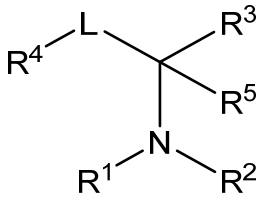
Sestrin1 or -2 is required for disruption of its interaction with GATOR2 and subsequent activation of mTORC1. Sestrin2 mutants incapable of binding leucine cannot signal the presence of leucine to mTORC1, and cells depleted of Sestrin2 and its homologs render mTORC1 insensitive to the absence of leucine (Wolfson et al., (2015) Science pii: ab2674 [Epub ahead of print]).

[0006] The Sestrins are three related proteins (Sestrin1, -2 and -3) of poorly characterized molecular functions (Buckbinder et al., (1994) Proc Natl Acad Sci U S A 91, 10640-10644; Budanov et al., (2002) Cell 134, 451-460; Peeters et al., (2003) Human genetics 112, 573-580). Sestrin2 inhibits mTORC1 signaling and has been proposed to activate AMPK upstream of TSC as well as interact with TSC (Budanov and Karin, (2008) Cell 134, 451-460), but later studies find inhibition of mTORC1 by Sestrin2 in the absence of AMPK (Peng et al., (2014) Cell 159(1):122-33) further emphasizing the important role the GATOR2 complex plays in modulating mTORC1 in response to Sestrin2.

[0007] Modulation of the Sestrin-GATOR2 complex represents a potential therapeutic target for selectively modulating mTORC1 activity indirectly.

SUMMARY

[0008] It has now been found that compounds of the present disclosure, and pharmaceutically acceptable compositions thereof, are effective as Sestrin-GATOR2 modulators. Such compounds have the general formula **I**:

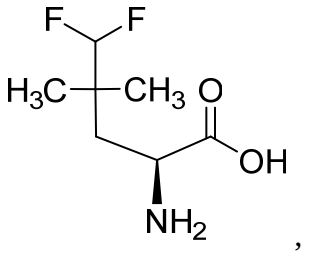


I

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

[0009] Compounds of the present disclosure, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with mTORC1. Such diseases, disorders, or conditions include diabetes, epilepsy, neurodegeneration, immune response, suppressed skeletal muscle growth, and cellular proliferative disorders (e.g., cancer) such as those described herein.

[0009A] In a first aspect, the present disclosure refers to a compound selected from:



,

I-90

or a pharmaceutically acceptable salt thereof.

[0009B] In a second aspect, the present disclosure refers to a pharmaceutically acceptable composition comprising the compound of the first aspect, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0009C] In a third aspect aspect, the present disclosure refers to a composition of the second aspectfor use in treating depression.

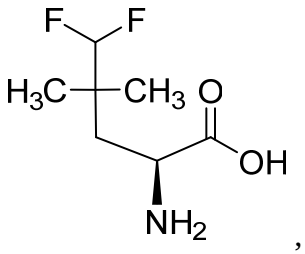
[0009D] In another aspect, the present disclosure refers to a use of a composition of the second aspect in the manufacture of a medicament for treating depression.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

CLAIMS

We claim:

1. A compound selected from:



,

I-90

or a pharmaceutically acceptable salt thereof.

2. A pharmaceutically acceptable composition comprising the compound according to claim 1, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

3. A composition of claim 2 for use in treating depression.

4. Use of a composition of claim 2 in the manufacture of a medicament for treating depression.