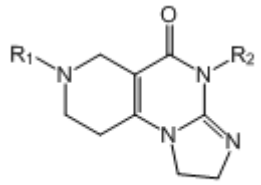
[0006] ONC201 (7-benzyl-4-(2-methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo [1,2-a]pyrido [3,4-e]pyrimidin-5(1H)-one) is the founding member of a class of anti-cancer compounds called imipridones that is in Phase II clinical trials in multiple advanced cancers. Since the discovery of ONC201 as a p53-independent inducer of TRAIL gene transcription, preclinical studies have determined that ONC201 has anti-proliferative and pro-apoptotic effects against a broad range of tumor cells but not normal cells. The mechanism of action of ONC201 involves engagement of PERK-independent activation of the integrated stress response, leading to tumor upregulation of DR5 and dual Akt/ERK inactivation, and consequent Foxo3a activation leading to upregulation of the death ligand TRAIL. ONC201 is orally active with infrequent dosing in animal models, causes sustained pharmacodynamic effects, and is not genotoxic. The first-in-human ONC201 clinical trial in advanced aggressive refractory solid tumors confirmed that it is well-tolerated. In summary, the imipridone family that comprises ONC201 and its chemical analogs represent a new class of therapeutic agents.

BRIEF SUMMARY OF THE INVENTION

[0007] In one aspect, provided herein are compounds of formula (**10**):



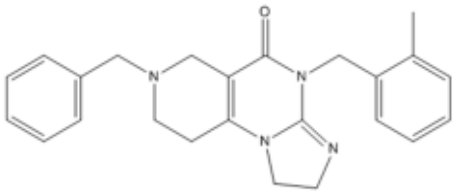
(**10**), wherein R_1 and R_2 are independently selected from H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl, alkoxycarbonyl, aralkoxy, aralkylthio, and acyl radicals. In one embodiment, when R_1 is CH_2Ph, R_2 is not CH_2-(2-CH_3-Ph). In one embodiment, R_1 is CH_2Ph and R_2 is CH_2-(2-CH_3-Ph) (i.e., ONC201). In one embodiment, R_1 is CH_2Ph and R_2 is CH_2-(2,4-di F-Ph) (i.e., ONC206). In one embodiment, R_1 is CH_2Ph and R_2 is CH_2-(4-CF_3-Ph) (i.e., ONC212). In one embodiment, R_1 is CH_2Ph and R_2 is CH_2-(3,4-di F-Ph) (i.e., ONC213). In one embodiment, R_1 is CH_2 (3,4-di-Cl-Ph and R_2 is CH_2-(4-CF_3-Ph) (i.e., ONC234). In one embodiment, R_1 is CH_2-3-thienyl and R_2 is CH_2-(4-CF_3-Ph) (i.e., ONC236).

[0008] In another aspect, provided herein are methods of treating or preventing a disease, disorder, or condition in a subject in need thereof, comprising: administering to the subject in need of such treatment a pharmaceutical composition comprising a therapeutically effective amount a compound of formula (**10**) or an analog thereof, or a pharmaceutically acceptable salt thereof. In one embodiment, the compound is selected from the group consisting of ONC201, ONC206, ONC212, ONC213, ONC234 and ONC236. In one embodiment, the subject has, or

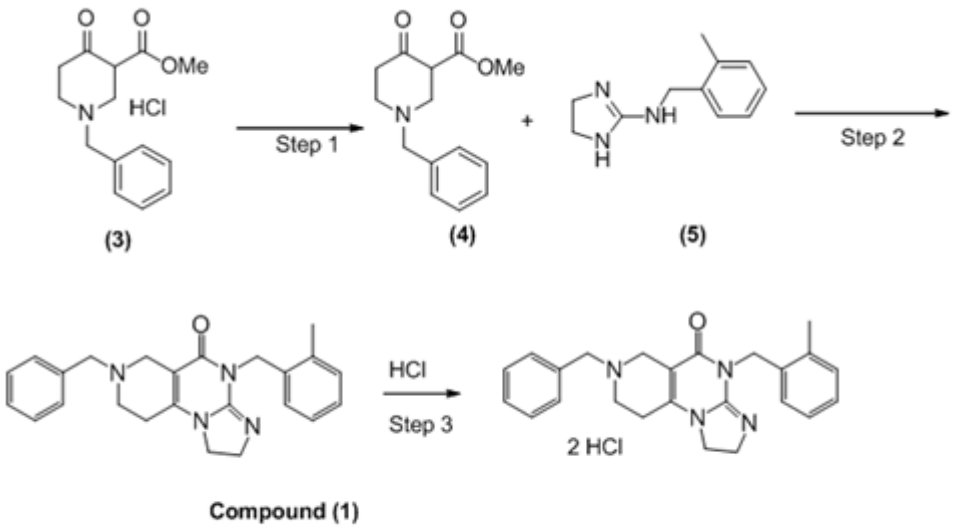
[00108] An optical response is detected by visual inspection, or by using one of the following devices: CCD camera, video camera, photographic film, laser-scanning devices, fluorometers, photodiodes, quantum counters, epifluorescence microscopes, scanning microscopes, flow cytometers, fluorescence microplate readers, or by means for amplifying the signal such as photomultiplier tubes. When a sample is examined using a flow cytometer, examination of it optionally includes sorting portions of it according to their fluorescence response.

[00109] When an indirectly detectable label is used, then illuminating typically includes adding a reagent to produce a detectable signal such as a colorimetric enzyme substrate. Radioisotopes are also considered indirectly detectable where an additional reagent is not needed, rather the radioisotope is exposed to X-ray film or other mechanism to record and measure the signal. This is true for some chemiluminescent signals that are observed after exposure to film.

I. ONC201 (COMPOUND (1)), SALTS THEREOF AND SYNTHESES THEREOF



[00110] ONC201 (compound (**1**)) and its analogs, and their pharmaceutically acceptable salts, as well as syntheses for them, are provided herein. In *in vitro* models, animal models, and human clinical trials, ONC201 has broad anti-cancer activity, low toxicity including few, if any, adverse effects, low genotoxicity, and high bioavailability including orally. These features allow ONC 201 and various analogs to be well suited for a variety of applications. ONC201 can be made by the synthesis shown in Scheme **1**.

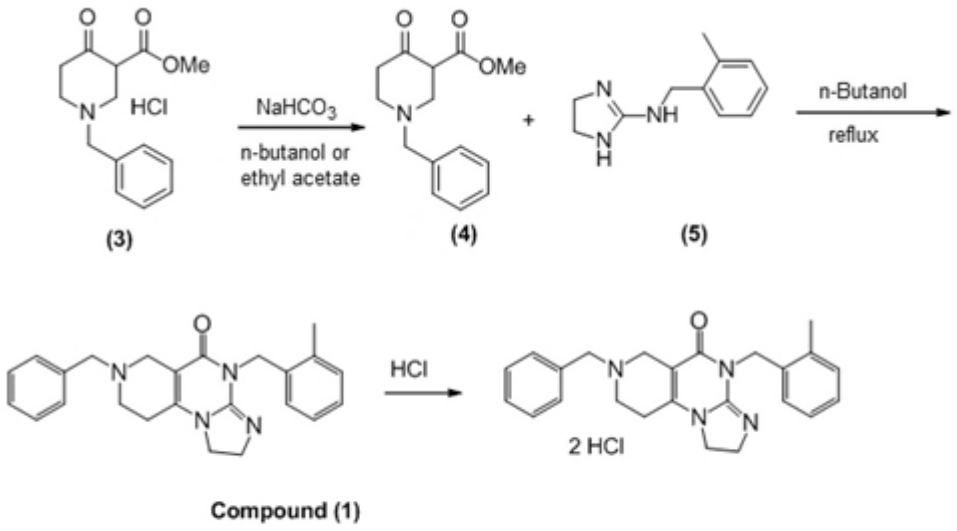


Scheme 1

[00111] Synthesis of an ONC201 dihydrochloride salt starts with commercially available intermediary N-Benzyl-3-carbomethoxy-4-piperidone hydrochloride, compound (**3**). In one embodiment, the synthesis includes neutralizing compound (**3**) with a base (Step **1**) to produce compound (**4**), a free base. In one embodiment, compound (**3**) is neutralized with an inorganic base to produce compound (**4**). In one embodiment, compound (**3**) is neutralized with an organic base to produce compound (**4**). In one embodiment, compound (**3**) is neutralized in the presence of an alcohol, for example, n-butanol. In one embodiment, compound (**3**) is neutralized in the presence of at least one organic solvent, for example, n-butanol and/or ethyl acetate. In one embodiment, compound (**3**) is neutralized in the presence of a base and at least one organic solvent, for example, $NaHCO_3$ and n-butanol. In one embodiment, compound (**3**) is neutralized in the presence of n-butanol and triethyl amine (Et_3N).

[00112] In one embodiment, the synthesis includes reacting compound (**4**) with compound (**5**) (Step **2**) to produce intermediary compound (**1**). In one embodiment, the reaction in Step **2** includes heating compound (**4**) with compound (**5**). In one embodiment, the reaction in Step **2** includes refluxing heating compound (**4**) and compound (**5**) in the presence of a solvent. In one embodiment, the reaction in Step **2** includes use of Dean-stark trap to remove water and/or methanol (MeOH) formed in the reaction.

[00113] In one embodiment, an ONC201 dihydrochloride salt is synthesized (Step **3**). In one embodiment, this reaction (Step **3**) includes treating ONC201 with HCl in dioxane. In one embodiment, Step **3** includes treating ONC201with 4N HCl in dioxane. In one embodiment, the synthesis optionally includes recrystallizing the ONC201 di-salt. In a preferred embodiment, the ONC201 di-hydrochloride salt is synthesized as shown in Scheme **2**.



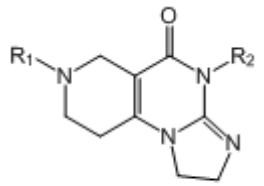
Scheme 2

neoplasms and metastasis. Methods and compositions described herein can be used for prophylaxis, as well as amelioration of cancer signs or symptoms. “Treatment” of a cancer in a subject includes: preventing, inhibiting or ameliorating cancer in the subject, such as slowing cancer progression or reducing or ameliorating a cancer sign or symptom. Examples of cancers treated using methods and compositions described herein include breast cancer, CNS cancers, colon cancer, ovarian cancer, prostate cancer, leukemia, lung cancer, and lymphoma.

III. COMPOUNDS OF FORMULA (10) AND SALTS THEREOF

[00118] In one aspect, provided herein are compounds and salts of formula (**10**) and methods of making them. Persons skilled in the art will understand that the general principles and concepts described here in conjunction with ONC201 (compound (**1**)) and its salts, including principles and concepts related to methods and pharmaceutical compositions, apply with equal force to compounds of formula (**10**) and salts thereof.

[00119] In one embodiment, provided herein are compounds of formula (**10**):



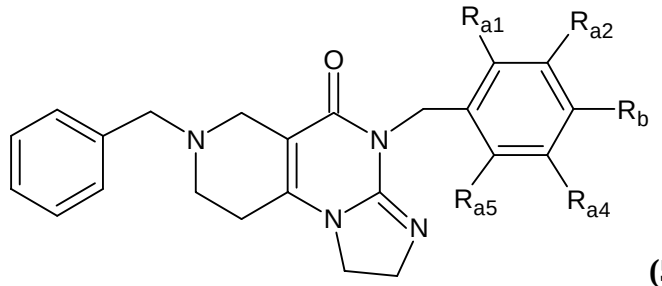
(10)

, wherein R_1 and R_2 are independently selected from H, alkyl, aryl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl, alkoxycarbonyl, aralkoxy, aralkylthio, and acyl radicals. In one embodiment, R_1 is CH_2Ph and R_2 is CH_2-(2-CH_3-Ph) (i.e., ONC201). In one embodiment, R_1 is CH_2Ph and R_2 is CH_2-(2,4-di F-Ph) (i.e., ONC206). In one embodiment, R_1 is CH_2Ph and R_2 is CH_2-(4-CF_3-Ph) (i.e., ONC212). In one embodiment, R_1 is CH_2Ph and R_2 is CH_2-(3,4-di F-Ph) (i.e., ONC213). In one embodiment, R_1 is CH_2 (3,4-di-Cl-Ph and R_2 is CH_2-(4-CF_3-Ph) (i.e., ONC234). In one embodiment, R_1 is CH_2-3-thienyl and R_2 is CH_2-(4-CF_3-Ph) (i.e., ONC236).

[00120] In one embodiment, R_1 and R_2 are independently selected from the group consisting of H, $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkylphenyl, $C_{1\text{-}4}$alkylphenylketone, $C_{1\text{-}4}$benzyl-piperazine, $C_{1\text{-}4}$alkylthienyl, $C_{1\text{-}4}$alkylpyridinyl, $C_{1\text{-}4}$alkylisoxazolidinyl, $C_{1\text{-}4}$alkylmorpholinyl, $C_{1\text{-}4}$alkylthiazolyl, and $C_{1\text{-}4}$alkylpyrazinyl wherein $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkylphenyl, $C_{1\text{-}4}$alkylphenylketone, $C_{1\text{-}4}$benzyl-piperazine, $C_{1\text{-}4}$alkylthienyl, $C_{1\text{-}4}$alkylpyridinyl, $C_{1\text{-}4}$alkylisoxazolidinyl, $C_{1\text{-}4}$alkylmorpholinyl, $C_{1\text{-}4}$alkylthiazolyl, and $C_{1\text{-}4}$alkylpyrazinyl are optionally substituted with $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkoxyl, hydroxyl, perhalogenated $C_{1\text{-}4}$alkyl, or halo. In one embodiment, R_1 and/or R_2 is a substituted or unsubstituted, arylalkyl or heteroarylalkyl. In one embodiment, the heteroarylalkyl is selected from $C_{1\text{-}4}$alkylpyrrolyl, $C_{1\text{-}4}$alkylfuryl,

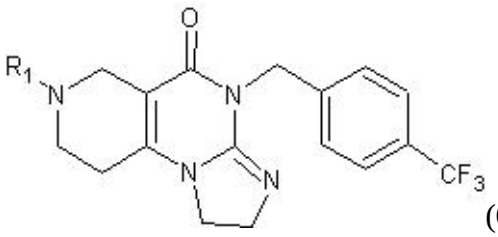
a benzyl or phenylethyl group. In one embodiment, the arylalkyl is substituted with C_{1-4}alkyl, C_{1-4}alkoxyl, hydroxyl, perhalogenated C_{1-4}alkyl, or halo. In one embodiment, R_b is selected from halo, CH_3, CF_3, and OCH_3. In one embodiment, one or more of R_{a1}, R_{a2}, R_{a4}, and R_{a5} is selected from halo, CH_3, CF_3, and OCH_3. In one embodiment, R_{a1}, R_{a2}, R_{a4}, and R_{a5} are H, and R_b is selected from halo, CH_3, CF_3, and OCH_3. In one embodiment, R_b is a halogen, *e.g.*, F, and R_{a1} is CH_3. In one embodiment, R_b is F or Cl, and R_{a2} is F or Cl. In one embodiment, R_b is CF_3. In one embodiment, R_b is OCH_3. In one embodiment, R_b and R_{a1} are Cl.

[00130] In one embodiment, compound (**50**) has the structure of compound (**55**):



(55), where R_{a1}, R_{a2}, R_{a4}, R_{a5}, and R_b are as defined above. In one embodiment, R_b is selected from halo, CH_3, CF_3, and OCH_3. In one embodiment, one or more of R_{a1}, R_{a2}, R_{a4}, and R_{a5} is selected from halo, CH_3, CF_3, and OCH_3. In one embodiment, R_{a1}, R_{a2}, R_{a4}, and R_{a5} are H, and R_b is selected from halo, CH_3, CF_3, and OCH_3. In one embodiment, R_b is halo, *e.g.*, F, and R_{a1} is CH_3. In one embodiment, R_b is F or Cl, and R_{a2} is F or Cl. In one embodiment, R_b is CF_3. In one embodiment, R_b is OCH_3. In one embodiment, R_b and R_{a1} are Cl.

[00131] In one embodiment, compound (**10**) has the structure of compound (**60**)



(**60**). In one embodiment, R_1 is H. In one embodiment, R_1 is a substituted or unsubstituted arylalkyl, such as benzyl or phenylethyl. In one embodiment, R_1 is a substituted or unsubstituted heterocycloalkylalkyl or a substituted or unsubstituted heteroarylalkyl, such as CH_2-(2-thienyl), CH_2-(3-thienyl), CH_2-4-methyl-2-thiazolyl, CH_2-2-pyrazinyl, CH_2CH_2(4-N-benzyl-piperazine), CH_2-(3-isoxazolidinyl), CH_2-2-pyridinyl, CH_2-3-pyridinyl, and CH_2CH_2-(4-morpholinyl). In one embodiment, the arylalkyl is substituted with C_{1-4}alkyl, C_{1-4}alkoxyl, hydroxyl, perhalogenated C_{1-4}alkyl, or halo. In one embodiment, the benzyl is substituted with one or more halogens. In one embodiment, the benzyl is substituted with one or more substituents selected from halo (*e.g.*, F), CH_3, CF_3, and OCH_3. In one embodiment, the benzyl is substituted at the para position with a halo, CH_3, CF_3, or OCH_3 substituent. In one embodiment, R_1 is fluorophenyloxobutyl or hydroxyphenylethyl

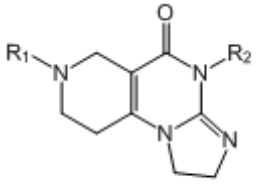
treatment. The levels for the pre-determined standard may be obtained from normal healthy subjects. Immunoassays can be used to assay protein levels in a sample.

[00146] In one aspect, provided herein are methods of treating and assessing the effectiveness of a treatment in a subject having a condition. In one embodiment, the method comprises (i) treating the subject according to a method of treatment described herein (ii) assessing as decribed herein the effectiveness of the treatment. In one embodiment, the subject has, or is at risk of having, cancer. In one embodiment, the treatment regimen comprises administering an effective amount of an imipridone, such as ONC201 or an analog thereof. In one embodiment, the treatment regimen comprises administering an effective amount of compound (**1**). In one embodiment, the treatment regimen comprises administering an effective amount of a compound of formula (**10**). In one embodiment, the compound of formula (**10**) is a compound of formula (**40**), *e.g.*, a compound of formula (**45**). In one embodiment, a compound of formula (**10**) is a compound of formula (**50**), *e.g.*, a compound formula (**55**). In one embodiment, the compound of formula (**10**) is a compound of formula (**80**). In one embodiment, the compound of formula (**10**) is a compound of formula (**90**). In one embodiment, the compound of formula (**10**) is a compound of formula (**60**). In one embodiment, analogs of compound (**1**) have a structure selected from the structures of formula (**25**), formula (**26**), formula (**27**), formula (**28**), formula (**29**), formula (**30**), or formula (**31**).

[00147] Other conditions that may be suitable for the methods described herein include Attention Deficit Disorder; Addiction; Epilepsy; Viral infection; Inflammation; Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis; Cardiovascular diseases such as coronary artery disease, cardiomyopathy, hypertensive heart disease, heart failure, pulmonary heart disease, cardiac dysrhythmias, inflammatory heart disease, endocarditis, inflammatory cardiomegaly, myocarditis, valvular heart disease, cerebrovascular disease, peripheral arterial disease, congenital heart disease, rheumatic heart disease; Diabetes; and light chain amyloidosis.

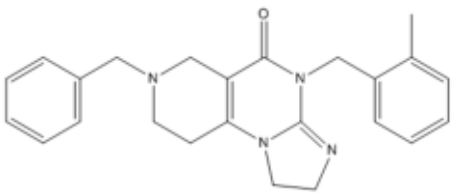
V. COMPOSITIONS

[00148] In one aspect, pharmaceutical compositions are provided, comprising compounds of formula (**10**):



(10)

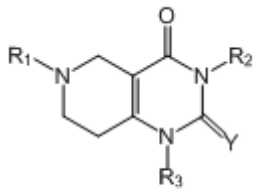
or of formula (**1**):



and their pharmaceutically acceptable saltsIn one embodiment, the salt is a pharmaceutically

general principles and concepts described above in conjunction with ONC201 and compounds of formula (**10)** and their salts, including principles and concepts related to methods and pharmaceutical compositions, apply with equal force to the following analogs and salts thereof.

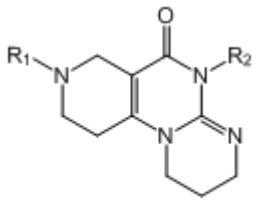
[00246] In one embodiment, the analogs have the structure of compound (**25**):



(25)

, wherein Y is NR_4 or O, and wherein R_1, R_2, R_3, and R_4 independently represent H, alkyl, cycloalkyl, cycloalkylalkyl, carboxyl, haloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, aralkyl, hydroxyalkyl, alkoxy, aryloxy, alkoxyalkyl, alkoxycarbonyl, aralkoxy, aralkylthio, alkanoyl, mercapto, alkylthio, arylthio, alkylsulfinyl, arylsulfinyl, alkylsulfonyl, arylsulfonyl, heteroaryl, acyl, and heterocycle radicals. In one embodiment, R_1, R_2, R_3, and R_4 are optionally substituted. In one embodiment, some or all hydrogens in R_1, R_2, R_3, and R_4 are substituted by deuterium. In other embodiments, R_1, R_2, R_3, and R_4 are independently selected from the group consisting of H, $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkylphenyl, $C_{1\text{-}4}$alkylphenylketone, $C_{1\text{-}4}$benzyl-piperazine, and $C_{1\text{-}4}$alkylthienyl, wherein $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkylphenyl, $C_{1\text{-}4}$alkylphenylketone, and $C_{1\text{-}4}$benzyl-piperazine are optionally substituted with $C_{1\text{-}4}$alkyl, hydroxyl, or halo. In still other embodiments, R_1, R_2, R_3, and R_4 are independently selected from the group consisting of H, CH_3, CH_2Ph, CH_2-((2-Cl)-Ph), CH_2-(2-thienyl), CH_2CH_2Ph, CH_2CH_2(4-N-benzyl-piperazine), CH_2-(2,4-di F-Ph), CH_2-((2-CH_3)-Ph), $CH_2CHOHPh$, and $(CH_2)_3CO$-4F-Ph.

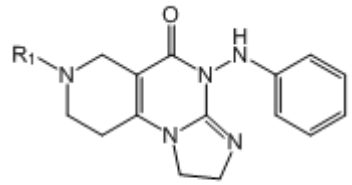
[00247] In one embodiment, the analogs have the structure of compound (**26**):



(26)

, wherein R_1 and R_2 independently represent H, alkyl, cycloalkyl, cycloalkylalkyl, carboxyl, haloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, aralkyl, hydroxyalkyl, alkoxy, aryloxy, alkoxyalkyl, alkoxycarbonyl, aralkoxy, aralkylthio, alkanoyl, mercapto, alkylthio, arylthio, alkylsulfinyl, arylsulfinyl, alkylsulfonyl, arylsulfonyl, heteroaryl, acyl, and heterocycle radicals. In one embodiment, R_1 and R_2 are independently selected from the group consisting of H, $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkylphenyl, $C_{1\text{-}4}$alkylphenylketone, $C_{1\text{-}4}$benzyl-piperazine, and $C_{1\text{-}4}$alkylthienyl, wherein $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkylphenyl,

[00251] In one embodiment, the analogs have the structure of compound (**27**):

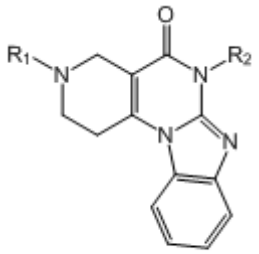


(27)

, wherein R_1 is H, alkyl, cycloalkyl, cycloalkylalkyl, carboxyl, haloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, aralkyl, hydroxyalkyl, alkoxy, aryloxy, alkoxyalkyl, alkoxycarbonyl, aralkoxy, aralkylthio, alkanoyl, mercapto, alkylthio, arylthio, alkylsulfinyl, arylsulfinyl, alkylsulfonyl, arylsulfonyl, heteroaryl, acyl, and heterocycle radicals. In one embodiment, R_1 is selected from the group consisting of H, $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkylphenyl, $C_{1\text{-}4}$alkylphenylketone, $C_{1\text{-}4}$benzyl-piperazine, and $C_{1\text{-}4}$alkylthienyl, wherein $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkylphenyl, $C_{1\text{-}4}$alkylphenylketone, and $C_{1\text{-}4}$benzyl-piperazine are optionally substituted with $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkoxyl, hydroxyl, perhalogenated $C_{1\text{-}4}$alkyl, or halo. In one embodiment, R_1 is selected from the group consisting of H, CH_3, CH_2Ph, CH_2-((2-Cl)-Ph), CH_2-(2-thienyl), CH_2CH_2Ph, CH_2CH_2(4-N-benzyl-piperazine), CH_2-(2,4-di F-Ph), CH_2-((2-CH_3)-Ph), $CH_2CHOHPh$, and $(CH_2)_3CO$-4F-Ph.

[00252] In one embodiment, R_1 is a benzyl optionally substituted with one or more of the following substituents alone or in combination in the ortho, meta, and/or para positions of the benzyl ring: -CH_3, -NO_2, -OCH_3, -CXH_2, -CX_2H, -CX_3, -$CH_2(CX_3)$, -$CH(CX_3)_2$, -$C(CX_3)_3$, -C_pX_{2p+1}, -OCX_3, or –OC_pX_{2p+1}, where p is an integer from 2 to 20 and where X is a halogen including F, Cl, Br, or I; preferably, F, Cl, or Br; more preferably, F or Cl. In one embodiment, R_1 is a H. In one embodiment, R_1 is a substituted or an unsubstituted arylalkyl, such as a benzyl or phenylethyl group. In one embodiment, the arylalkyl is substituted with $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkoxyl, hydroxyl, perhalogenated $C_{1\text{-}4}$alkyl, or halo.

[00253] In one embodiment, the analogs have the structure of compound (**28**):

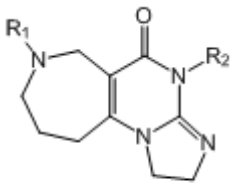


(28)

, wherein R_1 and R_2 independently represent H, alkyl, cycloalkyl, cycloalkylalkyl, carboxyl, haloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, aralkyl, hydroxyalkyl, alkoxy, aryloxy, alkoxyalkyl, alkoxycarbonyl, aralkoxy, aralkylthio, alkanoyl, mercapto, alkylthio, arylthio, alkylsulfinyl, arylsulfinyl, alkylsulfonyl, arylsulfonyl, heteroaryl,

or halo. In one embodiment, the heterocycloalkylalkyl or heteroarylalkyl is substituted with one or more substituents selected from the group consisting of halo, $-CH_3$, $-CF_3$, and $-OCH_3$.

[00257] In one embodiment, the analogs have the structure of compound (**29**):



(29)

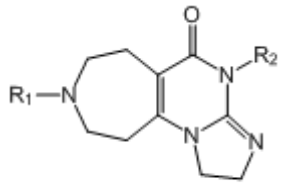
, wherein R_1 and R_2 independently represent H, alkyl, cycloalkyl, cycloalkylalkyl, carboxyl, haloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, aralkyl, hydroxyalkyl, alkoxy, aryloxy, alkoxyalkyl, alkoxycarbonyl, aralkoxy, aralkylthio, alkanoyl, mercapto, alkylthio, arylthio, alkylsulfinyl, arylsulfinyl, alkylsulfonyl, arylsulfonyl, heteroaryl, acyl, and heterocycle radicals. In one embodiment, R_1 and R_2 are independently selected from the group consisting of H, $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkylphenyl, $C_{1\text{-}4}$alkylphenylketone, $C_{1\text{-}4}$benzyl-piperazine, and $C_{1\text{-}4}$alkylthienyl, wherein $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkylphenyl, $C_{1\text{-}4}$alkylphenylketone, and $C_{1\text{-}4}$benzyl-piperazine are optionally substituted with $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkoxyl, hydroxyl, perhalogenated $C_{1\text{-}4}$alkyl, or halo. In one embodiment, R_1 is selected from the group consisting of H, CH_3, CH_2Ph, CH_2-((2-Cl)-Ph), CH_2-(2-thienyl), CH_2CH_2Ph, CH_2CH_2(4-N-benzyl-piperazine), CH_2-(2,4-di F-Ph), CH_2-((2-CH_3)-Ph), $CH_2CHOHPh$, and $(CH_2)_3$CO-4F-Ph. In one embodiment, R_2 is selected from the group consisting of H, CH_3, CH_2Ph, CH_2-((2-Cl)-Ph), CH_2-(2-thienyl), CH_2CH_2Ph, CH_2CH_2(4-N-benzyl-piperazine), CH_2-(2,4-di F-Ph), CH_2-((2-CH_3)-Ph), $CH_2CHOHPh$, and $(CH_2)_3$CO-4F-Ph. In one embodiment, when R_1 is CH_2Ph, R_2 is not CH_2-(2-CH_3-Ph). In one embodiment, R_1 is CH_2Ph and R_2 is CH_2-(2-CH_3-Ph). In one embodiment, R_1 is CH_2Ph and R_2 is CH_2-(2,4-di F-Ph). In one embodiment, R_1 is CH_2Ph and R_2 is CH_2-(4-CF_3-Ph).

[00258] In one embodiment, R_1 is a benzyl optionally substituted with one or more of the following substituents alone or in combination in the ortho, meta, and/or para positions of the benzyl ring: $-CH_3$, $-NO_2$, $-OCH_3$, $-CXH_2$, $-CX_2H$, $-CX_3$, $-CH_2(CX_3)$, $-CH(CX_3)_2$, $-C(CX_3)_3$, $-C_pX_{2p+1}$, $-OCX_3$, or $-OC_pX_{2p+1}$, where p is an integer from 2 to 20 and where X is a halogen including refers to F, Cl, Br, or I; preferably, F, Cl, or Br; more preferably, F or Cl. In one embodiment, R_2 is a benzyl substituted with one or more of the following substituents alone or in combination in the ortho, meta, and/or para positions of the benzyl ring: $-CH_3$, $-NO_2$, $-OCH_3$, $-CXH_2$, $-CX_2H$, $-CX_3$, $-CH_2(CX_3)$, $-CH(CX_3)_2$, $-C(CX_3)_3$, $-C_pX_{2p+1}$, $-OCX_3$, or $-OC_pX_{2p+1}$, where p is an integer from 2 to 20 and where X is a halogen.

[00259] In one embodiment, R_1 is a H. In one embodiment, R_1 is a substituted or an unsubstituted arylalkyl, such as a benzyl or phenylethyl group. In one embodiment, the arylalkyl is substituted with C_{1-4}alkyl, C_{1-4}alkoxyl, hydroxyl, perhalogenated C_{1-4}alkyl, or halo.

[00260] In one embodiment, R_2 is a substituted or an unsubstituted arylalkyl, such as a benzyl or phenylethyl group. In one embodiment, the arylalkyl is substituted with C_{1-4}alkyl, C_{1-4}alkoxyl, hydroxyl, perhalogenated C_{1-4}alkyl, or halo. In one embodiment, the arylalkyl is substituted with one or more substituents selected from the group consisting of halo, $-CH_3$, $-CF_3$, and $-OCH_3$. In one embodiment, R_2 is a substituted or an unsubstituted heterocycloalkylalkyl, such as a morpholinoalkyl or piperazinylalkyl group. In one embodiment, R_2 is a substituted or an unsubstituted heteroarylalkyl, such as an isoxazolidinylmethyl or pyridylmethyl group. In one embodiment, the heterocycloalkylalkyl or heteroarylalkyl is substituted with C_{1-4}alkyl, C_{1-4}alkoxyl, hydroxyl, perhalogenated C_{1-4}alkyl, or halo. In one embodiment, the heterocycloalkylalkyl or heteroarylalkyl is substituted with one or more substituents selected from the group consisting of halo, $-CH_3$, $-CF_3$, and $-OCH_3$.

[00261] In one embodiment, the analogs have the structure of compound (**30**):



(30)

, wherein R_1 and R_2 independently represent H, alkyl, cycloalkyl, cycloalkylalkyl, carboxyl, haloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, aralkyl, hydroxyalkyl, alkoxy, aryloxy, alkoxyalkyl, alkoxycarbonyl, aralkoxy, aralkylthio, alkanoyl, mercapto, alkylthio, arylthio, alkylsulfinyl, arylsulfinyl, alkylsulfonyl, arylsulfonyl, heteroaryl, acyl, and heterocycle radicals. In one embodiment, R_1 and R_2 are independently selected from the group consisting of H, C_{1-4}alkyl, C_{1-4}alkylphenyl, C_{1-4}alkylphenylketone, C_{1-4}benzyl-piperazine, and C_{1-4}alkylthienyl, wherein C_{1-4}alkyl, C_{1-4}alkylphenyl, C_{1-4}alkylphenylketone, and C_{1-4}benzyl-piperazine are optionally substituted with C_{1-4}alkyl, C_{1-4}alkoxyl, hydroxyl, perhalogenated C_{1-4}alkyl, or halo. In one embodiment, R_1 is selected from the group consisting of H, CH_3, CH_2Ph, CH_2-((2-Cl)-Ph), CH_2-(2-thienyl), CH_2CH_2Ph, CH_2CH_2(4-N-benzyl-piperazine), CH_2-(2,4-di F-Ph), CH_2-((2-CH_3)-Ph), $CH_2CHOHPh$, and $(CH_2)_3CO$-4F-Ph. In one embodiment, R_2 is selected from the group consisting of H, CH_3, CH_2Ph, CH_2-((2-Cl)-Ph), CH_2-(2-thienyl), CH_2CH_2Ph, CH_2CH_2(4-N-benzyl-piperazine), CH_2-(2,4-di F-Ph), CH_2-((2-CH_3)-Ph), $CH_2CHOHPh$, and $(CH_2)_3CO$-4F-Ph. In one embodiment, when R_1 is CH_2Ph, R_2 is not CH_2-(2-CH_3-Ph). In one embodiment, R_1 is CH_2Ph

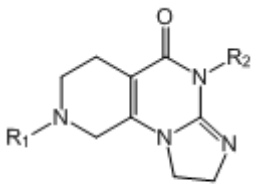
and R_2 is CH_2-(2-CH_3-Ph). In one embodiment, R_1 is CH_2Ph and R_2 is CH_2-(2,4-di F-Ph). In one embodiment, R_1 is CH_2Ph and R_2 is CH_2-(4-CF_3-Ph).

[00262] In one embodiment, R_1 is a benzyl optionally substituted with one or more of the following substituents alone or in combination in the ortho, meta, and/or para positions of the benzyl ring: $-CH_3$, $-NO_2$, $-OCH_3$, $-CXH_2$, $-CX_2H$, $-CX_3$, $-CH_2(CX_3)$, $-CH(CX_3)_2$, $-C(CX_3)_3$, $-C_pX_{2p+1}$, $-OCX_3$, or $-OC_pX_{2p+1}$, where p is an integer from 2 to 20 and where X is a halogen including refers to F, Cl, Br, or I, preferably, F, Cl, or Br, more preferably, F or Cl. In one embodiment, R_2 is a benzyl substituted with one or more of the following substituents alone or in combination in the ortho, meta, and/or para positions of the benzyl ring: $-CH_3$, $-NO_2$, $-OCH_3$, $-CXH_2$, $-CX_2H$, $-CX_3$, $-CH_2(CX_3)$, $-CH(CX_3)_2$, $-C(CX_3)_3$, $-C_pX_{2p+1}$, $-OCX_3$, or $-OC_pX_{2p+1}$, where p is an integer from 2 to 20 and where X is a halogen.

[00263] In one embodiment, R_1 is a H. In one embodiment, R_1 is a substituted or an unsubstituted arylalkyl, such as a benzyl or phenylethyl group. In one embodiment, the arylalkyl is substituted with $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkoxyl, hydroxyl, perhalogenated $C_{1\text{-}4}$alkyl, or halo.

[00264] In one embodiment, R_2 is a substituted or an unsubstituted arylalkyl, such as a benzyl or phenylethyl group. In one embodiment, the arylalkyl is substituted with $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkoxyl, hydroxyl, perhalogenated $C_{1\text{-}4}$alkyl, or halo. In one embodiment, the arylalkyl is substituted with one or more substituents selected from the group consisting of halo, $-CH_3$, $-CF_3$, and $-OCH_3$. In one embodiment, R_2 is a substituted or an unsubstituted heterocycloalkylalkyl, such as a morpholinoalkyl or piperazinylalkyl group. In one embodiment, R_2 is a substituted or unsubstituted heteroarylalkyl, such as an isoxazolidinylmethyl or pyridylmethyl group. In one embodiment, the heterocycloalkylalkyl or heteroarylalkyl is substituted with $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkoxyl, hydroxyl, perhalogenated $C_{1\text{-}4}$alkyl, or halo. In one embodiment, the heterocycloalkylalkyl or heteroarylalkyl is substituted with one or more substituents selected from the group consisting of halo, $-CH_3$, $-CF_3$, and $-OCH_3$.

[00265] In one embodiment, the analogs have the structure of compound (**31**):

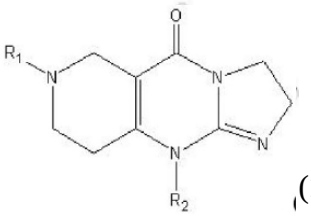


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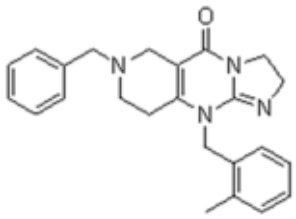
, wherein R_1 and R_2 independently represent H, alkyl, cycloalkyl, cycloalkylalkyl, carboxyl, haloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, aralkyl, hydroxyalkyl, alkoxy, aryloxy, alkoxyalkyl, alkoxycarbonyl, aralkoxy, aralkylthio, alkanoyl, mercapto, alkylthio, arylthio, alkylsulfinyl, arylsulfinyl, alkylsulfonyl, arylsulfonyl, heteroaryl,

or halo. In one embodiment, the heterocycloalkylalkyl or heteroarylalkyl is substituted with one or more substituents selected from the group consisting of halo, $-CH_3$, $-CF_3$, and $-OCH_3$.

[00269] In one embodiment, provided herein are compounds of formula (**100**):



(**100**), wherein R_1 and R_2 are independently selected from H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl, alkoxycarbonyl, aralkoxy, aralkylthio, and acyl radicals. In one embodiment, R_1 is CH_2Ph and R_2 is CH_2-(2-CH_3-Ph), which is an ONC201 linear isomer (i.e., TIC-10)



TIC-10, which lacks anti-cancer activity (Jacob *et al.*, *Angew. Chem. Int. Ed.*, (2014) **53**:6628; Wagner *et al.*, *Oncotarget* (2015) **5**(24):12728). But as shown in the Examples TIC-10 is a CXCR7 agonist. CXCR7 agonists can be used for liver regeneration and preventing or treating liver fibrosis (*Nature* (2014) **505**:97).

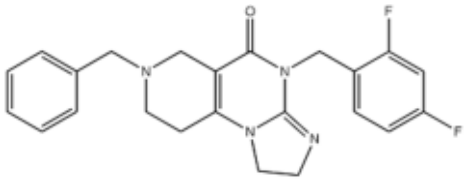
[00270] In one embodiment, R_1 and R_2 are independently selected from the group consisting of H, $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkylphenyl, $C_{1\text{-}4}$alkylphenylketone, $C_{1\text{-}4}$benzyl-piperazine, $C_{1\text{-}4}$alkylthienyl, $C_{1\text{-}4}$alkylpyridinyl, $C_{1\text{-}4}$alkylisoxazolidinyl, $C_{1\text{-}4}$alkylmorpholinyl, $C_{1\text{-}4}$alkylthiazolyl, and $C_{1\text{-}4}$alkylpyrazinyl wherein $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkylphenyl, $C_{1\text{-}4}$alkylphenylketone, $C_{1\text{-}4}$benzyl-piperazine, $C_{1\text{-}4}$alkylthienyl, $C_{1\text{-}4}$alkylpyridinyl, $C_{1\text{-}4}$alkylisoxazolidinyl, $C_{1\text{-}4}$alkylmorpholinyl, $C_{1\text{-}4}$alkylthiazolyl, and $C_{1\text{-}4}$alkylpyrazinyl are optionally substituted with $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkoxyl, hydroxyl, perhalogenated $C_{1\text{-}4}$alkyl, or halo. In one embodiment, R_1 and/or R_2 is a substituted or unsubstituted, arylalkyl or heteroarylalkyl. In one embodiment, the heteroarylalkyl is selected from $C_{1\text{-}4}$alkylpyrrolyl, $C_{1\text{-}4}$alkylfuryl, $C_{1\text{-}4}$alkylpyridyl, $C_{1\text{-}4}$alkyl-1,2,4-thiadiazolyl, $C_{1\text{-}4}$alkylpyrimidyl, $C_{1\text{-}4}$alkylthienyl, $C_{1\text{-}4}$alkylisothiazolyl, $C_{1\text{-}4}$alkylimidazolyl, $C_{1\text{-}4}$alkyltetrazolyl, $C_{1\text{-}4}$alkylpyrazinyl, $C_{1\text{-}4}$alkylpyrimidyl, $C_{1\text{-}4}$alkylquinolyl, $C_{1\text{-}4}$alkylisoquinolyl, $C_{1\text{-}4}$alkylthiophenyl, $C_{1\text{-}4}$alkylbenzothienyl, $C_{1\text{-}4}$alkylisobenzofuryl, $C_{1\text{-}4}$alkylpyrazolyl, $C_{1\text{-}4}$alkylindolyl, $C_{1\text{-}4}$alkylpurinyl, $C_{1\text{-}4}$alkylcarbazolyl, $C_{1\text{-}4}$alkylbenzimidazolyl, and $C_{1\text{-}4}$alkylisoxazolyl.

[00271] In one embodiment, R_1 and/or R_2 is a benzyl optionally substituted with one or more of the following substituents on the benzyl ring: X, $-CH_3$, $-NO_2$, $-OCH_3$, $-CN$, $-CXH_2$, $-CX_2H$, C_2-C_4 alkyl, $-CX_3$, $-CH_2(CX_3)$, $-CH(CX_3)_2$, $-C(CX_3)_3$, $-C_pX_{2p+1}$, $-OCX_3$, $-OC_pH_{2p+1}$, $-OC_pX_{2p+1}$,

[00294] ONC212 efficacy was determined in a leukemia xenograft model with MV411 AML cells resistant to standard-of-care cytarabine (Fig 30). ONC212 50 mg/kg significantly reduced leukemia xenograft tumor growth with oral weekly administration while ONC201 was not efficacious in this model at similar doses (Fig 30A). Interesting, biweekly ONC212 dosing with 25 mg/kg and weekly/biweekly dosing with 5 mg/kg was not efficacious (Fig 30B). None of these ONC212 administration regimens were associated with body weight loss (Fig 30C) or gross observations.

[00295] ONC212 25 mg/kg represents NOAEL in mouse and rat non-GLP oral single dose studies which is also the efficacious dose in mouse xenograft studies. ONC212 is approximately 10 fold more toxic compared to ONC201 (NOAEL 225 mg/kg in rat non-GLP oral single dose study).

ONC206



[00296] ONC206 demonstrated efficacy in a Ewing's sarcoma xenograft model (Fig. 31). MHH-ES-1 Ewing's sarcoma cells (5×10^6) were subcutaneously implanted in the flanks of athymic nude mice. ONC206 (PO) and methotrexate (IV) were administered on day 1 and day 13 as indicated. Tumor volume (Fig. 31A) and body weight (Fig. 31B) (n=4) was measured on indicated days.

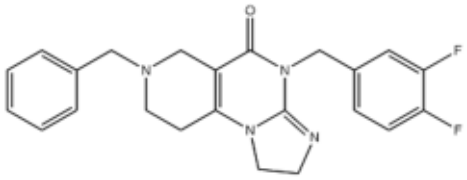
[00297] In addition, the IC_{50} of ONC201 and ONC206 (5nM - 5μM, 72h) upon treatment of several cell lines (n=3) were determined and shown below in Table 11.

TABLE 12

Cell line	ONC201 IC_{50} (μM)	ONC206 IC_{50} (μM)
MV411 (AML)	3.25	0.2
K562 (CML)	>5	0.22
MOLM14 (AML)	3.92	0.27
MHH-ES-1 (Ewing's sarcoma)	5.65	0.61
HFF (Normal Fibroblast)		>5

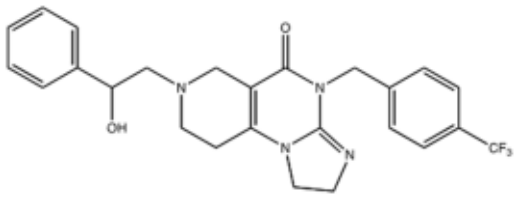
[00298] ONC206 showed up to 20 fold improvement compared to ONC201 in *in vitro* potency with no in vitro toxicity to normal cells at therapeutic doses (Table 12). With ONC206, only 2-fold increased toxicity (NOAEL 125 mg/kg) was noted overall relative to ONC201 (NOAEL 225 mg/kg) in rat non-GLP oral single dose study. *In vivo* efficacy in Ewing's sarcoma model with no toxicity (Fig 31). ONC206 efficacy was comparable to chemotherapy methotrexate, but chemotherapy was associated with body weight loss.

ONC213



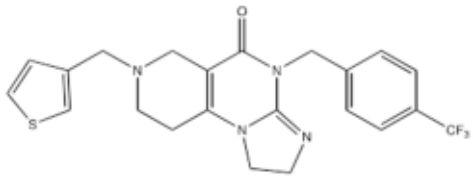
[00299] *In vitro* profiling of GPCR activity using a hetereologous reporter assay for arrestin recruitment, a hallmark of GPCR activation, indicated that ONC213 selectively targets DRD2/3 and GPR132/91 (Figure 32). Dual targeting of DRD2/3 and GPR132/91 represents a novel strategy for anti-cancer efficacy without toxicity. ONC213 is a DRD2/3 inhibitor and a GPR132/91 agonist. DRD2/3 potency of ONC213 is more than ONC201 but less than ONC206. GPR132 potency of ONC213 is less than ONC212. Specifically, ONC213 demonstrated *in vitro* anti-cancer potency in HCT116/RPMI8226 cancer cells similar to ONC212, but *in vitro* toxicity to normal cells was reduced compared to ONC212 (Figure 33). The safety profile of ONC213 confirmed in mouse MTD study with NOAEL 75 mg/kg three times that of ONC212 (25mg/kg). The GPR91 agonist activity of ONC213 provides an opportunity for immunology, immune-oncology and hematopoietic applications (*Nature Immunology* **9**:1261 (2008); *J Leukoc Biol.* **85**(5):837 (May 2009)).

ONC237



[00300] *In vitro* profiling of GPCR activity using a hetereologous reporter assay for arrestin recruitment, a hallmark of GPCR activation, indicated that ONC237 selectively targets DRD5 and GPR132 (Figure 34). ONC237 is a GPR132 agonist and DRD5 antagonist and has reduced anticancer efficacy (IC_{50} 31.2 µM) compared to ONC201. This data show that combining GPR132 agonist activity with DRD5 (D1-like dopamine receptor) antagonist activity results in poor anti-cancer effects compared to ONC213 which combines GPR132 agonist and DRD2/3 antagonist activity.

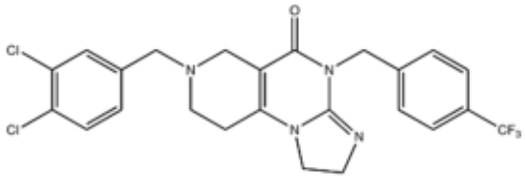
ONC236



[00301] *In vitro* profiling of GPCR activity using a hetereologous reporter assay for arrestin recruitment, a hallmark of GPCR activation, indicated that ONC236 is a highly selective

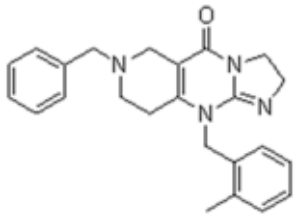
GPR132 agonist (Figure 35). ONC236 has anticancer efficacy (IC_{50} 88nM) comparable to ONC212 (10nM) better than ONC206/ONC201, completeness of response is better than ONC201 but not ONC212 in HCT116 cells.

ONC234



[00302] *In vitro* profiling of GPCR activity using a hetereologous reporter assay for arrestin recruitment, a hallmark of GPCR activation, indicated that ONC234 is a broad spectrum and potent GPCR targeting small molecule (Figures 36 and 38). ONC234 hits several GPCRs including activity as an antagonist activity for adrenergic, histamine, serotonin, CHRM, CCR, DRD2/5 receptors, as well as CXCR7 agonist activity.ONC236 has anticancer efficacy (IC_{50} 234nM) similar to ONC206, completeness of response same as ONC212, and better than ONC201 in HCT116 cells.

ONC201 LINEAR ISOMER (TIC-10)



(TIC-10)

[00303] *In vitro* profiling of GPCR activity using a hetereologous reporter assay for arrestin recruitment, a hallmark of GPCR activation, indicated that the ONC201 linear isomer (TIC-10) is a CXCR7 agonist (Figure 37). CXCR7 agonists can be used for liver regeneration and preventing/treating fibrosis, such as liver fibrosis (*Nature* **505**:97 (2014)). Fibrosis is the formation of excess fibrous connective tissue in an organ or tissue, including as a result of wound healing. Examples of fibrosis includes, pulmonary fibrosis, including cystic fibrosis and idiopathic pulmonary fibrosis; radiation-induced lung injury following treatment for cancer; liver fibrosis (cirrhosis); heart fibrosis, including atrial fibrosis, endomyocardial fibrosis, and old myocardial infarction; glial scar; arthrofibrosis; Crohn's Disease; dupuytren's contracture; keloids; mediastinal fibrosis; myelofibrosis; Peyronie’s disease; nephrogenic systemic fibrosis; progressive massive fibrosis; retroperitoneal fibrosis; scleroderma/systemic sclerosis; and adhesive capsulitis.