INHIBITORS OF ERK NUCLEAR TRANSLOCATION

RELATED APPLICATIONS

[0001] This application is a Continuation patent application of PCT Application No. PCT/IL2019/051326 filed on Dec. 3, 2019 which claims the benefit of priority under 35 USC § 119(e) of U.S. Provisional Patent Application No. 62/774,360 filed on Dec. 3, 2018. The contents of the above applications are all incorporated by reference as if fully set forth herein in their entirety.

SEQUENCE LISTING STATEMENT

[0002] The ASCII file, entitled 87819Sequence Listing.txt, created on Jun. 3, 2021, comprising 1,264 bytes, submitted concurrently with the filing of this application is incorporated herein by reference.

FIELD AND BACKGROUND OF THE INVENTION

[0003] The present invention, in some embodiments thereof, relates to therapy, and more particularly, but not exclusively, to compounds that inhibit ERK1/2 nuclear translocation and to uses thereof in treating proliferative diseases and disorders such as cancer.

[0004] The ERK cascade plays a central role in the regulation of various cellular processes, including proliferation and differentiation. Therefore, its dysregulation is associated with diseases such as cancer. One of the hallmarks of the cascade is the nuclear translocation of ERK1/2, which is important mainly for the induction of proliferation, but less so for other ERK1/2-induced processes. The nuclear translocation of ERK1/2 is mediated by the phosphorylation of their nuclear translocation signal (NTS). This phosphorylation allows interaction of ERK1/2 with importin7, which carries ERK1/2 into the nucleus, where the ERK1/2 phosphorylates transcription factors.

[0005] Plotnikov et al. [*Nat Commun* 2015, 6:6685] describes an NTS-derived myristoylated phosphomimetic EPE (Glu-Pro-Glu) peptide which blocks the interaction of importin7 and ERK1/2, and consequently the nuclear translocation of ERK1/2.

[0006] Arafeh et al. [*Sci Rep* 2017, 7:16345] reports that the EPE peptide significantly reduced the viability of BRAF-mutant melanoma, as well as NRAS-mutant and NF1-mutant melanomas which are resistant to other ERK cascade inhibitors; and that EPE peptide exhibited synergy in combination with the MEK inhibitor trametinib in reducing the viability of NRAS-mutant melanomas.

[0007] Samadani et al. [*Biochem J* 2015, 467:425-438] describes compounds with a thienyl benzenesulfonate scaffold which were designed to inhibit ERK1/2 substrates containing an F-site or DEF motif. A crystallographic structure of 1,1-dioxo-2,3-dihydrothiophen-3-yl benzenesulfonate (also referred to therein as SF-3-026) bound to the inactive form of ERK2 was obtained and deposited in the PDB (Protein Data Bank) under accession code 3QYI. Analogs of SF-3-026 were prepared and compared with SF-3-026, and the naphthyl analog of SF-3-026 (SF-3-030) was reported to be the most potent inhibitor.

[0008] U.S. Patent Application Publication No. 2014/0179743, by some of the coauthors of Samadani et al. [*Biochem J* 2015, 467:425-438], describes non-ATP-dependent inhibitors of ERK which comprise a —S(═O)$_2$— linking group; and more particularly, compounds with a 1,1-dioxo-2,3-dihydrothiophen-3-yl or 1,1-dioxo-tetrahydrothiophen-3-yl moiety attached to a —O—S(═O)$_2$— or —N(R)—S(═O)$_2$— linking group, including SF-3-026 and SF-3-030.

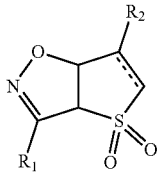
[0009] Albini et al. [*Tetrahedron* 1982, 38:3629-3639] describes regioselective cycloaddition of thiophene-1,1-dioxide and 2,3-dihydrothiophene-1,1-dioxide to benzonitrile oxides.

[0010] Additional background art includes Ananthan et al. [*Tuberculosis* (*Edinb*) 2009, 89:334-353]; Birkner et al. [*Int J Mol Sci* 2017, 18:E1990]; Bryant et al. [*Trends Biochem Sci* 2014, 39:91-100]; Campbell et al. [*Cancer Res* 2007, 67:2098-2106]; Deer et al. [*Pancreas* 2010, 39:425-435]; Flores & Seger [F1000*Prime Rep* 2013, 5:41]; Glowienke et al. [*Mutat Res* 2005, 581:23-34]; Michailovici et al. [*Development* 2014, 141:2611-2620]; Plotnikov et al. [*Mol Cell Biol* 2011, 31:3515-3530]; and Schevzov et al. [*Mol Biol Cell* 2015, 26:2475-2490].

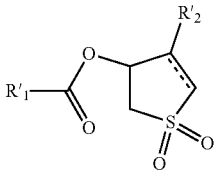
SUMMARY OF THE INVENTION

[0011] According to an aspect of some embodiments of the invention, there is provide a compound for use in treating a disease or disorder associated with nuclear translocation of ERK1/2, the compound being represented by Formula I or Formula II:

Formula I



Formula II



wherein:

[0012] each dashed line independently represents a saturated or unsaturated bond;

[0013] R_1 and R'_1 are each independently an aryl or heteroaryl, which is substituted or non-substituted; and

[0014] R_2 and R'_2 are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, halo, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, sulfonate, sulfate, cyano, nitro, azide, phosphonyl, phosphinyl, carbonyl, thiocarbonyl, a urea group, a thiourea group, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, C-carboxy, O-carboxy, sulfonamido, guanyl, guanidinyl, hydrazine, hydrazide, thiohydrazide, and amino,

[0015] wherein when R_2 is hydrogen, the dashed line in Formula I represents an unsaturated bond, and when R'_2 is hydrogen, the dashed line in Formula II represents an unsaturated bond.