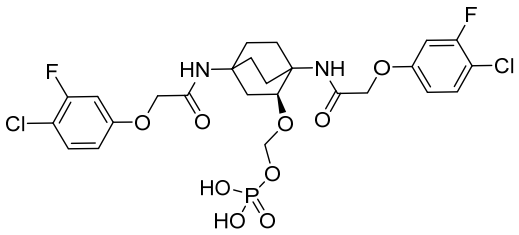
exchange of GDP with GTP in eIF2 is catalyzed by its dedicated guanine nucleotide exchange factor (GEF) eIF2B. eIF2B exists as a decamer ($B1_2\ B2_2\ B3_2\ B4_2\ B5_2$) or dimer of two pentamers in cells (Gordiyenko, Y. et al, *Nat Commun* (2014) 5:3902; Wortham, N.C. et al, *FASEB J* (2014) 28:2225-2237). Molecules such as ISRIB interact with and stabilize the eIF2B dimer conformation, thereby enhancing intrinsic GEF activity and making cells less sensitive to the cellular effects of phosphorylation of eIF2α (Sidrauski, C. et al, *eLife* (2015) e07314; Sekine, Y. et al, *Science* (2015) 348:1027-1030). As such, small molecule therapeutics that can modulate eIF2B activity may have the potential to attenuate the PERK branch of the UPR and the overall ISR, and therefore may be used in the prevention and/or treatment of various diseases, such as a neurodegenerative disease, a leukodystrophy, a cancer, an inflammatory disease, an autoimmune disease, a viral infection, a skin disease, a fibrotic disease, a hemoglobin disease, a kidney disease, a hearing loss condition, an ocular disease, a musculoskeletal disease, or a metabolic disease.

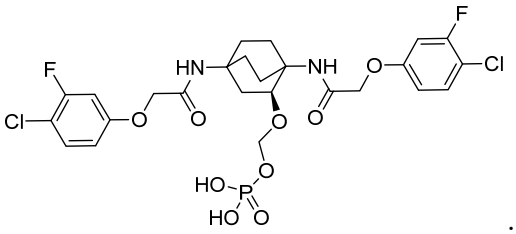
SUMMARY

[004a] In one aspect of the present disclosure, there is provided a compound represented by compound, wherein the compound is:



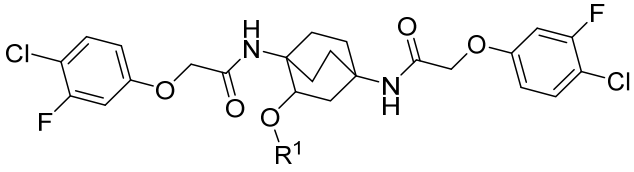
, or a pharmaceutically acceptable salt, thereof.

[004b] In another aspect of the present disclosure, there is provided a compound represented by a compound, wherein the compound is



.

[005] In one example, described herein is a compound represented by Formula (I):



(I);

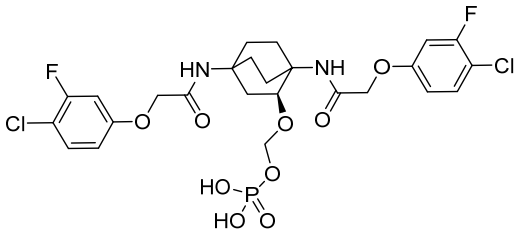
or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof, wherein:

R^1 is selected from the group consisting of -C(O)-C_{1-4}alkyl, -C(O)-O-C_{1-4}alkyl, -C(O)-N(R^a)-C_{1-4}alkyl, -C(O)-C_{1-4}alkylene-C_{1-4}alkoxy, -C(O)-C_{1-4}alkylene-O-C_{1-4}alkylene-C_{1-4}alkoxy, -methylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-O-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-N(R^a)-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2)_2$, -C(O)-C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2$)(O-C_{1-5}alkylene-P(O)$(OH)_2$), -methylene-O-C(O)C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$, -methylene-O-C(O)C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2)_2$, -C(O)-O-C_{1-5}alkylene-O-C(O)C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$, -C(O)-N(R^a)-heteroarylene-C_{1-2}alkylene-O-P(O)$(OH)_2$, -P(O)$(OH)_2$, -SO_3H, -$SO_2NR^aR^b$, -C(O)-heteroaryl, -C(O)-C_{1-5}alkylene-O-C_{1-5}alkylene-phenyl and methylene-C_{1-5}alkoxide;

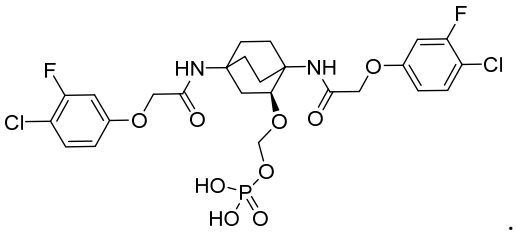
wherein -C(O)-C_{1-4}alkyl is substituted by one or two substituents each independently selected from the group consisting of –NR^aR^b and -CO_2H; and wherein -C(O)-O-C_{1-4}alkyl, -C(O)-N(R^a)-C_{1-4}alkyl, -C(O)-C_{1-4}alkylene-C_{1-4}alkoxy, -C(O)-C_{1-4}alkylene-O-C_{1-4}alkylene-C_{1-}

CLAIMS

1. A compound, wherein the compound is:



, or a pharmaceutically acceptable salt, thereof.

2. A compound, wherein the compound is  .