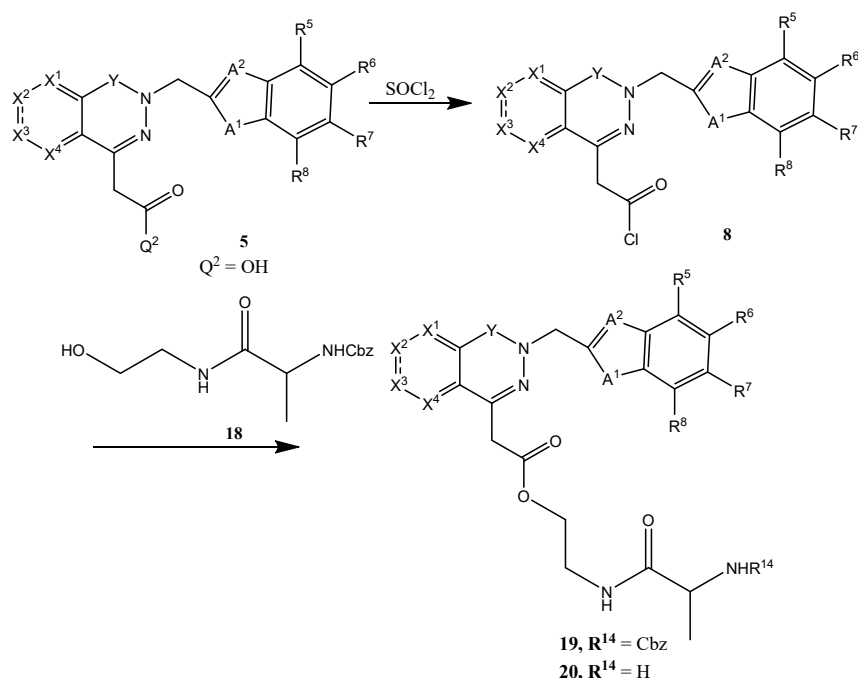


[0179] In certain embodiments, the reaction with compound **13** or **14** according to Scheme 7 can be carried out in the presence of an additive, such as DMAP, and the like. In certain embodiments, the reaction with compound **9** can be carried out in the absence of an additive.

[0180] In certain embodiments, the reaction with compound **13** or **14** according to Scheme 7 can be carried out using aprotic solvents, such as DMF, THF, and the like.

[0181] In certain embodiments, compounds such as **13** or **14** comprise protecting groups, which can be removed as described, for example, in Greene *et al.*, *Protective Groups in Organic Synthesis* (4th ed. 2006). For example, compounds having carboxylic acid group as Q² (e.g., (**5**)) can be reacted with a suitable reagent, such as thionyl chloride (SOCl₂), oxalyl chloride (COCl)₂, phosphoryl chloride (POCl₃), or the like, followed by reaction with a suitable reagent, such as benzyl (1-((2-aminoethyl) amino)-1-oxopropan-2-yl) carbamate (**18**), or the like, to obtain compound **19**. Deprotection of compound **19** provides a compound of formula **20**.

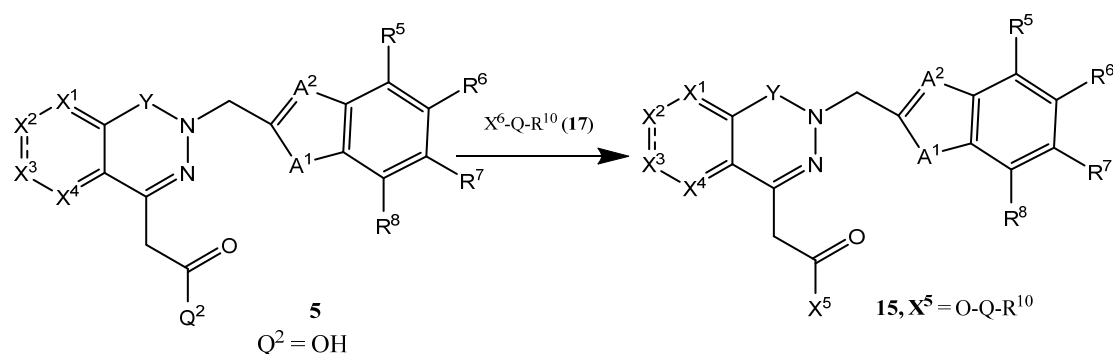
[0182] For example, the following exemplary synthesis can be carried out according to Scheme 8.



[0187] In certain embodiments, the reaction according to Scheme 9 can be carried out using aprotic solvents, such as DMF, THF, and the like.

[0188] Other suitable reactions of the compound of Formula (5), (6), or (7) are possible to obtain different forms of the compound of Formula (I-1), (I-2), or (I-3), respectively. For example, compounds having carboxylic acid group as Q^2 (e.g., 5) can be reacted with a suitable reagent, such as X^6-Q-R^{10} (17), where X^6 is a halogen, in the presence of an additive such as tetra-*n*-butylammonium bromide (TBAB), tetra-*n*-butylammonium iodide (TBAI), tetra-*n*-butylammonium chloride (TBAC), or the like, to obtain a compound of Formula (I-1), such as compound 15.

[0189] For example, the following exemplary synthesis can be carried out according to Scheme 10.



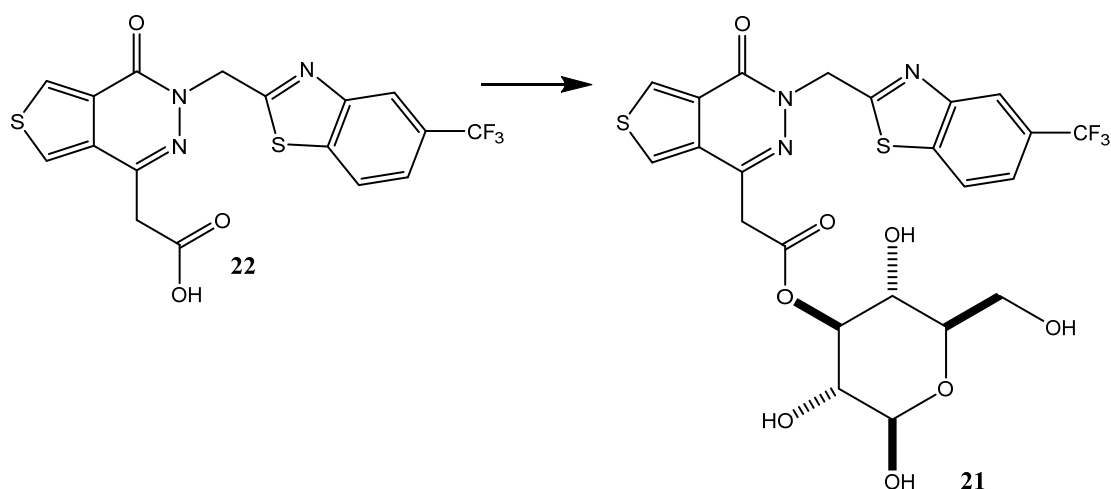
Scheme 10

[0190] In certain embodiments, X^6-Q-R^{10} (17) is Cl-Q-R^{10} . In certain embodiments, X^6-Q-R^{10} (17) is Br-Q-R^{10} . In certain embodiments, X^6-Q-R^{10} (17) is I-Q-R^{10} .

[0191] In certain embodiments, the reaction according to Scheme 10 can be carried out in the presence of a base, such as triethylamine, diisopropylethylamine, imidazole, pyridine, and the like.

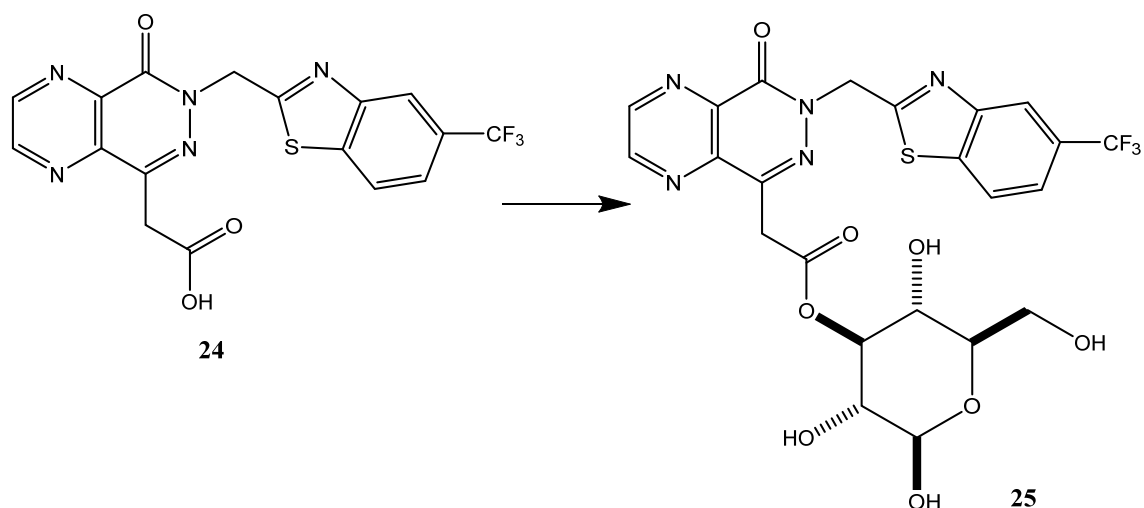
[0192] In certain embodiments, the reaction according to Scheme 10 can be carried out in the absence of TBAI, TBAB, or TBAC.

(trifluoromethyl)benzo[d]thiazol-2-yl)methyl)-3,4-dihydrothieno[3,4- d]pyridazin-1-yl)acetate (Compound **21**):



[0242] 2-(4-oxo-3-((5-(trifluoromethyl)benzo[d]thiazol-2-yl)methyl)-3,4-dihydrothieno[3,4-d]pyridazin-1-yl)acetic acid (Compound **22**) is prepared using the same method described previously in WO2017/038505.

[0243] (2R,3R,4S,5R,6R)-2,3,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-4-yl 2-((4-oxo-3-((5-(trifluoromethyl)benzo[d]thiazol-2-yl)methyl)-3,4-dihydrothieno[3,4- d]pyridazin-1-yl)acetate (Compound **21**): (Step 1) To a stirred solution of Compound **22** and (3aR,5S,6S,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3- d][1,3]dioxol-6-ol (Compound **9**) in THF is added 1-ethyl-3-(3- dimethylaminopropyl)carbodiimide, NEt_3 , and DMAP (catalytic). The reaction is stirred at room temperature until completion, as monitored by TLC. The reaction mixture is concentrated *in vacuo*. (Step 2) The crude residue is taken up in CH_2Cl_2 and trifluoroacetic acid is added. The reaction mixture is stirred at ambient temperature for 2 hours. The reaction mixture is concentrated *in vacuo* and the residue partitioned between ether and saturated aqueous NaHCO_3 . The layers were separated and the ethereal layer washed with saturated aqueous NaHCO_3 (1x). The ethereal layers are combined and concentrated *in vacuo*. The resulting residue is purified via flash column chromatography over silica gel to give (2R,3R,4S,5R,6R)-2,3,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-4-yl 2-((4- oxo-3-((5-



[0247] 2-(8-oxo-7-((5-(trifluoromethyl)benzo[d]thiazol-2-yl)methyl)-7,8-dihydropyrazino[2,3-*d*]pyridazin-5-yl)acetic acid (Compound **24**) is prepared using the same method described previously in U.S. Patent No. 8,9 16,563.

[0248] (2*R*,3*R*,4*S*,5*R*,6*R*)-2,3,5-trihydroxy-6-(hydroxymethyl) tetrahydro-2*H*-pyran-4-yl 2-(8-oxo-7-((5-(trifluoromethyl)benzo[d]thiazol-2-yl)methyl)-7,8-dihydropyrazino[2,3-*d*]pyridazin-5-yl)acetate (Compound **25**): To a stirred solution of Compound **24** and (3*aR*,5*S*,6*S*,6*aR*)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-ol (Compound **9**) in THF is added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, NEt₃, and DMAP (catalytic). The reaction is stirred at room temperature until completion, as monitored by TLC. The reaction mixture is concentrated *in vacuo*. The crude residue is taken up in CH₂Cl₂ and trifluoroacetic acid is added. The reaction mixture is stirred at ambient temperature for 2 hours. The reaction mixture is concentrated *in vacuo* and the residue partitioned between ether and saturated aqueous NaHCO₃. The layers were separated and the ethereal layer washed with saturated aqueous NaHCO₃ (1x). The ethereal layers are combined and concentrated *in vacuo*. The resulting residue is purified *via* flash column chromatography over silica gel to give (2*R*,3*R*,4*S*,5*R*,6*R*)-2,3,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-4-yl 2-(8-oxo-7-((5-(trifluoromethyl)benzo[d]thiazol-2-yl)methyl)-7,8-dihydropyrazino[2,3-*d*]pyridazin-5-yl)acetate (Compound **25**).