# PRODRUGS OF STAT3 INHIBITORS

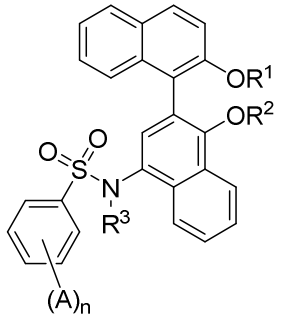
## CROSS REFERENCE

**[0001]** This application claims the benefit of and priority to U.S. Provisional Patent Application No. 63/366,437, filed June 15, 2022, which is incorporated by reference in its entirety herein.

## SUMMARY

**[0002]** Disclosed herein, in certain examples, are compounds of Formula I, or pharmaceutically acceptable salts or solvates thereof, and compositions comprising a compound of Formula I, or a pharmaceutically acceptable salt or a solvate thereof, and a pharmaceutically acceptable carrier. In certain examples, the compounds and compositions disclosed herein are effective at inhibiting signal transducer and activator of transcription 3 (STAT3) and thus are useful in methods of treating, preventing, or reducing the risk or severity of certain diseases or disorders such as cancer, fibrosis, and inflammatory diseases or disorders.

**[0003]** In one aspect, provided herein is a compound of Formula I:

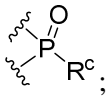



(I),

or a pharmaceutically acceptable salt or a solvate thereof, wherein

A is halo, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$haloalkyl, or $C_{1-4}$haloalkoxy;

$R^1$, $R^2$, and $R^3$ are each independently H, $C(=O)NR^AR^B$, $P(=O)(OH)(R^C)$, or $C_{1-4}$alkylene-O-$P(=O)(OH)(R^C)$; or

$R^1$ and $R^2$ together form: 

;

provided that $R^1$, $R^2$ and $R^3$ are not simultaneously H;

$R^A$ is H or $C_{1-4}$alkyl;

$R^B$ is $C_{1-6}$alkylene-N(H)($C_{1-6}$alkyl), $C_{1-6}$alkylene-(5-8 membered heterocyclyl), $C_{1-6}$alkylene-C(=O)OH optionally substituted with amine, $C_{1-4}$alkyl, or benzyl;

$R^C$ is $C_{1-4}$alkyl or hydroxy; and

n is an integer 0, 1, 2, or 3.

**[0004]** In certain examples, provided herein are pharmaceutical compositions comprising a compound as described herein, or a pharmaceutically acceptable salt or a solvate thereof, and a pharmaceutically acceptable carrier. In one aspect, provided herein is a pharmaceutical composition comprising: a) a compound as disclosed herein, or a pharmaceutically acceptable salt or a solvate thereof, and b) a pharmaceutically acceptable carrier.

**[0005]** In certain examples, provided herein are methods that involve the use of (e.g., comprise the administration of) a compound of formula (I), a STAT3 inhibitor, wherein the compound of formula (I) is formulated in a manner described herein (e.g., is present in a composition as described herein). In one aspect, provided herein is a compound as disclosed herein, or a pharmaceutically acceptable salt or a solvate thereof, for use in therapy. In specific examples, provided herein are methods of treating, preventing, or reducing the risk or severity of cancer. In one aspect, provided herein is use of a compound as disclosed herein, or a pharmaceutically acceptable salt or a solvate thereof, in the manufacture of a medicament for treating cancer in an individual in need thereof. In other specific examples, provided herein are methods of treating, preventing, or reducing the risk or severity of fibrosis. In one aspect, provided herein is use of a compound as disclosed herein, or a pharmaceutically acceptable salt or a solvate thereof, in the manufacture of a medicament for treating fibrosis in an individual in need thereof. In still other specific examples, provided herein are methods of treating, preventing, or reducing the risk or severity of an inflammatory disease/disorder. In one aspect, provided herein is use of a compound as disclosed herein, or a pharmaceutically acceptable salt or a solvate thereof, in the manufacture of a medicament for treating inflammatory disease or disorder in an individual in need thereof. In one aspect, provided herein is use of a compound

as disclosed herein, or a pharmaceutically acceptable salt or a solvate thereof, in the manufacture of a medicament for treating neurodegenerative disease or disorder in an individual in need thereof. In one aspect, provided herein is use of a compound as disclosed herein, or a pharmaceutically acceptable salt or a solvate thereof, in the manufacture of a medicament for treating non-alcoholic fatty liver disease or steatohepatitis in an individual in need thereof. In one aspect, provided herein is use of a compound as disclosed herein, or a pharmaceutically acceptable salt or a solvate thereof, in the manufacture of a medicament for treating cachexia in an individual in need thereof. In one aspect, provided herein is use of a compound as disclosed herein, or a pharmaceutically acceptable salt or a solvate thereof, in the manufacture of a medicament for treating anaphylaxis in an individual in need thereof.

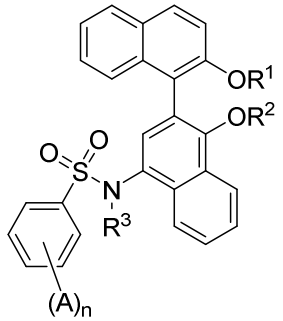
**[0006]** Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing **Detailed Description**, **Examples**, and **Claims**.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0007] FIG. 1** shows the comparison of exposures of TTI-101 SEDD and Compound 9 (in PBS) in H22 syngeneic mice.

## DETAILED DESCRIPTION

**[0008]** The present disclosure provides, in certain embodiments, compounds of Formula I,




(I)

or pharmaceutically acceptable salts or solvates thereof, and compositions comprising a compound of Formula I, or a pharmaceutically acceptable salt or a solvate thereof, and a