halogen, cyano, nitro, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

R_2 is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkylthio, substituted or unsubstituted C_{1-6} haloalkoxy, substituted or unsubstituted C_{1-6} haloalkylthio, substituted or unsubstituted C_{1-6} alkylamino, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} haloalkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{2-6} haloalkynyl, halogen, cyano, nitro, or a substituted or unsubstituted 3- to 10-

membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

R_3 is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkylthio, substituted or unsubstituted C_{1-6} haloalkoxy, substituted or unsubstituted C_{1-6} haloalkylthio, substituted or unsubstituted C_{1-6} alkylamino, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} haloalkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{2-6} haloalkynyl, halogen, cyano, nitro, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

X is CO or SO_2;

Y is CH or N;

R_4 is selected from the group consisting of a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

R_5 is $(L_1)_nR_a$, wherein L_1 is a C_{1-6} alkylene chain, n is 0 or 1, and R_a is OR_b, C_{1-6} alkylamino, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

R_b is hydrogen, $C(O)NHR_c$, or $C(O)R_d$;

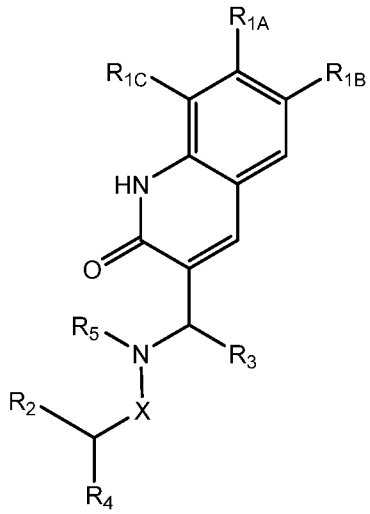
R_c is aryl; and

R_d is substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkylthio, substituted or unsubstituted C_{1-6} haloalkoxy, substituted or unsubstituted C_{1-6} haloalkylthio, substituted or unsubstituted C_{1-6} alkylamino, substituted or unsubstituted C_{1-6} alkylaminoalkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} haloalkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{2-6} haloalkynyl, halogen, cyano, nitro, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation,

or a glucuronide thereof,

or a pharmaceutically acceptable salt thereof.

One embodiment of the present disclosure includes a compound of formula (IG):



(IG)

wherein

each of R_{1A}, R_{1B}, R_{1C} independently is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkylthio, substituted or unsubstituted C_{1-6} haloalkoxy, substituted or unsubstituted C_{1-6} haloalkylthio, substituted or unsubstituted C_{1-6} alkylamino, substituted or unsubstituted C_{1-6} alkylaminoalkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} haloalkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{2-6} haloalkynyl, halogen, cyano, nitro, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

R_2 is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkylthio, substituted or unsubstituted C_{1-6} haloalkoxy, substituted or unsubstituted C_{1-6} haloalkylthio, substituted or unsubstituted C_{1-6} alkylamino, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} haloalkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{2-6} haloalkynyl, halogen, cyano, nitro, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

R_3 is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkylthio, substituted or unsubstituted C_{1-6} haloalkoxy, substituted or unsubstituted C_{1-6} haloalkylthio, substituted or unsubstituted C_{1-6} alkylamino,

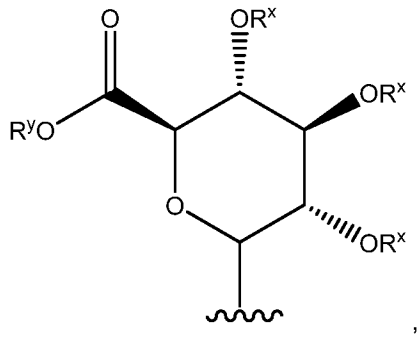
substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} haloalkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{2-6} haloalkynyl, halogen, cyano, nitro, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

X is CO or SO_2;

Y is CH or N;

R_4 is selected from the group consisting of a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

R_5 is $(L_1)_nR_a$, wherein L_1 is a C_{1-6} alkylene chain, n is 0 or 1, and R_a is OR_b, C_{1-6} alkylamino, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;



R_b is hydrogen, $C(O)NHR_c$, $C(O)R_d$, or , where each R^x independently is hydrogen or $C(O)R^z$,

R^y is H or R^z, and

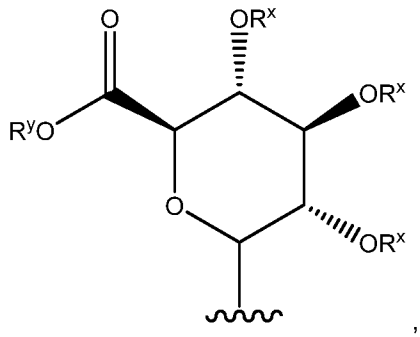
each R^z independently is C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{9-20} alkyl, C_{9-20} alkenyl, or C_{9-20} alkynyl;

R_c is aryl; and

R_d is substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkylthio, substituted or unsubstituted C_{1-6} haloalkoxy, substituted or unsubstituted C_{1-6} haloalkylthio, substituted or unsubstituted C_{1-6} alkylamino, substituted or unsubstituted C_{1-6} alkylaminoalkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} haloalkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{2-6} haloalkynyl, halogen, cyano, nitro, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation,

or a pharmaceutically acceptable salt thereof.

One aspect of the present disclosure includes wherein R_{1A} is hydrogen. One aspect of the present disclosure includes wherein R_{1B} is substituted or unsubstituted C_{1-6} alkyl. One aspect of the present disclosure includes wherein R_{1C} is substituted or unsubstituted C_{1-6} alkyl. One aspect of the present disclosure includes wherein R_2 is hydrogen or C_{1-6} alkyl. One aspect of the present disclosure includes wherein R_3 is hydrogen. One aspect of the present disclosure includes wherein R_4 is substituted or unsubstituted phenyl. One aspect of the present disclosure includes wherein R_4 is substituted phenyl. One aspect of the present disclosure includes wherein R_4 is phenyl substituted with one or more C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, halogen, or SO_2R_e, where R_e is hydrogen or C_{1-6} alkyl. One aspect of the present disclosure includes wherein R_4 is phenyl and is monosubstituted. One aspect of the present disclosure includes wherein R_4 is phenyl and is disubstituted. One aspect of the present disclosure includes wherein R_5 is $(L_1)_nR_a$, wherein L_1 is a C_2 alkylene, n is 1, and R_a is OR_b, wherein R_b is hydrogen. One aspect of the present disclosure includes wherein R_b



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where each R^x is hydrogen, and R^y is hydrogen. One aspect of the present disclosure includes wherein each R^x is $C(O)R^z$, and R^y is R^z. One aspect of the present disclosure include wherein each R^z is C_{1-6} alkyl.

One embodiment of the present disclosure includes a compound selected from:

N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)-2-(o-tolyl)acetamide;

N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)-2-(2-iodophenyl)acetamide;

N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)-2-phenyl-acetamide;

2-(2-bromophenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)acetamide;

2-(2-bromophenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)propanamide;
2-(3-bromophenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)acetamide;
N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)-2-(3-methylsulfonylphenyl)acetamide;
2-(2-chlorophenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)acetamide;
N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)-2-(3-methoxyphenyl)acetamide;
2-(2-chloro-5-methoxy-phenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)acetamide;
2-(2-chloro-4-methoxy-phenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)acetamide; 2-(2-bromo-5-methoxy-phenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)acetamide;
1-(3-bromophenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)methanesulfonamide;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-3-(4-ethoxyphenyl)-1-(2-hydroxyethyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(4-(trifluoromethyl)phenyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(4-(trifluoromethoxy)phenyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(4-methoxyphenyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(3-(trifluoromethyl)phenyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(o-tolyl)urea;
3-(4-bromophenyl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(2-(trifluoromethyl)phenyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-3-(2,6-dimethylphenyl)-1-(2-hydroxyethyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(2-

methoxyphenyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(2-isopropylphenyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(4-isopropylphenyl)urea;
3-(2-bromophenyl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea;
6,8-dibromo-3-(hydroxymethyl)quinolin-2(1H)-one;
6,8-dibromo-2-oxo-1,2-dihydroquinoline-3-carbaldehyde;
3-(2-cyclopropylphenyl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea;
3-([1,1'-biphenyl]-2-yl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(pyridin-3-yl)urea; 1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(2-iodophenyl)urea; 1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-3-(4-fluoro-2-iodophenyl)-1-(2-hydroxyethyl)urea;
1-(1-(2-chloro-6,8-dimethylquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(2-isopropylphenyl)urea;
1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(2-isopropylphenyl)urea;
1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-3-(4-fluoro-2-iodophenyl)-1-(2-hydroxyethyl)urea;
1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(o-tolyl)urea;
1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(4-methoxyphenyl)urea;
1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(3-methoxyphenyl)urea;
1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(m-tolyl)urea;
1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(3-isopropylphenyl)urea;
1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-3-(3-ethynyl-4-fluorophenyl)-1-(2-hydroxyethyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-3-(4-fluoro-2-

((trimethylsilyl)ethynyl)phenyl)-1-(2-hydroxyethyl)urea;
3-([1,1'-biphenyl]-2-yl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea;
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-(o-tolyl)acetamide;
2-bromo-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)benzamide; N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-(2-iodophenyl)acetamide;
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-phenylacetamide;
2-(2-bromophenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)acetamide;
3-bromo-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)benzamide;
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-3-iodobenzamide;
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-iodobenzamide;
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-3-iodobenzamide;
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-iodobenzamide;
2-(2-bromophenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)propanamide;
1-(3-bromophenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)methanesulfonamide;
2-(2-bromo-5-methoxyphenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)acetamide;
3-(2-bromo-5-methoxyphenyl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea;
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-(3-(methylsulfonyl)phenyl)acetamide;
2-(2-chlorophenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)acetamide;
2-(2-(tert-butyl)phenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)acetamide;

N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-(3-methoxyphenyl)acetamide;

3-(2-chloro-5-methoxyphenyl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea;

1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(3-(trifluoromethoxy)phenyl)urea;

N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-(3-methoxyphenyl)acetamide;

N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-(3-methoxyphenyl)acetamide;

2-(2-chloro-4-methoxyphenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)acetamide;

6-(2-(1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-3-(4-ethoxyphenyl)ureido)ethoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid;

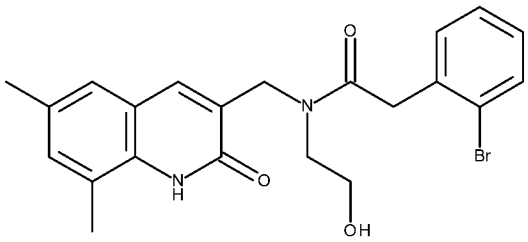
6-(2-(1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-3-(2-isopropylphenyl)ureido)ethoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid;

6-(2-(2-(2-(tert-butyl)phenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)acetamido)ethoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid;

6-(2-(2-(2-chlorophenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)acetamido)ethoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid;

or a glucuronide thereof, or a pharmaceutically acceptable salt thereof.

One embodiment of the present disclosure is a compound selected from:



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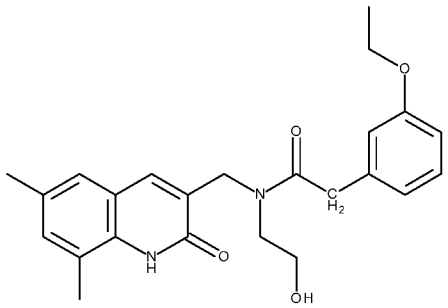

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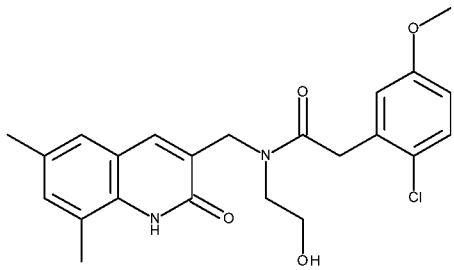

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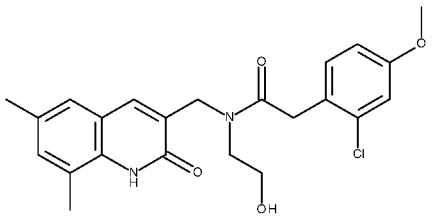

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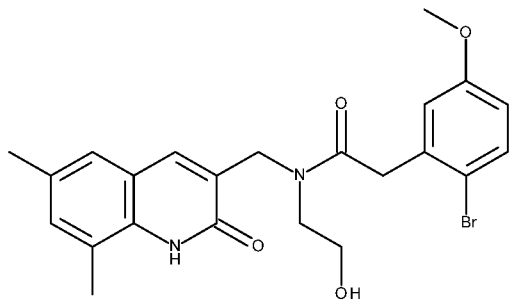

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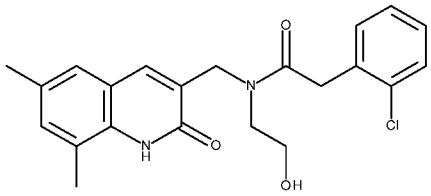

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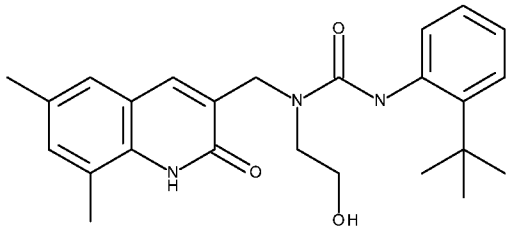
or a glucuronide thereof, or pharmaceutically acceptable salt thereof.

One embodiment of the present disclosure is a compound selected from:



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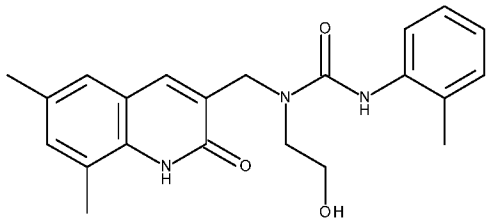

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or a glucuronide thereof, or pharmaceutically acceptable salt thereof.

Compositions that Inhibit β-glucuronidase Activity

One embodiment described in the present disclosure provides compositions that inhibit β-glucuronidase activity. Generally, the compositions that inhibit β-glucuronidase activity in humans and animals will comprise a pharmaceutically acceptable excipient or diluent and a compound having the formula provided above as formula (I).

In one embodiment described herein is a composition comprising one or more compounds as described herein and one or more pharmaceutically acceptable carriers.

The term “composition” as used herein is intended to encompass a product comprising specific ingredients in specified amounts, as well as any product which

results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The pharmaceutical compositions for the administration of the compounds of this disclosure may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions and self-emulsifications as described in U.S. Pat. No. 6,451,339, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with other non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents such as cellulose, silicon dioxide, aluminum oxide, calcium carbonate, sodium carbonate, glucose, mannitol, sorbitol, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example PVP, cellulose, PEG, starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated enterically or otherwise by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Pat.

Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil. Additionally, emulsions can be prepared with a non-water miscible ingredient such as oils and stabilized with surfactants such as mono-diglycerides, PEG esters and the like.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by

those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the disclosure may also be in the form of oil in water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative. and flavoring and coloring agents. Oral solutions can be prepared in combination with, for example, cyclodextrin, PEG and surfactants.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, axed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of the present disclosure may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient, which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols. Additionally, the compounds can be administered via ocular delivery by means of solutions or ointments. Still further, transdermal delivery of the subject compounds can be accomplished by means of iontophoretic patches and the like.

For topical use, creams, ointments, jellies, solutions or suspensions containing the compounds of the present disclosure are employed. As used herein,

topical application is also meant to include the use of mouth washes and gargles. Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions, which may contain anti-oxidants, buffers, bacteriostats and solutes, which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

The formulations may be packaged in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water, for injection immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

The subject matter further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefore. Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered parenterally, orally or by any other desired route.

In particular embodiments, a preferred pharmaceutical composition includes one or more of the presently disclosed compounds and one or more chemotherapeutic agent.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material

which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Methods of Inhibiting β-glucuronidase Activity and Attenuating Side Effects from Drugs

In yet another aspect, the present disclosure provides methods of attenuating the side effects of one or more drugs comprising administering to a subject an effective amount of one or more compounds of formula (I) as described herein. Compounds for use in the present methods include those compounds according to formula (I), those provided above as embodiments, those specifically exemplified in the Examples below, and those provided with specific structures herein.

In one embodiment described herein is a method for attenuating the side effects of one or more drug comprising administering to a subject an effective amount of one or more of any of the compounds described herein. In one aspect of the embodiment, the compounds described herein selectively inhibit β-glucuronidase. In one aspect described herein, the compounds can be co-administered with one or more drug.

The pharmaceutical compositions and methods of the present disclosure may further comprise other therapeutically active compounds as noted herein, including but not limited to treatment of 1) allergic diseases such as systemic anaphylaxis or hypersensitivity responses, drug allergies, insect sting allergies and food allergies, (2) inflammatory bowel diseases, such as Crohn's disease, ulcerative colitis, ileitis and enteritis, (3) vaginitis, (4) psoriasis and inflammatory dermatoses such as dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria and pruritus, (5) vasculitis, (6) spondyloarthropathies, (7) scleroderma, (8) asthma and respiratory allergic diseases such as allergic asthma, allergic rhinitis, hypersensitivity lung diseases and the like, (9) autoimmune diseases, such as fibromyalagia, scleroderma, ankylosing spondylitis, juvenile RA, Still's disease, polyarticular juvenile RA, pauciarticular juvenile RA, polymyalgia rheumatica, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, polyarticular arthritis, multiple sclerosis, systemic lupus erythematosus, type I diabetes, type II diabetes, glomerulonephritis, and the like, (10) graft rejection (including allograft rejection), (11) graft-v-host disease (including

both acute and chronic), (12) other diseases in which undesired inflammatory responses are to be inhibited, such as atherosclerosis, myositis, neurodegenerative diseases (e.g., Alzheimer's disease), encephalitis, meningitis, hepatitis, nephritis, sepsis, sarcoidosis, allergic conjunctivitis, otitis, chronic obstructive pulmonary disease, sinusitis, Behcet's syndrome and gout, (13) immune mediated food allergies such as Coeliac (Celiac) disease (14) pulmonary fibrosis and other fibrotic diseases, and (15) irritable bowel syndrome.

In another group of embodiments, diseases or conditions that induce side effects that can be treated with β-glucuronidase inhibitor compound include but are not limited to cancers, including but not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia or lymphoid malignancies. More particular examples of such cancers include melanoma, squamous cell cancer (e.g., epithelial squamous cell cancer), lung cancer including melanoma, multiple myeloma, small-cell lung cancer, non-small cell lung cancer ("NSCLC"), adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer, pancreatic cancer, glioblastoma, glioblastoma multiforme, KRAS mutant solid tumors, indolent non-Hodgkin's lymphoma, chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma, thyroid cancer, non-Hodgkin's lymphoma, basal cell carcinoma, hematological tumors, B-cell non-Hodgkin's lymphoma, acute myeloid leukemia (AML), cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, including triple negative breat cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, as well as head and neck cancer. Also included are "hematological malignancies" or "hematological cancer," which are the types of cancer that affect blood, bone marrow, and lymph nodes. Hematological malignancies may derive from either of the two major blood cell lineages: myeloid and lymphoid cell lines. The myeloid cell line normally produces granulocytes, erythrocytes, thrombocytes, macrophages and mast cells; the lymphoid cell line produces B, T, NK and plasma cells. Lymphomas, lymphocytic leukemias, and myeloma are from the lymphoid line, while acute and chronic myelogenous leukemia, myelodysplastic syndromes and myeloproliferative diseases are myeloid in origin. Leukemias include Acute lymphoblastic leukemia (ALL), Acute myelogenous leukemia (AML), Chronic lymphocytic leukemia (CLL), Chronic myelogenous leukemia (CML), Acute monocytic leukemia (AMOL) and small lymphocytic

lymphoma (SLL). Lymphomas include Hodgkin's lymphomas (all four subtypes) and Non-Hodgkin's lymphomas (NHL, all subtypes), cardiovascular diseases, diseases in which angiogenesis or neovascularization play a role (neoplastic diseases, retinopathy and macular degeneration), infectious diseases (viral infections, e.g., HIV infection, and bacterial infections) and immunosuppressive diseases such as organ transplant conditions and skin transplant conditions, chronic inflammation, autoimmune diseases such as rheumatoid arthritis and immune-mediated food allergies such as Coelaic disease.

Another embodiment described herein include methods for improving the treatment of a variety of diseases including neoplasms of the bone, brain, breast, cervix, colon, intestines, kidney, liver, lung, pancreatic, prostrate, rectum, stomach, throat, uterus, and the like.

Another embodiment described herein include methods for improving the efficacy of other drugs including but not limited to: chemotherapeutic drugs including but not limited to camptothecin, indolizino, irinotecan, diflomotecan, exatecan, gimatecan, irinotecan, karenitecin, lurtorecan, rubitecan, silatecan, topotecan, NSAIDs, sorafenib, alkylating agents such as thiotepa and cyclophosphamide (CYTOXAN®); alkyl sulfonates such as busulfan, improsulfan, and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); delta-9-tetrahydrocannabinol (dronabinol, MARINOL®); beta-lapachone; lapachol; colchicines; betulinic acid; a camptothecin (including the synthetic analogue topotecan (HYCAMTIN®), CPT-11 (irinotecan, CAMPTOSAR®), acetylcamptothecin, scopolectin, and 9-aminocamptothecin); bryostatin; pemetrexed; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); podophyllotoxin; podophyllinic acid; teniposide; cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; TLK-286; CDP323, an oral alpha-4 integrin inhibitor; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as

anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX®; tamoxifen citrate), raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and FARESTON® (toremifine citrate); aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, MEGASE® (megestrol acetate), AROMASIN® (exemestane; Pfizer), formestanie, fadrozole, RIVISOR® (vorozole), FEMARA® (letrozole; Novartis), and ARIMIDEX® (anastrozole; AstraZeneca); anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; as well as troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); (iv) protein kinase inhibitors; lipid kinase inhibitors; (vi) antisense oligonucleotides, particularly those which inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, such as, for example, PKC-alpha, Ralf and H-Ras; (vii) ribozymes such as VEGF expression inhibitors (e.g., ANGIOZYME®) and HER2 expression inhibitors; (viii) vaccines such as gene therapy vaccines, for example, ALLOVECTIN®, LEUVECTIN®, and VAXID®; PROLEUKIN® rIL-2; a topoisomerase 1 inhibitor such as LURTOTECAN®; ABARELIX® rmRH; (ix) anti-angiogenic agents such as bevacizumab (AVASTIN®, Genentech); and (x) pharmaceutically acceptable salts, acids and derivatives of any of the above; NSAIDs including but not limited to salicylates, p-amino phenol derivatives, propionic acid derivatives, carboxylic acid derivatives, enolic acid derivatives, fenamic acid derivatives, sulphonanilides, and selective COX-2 inhibitors. "NSAID salicylates" include, but are not limited to, aspirin (acetylsalicylic acid), diflunisal, and salsalate. "NSAID p-amino phenol derivatives" include, but are not limited to, paracetamol and phenacetin. "NSAID propionic acid derivatives" include, but are not limited to, ibuprofen, naproxen, fenoprofen, ketoprofen, dexketoprofen, fluribiprofen, oxaprozin, and loxoprofen. "NSAID carboxylic acid derivatives" include, but are not limited to, indomethacin, sulindac, etodolac, ketorolac, diclofenac. NSAID carboxylic acid derivatives include NSAID acetic acid derivatives. NSAID carboxylic acid derivatives are also referred to herein as "carboxylic acid NSAIDs." "NSAID enolic acid derivatives" include, but are not limited to, piroxicam, meloxicam, tenoxicam, droxicam, lomoxicam, and isoxicam. "NSAID fenamic acid derivatives" include, but are not limited to, mefenamic acid, meclofenamic acid, flufenamic acid, and tolfenamic acid. "NSAID sulphonanilides" include, but are not limited to, nimesulide. "NSAID selective COX-2 inhibitors" include, but are not limited to, celecoxib, rofecoxib, valdecoxib, parecoxib, lumiracoxib, etoricoxib, and firocoxib; antibiotics including not limited to

cephalosporins such as cefixime and cefpodoxime, clindamycin, penicillins, fluoroquinolones such as ciprofloxacin and levofloxacin, the enediyne antibiotics (*e.g.*, calicheamicin, especially calicheamicin gamma1I and calicheamicin omegaI1 (see, *e.g.*, Nicolaou *et al.*, *Angew. Chem Intl. Ed. Engl.*, 33: 183-186 (1994)); dynemicin, including dynemicin A; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including ADRIAMYCIN®, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin, doxorubicin HCl liposome injection (DOXIL®) and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate, gemcitabine (GEMZAR®), tegafur (UFTORAL®), capecitabine (XELODA®), an epothilone, and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, and floxuridine; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine (ELDISINE®, FILDESIN®); dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); thiotepa; taxoids, *e.g.*, paclitaxel (TAXOL®), albumin-engineered nanoparticle formulation of paclitaxel (ABRAXANE™), and doxetaxel (TAXOTERE®); chloranbucil; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine (VELBAN®); platinum; etoposide (VP-16); ifosfamide; mitoxantrone;

vincristine (ONCOVIN®); oxaliplatin; leucovovin; vinorelbine (NAVELBINE®); novantrone; edatrexate; daunomycin; aminopterin; ibandronate; topoisomerase inhibitor RFS 2000; difluorometlhylornithine (DMFO); retinoids such as retinoic acid; pharmaceutically acceptable salts, acids or derivatives of any of the above; as well as combinations of two or more of the above such as CHOP, an abbreviation for a combined therapy of cyclophosphamide, doxorubicin, vincristine, and prednisolone, and FOLFOX, an abbreviation for a treatment regimen with oxaliplatin (ELOXATIN™) combined with 5-FU and leucovovin; vaccines such as THERATOPE® vaccine and gene therapy vaccines, for example, ALLOVECTIN® vaccine, LEUVECTIN® vaccine, and VAXID® vaccine; topoisomerase 1 inhibitor (e.g., LURTOTECAN®); an anti-estrogen such as fulvestrant; EGFR inhibitor such as erlotinib or cetuximab; an anti-VEGF inhibitor such as bevacizumab; arinotecan; rmRH (e.g., ABARELIX®); 17AAG (geldanamycin derivative that is a heat shock protein (Hsp) 90 poison), and pharmaceutically acceptable salts, acids or derivatives of any of the above; anti-hormonal agents that act to regulate, reduce, block, or inhibit the effects of hormones that can promote the growth of cancer, and are often in the form of systemic, or whole-body treatment. They may be hormones themselves. Examples include anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX® tamoxifen), raloxifene (EVISTA®), droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and toremifene (FARESTON®); anti-progesterones; estrogen receptor down-regulators (ERDs); estrogen receptor antagonists such as fulvestrant (FASLODEX®); agents that function to suppress or shut down the ovaries, for example, leutinizing hormone-releasing hormone (LHRH) agonists such as leuprolide acetate (LUPRON® and ELIGARD®), goserelin acetate, buserelin acetate and tripterelin; anti-androgens such as flutamide, nilutamide and bicalutamide; and aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, megestrol acetate (MEGASE®), exemestane (AROMASIN®), formestanie, fadrozole, vorozole (RIVISOR®), letrozole (FEMARA®), and anastrozole (ARIMIDEX®). In addition, such definition of chemotherapeutic agents includes bisphosphonates such as clodronate (for example, BONEFOS® or OSTAC®), etidronate (DIDROCAL®), NE-58095, zoledronic acid/zoledronate (ZOMETA®), alendronate (FOSAMAX®), pamidronate (AREDIA®), tiludronate (SKELID®), or risedronate (ACTONEL®); as well as troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); anti-sense oligonucleotides, particularly those that inhibit expression of genes in signaling

pathways implicated in abherant cell proliferation, such as, for example, PKC-alpha, Raf, H-Ras, and epidermal growth factor receptor (EGF-R); immunosuppressants and anti-rejection drugs including but not limited to tacrolimus and cyclosporine, mycophenolate mofetil, mycophenolate sodium, azathioprine, sirolimus and prednisone; other β-glucuronidase substrate drugs including but not limited to morphine, paracetamol, oxazepam, androsterone, carbamazepine, codeine, lamotrigine, lorazepam, temazepam, testosterone, and zidovudine.

Preparation of the β-glucuronidase inhibitors

The following examples are offered to illustrate, but not to limit, the claimed disclosure.

Additionally, those skilled in the art will recognize that the molecules claimed in this patent may be synthesized using a variety of standard organic chemistry transformations. Such methods can be carried out utilizing corresponding deuterated and optionally, other isotope-containing reagents and/or intermediates to synthesize the compounds delineated herein, or invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure.

Certain general reaction types employed widely to synthesize target compounds in this disclosure are summarized in the examples. Specifically, generic procedures for sulfonamide formation, pyridine N-oxide formation and 2-aminophenyl-arylmethanone synthesis via Friedel-Crafts type approaches are given, but numerous other standard chemistries are described within and were employed routinely.

While not intended to be exhaustive, representative synthetic organic transformations which can be used to prepare compounds of the disclosure are included below.

These representative transformations include; standard functional group manipulations; reductions such as nitro to amino; oxidations of functional groups including alcohols and pyridines; aryl substitutions via *IPSO* or other mechanisms for the introduction of a variety of groups including nitrile, methyl and halogen; protecting group introductions and removals; Grignard formation and reaction with an electrophile; metal-mediated cross couplings including but not limited to Buckwald, Suzuki and Sonigashira reactions; halogenations and other electrophilic aromatic substitution reactions; diazonium salt formations and reactions of these species; etherifications; cyclative condensations, dehydrations, oxidations and reductions leading to heteroaryl groups; aryl metallations and transmetallations and reaction of the ensuing aryl-metal species with an electrophile such as an acid chloride or

Weinreb amide; amidations; esterifications; nucleophilic substitution reactions; alkylations; acylations; sulfonamide formation; chlorosulfonylations; ester and related hydrolyses, and the like.

Certain molecules claimed in this patent can exist in different enantiomeric and diastereomeric forms and all such variants of these compounds are within the scope of the disclosure.

In the descriptions of the syntheses that follow, some precursors may be obtained from commercial sources. These commercial sources include Aldrich Chemical Co., Acros Organics, Ryan Scientific Incorporated, Oakwood Products Incorporated, Lancaster Chemicals, Sigma Chemical Co., Lancaster Chemical Co., TCI-America, Alfa Aesar, Davos Chemicals, and GFS Chemicals.

Compounds of the present disclosure can be made by the methods and approaches described in the following experimental section and by the use of standard organic chemistry transformations that are well known to those skilled in the art.

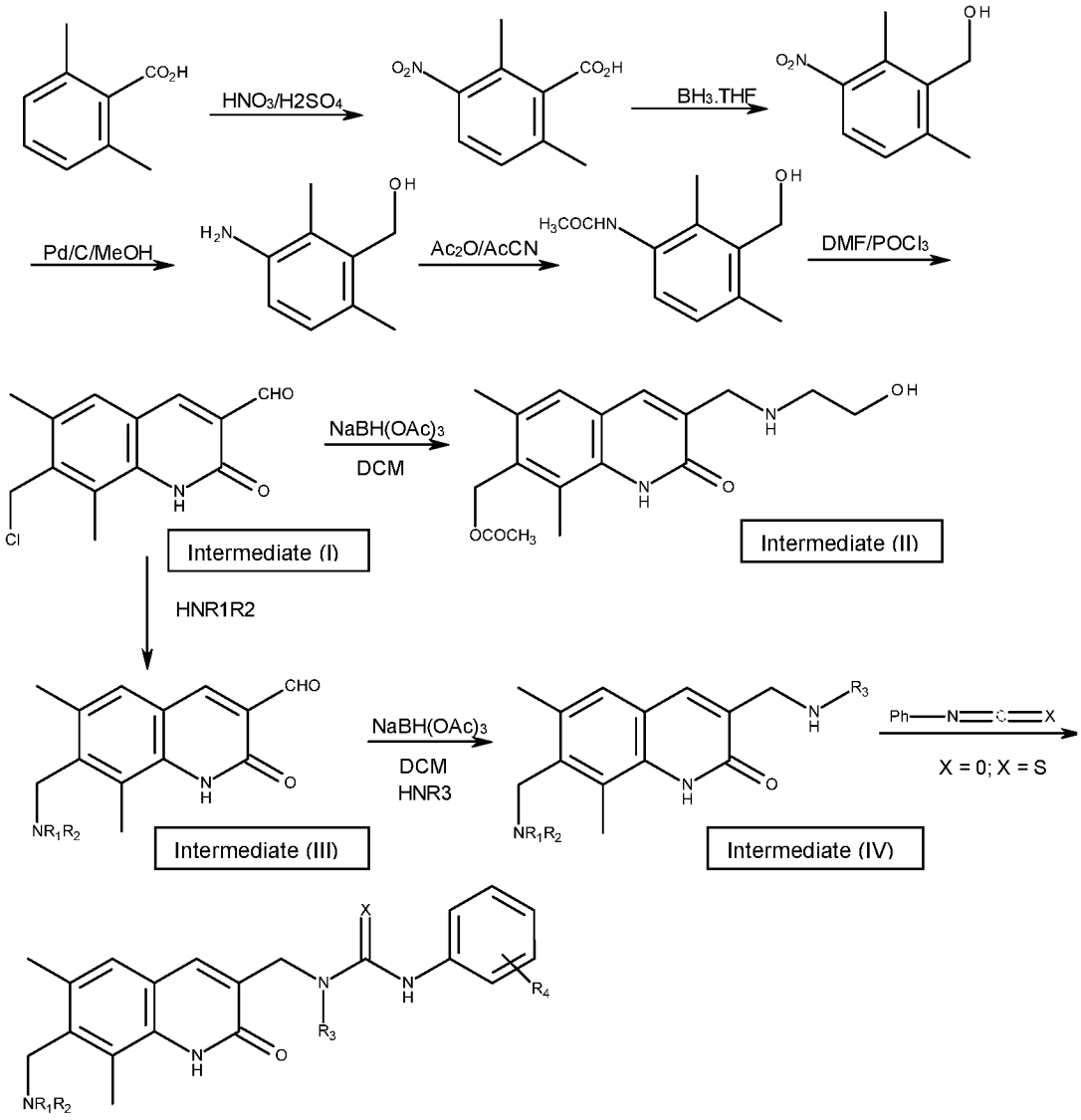
Examples

The present disclosure explicitly encompasses those compounds herein presented. A composition comprising a therapeutically acceptable amount of any of these compounds is also within the scope of the invention. The compounds may be synthesized using the techniques described and exemplified herein.

Substituent groups and variables used in the schemes of the present disclosure are not intended to be idenitical to the substitutent groups and variables used to define the compounds of Formula (I) and (IG) of the present disclosure. While not identical, the respective definitions are clear.

Schemes from PCT/US2018/048891, the entirety of which is herein incorporated by reference with regard to any synthetic teaching, may be useful for reference:

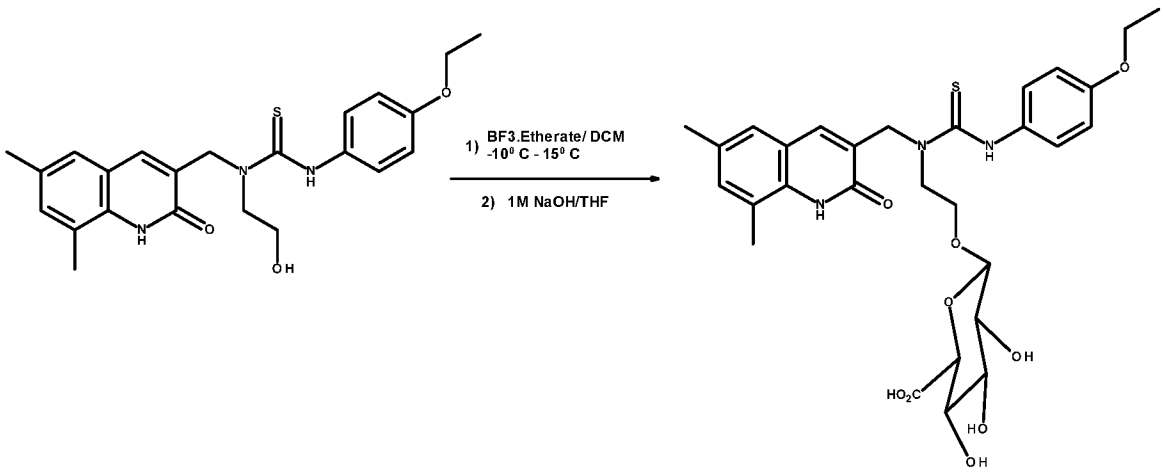
Synthesis Scheme 1:



2,6-dimethylbenzoic acid was treated with nitric acid/sulfuric acid to afford the nitro compound which was then subjected to borane reduction to provide the alcohol. The nitro group was then reduced and then acetylated tp provide the N-acetyl derivative. The N-acetylated compound was then subjected to DMF/POCl3 conditions to directly provide 7-(chloromethyl)-6,8-dimethyl-2-oxo-1H-quinoline-3-carbaldehyde (I). Intermediate (I) was then treated with ethanol amine to afford intermediate (II) or treated with various amines to afford intermediate (III). Intermediate (III) was subjected to reductive amination with various amines to afford intermediate (IV). Intermediate (IV) was then reacted with various isocyanates or isothiocyanates to provide the final compounds (V).

Synthesis Scheme 2:

Scheme for Inh-1 glucuronide synthesi



Inh-1 in dichloromethane was cooled to -10 degrees and was treated with 2,3,4-Tri-O-acetyl-1-O-trichloroacetimidoyl-α-D-glucopyranuronic acid methyl ester followed by borontrifluoride etherate solution. After stirring for 30 minutes the reaction was warmed to room temperature, stirred for 3 hours and then quenched with saturated $NaHCO_3$. After separation of the organics layer and drying, the crude reaction was taken to the next step. Hydrolysis of the acetate's and methyl ester with 1N NaOH afforded the desired Inh-1 glucuronide. LCMS (ESI) 602 (M+H).

Alternative glucuronide synthesis:

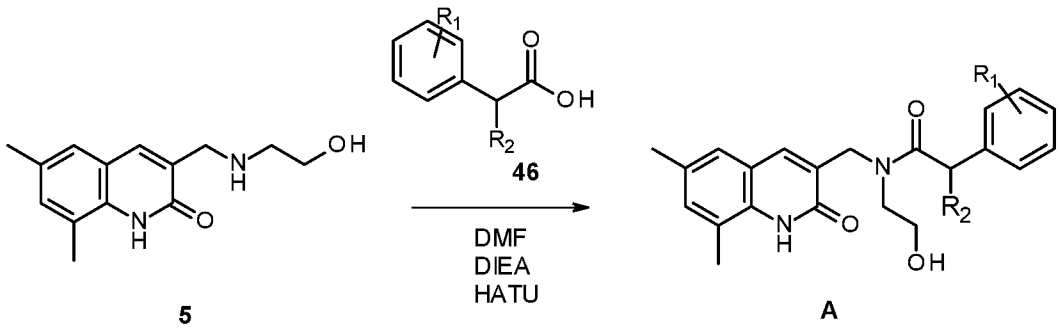
To generate inhibitor-glucuronides using non-chemical synthesis, biosynthetic techniques are utilized, using Corning® Supersomes™ UGT. UGT supersomes are baculovirus generated UGTs, and far more pure than normal microsomal fractions. Briefly, supersome activation requires alamethicin (pore forming molecule), UGT supersomes, BSA, microsome buffer (100 mM Tris ph 7.5, 100 mM NaCl) and $MgCl_2$. This mixture was incubated on ice for 30 minutes to allow for pore formation followed by addition of the acceptor parent drug substrate, incubated for an additional 5 minutes at 37 °C. Addition of the UGT cofactor UDP-glucuronic acid (UDP-GA) initiates the reaction, incubated at 37 °C, for an overnight incubation.

Since it was unclear which specific UGT form conjugates with the inhibitors, a master mix of all available UGTs was created (14 in total from both the UGT1 and UGT2 line) to use in the UGT reactions.

A UDP-Glo™ assay kit from Promega was used to quantitate the amount of inhibitor glucuronide production. A luciferase reaction detects the formation of UDP molecules, which is generated during the UGT reaction converting UDP-GA to UDP, in a one-to-one molar ratio as production of inhibitor-glucuronide.

Examples of Compound Synthesis

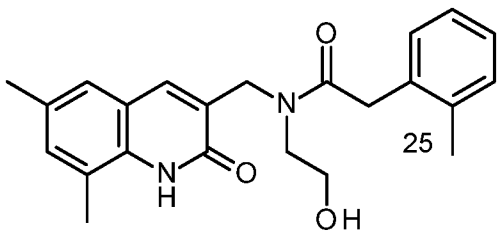
Scheme 3



General procedure for compounds with structure A: Compound 5 (0.1 g, 0.4 mmol) was dissolved in DMF (2 ml), then DIEA (0.1 ml, 0.6 mmol), compound 46 (1 eq), and HATU (0.18 g, 0.48 mmol) were added. The mixture was stirred at room temperature overnight. Ethyl acetate and water were added to the reaction mixture and the organic layer was separated, dried over MgSO4 and the solvent removed. The crude was purified by column chromatography (12 g, silica gel) using gradient MeOH/DCM 0 to 4 % to give compound A.

The following compounds were synthesized according to the general procedure.

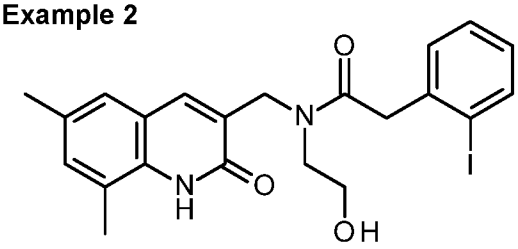
Example 1



Example 1

N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)-2-(o-tolyl)acetamide: LCMS ESI (M+H) 379

Example 2

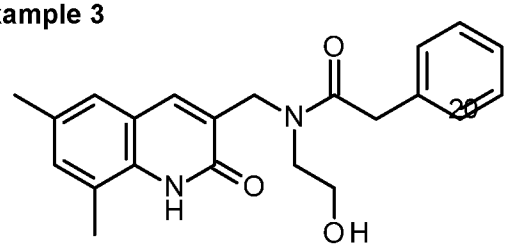


Example 2

N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)-2-(2-iodophenyl)acetamide:

1H NMR (500 MHz, DMSO-d_6) δ ppm 2.25 - 2.32 (m, 3 H) 2.35 - 2.41 (m, 3 H) 3.39 - 3.68 (m, 4 H) 3.80 - 4.03 (m, 1 H) 4.38 - 4.56 (m, 1 H) 6.92 - 7.02 (m, 1 H) 7.11 - 7.18 (m, 1 H) 7.22 - 7.36 (m, 2 H) 7.55 - 7.61 (m, 1 H) 7.66 - 7.71 (m, 1 H) 7.74 - 7.89 (m, 1 H) 10.91 - 11.05 (m, 1 H); LCMS ESI (M+H) 491

Example 3

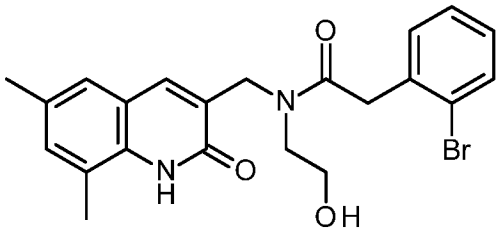


Example 3

N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)-2-phenyl-acetamide:

1H NMR (500 MHz, DMSO-d_6) δ ppm 2.25 - 2.31 (m, 3 H) 2.35 - 2.39 (m, 3 H) 3.34 - 3.59 (m, 4 H) 3.70 - 3.89 (m, 2 H) 4.34 - 4.51 (m, 2 H) 7.07 (s, 1 H) 7.11 - 7.20 (m, 2 H) 7.22 - 7.36 (m, 5 H) 10.81 - 11.14 (m, 1 H); LCMS ESI (M+H) 365.

Example 4

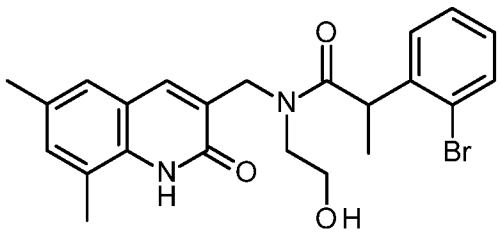


Example 4

2-(2-bromophenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)acetamide:

1H NMR (500 MHz, DMSO-d_6) δ ppm 2.28 - 2.30 (m, 3 H) 2.37 - 2.40 (m, 3 H) 3.38 - 3.70 (m, 4 H) 3.81 - 4.08 (m, 2 H) 4.31 - 4.58 (m, 2 H) 7.09 - 7.23 (m, 3 H) 7.25 - 7.39 (m, 3 H) 7.48 - 7.69 (m, 2 H) 10.94 (br. s., 1 H); LCMS ESI (M+H) 443.

Example 5

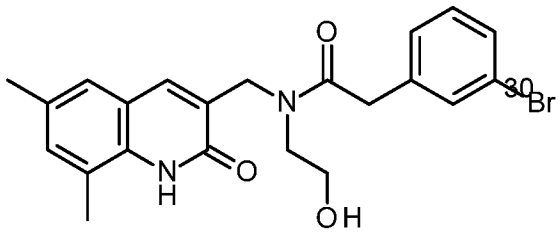


Example 5

2-(2-bromophenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)propanamide:

LCMS ESI (M+H) 457, 459.

Example 6

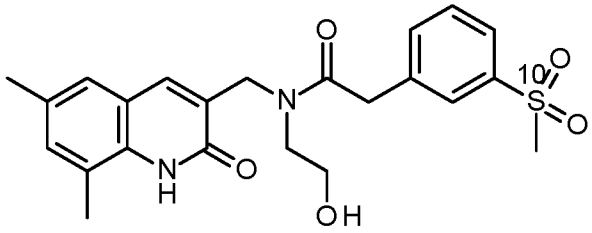


Example 6

2-(3-bromophenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)acetamide:

1H NMR (500 MHz, DMSO-d_6) δ ppm 2.28 (s, 3 H) 2.36 - 2.40 (m, 3 H) 3.38 - 3.64 (m, 4 H) 3.75 - 3.93 (m, 2 H) 4.35 - 4.54 (m, 2 H) 7.10 - 7.21 (m, 2 H) 7.26 - 7.39 (m, 3 H) 7.42 - 7.54 (m, 2 H) 10.87 - 11.07 (m, 1 H); LCMS ESI (M+H) 443,445.

Example 7

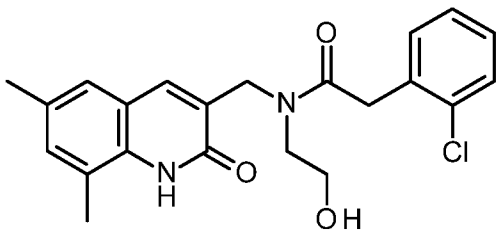


Example 7

N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)-2-(3-methylsulfonylphenyl)acetamide:

1H NMR (500 MHz, DMSO-d_6) δ ppm 2.25 - 2.29 (m, 3 H) 2.34 - 2.38 (m, 3 H) 3.13 - 3.16 (m, 3 H) 3.17 - 3.19 (m, 1 H) 3.35 - 3.63 (m, 4 H) 3.88 - 4.07 (m, 2 H) 4.30 - 4.58 (m, 2 H) 7.10 - 7.41 (m, 2 H) 7.45 - 7.63 (m, 3 H) 7.68 - 7.85 (m, 2 H) 10.90 (br. s., 1 H); LCMS ESI (M+H) 443.

Example 8

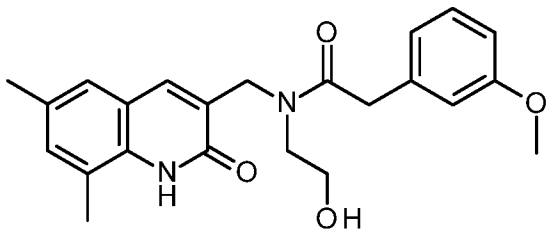


Example 8

2-(2-chlorophenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)acetamide:

LCMS ESI (M+H) 399.

Example 9

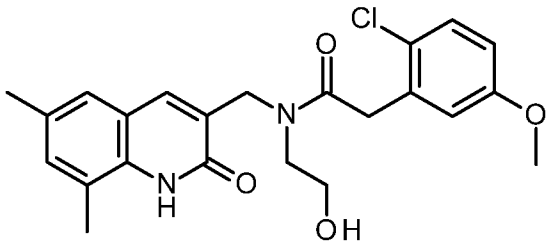


Example 9

N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)-2-(3-methoxyphenyl)acetamide:

LCMS ESI (M+H) 395.

Example 10

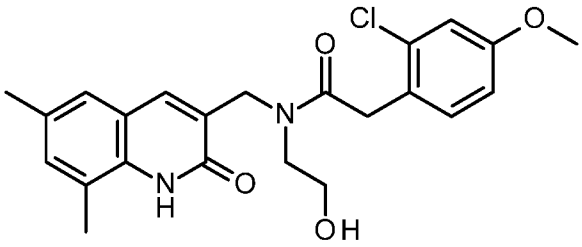


Example 10

2-(2-chloro-5-methoxy-phenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)acetamide:

1H NMR (500 MHz, DMSO-d_6) δ ppm 2.29 - 2.36 (m, 3 H) 2.41 - 2.46 (m, 3 H) 3.40 - 3.71 (m, 4 H) 3.76 (s, 3 H) 3.84 - 4.05 (m, 2 H) 4.42 - 4.63 (m, 2 H) 6.81 - 6.99 (m, 2 H) 7.17 - 7.40 (m, 3 H) 7.51 - 7.70 (m, 1 H) 10.89 - 11.19 (m, 1 H); LCMS ESI (M+H) 429, 431.

Example 11

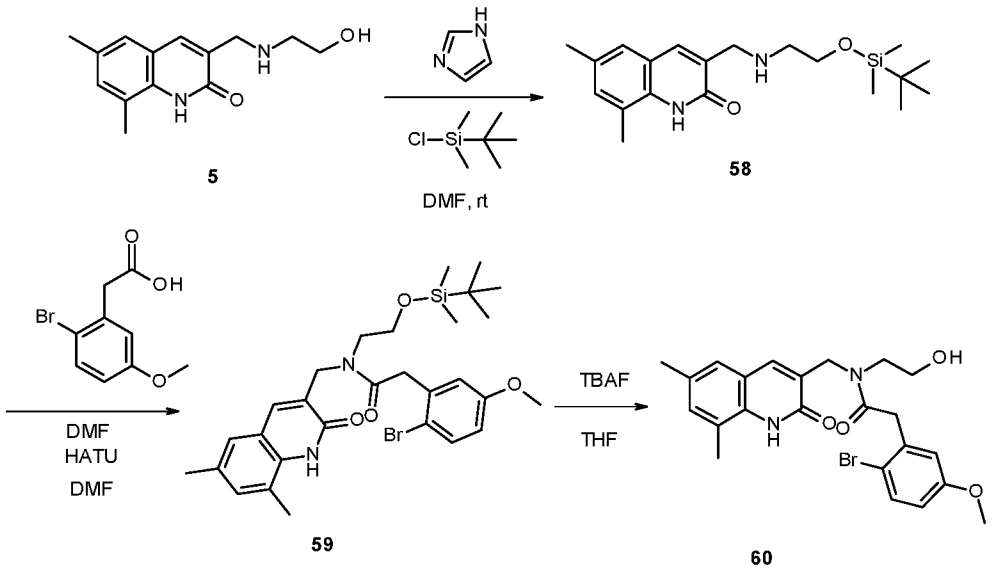


Example 11

2-(2-chloro-4-methoxy-phenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)acetamide:

1H NMR (500 MHz, DMSO-d_6) δ ppm 2.25 - 2.32 (m, 3 H) 2.35 - 2.41 (m, 3 H) 3.35 - 3.63 (m, 4 H) 3.66 - 3.95 (m, 5 H) 4.30 - 4.57 (m, 2 H) 6.80 - 7.05 (m, 2 H) 7.04 - 7.60 (m, 4 H) 10.88 - 11.07 (m, 1 H); LCMS ESI (M+H) 429.

Scheme 4



Compound 58, Scheme 4

3-[[2-[tert-butyl(dimethyl)silyl]oxyethylamino]methyl]-6,8-dimethyl-1H-quinolin-2-one: To a solution of compound 5 (0.6 g, 2.4 mmol) in DMF (6 mL) was added imidazole (0.4 g, 0.06 mol) and TBDMS-Cl (0.44 g, 2.9 mmol) and the mixture stirred at rt overnight. Then more imidazole (0.4 g) and TBDMS-Cl (0.44 g) were added and

the mixture stirred at rt overnight. Water (100 mL) and ethyl acetate (200 mL) were added to the reaction mixture. The organic layer was separated and washed with water, dried over $MgSO_4$, filtered and solvent evaporated under reduced pressure. The crude was purified by silica plug using gradient MeOH/DCM 0 to 10% to give 660 mg of compound 58 as a yellow solid (75%). LCMS ESI (M+H)

Compound 59, Scheme 4

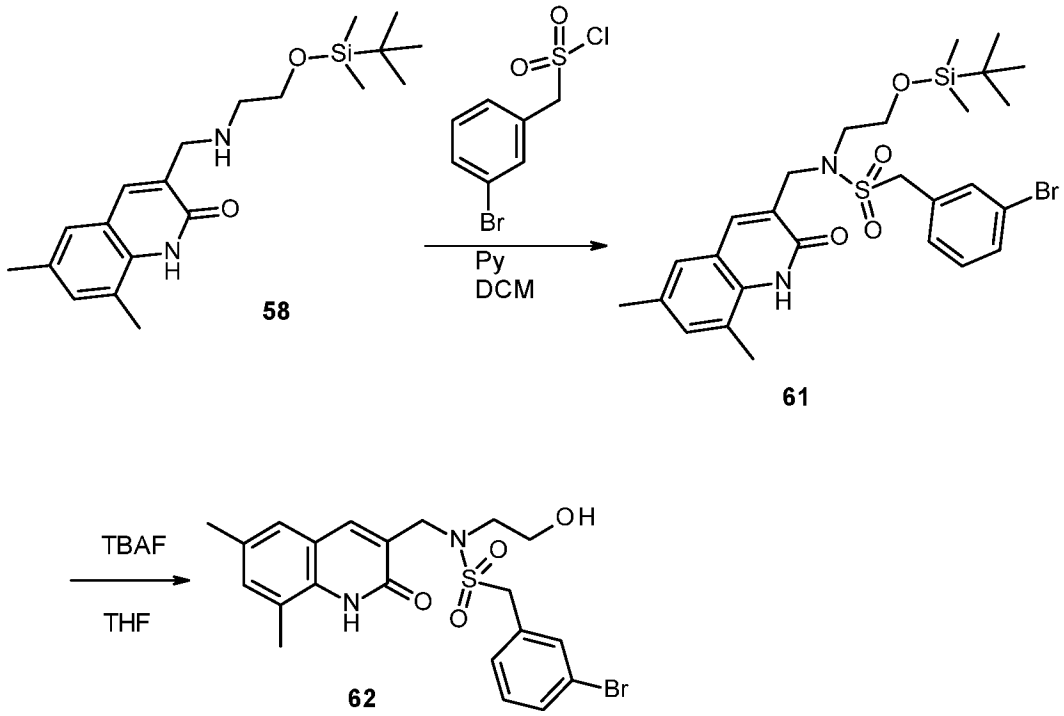
2-(2-bromo-5-methoxy-phenyl)-N-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]acetamide: Compound 5 (0.075 g, 0.2 mmol) was dissolved in DMF (2 ml), then DIEA (0.05 ml, 0.3 mmol), 2-(2-bromo-5-methoxy-phenyl)acetic acid (0.051, 0.2 mmol), and HATU (0.091 g, 0.24 mmol) were added. The mixture was stirred at room temperature overnight. Ethyl acetate and water were added to the reaction mixture and the organic layer was separated, dried over MgSO4 and the solvent removed to give crude 59 as a yellow oil. LCMS ESI (M+H) 587

Example 12

2-(2-bromo-5-methoxy-phenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)acetamide: To a solution of crude 59 in THF (3 mL), was added 0.19 g of TBAF. $3H_2O$ (3 eq assuming 100% yield for 59) and the mixture was stirred at rt for 1 hour. Then water ansd ethyl acetate added, the organic layer was separated, dried over MgSO4 and solvent evaporated under reduced pressure. The crude was purified by column chromatography (silica gel, 12 g) using gradient MeOH/DCM 0-12 % to give 100 mg of compound 60 as a white solid (~100%) from compound 58).

1H NMR (500 MHz, DMSO-d_6) δ ppm 2.24 - 2.28 (m, 3 H) 2.32 - 2.38 (m, 3 H) 3.46 - 3.62 (m, 4 H) 3.67 (s, 3 H) 3.74 - 4.00 (m, 2 H) 4.26 - 4.52 (m, 2 H) 6.61 - 6.91 (m, 2 H) 7.08 - 7.68 (m, 4 H) 10.82 - 11.05 (m, 1 H); LCMS ESI (M+H) 473.

Scheme 5



Compound 61, Scheme 5

1-(3-bromophenyl)-N-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]methanesulfonamide: To a solution of compound 58 (0.1 g, 0.28 mmol) in DCM (2 mL) was added pyridine (0.135 mL, 0.0017 mol) and (3-bromophenyl)methanesulfonyl chloride (0.11 g, 0.42 mmol) and the reaction mixture was stirred at room temperature overnight. Water was added and the organic layer separated. The aqueous layer was extracted with ethyl acetate, organic layers combined, dried over $MgSO_4$ and concentrated under reduced pressure to give crude 61 as a white solid (170 mg). LCMS ESI (M+H) 593.

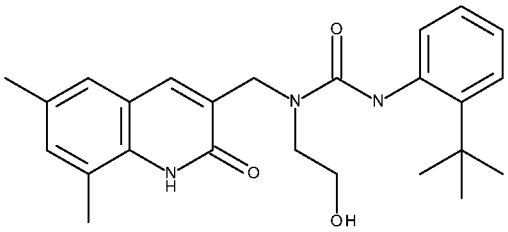
Example 13

1-(3-bromophenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)methanesulfonamide: To a solution of crude 61 in THF (3 mL), was added 0.18 g of TBAF. $3H_2O$ (3 eq assuming 100% yield for 61) and the mixture was stirred at rt overnight. Then water and ethyl acetate added, the organic layer was separated, dried over MgSO4 and solvent evaporated under reduced pressure. The crude was purified by column chromatography (silica gel, 12 g) using gradient

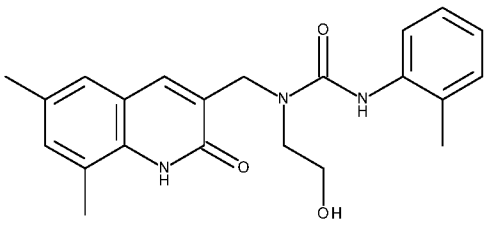
MeOH/DCM 0-5 % to give 8 mg of compound 62 as a white solid (6%) from compound 58. LCMS ESI (M+H) 479.

With reference to the general synthetic description provided in PCT/US2018/48891, herein incorporated by reference with regard to such teaching, the following additional compounds were made:

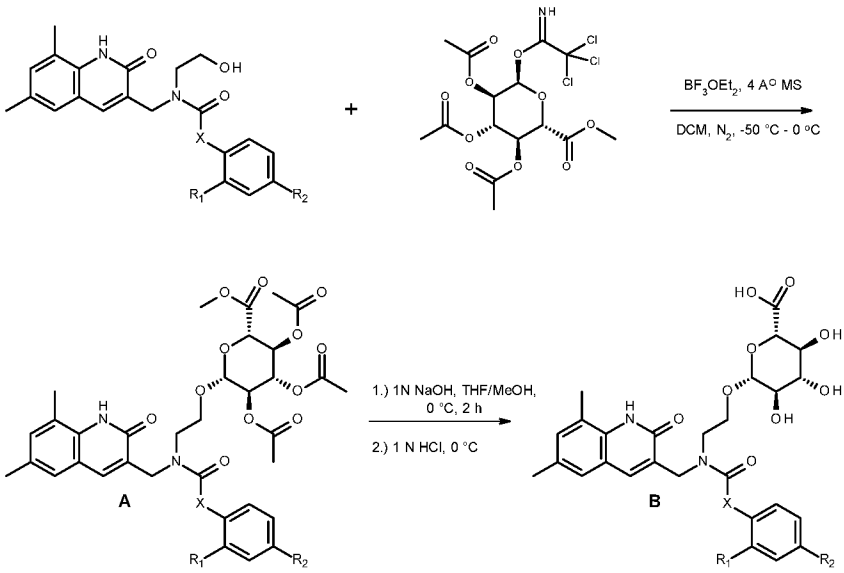
Example 14



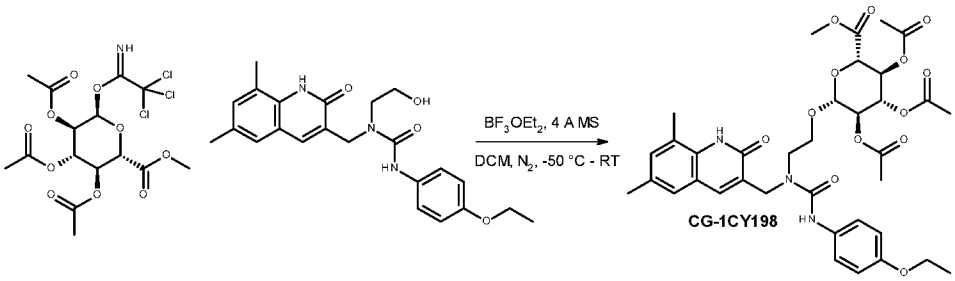
Example 15



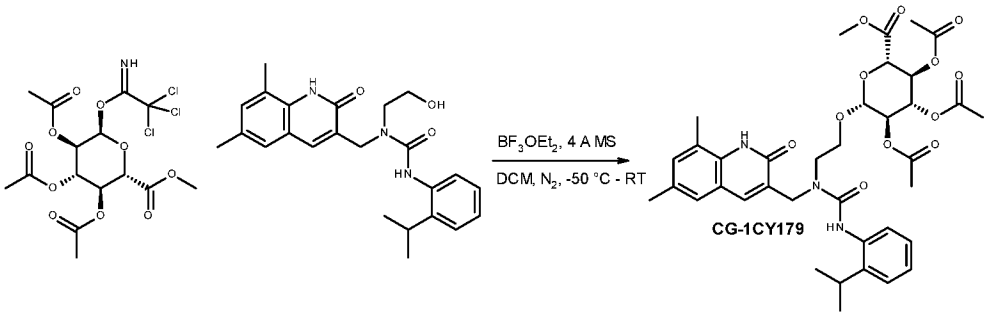
Scheme 6:



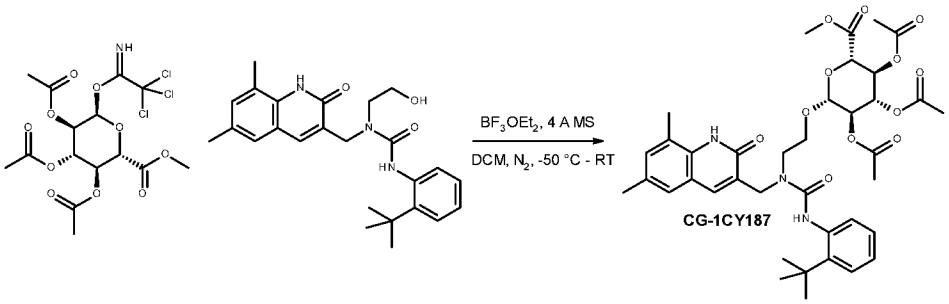
General Glucuronidation Procedure: The (2-hydroxyethyl) intermediate **3X** (1.1 mmol) and methyl 2,3,4-tri-*O*-acetyl-1-*O*-(trichloroacetimidoyl)-α-D-glucuronate (1.26 mmol) are dissolved in anhydrous DCM (20 mL/1 mmol of **3x**) in the presence of oven-dried 4 Å molecular sieve. The reaction is stirred at RT for 30 minutes and then cooled at -50 °C for 15 minutes. A solution of BF_3-etherate (1.1 mmol) in anhydrous DCM (2 mL) is added dropwise via a syringe. The reaction is stirred while warming to RT over 2 h as the chalky solution tuned clear, then quenched with saturated $NaHCO_3$ and extracted with DCM, washed with brine, dried over $MgSO_4$ and evaporated. Purification by flash chromatography (silica gel, 0-100% EA/Hexanes) provided the desired product as a white solid; yield 45-80%.



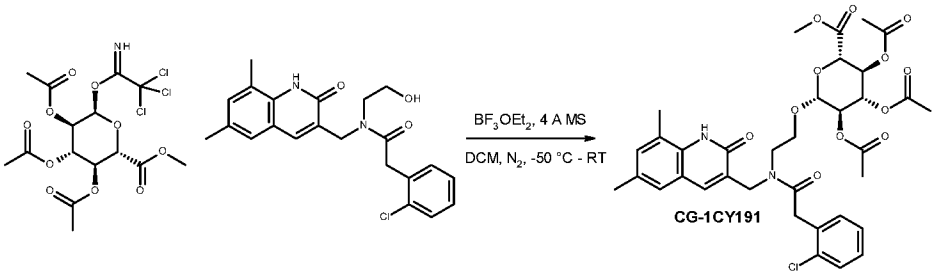
CG-1CY198: Methyl (2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-[2-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl-[(4-ethoxyphenyl)carbamoyl]amino]ethoxy]tetrahydropyran-2-carboxylate. 1H NMR (500 MHz, DMSO-d 6) δ ppm 1.28 (t, J=7.09 Hz, 3 H) 1.94 (s, 3 H) 1.97 (s, 3 H) 1.98 (s, 3 H) 2.30 (s, 3 H) 2.41 (s, 3 H) 3.38 - 3.52 (m, 2 H) 3.61 (s, 3 H) 3.68 - 3.75 (m, 1 H) 3.83 - 3.90 (m, 1 H) 3.94 (q, J=7.01 Hz, 2 H) 4.01 (q, J=7.34 Hz, 1 H) 4.32 - 4.39 (m, 1 H) 4.40 - 4.48 (m, 2 H) 4.78 - 4.84 (m, 1 H) 4.90 4.97 (m, 2 H) 5.33 (t, J=9.54 Hz, 1 H) 6.80 (d, J=8.80 Hz, 2 H) 7.20 (s, 1 H) 7.31 (d, J=8.80 Hz, 2 H) 7.35 (s, 1 H) 7.78 (s, 1 H) 11.29 (br. s., 1 H); LCMS ESI (M+H) 726.4.



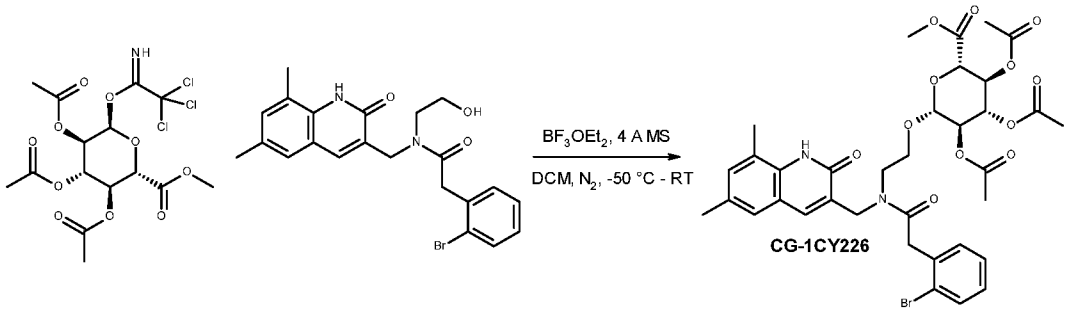
CG-1CY179: Methyl (2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-[2-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl-[(2-isopropylphenyl)carbamoyl]amino]ethoxy]tetrahydropyran-2-carboxylate. 1H NMR (500 MHz, DMSO-d 6) δ ppm 1.09 (d, J=6.85 Hz, 6 H) 1.95 (s, 3 H) 1.97 (s, 3 H) 2.00 (s, 3 H) 2.31 (s, 3 H) 2.41 (s, 3 H) 3.13 - 3.21 (m, 1 H) 3.42 - 3.52 (m, 2 H) 3.60 (s, 3 H) 3.72 (ddd, J=11.00, 5.87, 5.62 Hz, 2 H) 3.89 (ddd, J=10.15, 5.01, 4.89 Hz, 1 H) 4.01 (q, J=6.85 Hz, 1 H) 4.35 - 4.41 (m, 1 H) 4.43 - 4.51 (m, 2 H) 4.79 - 4.85 (m, 1 H) 4.91 - 4.98 (m, 2 H) 5.35 (t, J=9.54 Hz, 1 H) 7.06 - 7.11 (m, 2 H) 7.19 (s, 1 H) 7.20 - 7.25 (m, 2 H) 7.32 (s, 1 H) 7.74 (br. s., 1 H) 11.17 (br. s., 1 H); LCMS ESI (M+H) 724.8.



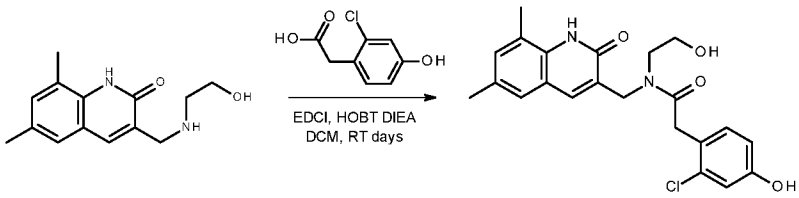
CG-1CY187: Methyl (2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-[2-[(2-tert-butylphenyl)carbamoyl-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]amino]ethoxy]tetrahydropyran-2-carboxylate. 1H NMR (500 MHz, DMSO-d 6) δ ppm 1.31 (s, 9 H) 1.95 (s, 3 H) 1.97 (s, 3 H) 2.01 (s, 3 H) 2.31 (s, 3 H) 2.39 (s, 3 H) 3.41 - 3.48 (m, 1 H) 3.50 - 3.58 (m, 1 H) 3.60 (s, 3 H) 3.67 - 3.74 (m, 1 H) 3.89 (ddd, J=10.15, 5.01, 4.89 Hz, 1 H) 4.39 (d, J=17.12 Hz, 1 H) 4.45 (d, J=10.27 Hz, 1 H) 4.50 (d, J=17.12 Hz, 1 H) 4.79 - 4.83 (m, 1 H) 4.90 - 4.97 (m, 2 H) 5.33 (t, J=9.54 Hz, 1 H) 7.01 - 7.06 (m, 1 H) 7.12 - 7.16 (m, 2 H) 7.19 (s, 1 H) 7.30 7.35 (m, 2 H) 7.73 (br. s., 1 H) 11.13 (br. s., 1 H); LCMS ESI (M+H) 738.3.



CG-1CY191: Methyl (2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-[2-[[2-(2-chlorophenyl)acetyl]-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]amino]ethoxy]tetrahydropyran-2-carboxylate. 1H NMR (500 MHz, DMSO-d 6) δ ppm 1.88 - 2.03 (m, 9 H) 2.30 (d, J=2.93 Hz, 3 H) 2.38 (d, J=9.29 Hz, 3 H) 3.59 (d, J=15.65 Hz, 3 H) 3.72 - 4.01 (m, 6 H) 4.32 - 4.56 (m, 4 H) 4.86 - 5.01 (m, 2 H) 7.11 - 7.44 (m, 8 H) 7.45 - 7.69 (m, 2 H) 10.93 - 11.11 (m, 2 H); LCMS ESI (M+H) 715.4.

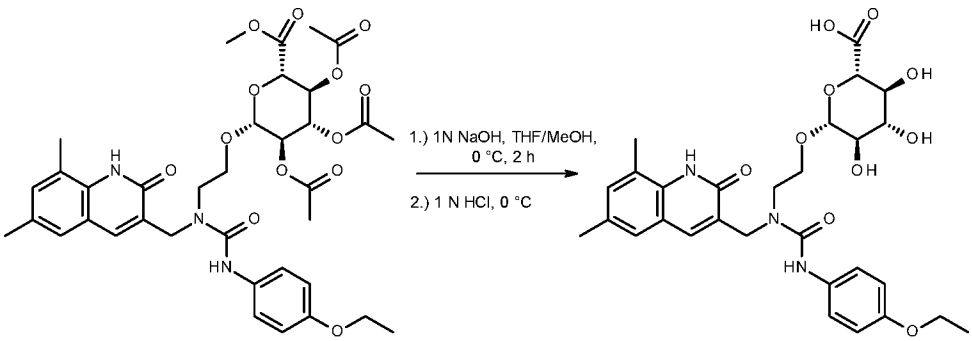


CG-1CY226: Methyl (2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-[2-[[2-(2-bromophenyl)acetyl]-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]amino]ethoxy]tetrahydropyran-2-carboxylate. 1H NMR (500 MHz, DMSO-d 6) δ ppm 2.29 (br. s., 4 H) 2.30 (br. s., 3 H) 2.37 (s, 3 H) 2.39 (s, 3 H) 3.58 (s, 3 H) 3.61 (s, 3 H) 3.88 (d, J=15.65 Hz, 2 H) 4.31 - 4.39 (m, 2 H) 4.41 - 4.49 (m, 2 H) 4.87 - 5.00 (m, 4 H) 5.29 5.38 (m, 2 H) 7.16 - 7.21 (m, 3 H) 7.30 (dd, J=11.49, 3.67 Hz, 2 H) 7.51 - 7.59 (m, 2 H) 7.65 - 7.70 (m, 1 H) 10.93 - 11.06 (m, 1 H); LCMS ESI (M+H) 759.5.

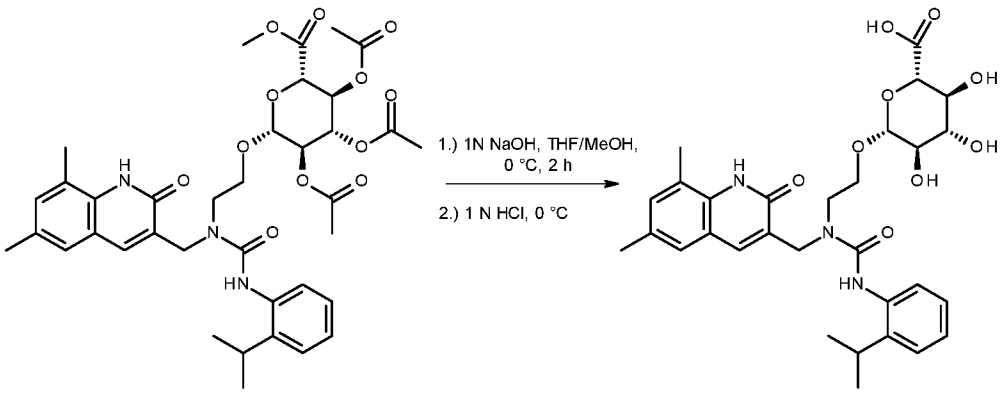


1CY225: 2-(2-chloro-4-hydroxy-phenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)acetamide. The coupling of 3-[(2-hydroxyethylamino)methyl]-6,8-dimethyl-1H-quinolin-2-one (60 mg, 0.2 mmol) with 2-(2-chloro-4-hydroxy-phenyl)acetic acid (37 mg, 0.2 mmol) in the presence of EDCI, HOBt And Hunig's base is currently progressing very sluggishly.

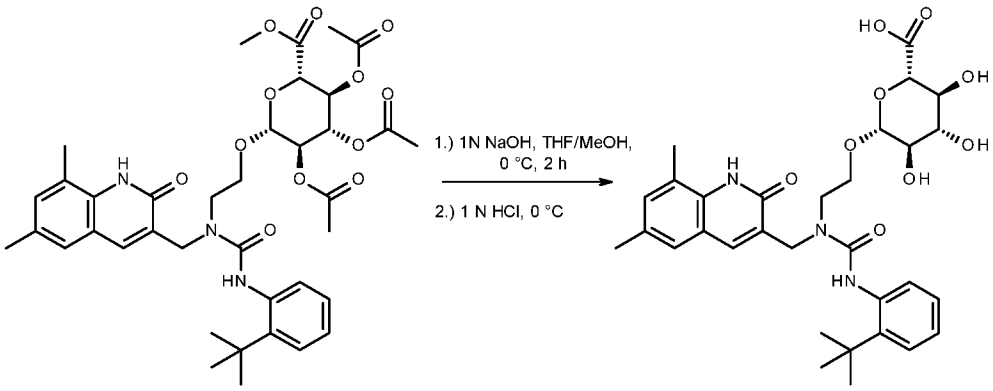
Representative Procedure for the Hydrolysis of the Methyl ester and the Acetyl Groups of the Glucuronic Acid Unit: The glucuronidtion products **A** (0.4 mmol) in a mixture of THF/MeOH (6:1; 21 mL) at 0 °C is treated slowly with 1 N NaOH (6 mL). The reaction is stirred in an ice-water bath for 2 h and the organic solvents removed *in vacuo* (no heat). The aqueous residue (a white suspension) is neutralized to pH 7 with1 N HCl, then chilled at -78 °C and lyophilized to give the sodium salt of the desired product as a white solid.



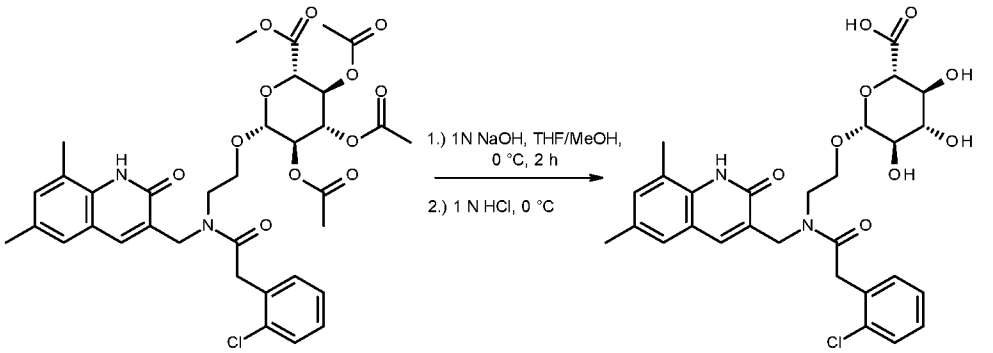
CG-1CY199: (2S,3S,4S,5R,6R)-6-[2-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl-[(4-ethoxyphenyl)carbamoyl]amino]ethoxy]-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid. 1H NMR (500 MHz, DMSO-d6) δ ppm 1.28 (t, J=6.85 Hz, 3 H) 2.29 (s, 3 H) 2.40 (s, 3 H) 2.97 (t, J=8.31 Hz, 1 H) 3.07 - 3.12 (m, 1 H) 3.16 (t, J=8.56 Hz, 1 H) 3.25 (d, J=9.78 Hz, 2 H) 3.44 - 3.50 (m, 2 H) 3.58 (d, J=3.91 Hz, 2 H) 3.78 (ddd, J=10.88, 5.62, 5.50 Hz, 1 H) 3.85 (ddd, J=10.52, 5.62, 5.38 Hz, 1 H) 3.94 (q, J=7.17 Hz, 2 H) 4.21 (d, J=7.83 Hz, 1 H) 4.46 (s, 2 H) 4.98 - 5.25 (m, 2 H) 6.78 (d, J=9.29 Hz, 2 H) 7.18 (s, 1 H) 7.33 (d, J=8.80 Hz, 2 H) 7.41 (s, 1 H) 7.96 (br. s., 1 H) 9.42 (br. s., 1 H) 11.24 (br. s., 1 H); LCMS ESI (M+H) 586.1.



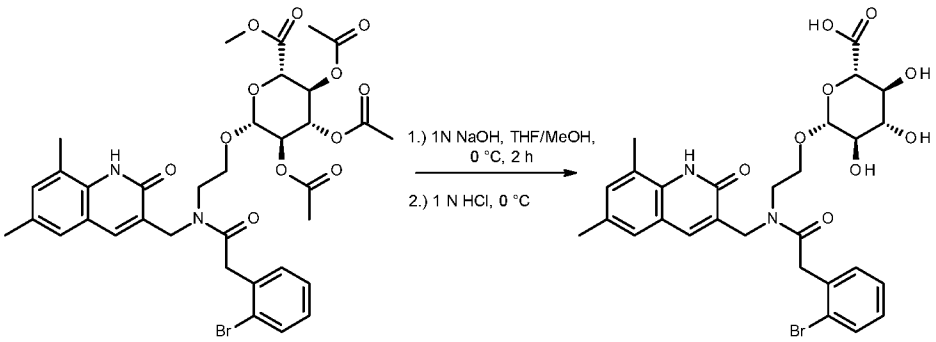
CG-1CY185: (2S,3S,4S,5R,6R)-6-[2-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl-[(2-isopropylphenyl)carbamoyl]amino]ethoxy]-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid. 1H NMR (500 MHz, DMSO-d6) δ ppm 1.10 (d, 6 H) 2.30 (s, 3 H) 2.40 (s, 3 H) 2.99 (t, J=8.07 Hz, 1 H) 3.05 3.10 (m, 1 H) 3.14 (d, J=8.80 Hz, 1 H) 3.16 - 3.21 (m, 1 H) 3.22 (d, J=9.78 Hz, 1 H) 3.51 (br. s., 2 H) 3.70 3.77 (m, 1 H) 3.84 - 3.90 (m, 1 H) 4.19 (d, J=7.83 Hz, 1 H) 4.44 - 4.56 (m, 3 H) 5.07 (br. s., 1 H) 5.17 (br. s., 1 H) 7.05 - 7.09 (m, 2 H) 7.17 (br. s., 1 H) 7.20 - 7.24 (m, 2 H) 7.36 (br. s., 1 H) 7.91 (br. s., 1 H) 8.79 (br. s., 1 H) 11.15 (br. s., 1 H); LCMS ESI (M+H) 584.4.



1CY188: (2S,3S,4S,5R,6R)-6-[2-[(2-tert-butylphenyl)carbamoyl-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]amino]ethoxy]-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid. 1H NMR (500 MHz, DMSO-d6) δ ppm 1.33 (s, 9 H) 2.31 (s, 3 H) 2.39 (s, 3 H) 2.95 (t, J=8.31 Hz, 1 H) 3.02 3.08 (m, 1 H) 3.10 - 3.15 (m, 1 H) 3.17 - 3.23 (m, 1 H) 3.55 (d, J=7.34 Hz, 2 H) 3.68 - 3.75 (m, 1 H) 3.83 3.90 (m, 1 H) 4.17 (d, J=7.83 Hz, 1 H) 4.46 - 4.59 (m, 2 H) 5.00 (br. s., 1 H) 5.08 (br. s., 1 H) 7.02 - 7.06 (m, 1 H) 7.10 - 7.15 (m, 2 H) 7.17 (br. s., 1 H) 7.27 - 7.41 (m, 2 H) 7.92 (br. s., 1 H) 8.58 (s, 1 H) 11.14 (s, 1 H); LCMS ESI (M+H) 598.7.

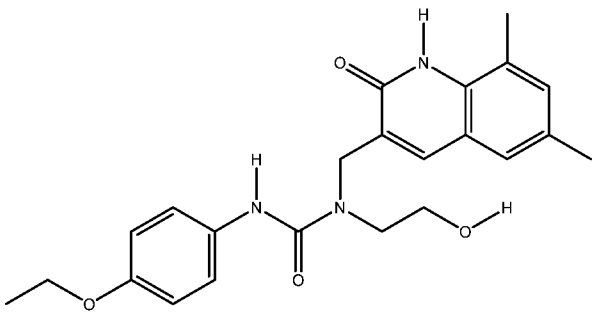


1CY192: (2S,3S,4S,5R,6R)-6-[2-[[2-(2-chlorophenyl)acetyl]-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]amino]ethoxy]-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid. 1H NMR (500 MHz, DMSO-d6) δ ppm 2.29 (br. s., 3 H) 2.39 (d, J=7.83 Hz, 3 H) 2.89 - 2.95 (m, 1 H) 2.99 3.06 (m, 2 H) 3.06 - 3.11 (m, 1 H) 3.14 (dd, J=9.54, 5.14 Hz, 2 H) 3.49 - 3.56 (m, 1 H) 3.62 (d, J=5.38 Hz, 1 H) 3.66 - 3.76 (m, 1 H) 3.84 (d, J=5.87 Hz, 1 H) 3.93 (br. s., 1 H) 4.08 (br. s., 1 H) 4.09 - 4.21 (m, 1 H) 4.30 4.47 (m, 1 H) 4.59 (d, J=7.83 Hz, 1 H) 5.00 - 5.45 (m, 2 H) 7.13 (br. s., 1 H) 7.20 - 7.29 (m, 2 H) 7.30 - 7.42 (m, 2 H) 7.51 - 7.79 (m, 1 H) 10.99 (br. s., 1 H); LCMS ESI (M+H) 575.4.



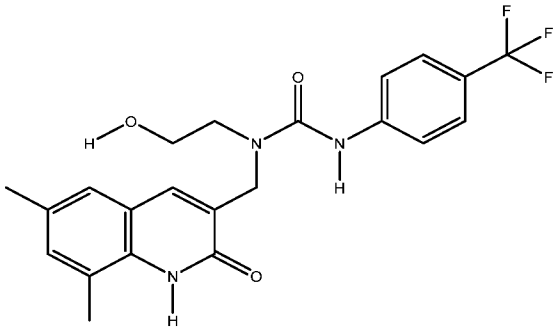
1CY228: (2S,3S,4S,5R,6R)-6-[2-[[2-(2-bromophenyl)acetyl]-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]amino]ethoxy]-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid. 1H NMR (500 MHz, DMSO-d6) δ ppm .....; LCMS ESI (M+H) 519.3.

Example 16



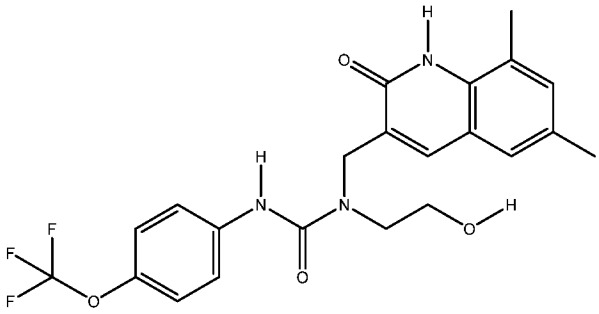
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-3-(4-ethoxyphenyl)-1-(2-hydroxyethyl)urea

Example 17



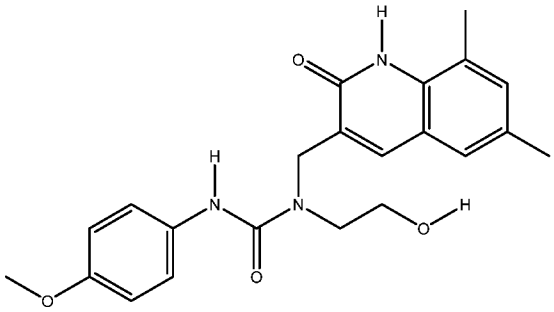
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(4-(trifluoromethyl)phenyl)urea

Example 18



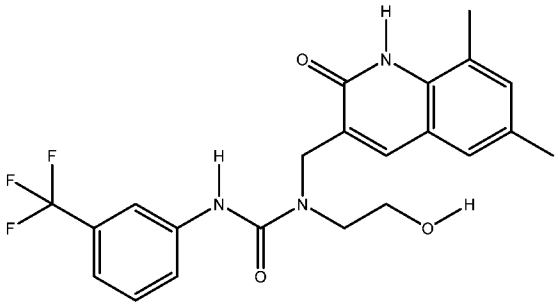
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(4-(trifluoromethoxy)phenyl)urea

Example 19



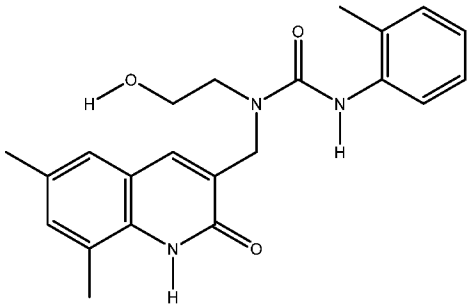
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(4-methoxyphenyl)urea

Example 20



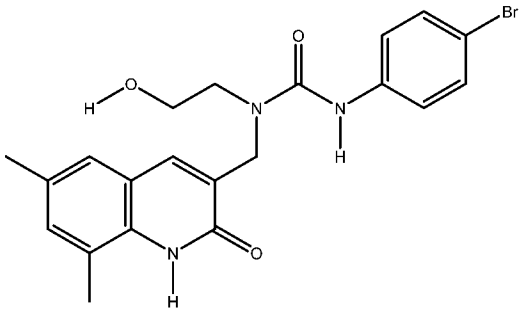
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(3-(trifluoromethyl)phenyl)urea

Example 21



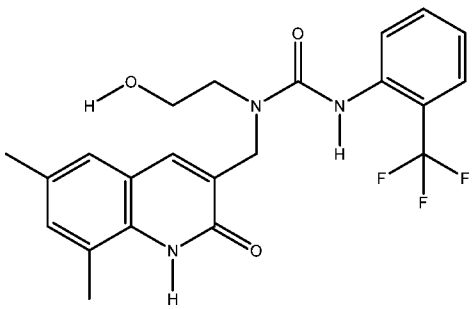
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(o-tolyl)urea

Example 22



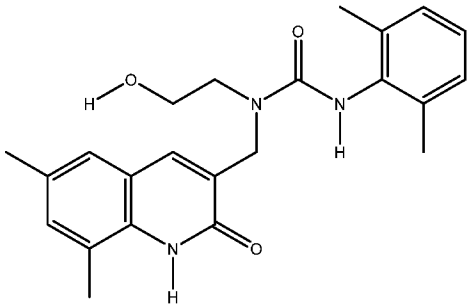
3-(4-bromophenyl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea

Example 23



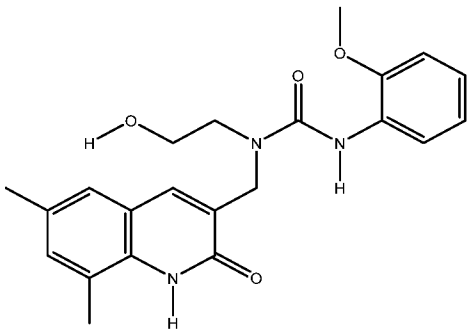
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(2-(trifluoromethyl)phenyl)urea

Example 24



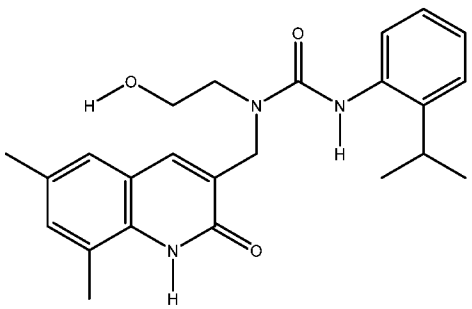
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-3-(2,6-dimethylphenyl)-1-(2-hydroxyethyl)urea

Example 25



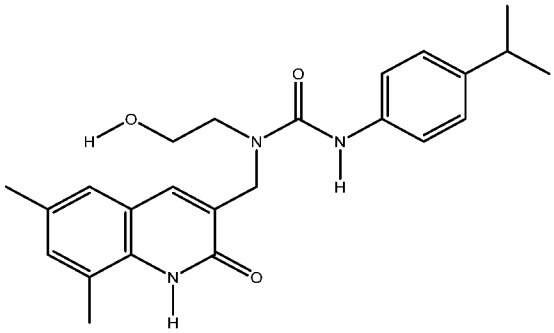
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(2-methoxyphenyl)urea

Example 26



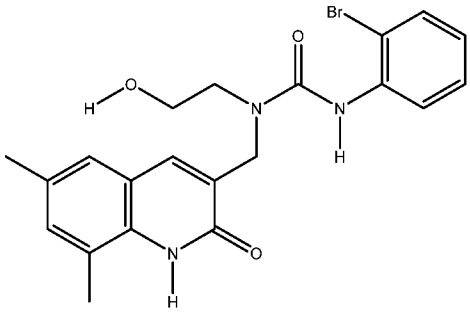
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(2-isopropylphenyl)urea

Example 27



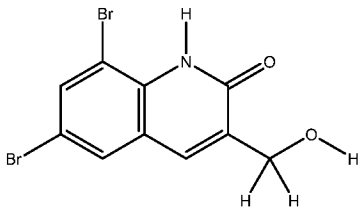
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(4-isopropylphenyl)urea

Example 28



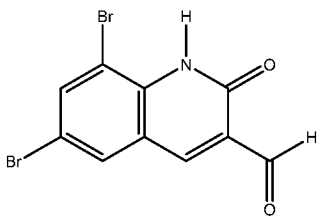
3-(2-bromophenyl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea

Example 29



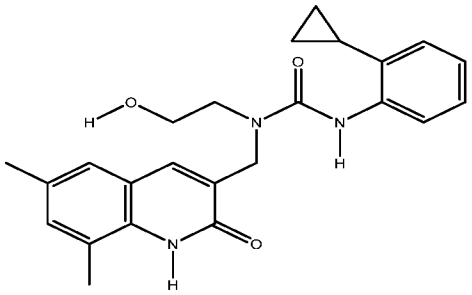
6,8-dibromo-3-(hydroxymethyl)quinolin-2(1H)-one

Example 30



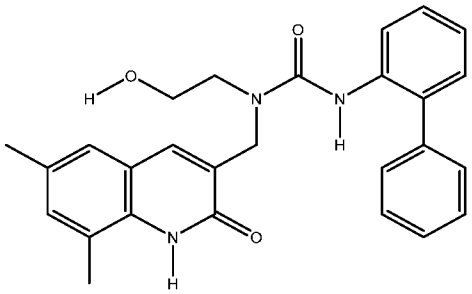
6,8-dibromo-2-oxo-1,2-dihydroquinoline-3-carbaldehyde

Example 31



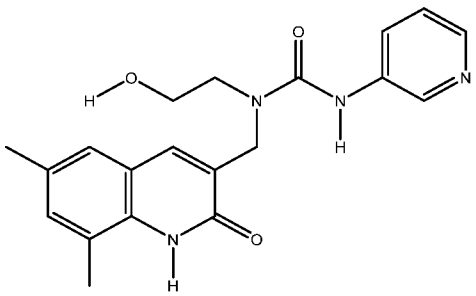
3-(2-cyclopropylphenyl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea

Example 32



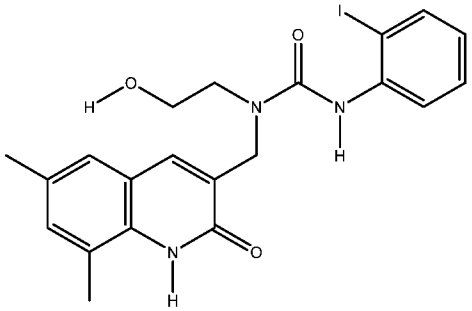
3-([1,1'-biphenyl]-2-yl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea

Example 33



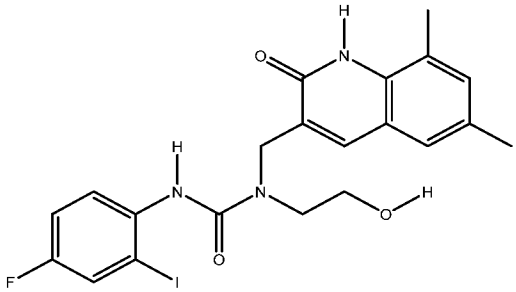
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(pyridin-3-yl)urea

Example 34



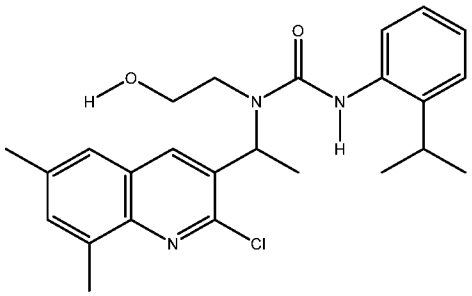
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(2-iodophenyl)urea

Example 35



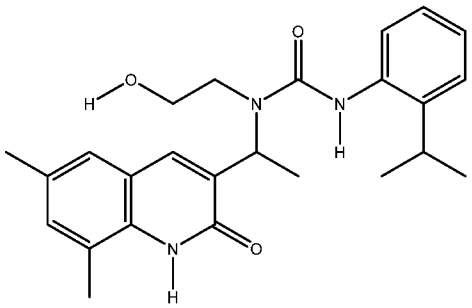
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-3-(4-fluoro-2-iodophenyl)-1-(2-hydroxyethyl)urea

Example 36



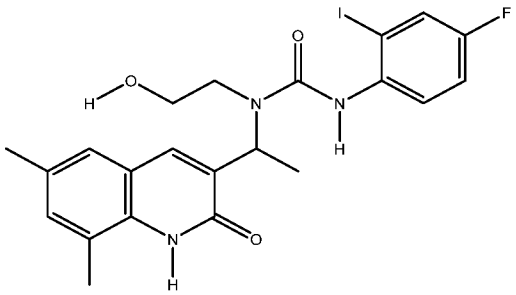
1-(1-(2-chloro-6,8-dimethylquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(2-isopropylphenyl)urea

Example 37



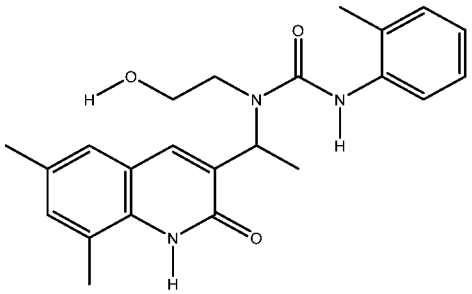
1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(2-isopropylphenyl)urea

Example 38



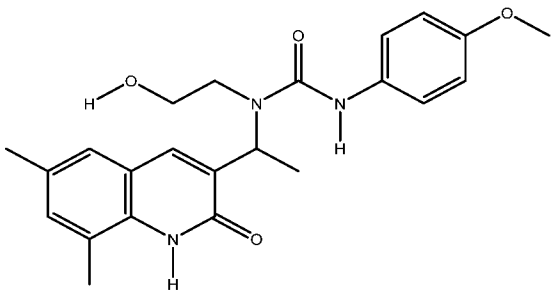
1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-3-(4-fluoro-2-iodophenyl)-1-(2-hydroxyethyl)urea

Example 39



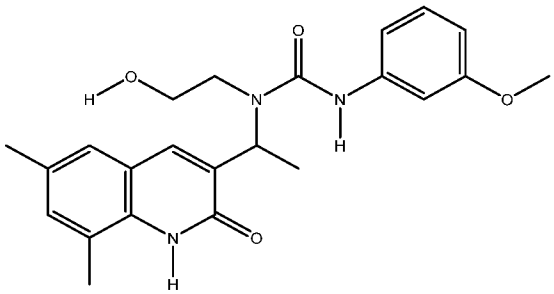
1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(o-tolyl)urea

Example 40



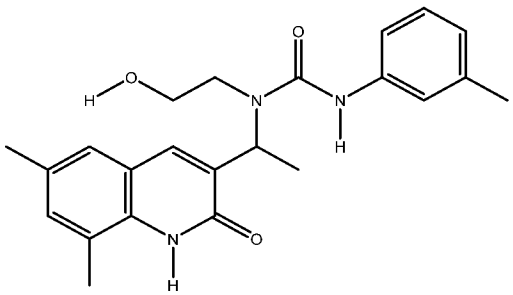
1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(4-methoxyphenyl)urea

Example 41



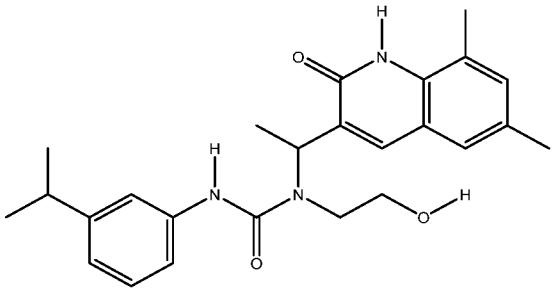
1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(3-methoxyphenyl)urea

Example 42



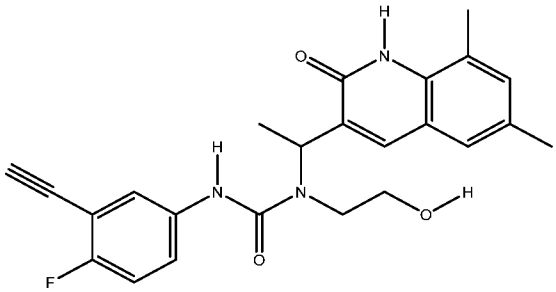
1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(m-tolyl)urea

Example 43



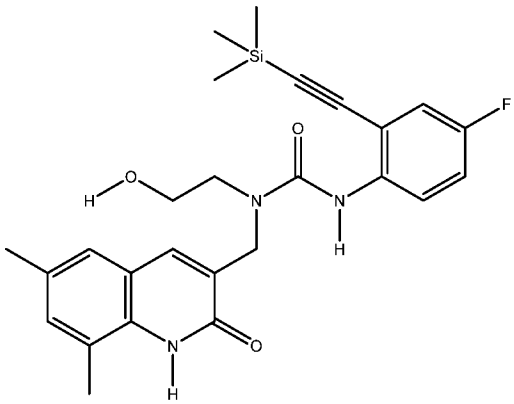
1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(3-isopropylphenyl)urea

Example 44



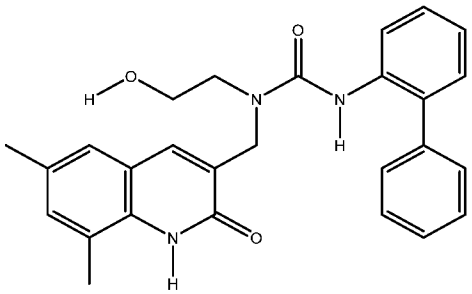
1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-3-(3-ethynyl-4-fluorophenyl)-1-(2-hydroxyethyl)urea

Example 45



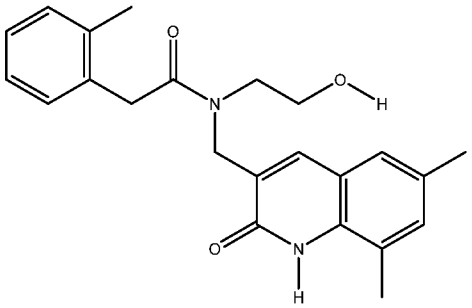
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-3-(4-fluoro-2-((trimethylsilyl)ethynyl)phenyl)-1-(2-hydroxyethyl)urea

Example 46



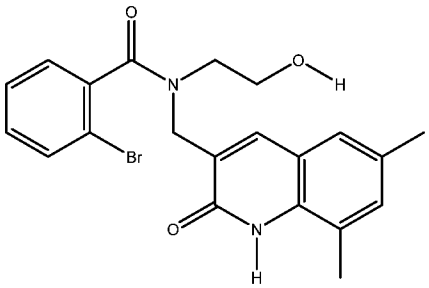
3-([1,1'-biphenyl]-2-yl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea

Example 47



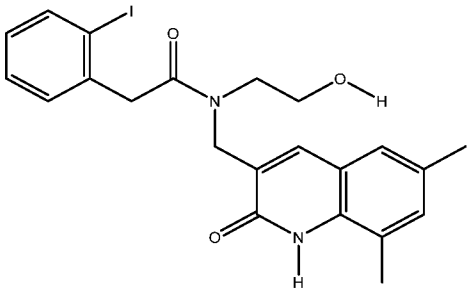
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-(o-tolyl)acetamide

Example 48



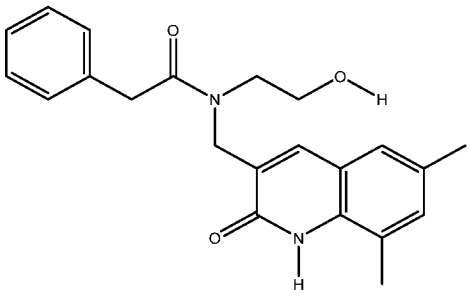
2-bromo-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)benzamide

Example 49



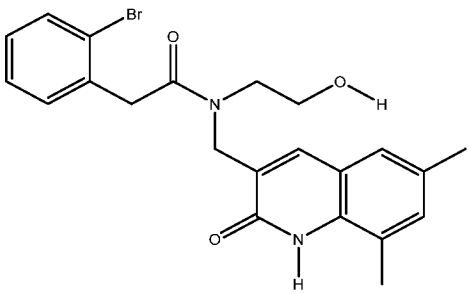
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-(2-iodophenyl)acetamide

Example 50



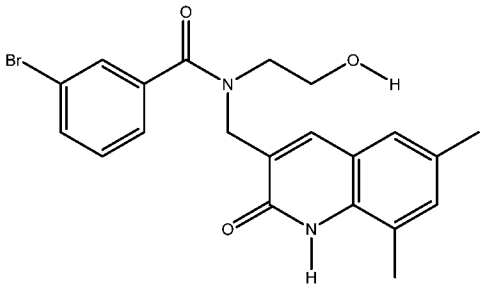
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-phenylacetamide

Example 51



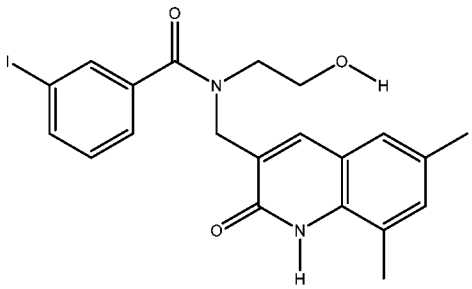
2-(2-bromophenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)acetamide

Example 52



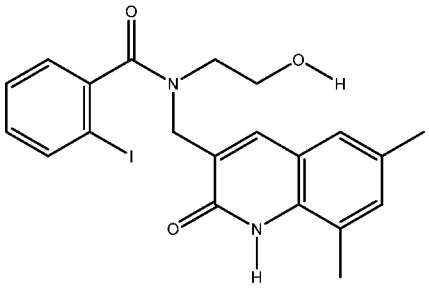
3-bromo-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)benzamide

Example 53



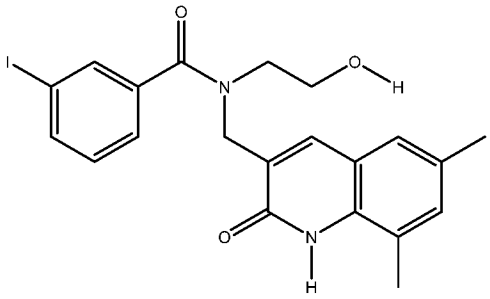
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-3-iodobenzamide

Example 54



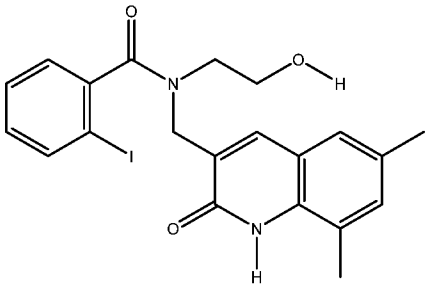
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-iodobenzamide

Example 55



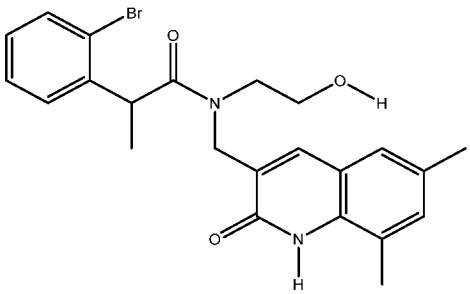
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-3-iodobenzamide

Example 56



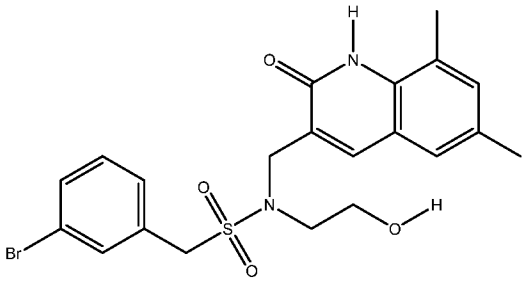
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-iodobenzamide

Example 57



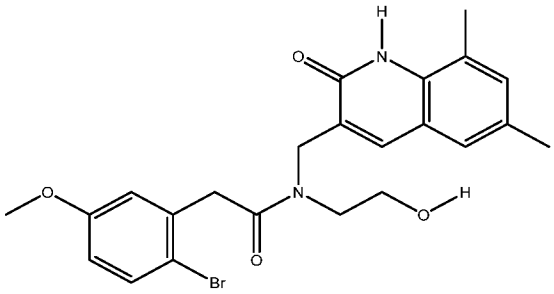
2-(2-bromophenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)propanamide

Example 58



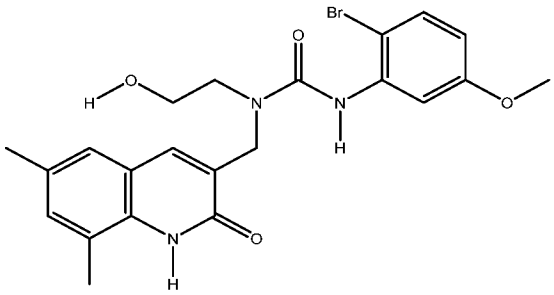
1-(3-bromophenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)methanesulfonamide

Example 59



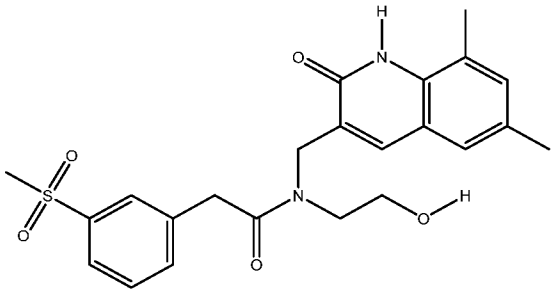
2-(2-bromo-5-methoxyphenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)acetamide

Example 60



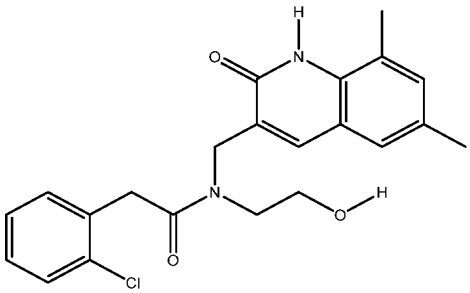
3-(2-bromo-5-methoxyphenyl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea

Example 61



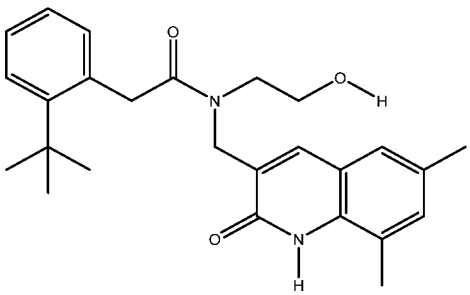
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-(3-(methylsulfonyl)phenyl)acetamide

Example 62



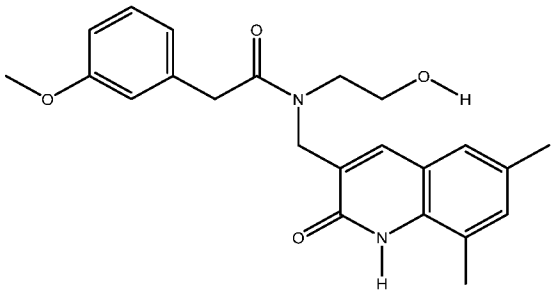
2-(2-chlorophenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)acetamide

Example 63



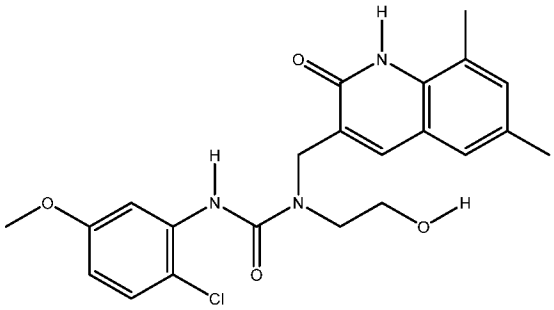
2-(2-(tert-butyl)phenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)acetamide

Example 64



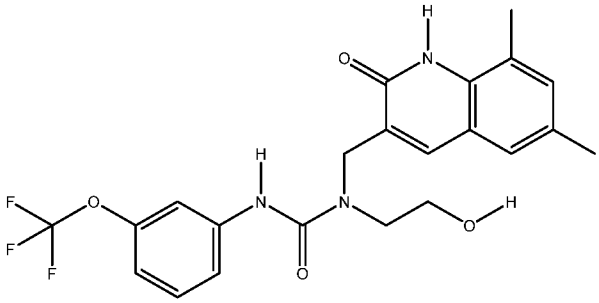
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-(3-methoxyphenyl)acetamide

Example 65



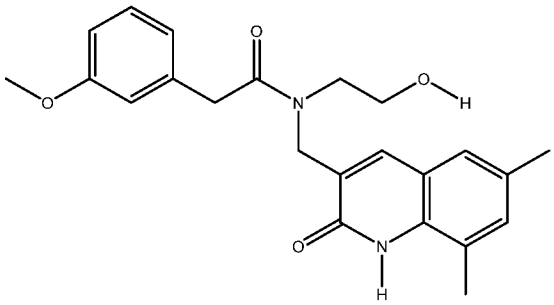
3-(2-chloro-5-methoxyphenyl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea

Example 66



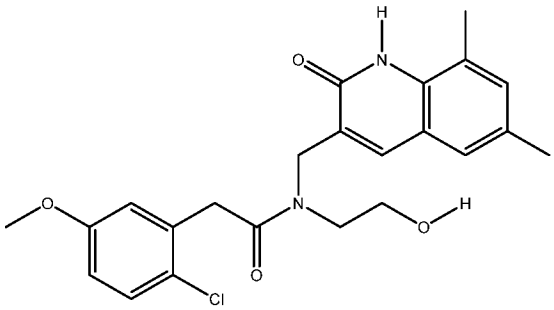
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(3-(trifluoromethoxy)phenyl)urea

Example 67



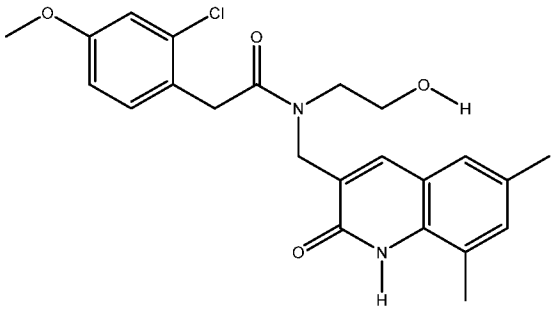
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-(3-methoxyphenyl)acetamide

Example 68



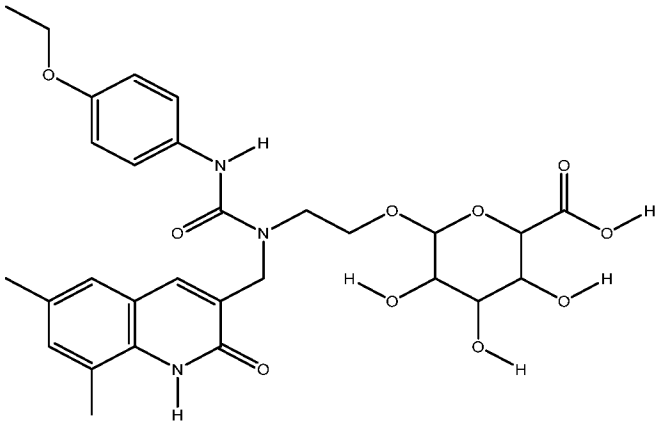
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-(3-methoxyphenyl)acetamide

Example 69



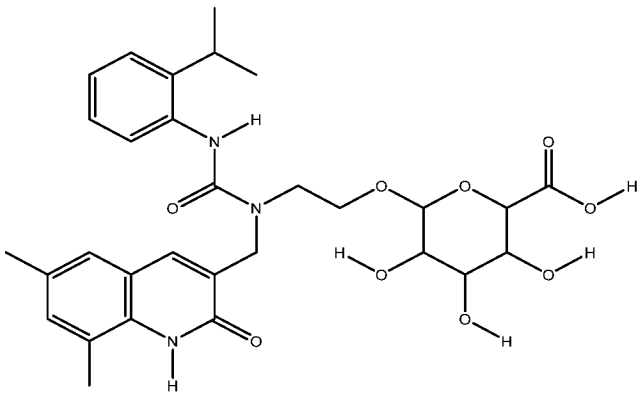
2-(2-chloro-4-methoxyphenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)acetamide

Example 70



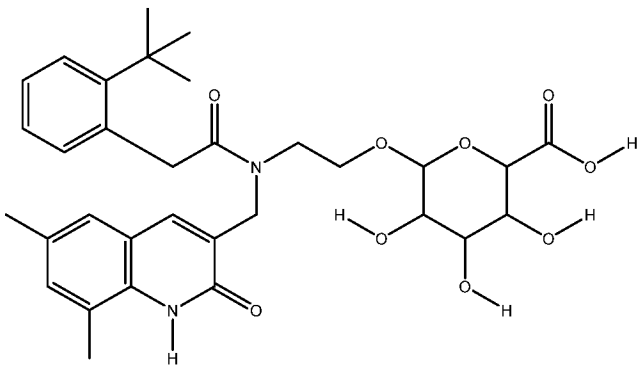
6-(2-(1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-3-(4-ethoxyphenyl)ureido)ethoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid

Example 71



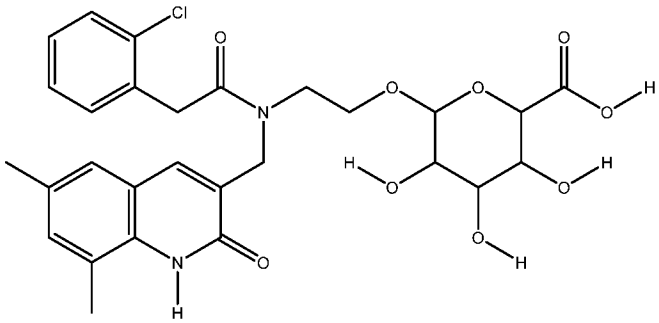
6-(2-(1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-3-(2-isopropylphenyl)ureido)ethoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid

Example 72



6-(2-(2-(2-(tert-butyl)phenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)acetamido)ethoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid

Example 73



6-(2-(2-(2-chlorophenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)acetamido)ethoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid

Biological Examples

The biological activity of the compounds of the present disclosure may be tested using the test methods described below.

Successful drug candidate compounds may be subjected to numerous biochemical and cellular assays. Purified bacterial β-glucuronidases may be challenged with compounds to determine inhibition properties in a standard, robust activity assay, utilizing p-nitrophenyl glucuronide (PNPG) as the enzymatic substrate. Reactions (n=3/inhibitor concentration) may be conducted in a 96-well assay, consisting of PNPG substrate (12 concentrations between 25 μM and 5 mM), inhibitor solution (8 concentrations between 0.1 nM and 100 μM), and 5 nM enzyme. Preferred compounds exhibited potent IC_{50} values with values <1 μM.

Additionally, preferred compounds exhibited negligible, if any, effect on purified mammalian β-glucuronidases, specifically, preferred compounds are >500-fold more selective and potent against purified bacterial enzymes. Purified bovine liver and human β-glucuronidase may be dissolved in a reaction mixture containing 1 μM enzyme and 1 mM PNPG as substrate.

Live, cultured bacterial cells (*E. coli, Bacteroides vulgatus, Clostridium ramosum*, as well as *Lactobacillus reuteri* and *Bifidobacterium infantis* as negative controls) mixed with the compounds (8 concentrations between 0.1 nM and 100 μM) may have reduced β-glucuronidase activity when challenged with 1 mM PNPG as a substrate. A potent inhibition profile was observed for the preferred compounds of the invention namely displaying EC50 values <500 nM.

Additionally, live cells may be incubated with drug candidates (1 μM to 10 mM in half-log units) for extended time-points and plated on LB-Agar plates to conduct standard colony-forming assays. There may be a determination regarding an observable or quantifiable impact on cellular growth and viability after extended incubations of NCEs and cultured bacteria. As such, preferred compounds of the present disclosure will not exhibit anti-microbial characteristics. Furthermore, cultured mammalian cells (HCT116 cells) incubated (6 to 24 hr incubation time-points) with drug candidates may continue to grow and be viable, as evidenced by the conversion of rezasurin to resorufin indicating mammalian cell viability. Critically, the compounds may be not cytotoxic to mammalian cells.

In vivo efficacy of the compounds may be determined in treated mouse models, developed by Symberix, Inc., Durham NC. Efficacy may be determined by reduction in bloody diarrhea (observed and scored) and reduced SN-38 levels in feces (determined bioanalytically). Compounds may be given p.o. at 0.1 mg/kg to 1

mg/kg dose-strength and twice daily, to multiple cohorts of mice, including untreated, vehicle, inhibitor-only, and treated groups. Treatment may be dosed at 50 mg/kg, unless otherwise noted. Compounds of the invention evidenced by a decrease in bloody diarrheal events in mice as well as diminished SN-38 levels in fecal matter, will represent a reduction in bacterial β-glucuronidase activity due to inhibition.

Table 1 describes data demonstrating the increased potency of inhibitor-glucuronides in the cellular assays described with a 2 hour incubation time.

Table 1.							
Sample	**Purified GUS**				**Live E. coli**		
	Orignial IC_{50}	Updated IC_{50} (Normalized)			Normalized IC_{50}		
	uM	Normalized	STDEV	N	Normalized	STDEV	N
Inh1	0.9	1	0	5	1	0	3
Ex. 8	0.57	0.51	0.41	2	0.97	0.46	3
Ex. 12	0.58	0.81	0.48	2	0.73	0.09	2
Ex. 4	0.92	0.83	0.01	2	1.2	0.31	3

Table 2			
Sample	**IC_{50} (uM)**	**Cell-Based**	**Cell-based (4 hour preincubation)**
Ex. 16	2.725	1.655413	0.89
Ex. 17	>100	>100	>100
Ex. 18	>100	>100	>100
Ex. 19	2.11	2.3066	0.601
Ex. 20	>100	>100	>100
Ex. 21	2.17	1.81725	0.504
Ex. 22	1.795	1.338458	0.55
Ex. 23	>100	>100	>100
Ex. 24	0.54	1.5044	0.666
Ex. 25	2.43	1.14	0.997
Ex. 26	0.51	2.03	1.539
Ex. 27	2.55	1.09	1.22
Ex. 28	0.855	0.485	0.324085
Ex. 29	>100	Untested	Untested
Ex. 30	>100	Untested	Untested
Ex. 31	0.759	Untested	Untested
Ex. 32	>50	Untested	Untested
Ex. 33	>50	Untested	Untested
Ex. 34	0.716	0.595	0.61
Ex. 35	0.1423	Untested	Untested
Ex. 36	>25	Untested	Untested
Ex. 37	6.44	Untested	Untested
Ex. 38	13.03	Untested	Untested
Ex. 39	>50	Untested	Untested
Ex. 40	>50	Untested	Untested
Ex. 41	3.712	Untested	Untested
Ex. 42	1.661	Untested	Untested
Ex. 43	6.731	Untested	Untested
Ex. 44	1.105	Untested	Untested
Ex. 45	19.058	Untested	Untested
Ex. 46	6.164	Untested	Untested
Ex. 47	4.96	Untested	Untested
Ex. 48	12.77	Untested	Untested
Ex. 49	0.81	0.705	0.575
Ex. 50	8.56	Untested	Untested
Ex. 51	0.965	0.98	0.872961
Ex. 52	>50	Untested	Untested
Ex. 53	>50	Untested	Untested
Ex. 54	>50	Untested	Untested
Ex. 55	>50	Untested	Untested
Ex. 56	>50	Untested	Untested
Ex. 57	10.888	Untested	Untested
Ex. 58	3.262	Untested	Untested
Ex. 59	0.935	0.729853	Untested
Ex. 60	3.308	Untested	Untested
Ex. 61	21.86	Untested	Untested
Ex. 62	0.575	1.469556	0.929

Ex. 63	0.905	1.2	1.352
Ex. 64	5.234	Untested	Untested
Ex. 65	3.6	Untested	Untested
Ex. 66	24.3	Untested	Untested
Ex. 67	>50	Untested	Untested
Ex. 68	3.34	Untested	Untested
Ex. 69	2.87	Untested	Untested
Ex. 70	Untested	0.114	0.013
Ex. 71	Untested	0.082	0.004
Ex. 72	Untested	0.077	0.008
Ex. 73	Untested	0.087	0.007

Glucuronide ester prodrugs can be activated by esterases to yield inhibitor glucuronides that have been shown to have increasing potencies in cell-based *E. coli* assays as described above. Without ester cleavage, these prodrugs remain inactive in cell. This is demonstrated using the example CG-1CY179 (SY65-G-Acetate) in the cell-based assay with and without pre-treatment with rabbit or porcine liver esterase. For esterase activation, the prodrug is treated with 5 mg/mL esterase for 30 mins at 37ºC to cleave the ester bonds yielding the glucuronide moiety. Following treatment, an inhibitor titration ranging from 10 uM to 10 pM is mixed and preincubated with live *E. coli* for 5 mins or 4 hours at 37ºC in a microplate with assay buffer (HEPES pH 7, NaCl). Chemically synthesized SY65-G is included as a positive control. Following preincubation, 4-methylumbelliferyl glucuronide (4MUG) is added at a final concentration of 100 uM to the cell and inhibitor mixture. The conversion of 4MUG to 4MU is detected via fluorescence (Ex./Em.: 360/460). As described in Table 3, esterase treated glucuronide prodrug is just as potent as the glucuronide positive control. The untreated prodrug is not active.

Table 3

Compound	Pre-incubation time	
	5 min (nM)	4 hour (nM)
SY65-G	125	0.53
SY65-G + Esterase	93	0.57
SY65-G-Ac	>10000	>10000
SY65-G-Ac + Esterase	156	0.52

All publications, patents and patent applications cited in this specification are incorporated herein by reference for the teaching to which such citation is used.

Test compounds for the experiments described herein may be employed in free or salt form.

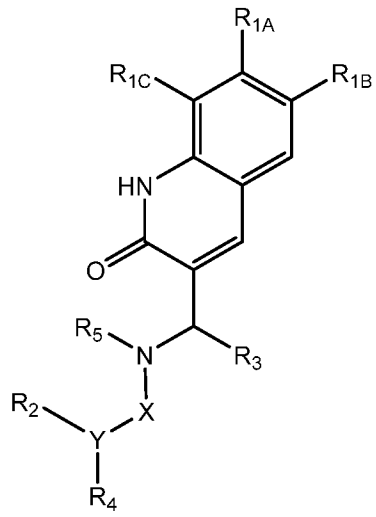
The specific responses observed may vary according to and depending on the particular active compound selected or whether there are present carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with practice of the present disclosure.

Although specific embodiments of the present disclosure are herein illustrated and described in detail, the invention is not limited thereto. The above detailed descriptions are provided as exemplary of the present disclosure and should not be construed as constituting any limitation of the invention. Modifications will be obvious to those skilled in the art, and all modifications that do not depart from the spirit of the invention are intended to be included with the scope of the appended claims.

CLAIMS

What is claimed is:

1. A compound of formula (I):



(I)

wherein

each of R_{1A}, R_{1B}, R_{1C} independently is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkylthio, substituted or unsubstituted C_{1-6} haloalkoxy, substituted or unsubstituted C_{1-6} haloalkylthio, substituted or unsubstituted C_{1-6} alkylamino, substituted or unsubstituted C_{1-6} alkylaminoalkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} haloalkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{2-6} haloalkynyl, halogen, cyano, nitro, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

R_2 is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkylthio, substituted or unsubstituted C_{1-6} haloalkoxy, substituted or unsubstituted C_{1-6} haloalkylthio, substituted or unsubstituted C_{1-6} alkylamino, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} haloalkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{2-6} haloalkynyl, halogen, cyano, nitro, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S,

and optionally having one or more degrees of unsaturation;

R_3 is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkylthio, substituted or unsubstituted C_{1-6} haloalkoxy, substituted or unsubstituted C_{1-6} haloalkylthio, substituted or unsubstituted C_{1-6} alkylamino, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} haloalkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{2-6} haloalkynyl, halogen, cyano, nitro, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

X is CO or SO_2;

Y is CH or N;

R_4 is selected from the group consisting of a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

R_5 is $(L_1)_nR_a$, wherein L_1 is a C_{1-6} alkylene chain, n is 0 or 1, and R_a is OR_b, C_{1-6} alkylamino, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

R_b is hydrogen, $C(O)NHR_c$, or $C(O)R_d$;

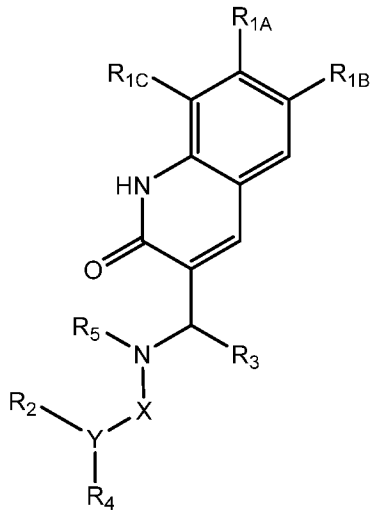
R_c is aryl; and

R_d is substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkylthio, substituted or unsubstituted C_{1-6} haloalkoxy, substituted or unsubstituted C_{1-6} haloalkylthio, substituted or unsubstituted C_{1-6} alkylamino, substituted or unsubstituted C_{1-6} alkylaminoalkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} haloalkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{2-6} haloalkynyl, halogen, cyano, nitro, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation,

or a glucuronide thereof,

or a pharmaceutically acceptable salt thereof.

2. A compound of formula (IG):



(IG)

wherein

each of R_{1A}, R_{1B}, R_{1C} independently is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkylthio, substituted or unsubstituted C_{1-6} haloalkoxy, substituted or unsubstituted C_{1-6} haloalkylthio, substituted or unsubstituted C_{1-6} alkylamino, substituted or unsubstituted C_{1-6} alkylaminoalkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} haloalkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{2-6} haloalkynyl, halogen, cyano, nitro, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

R_2 is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkylthio, substituted or unsubstituted C_{1-6} haloalkoxy, substituted or unsubstituted C_{1-6} haloalkylthio, substituted or unsubstituted C_{1-6} alkylamino, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} haloalkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{2-6} haloalkynyl, halogen, cyano, nitro, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

R_3 is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkylthio, substituted or unsubstituted C_{1-6} haloalkoxy, substituted or unsubstituted C_{1-6} haloalkylthio, substituted or unsubstituted C_{1-6} alkylamino,

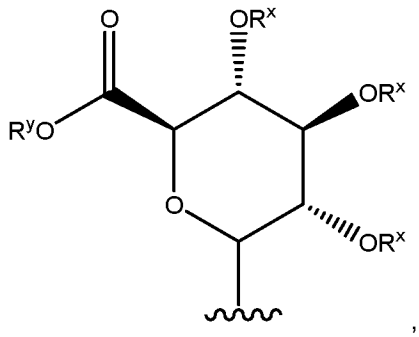
substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} haloalkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{2-6} haloalkynyl, halogen, cyano, nitro, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

X is CO or SO_2;

Y is CH or N;

R_4 is selected from the group consisting of a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;

R_5 is $(L_1)_nR_a$, wherein L_1 is a C_{1-6} alkylene chain, n is 0 or 1, and R_a is OR_b, C_{1-6} alkylamino, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation;



R_b is hydrogen, $C(O)NHR_c$, $C(O)R_d$, or , where each R^x independently is hydrogen or $C(O)R^z$,

R^y is H or R^z, and

each R^z independently is C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{9-20} alkyl, C_{9-20} alkenyl, or C_{9-20} alkynyl;

R_c is aryl; and

R_d is substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkylthio, substituted or unsubstituted C_{1-6} haloalkoxy, substituted or unsubstituted C_{1-6} haloalkylthio, substituted or unsubstituted C_{1-6} alkylamino, substituted or unsubstituted C_{1-6} alkylaminoalkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} haloalkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{2-6} haloalkynyl, halogen, cyano, nitro, or a substituted or unsubstituted 3- to 10-membered ring, optionally having one or more heteroatoms selected from N, O, or S, and optionally having one or more degrees of unsaturation,

or a pharmaceutically acceptable salt thereof.

3. The compound of any one of claims 1 or 2, wherein R_{1A} is hydrogen.

4. The compound of any one of claims 1 – 3, wherein R_{1B} is substituted or unsubstituted C_{1-6} alkyl.

5. The compound of any one of claims 1 – 4, wherein R_{1C} is substituted or unsubstituted C_{1-6} alkyl.

6. The compound of any one of claims 1 – 5, wherein R_2 is hydrogen or C_{1-6} alkyl.

7. The compound of any one of claims 1 – 6, wherein R_3 is hydrogen.

8. The compound of any one of claims 1 – 7, wherein R_4 is substituted or unsubstituted phenyl.

9. The compound of any one of claims 1 – 8, wherein R_4 is substituted phenyl.

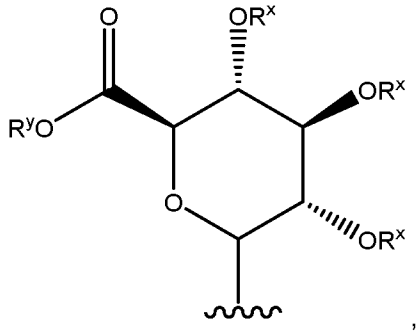
10. The compound of claim 9, wherein R_4 is phenyl substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} alkynyl substituted with $Si(CH_3)_3$, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, halogen, aryl, C_{3-6} cycloalkyl, or SO_2R_e, where R_e is hydrogen or C_{1-6} alkyl.

11. The compound of claim 10, wherein R_4 is phenyl and is monosubstituted.

12. The compound of claim 10, wherein R_4 is phenyl and is disubstituted.

13. The compound of any one of claims 1 – 12, wherein R_5 is $(L_1)_nR_a$, wherein L_1 is a C_2 alkylene, n is 1, and R_a is OR_b, wherein R_b is hydrogen.

14. The compound of any of any one of claims 1 – 13, wherein R_b is



where each R^x is hydrogen, and R^y is hydrogen.

15. The compound of claim 14, wherein each R^x is $C(O)R^z$, and R^y is R^z.

16. The compound of claim 15, wherein each R^z is C_{1-6} alkyl.

17. A compound selected from:

N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)-2-(o-tolyl)acetamide;

N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)-2-(2-iodophenyl)acetamide;

N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)-2-phenyl-acetamide;

2-(2-bromophenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)acetamide;

2-(2-bromophenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)propanamide;

2-(3-bromophenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)acetamide;

N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)-2-(3-methylsulfonylphenyl)acetamide;

2-(2-chlorophenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)acetamide;

N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)-2-(3-methoxyphenyl)acetamide;

2-(2-chloro-5-methoxy-phenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)acetamide;

2-(2-chloro-4-methoxy-phenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-

hydroxyethyl)acetamide; 2-(2-bromo-5-methoxy-phenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)acetamide;
1-(3-bromophenyl)-N-[(6,8-dimethyl-2-oxo-1H-quinolin-3-yl)methyl]-N-(2-hydroxyethyl)methanesulfonamide;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-3-(4-ethoxyphenyl)-1-(2-hydroxyethyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(4-(trifluoromethyl)phenyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(4-(trifluoromethoxy)phenyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(4-methoxyphenyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(3-(trifluoromethyl)phenyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(o-tolyl)urea;
3-(4-bromophenyl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(2-(trifluoromethyl)phenyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-3-(2,6-dimethylphenyl)-1-(2-hydroxyethyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(2-methoxyphenyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(2-isopropylphenyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(4-isopropylphenyl)urea;
3-(2-bromophenyl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea;
6,8-dibromo-3-(hydroxymethyl)quinolin-2(1H)-one;
6,8-dibromo-2-oxo-1,2-dihydroquinoline-3-carbaldehyde;
3-(2-cyclopropylphenyl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea;
3-([1,1'-biphenyl]-2-yl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea;

1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(pyridin-3-yl)urea; 1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(2-iodophenyl)urea; 1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-3-(4-fluoro-2-iodophenyl)-1-(2-hydroxyethyl)urea;

1-(1-(2-chloro-6,8-dimethylquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(2-isopropylphenyl)urea;

1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(2-isopropylphenyl)urea;

1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-3-(4-fluoro-2-iodophenyl)-1-(2-hydroxyethyl)urea;

1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(o-tolyl)urea;

1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(4-methoxyphenyl)urea;

1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(3-methoxyphenyl)urea;

1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(m-tolyl)urea;

1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-1-(2-hydroxyethyl)-3-(3-isopropylphenyl)urea;

1-(1-(6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-3-(3-ethynyl-4-fluorophenyl)-1-(2-hydroxyethyl)urea;

1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-3-(4-fluoro-2-((trimethylsilyl)ethynyl)phenyl)-1-(2-hydroxyethyl)urea;

3-([1,1'-biphenyl]-2-yl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea;

N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-(o-tolyl)acetamide;

2-bromo-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)benzamide; N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-(2-iodophenyl)acetamide;

N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-phenylacetamide;

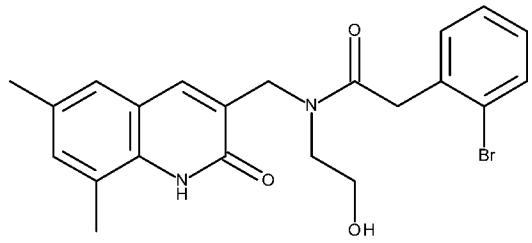
2-(2-bromophenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)acetamide;

3-bromo-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-

hydroxyethyl)benzamide;
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-3-iodobenzamide;
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-iodobenzamide;
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-3-iodobenzamide;
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-iodobenzamide;
2-(2-bromophenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)propanamide;
1-(3-bromophenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)methanesulfonamide;
2-(2-bromo-5-methoxyphenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)acetamide;
3-(2-bromo-5-methoxyphenyl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea;
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-(3-(methylsulfonyl)phenyl)acetamide;
2-(2-chlorophenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)acetamide;
2-(2-(tert-butyl)phenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)acetamide;
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-(3-methoxyphenyl)acetamide;
3-(2-chloro-5-methoxyphenyl)-1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)urea;
1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-(2-hydroxyethyl)-3-(3-(trifluoromethoxy)phenyl)urea;
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-(3-methoxyphenyl)acetamide;
N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)-2-(3-methoxyphenyl)acetamide;
2-(2-chloro-4-methoxyphenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-N-(2-hydroxyethyl)acetamide;
6-(2-(1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-3-(4-

ethoxyphenyl)ureido)ethoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid;
6-(2-(1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-3-(2-isopropylphenyl)ureido)ethoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid;
6-(2-(2-(2-(tert-butyl)phenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)acetamido)ethoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid;
6-(2-(2-(2-chlorophenyl)-N-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)acetamido)ethoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid;
or a glucuronide thereof, or a pharmaceutically acceptable salt thereof.

18. A compound selected from:



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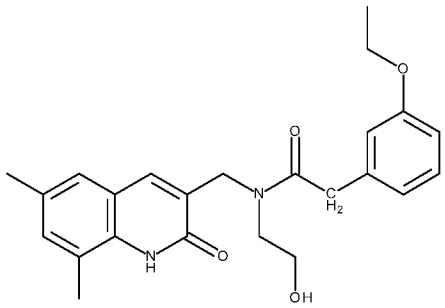

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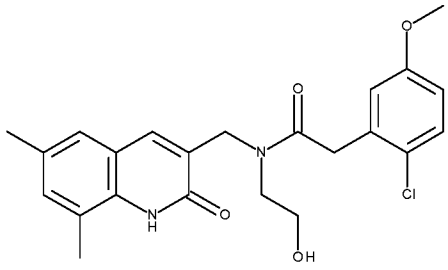

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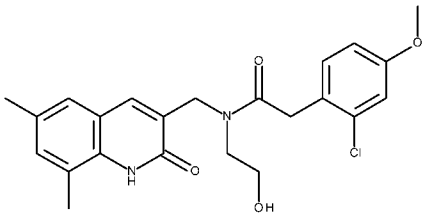

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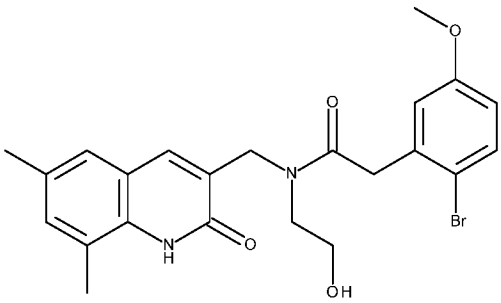
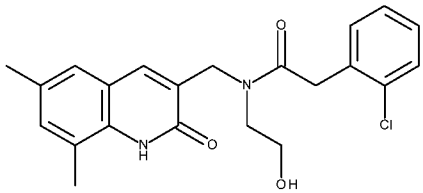


; and



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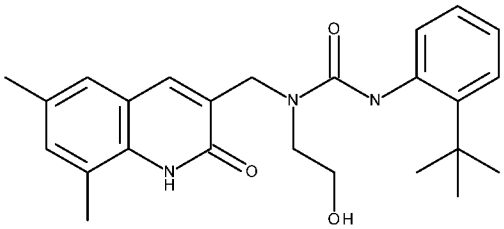
or a glucuronide thereof, or pharmaceutically acceptable salt thereof.

19. A compound selected from:



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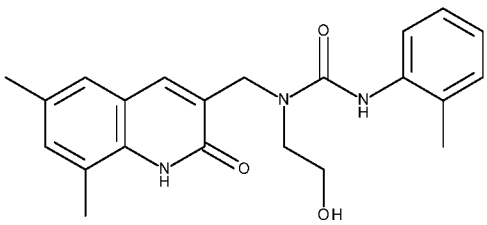

,

or a glucuronide thereof, or pharmaceutically acceptable salt thereof.

20. A composition comprising: one or more compounds of any one of claims 1 – 19, and one or more pharmaceutically acceptable carriers.

21. A method for attenuating the side effects of one or more drug, said method comprising: administering to a subject in need thereof an effective amount of one or more compounds of any one of claims 1 - 19.

22. The method of claim 21, wherein the one or more compounds selectively inhibit β-glucuronidase.

23. The method of claims 21 or 22, wherein the one or more compounds can be co-administered with the one or more therapeutic compound or product.

24. A compound of any one of claims 1 – 19 for use in medicine.

25. The compound of claim 24 wherein the compound selectively inhibits β-glucuronidase.

26. A compound of any one of claims 1 – 19 for the manufacture of a medicament for attenuating side effects of one or more drug.

27. The compound of claim 26 wherein the compound selectively inhibits β-glucuronidase.

28. Use of a compound of any one of claims 1 – 19 for attenuating the side effects of one or more drug.

29. The use of claim 28, wherein the compound selectively inhibits β-glucuronidase.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/021416

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

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

1. ☒ Claims Nos.: 21-23
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 21-23 pertain to methods for treatment of the human body by surgery or therapy, as well as diagnostic methods(PCT Article 17(2)(a)(i) and Rule 39.1(iv)).

2. ☒ Claims Nos.: 10-12, 15-16, 22, 25, 27, 29
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 10-12, 15-16, 22, 25, 27, 29 are regarded to be unclear because they refer to claims which do not comply with PCT Rule 6.4(a).

3. ☒ Claims Nos.: 4-9, 13-14, 20-21, 23-24, 26, 28
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/021416

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/4704(2006.01)i, A61P 1/00(2006.01)i, A61P 1/12(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 31/4704; A61K 31/38; A61K 31/435; A61K 31/4709; A61K 31/5377; A61K 45/06; A61P 1/00; A61P 1/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal), STN(Registry, Caplus) & keywords: β-glucuronidase inhibitor, dihydroquinoline, urea, acetamide

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011-072127 A1 (THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL et al.) 16 June 2011 claim 1	1-3,17-19
X	US 2015-0011542 A1 (UNIVERSITY OF CONNECTICUT) 08 January 2015 claims 1, 8	1-3,17-19
X	ROBERTS, A. B. et al., "Molecular Insights into Microbial β-Glucuronidase Inhibition to Abrogate CPT-11 Toxicity", Mol. Pharmacol., 2013, Vol. 84, pages 208-217 abstract; figure 1	1-3,17-19
X	AHMAD, S. et al., "A High Throughput Assay for Discovery of Bacterial β-Glucuronidase Inhibitors", Current Chemical Genomics, 2011, Vol. 5, pages 13-20 abstract; table 1	1-3,17-19
PX	WO 2019-051185 A1 (SYMBERIX, INC.) 14 March 2019 claims 1, 27-35	1-3,17-19

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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

Date of the actual completion of the international search	Date of mailing of the international search report
24 June 2020 (24.06.2020)	**24 June 2020 (24.06.2020)**

Name and mailing address of the ISA/KR	Authorized officer
International Application Division Korean Intellectual Property Office 189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea	HEO, Joo Hyung
Facsimile No. +82-42-481-8578	Telephone No. +82-42-481-8150

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2020/021416

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011-072127 A1	16/06/2011	CA 2783701 A1	16/06/2011
		EP 2509597 A1	17/10/2012
		EP 2509597 A4	10/04/2013
		US 2012-0322797 A1	20/12/2012
		US 2015-0051205 A1	19/02/2015
		US 8557808 B2	15/10/2013
		US 9334288 B2	10/05/2016
US 2015-0011542 A1	08/01/2015	WO 2013-106656 A2	18/07/2013
WO 2019-051185 A1	14/03/2019	None	